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"The effects of morphine and oxycodone on memory in humans"

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Overview

The side effects of opiates are an important area of study as detriments to activities of daily living and to quality of life might outweigh detriments caused by untreated pain. Furthermore there has been relatively little research into the cognitive effects of opiates. This thesis aims to explore the effects of morphine and oxycodone on memory. Part one of the thesis comprises a literature review of the cognitive effects of opiates. It presents an overview of the current levels of understanding as well as highlighting the clinical importance of furthering our understanding. It also briefly raises the question of how gender may interact with the drug effects.

Part 2 comprises the empirical paper. It reports a randomised, placebo-controlled, double-blind study comparing the effects of 10mg morphine, 5 mg oxycodone and placebo on 18 healthy volunteers. The findings were that these doses did not produce significant impairments in most cognitive measures, and there was no retrograde memory impairment as was seen in a previous similar study involving cancer patients. It found some subtle drug effects on working memory, episodic memory and subjective experiences. More importantly, it revealed some subtle interactions of gender and weight with drug implying that the current practice of prescribing doses of oral opiates that are not determined by weight and gender may be inappropriate. Part 3 comprises a critical appraisal of the research. It includes a description of my personal experience during the research process as well as exploring further issues of validity within the study.

Table of Contents

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Part 1

Literature Review

"How do opiates affect memory?"

Abstract

Opiates have been commonly used for the management of pain for many years. Despite this, there is a surprising lack of research into the effects of opiates on cognition, with far more research having been carried out on other classes of psychotropic drugs. This paper will outline why it is important to understand the cognitive effects of opiates, in particular the short acting opiates morphine and oxycodone. It will review past research into the area to demonstrate the level of current understanding. The author is particularly interested in the results of a recent paper (Kamboj et al., 2005) that demonstrated an apparent retrograde memory impairment caused by morphine. As well as providing clinically relevant information about the cognitive effects of opiates, this finding also provides us with some theoretical insights into the normal workings of memory and has implications for future research.

1. Introduction

The following review investigates both the importance of furthering our knowledge of the cognitive side effects of opiates and the current understanding of these effects. The bulk of the paper reviews studies that have investigated the cognitive effects of opiates in a variety of settings. The review will then attempt to synthesise the current knowledge of the effects of opiates on memory with current understanding of memory function. Finally, some recent articles relating to how weight and gender can mediate the effects of opiates are presented.

Two databases were searched: PsychINFO 1966 to April 2006 and MEDLINE 1966 to April 2006. The search parameters provided articles with any one of the following key words; opiate, opioid, morphine, oxycodone with any of these key words; memory, cognitive, cognition, amnesia. The abstracts from these articles were read by the author, studies using scientific method for assessing the cognitive effects of opiates were included.

2. Why is it important to understand the effects of opiates?

2.1. Clinical use of opiates

Opiates are commonly used as analgesia in the treatments of both acute pain (following injury or surgical procedures) and persistent pain (including cancer-pain and chronic non-cancer pain). In the past there has been a reluctance to prescribe opiates, especially on an outpatient basis for chronic non-cancer pain, for three main reasons. Firstly there is concern that patients may suffer too much from the side effects, including sedation and cognitive impairment. Secondly, there are fears that patients may build up a tolerance to the drugs or may become addicted. Finally, there

is some concern that increased prescribing of these drugs on an outpatient basis would lead to higher rates of drug abuse in the general population due to the greater number of opiates available outside of clinical settings. It is estimated that in the UK, 2 – 6 million people have persistent severe non-cancer pain (British Pain Society, 2004), with an estimated 30 million adults in the USA (Joranson, Tyan, Gilson & Dahl, 2000) showing that in this clinical population alone there are a significant number of people who may be have a potential benefit or risk due to opiate use.

Recent research has addressed some of these concerns, indicating that some of the reasons for the reluctance in prescribing may be unfounded. Whilst there is some evidence that patients may develop tolerance to opiates, the increase in dose needed to produce adequate analgesia is often associated with an increase in pain symptoms as illness progresses and it can be difficult to deduce whether higher doses needed are due to tolerance or increased pain (Houde, 1985). Fears that clinical opioid use for pain management may lead to drug addiction may be assuaged by evidence showing that the typical drug seeking behaviour demonstrated by addicts does not occur in patients after opioid prescription for childbirth, operations and myocardial infarctions (Gould et al., 1992) and addiction rates in general clinical populations taking opioids have been shown to be less than 1% (Melzack, 1992). Furthermore, an increase in the amount of oral opiates given to outpatients was not associated with an increase in street addiction in Sweden (Agenas, 1982 in Mcquay, 1997).

Thus, the main barrier to opiate prescribing is the risk of adverse side effects. Clinicians attempt to strike the correct balance between adequate pain relief and unwanted side effects. This has lead to legal cases with patients complaining of either

inadequate pain relief or intolerable side effects. Indeed the British Pain Society (2004) states that: "*Complete pain relief is rarely achievable, and then only at the expense of side effects such as cognitive impairment*".

The British National Formulary (BNF; Joint Formulary Committee, 2006) states that the most common side effects experienced by patients taking opiates are nausea, vomiting, constipation and drowsiness, with a risk of respiratory depression and hypotension at higher doses. However, a recent review of the safety and efficacy of long-acting opioids for chronic non-cancer pain found that the most common adverse effects were abuse, addiction, respiratory depression, nausea, vomiting, constipation, somnolence, confusion and dizziness, with little further evidence of cognitive impairment (Chou, Clark & Helfand, 2003).

In a review of opioid use for neuropathic pain, the most common side effects were constipation, nausea, drowsiness, dizziness, sweating, dry mouth and sedation. In most patients these side effects alleviated after three months of opiate use (Kalso, 2003). The British Pain Society acknowledges the potential cognitive effects of opiate use by recommending that patients do not drive if they are titrating their dose or if they feel "cognitively impaired", and they also suggest that patients modify their work and domestic duties when taking opiates. However, there is a lack of clear guidelines explaining what type of cognitive impairment a person may experience and what they should expect to be able to do.

Recently, both the British and American Pain Societies published guidelines endorsing the use of opiates for non-cancer pain with the proviso that patients are

monitored by a multidisciplinary team to look out for potential risks outlined above (British Pain Society, 2004; American Pain Society, 1998). However it is acknowledged that there is a lack of good quality research about the benefits and risks associated with opioid use for persistent non-cancer pain.

The cognitive side effects of opiate use on an acute basis are also poorly understood, with patients reporting the effects anecdotally with terms such as 'mental slowness'. Thousands of people in UK are prescribed short acting opiates every year, so it would be prudent to understand exactly what the cognitive side effects are. This is of increasing relevance now, with more people taking opiates on an outpatient basis. It raises issues of safety, in relation to tasks such as driving, and also issues about quality of life. Also, if the drug is affecting their cognitive state, then this needs to be taken into account if patients are required to make important decisions, for example, it may affect their ability to give informed consent to treatment. Hence the possible detriments to quality of life caused by the opiates need to be weighed up with the detriments to quality of life if someone has undertreated pain.

There are a range of opiates available for analgesia and morphine has been the most widely used for many years. However, the clinical use of oxycodone is on the increase. Animal studies have shown that while morphine produces its effects primarily via the mu-opioid receptors, oxycodone also has an effect on the kappa-opioid receptors (Smith, Ross, Nielsen & Saini, 2001) indicating that oxycodone may produce its analgesic effects through slightly different mechanisms. Oxycodone produces a longer lasting analgesia and is associated with fewer side effects. Recently, Staahl, Christrup, Anderson, Arendt-Nielsen, and Drewes (2006) compared the analgesic effects of

morphine and oxycodone by inducing different types of pain in healthy volunteers. Whilst both drugs had equal analgesic properties on skin and muscle pain, oxycodone produced superior analgesia on thermal and mechanical stimulation of the oesophagus. They concluded that oxycodone may be a useful alternative to morphine in the treatment of visceral pain.

2.2. Recreational and dependent use of opiates

Heroin is the most commonly abused opiate, with an estimated nine million heroin users worldwide (United Nations Office for Drugs and Crime, 2004) and almost a million chronic heroin users in the US. Furthermore, the estimated number of first time users of prescription pain killers for recreational purposes in the US has risen dramatically in the past few years, from less than half a million in 1996 to nearly 2.5 million in 2002 (Centre for Substance Abuse Research [CESAR], 2004). This is nearly as high as the estimated incidence of first time cannabis use (2.6 million in the same year) and more than twice as much as the number of new ecstasy users (1.1 million) (CESAR, 2004). Recently, one of the newer opiates, oxycodone, has gained popularity as a drug of abuse (Substance Abuse and Mental Health Services Administration [SAMHSA], 2002). Trends in recreational use indicate that drug use in the UK often follows that in the US, so recreational use of oxycodone is likely to increase in UK. Even less is known about the cognitive effects of oxcycodone than morphine, and this highlights the importance of investigating the area further.

3. Evidence from pre-clinical studies

There are severe limitations of using research from animal studies to extrapolate to human cognitive functioning. Most animal studies use mice or rats, whose cortices are

vastly smaller and simpler than those of humans. However, more invasive procedures than can be carried out on humans have been done, providing insight into some of the basic neurochemical mechanisms involved. Whilst these studies with opiates have been able to demonstrate at which part of the brain the opiate is having its effect, which receptors and which neurochemical systems are involved, care must be taken if extrapolating these findings to humans.

Several studies have demonstrated memory impairments following morphine administration in animals. Rats have been shown to be impaired in memory performance following morphine in the shuttle avoidance test (Izqiurdo, 1980), the radial maze (Spain and Newson, 1991) and the Morris Water maze (Sala et al., 1994). Some of these have specifically investigated the retrograde amnesic affect of opiates in variety of tasks. Impaired retention of material encoded before being given an opiate has been demonstrated in mice (Castellano, 1975) and rats (Izquierdo, 1979). These researchers have concluded that the impaired performance is due to a disruption in memory consolidation, as they were able to control for other possible causes including sedation and possible interference from increased distractibility.

The effects of morphine on memory have been shown to be mediated via the hippocampus. In rats, extracellular glucose levels reduce in the hippocampus while performing a memory task and morphine injections lead to less reduction in glucose, implying that the hippocampal cells are not as active (McNay, Canal, Sherwin & Gold, 2006). More precisely, Meilandt, Barea. Harvey and Martinez (2004) demonstrated that morphine produces its amnesic effect due to its action on the mu-opioid receptors in the CA3 field of the hippocampus. Further research has implicated the involvement

of the dopamine system (Costanzi, Battaglia, Rossi-Arnaud, Cestari & Castellano, 2004) and the cholinergic system (Li, Wu, Pei & Xu, 2001) in mice.

If similar effects are found in humans, one could expect that opiates would cause memory impairments, and that these impairments might be similar to patients with hippocampal dysfunction.

4. A review of the Cognitive effects of opiates

4.1. Methodological Issues

There have been several studies aiming to investigate the cognitive effects of opiates, but findings have been varied, with some reporting impairments and others reporting cognitive enhancement following opiate treatment. There are several methodological problems with most studies investigating the effects of opiates on cognition and these concern the cognitive tests used, the types of opiates given and the characteristics of the people who were given the opiates. Firstly, the majority of studies have used a limited range of measures, with some only assessing one function such as psychomotor speed or word list recall. Any impairment or lack of impairment found following the administration of an opiate has then been erroneously generalised to conclude that the opiate did or did not have any effect on cognition and/or memory as a whole (e.g. Lorenz, Beck & Bromm, 1997). Secondly, studies have varied in the types of opiate used, showing differing effects of short-acting compared to long-acting opiates or with morphine like agonists compared to mixed action agonists. Thirdly, studies have varied in their use of comparison groups: some use repeated measures designs, comparing people on opiates with themselves on placebo or another psychotropic drug; others use between subject designs, comparing clinical or

drug abusing populations with either opiate free patients or with healthy volunteers. These clinical studies have limited generalisability as control groups often differ from the clinical populations across a range of variables (e.g. psychopathology, education, pre-morbid intelligence). Related to this is the issue of whether a participant is actually experiencing pain or not. Pain itself can modulate cognition with evidence (described below) indicating that it can have both an enhancing effect (Sjøgren, Thomsen & Olsen, 2000) and an impairing effect (Veldhuijzen et al. 2006). When comparing different groups one must take into account further confounding factors that can influence the effect an opiate exerts on cognition including their prior experience of (and therefore tolerance of) opiates, their age, their illness and levels of sedation.

There are drawbacks associated with relying on any of these particular patient groups, and whilst testing opiate naïve participants may seem most beneficial, several side effects that can influence performance on cognitive tasks such as nausea and sedation subside once a person has received opiates on a number of occasions. Despite these drawbacks, it is still relevant to review the cognitive effects found in the various different participant groups so long as one is aware of the other factors which may be contributing to performance changes on cognitive tasks.

4.2 Zacny's (1995) Review of the Effects of Opioids on Psychomotor and Cognitive Functioning

A comprehensive review of the effects of opioids on psychomotor and cognitive functioning in humans was carried out by Zacny (1995). The relevant findings from this review will be discussed, and then more recent studies will be reviewed.

Overall, Zacny found that mixed agonist-antagonists cause greater impairment than other opiates (including morphine and oxycodone) with opiate naive participants displaying greater levels of cognitive or psychomotor impairment than habitual or occasional users. In studies investigating the effects of morphine, some studies showed impairments of motor performance and some showed impaired sustained attention in patients, drug abusers and healthy volunteers.

Morphine had fewer effects on accuracy of responding, ability to process information and intellectual functioning than would be expected from the subjective effects often reported by patients (including mental clouding, confusion, grogginess and light headedness). Only eight studies specifically investigated the effects of morphine on memory. Digit span was impaired in cancer patients following morphine dose escalation (Bruera, Macmillan, Hanson & MacDonald, 1989), but unaffected in healthy volunteers (Saddler, James & Harington, 1985). Immediate free recall was found to be unaffected in five studies of opioid dependent drug abusers (Preston, Bigelow & Liebson, 1988a, 1988b, 1989; Strain, Preston, Liebson & Bigelow, 1992, 1993), but was impaired in a study of former drug addicts (Preston et al., 1987) and in cancer patients following dose escalation (Bruera et al., 1989). Only one study investigated delayed recall and found that this was impaired by morphine infusions in healthy volunteers (Kerr et al., 1991).

In the only study that Zacny found assessing the effects of oxycodone, healthy volunteers given intra-muscular injections of oxycodone displayed impairments in choice reaction time, whilst performance on other measures of cognition remained

intact (Saarialho-Kere, Mattila, & Seppala,1989). The only impairments in this study were to physiological responses such as exophoria and body sway. One study investigated healthy volunteers' reactions to dihydrocodeine, which is another codeine derivative like oxycodone. This study actually demonstrated an improvent in a test of working memory (Digit Span forwards and backwards) and speed of processing (Symbol Cancellation test) (Svekely, Torok, Karczag, Tolna & Till, 1986).

As well as reviewing papers that tested cognitive performance following opiates in laboratory conditions, Zacny also reviewed epidemiological data, and found that most studies showed no evidence of gross neuropsychological impairments following opioid use and that people taking opioids were not at increased risk or accidents. This seems to be in accordance with the experimental data discussed above.

Zacny provided several suggestions for important future research into this area. Over the past decade since his review, a number of studies have been carried out, attempting to clarify further the cognitive effects of opiates.

4.3. Healthy Volunteers

As described above, there are two main difficulties with using data on the effects of opiates in healthy volunteers. Firstly, the presence or absence of pain is likely to modulate the physiological and cognitive effects of the opiates. Secondly, tolerance to the side effects of opiates develops over time, with relatively greater side effects occurring following an acute dose in opiate naïve participants. Thus, generalizing effects in healthy volunteers to the more clinically relevant effects in patients receiving opiates for pain needs to be done extremely cautiously. Nevertheless,

investigating the effects in opiate naïve volunteers can provide valuable insights into the effects that morphine has on cognitive processes.

However, very few studies to date have tested the cognitive effects of opiates in healthy volunteers. In one study, healthy volunteers given a continuous morphine infusion showed decrements both in the ability to process serially presented material and in a test of fine motor control (Coda et al., 1994). In a previous study, the same researchers also found that a single dose of morphine was associated with memory deficits in opiate naïve participants (Kerr et al., 1991). Specifically, participants were impaired at encoding, processing and recalling serial verbal information, with delayed recall also being impaired. In both of these studies, participants received steady infusions providing them with morphine plasma concentrations of 20-80ng/ml (equivalent to 1.5-6mg injections).

O'Neill et al. (2000) investigated the effects of morphine in healthy volunteers in a cross-over trial comparing the effects of oral morphine, detropropoxyphene, lorazepam and placebo. Overall they found that 10mg of oral morphine did not cause substantial detriments in participants' performance on their cognitive measures and actually caused an improvement in accuracy on a choice reaction task. Whilst they did not find any impairment in immediate or delayed recall, the memory test used was relatively concise (short word list recall) so it is possible that there were ceiling effects. However, this was difficult to evaluate as the paper does not report any actual scores.

4.4. Drug Abusing Populations

Studies investigating the effects of opiates in drug abusing populations typically assess performance effects in abstinent heroin addicts on methadone treatment programmes. This is done either by using comparison groups (i.e. former opiate dependent volunteers not on methadone, current heroin users or non drug abusing volunteers) to assess the long term effects of opiates or by varying the methadone dose using within subjects designs. It is important to note that whilst there are similarities with morphine, methadone is a long-acting synthetic opiate, with a different mode of action to morphine. Some methodological difficulties arise when deciding how to assess the effects of methadone. When using within subjects designs, comparing the effects of methadone with that of placebo in this population is troublesome as the withdrawal symptoms and craving experienced by withdrawing the methadone may explain some of the neuropsychological deficits (Curran, Bolton, Wanigaratne & Smyth, 1999). However, when comparing former heroin dependent individuals in methadone treatment with healthy volunteers, the long-term detriment to cognitive function due to chronic prior heroin use can potentially contaminate the results. Indeed, in a study investigating the neuropsychological deficits of opiate abusers, Davis, Liddiard and McMillan (2002) found that former addicts displayed cognitive impairment whether they were on a methadone programme or not. Whist the cognitive impairment was worse for those taking methadone, the difference was not statistically significant.

A within-subjects method used in a study by Curran, Kleckham, Bearn, Strang and Wanigaratne (2001) to elucidate the effects of methadone administration separately from the effects of chronic opiate use. This was done by using a repeated measures

design with patients who usually received their methadone in two equal doses in the day. They were given the same amount of methadone overall in a day, but it was administered in two preparations per day, with each linctus preparation containing 100%, 50% or 0% (placebo) of their daily dose. Patients did not report any subjective differences including craving and mood due to their drug administration regime, indicating that they were not experiencing withdrawal effects. Furthermore, they were not able to differentiate between when they received methadone and when they received placebo. However, patients receiving 100% of their daily dose were impaired on a task of episodic verbal memory (delayed prose recall).

More recently two studies have highlighted impairments due to methadone by comparing former heroin addicts who were not participating in methadone treatment programmes with those that were. Verdejo, Toribio, Orozco, Puente and Pérez-Garcia (2005) found that patients taking methadone performed worse on tests of processing speed, visual spatial attention, working memory and tests sensitive to executive function deficits (assessing cognitive flexibility, and analogical reasoning). In a study comparing methadone maintained patients with both abstinent users not taking methadone and healthy controls, Mintzer, Copersine and Stitzer (2005) found deficits in tests of motor and cognitive speed, working memory, decision making and executive function that could be ascribed to the methadone alone rather than long term heroin abuse. This study did not find an impairment in verbal recall or recognition.

Overall therefore, whilst no deficits in episodic memory have been found in patients receiving stable doses for methadone, an acute administration of twice the usual dose was associated with verbal recall deficits.

4.5. The Effects of Opiates in Clinical Populations

In testing the cognitive performance of patients taking opiate medication for pain, the methodological problem of assessing the side effects of someone not experiencing pain are eliminated. However, patients have a variety of characteristics that may make them different to comparison control groups (e.g. illness and mood). Furthermore, attempts to assess the effects of opiates using repeated measures designs are difficult for the ethical reasons that giving someone a placebo is likely to lead to them experiencing further pain.

4.5.1. Non-Cancer Pain

Chronic non-cancer pain affects an estimated 30 million adults in USA (Joranson et al., 2000). As explained above, both British and American guidelines now endorse opiate treatment as being appropriate (British Pain Society, 2004). In a randomized controlled trial comparing the efficacy of opiates against tricylic antidepressants (TCA) for the treatment of post therapeutic neuralgia, both treatments were considered superior to placebo in pain reduction, with opiates having a nearly significant superior effect ($p=0.06$) to that of TCAs (Raja et al., 2002). Also, significantly more patients in this study preferred the opiate treatment. However, this finding must be treated cautiously, as the preferential effects of morphine may not have been due to its analgesic effects.

However, there is still a reluctance to prescribe opiates for this type of pain, due to fears of cognitive impairment. Subjectively, 54% of patients receiving opiates for the treatment of chronic pain complained of difficulties with short term memory, concentration and attention (McCracken and Iverson, 2001). However, from this study it was not possible to ascertain whether the impairments actually existed, or whether it was merely the patients' perception of the impairments.

It is has also been commonly acknowledged that the administration of opiate analgesics following surgery can lead to an increased prevalence and intensity of post operative delirium. In the past, this has led some physicians to prescribe weaker painkillers, particularly to patients already thought to be at risk (e.g. elderly patients or patients with dementia). However, in a study investigating the relationship between pain and opiate use on the development of post operative delirium following hip fracture, Morrison et al. (2003) found that under-treated pain was the most significant factor in the development of delirium. Patients who were "cognitively intact" pre-morbidly were nine times more likely to develop delirium if their pain was under-treated and overall, patients receiving less than 10mg of parenteral morphine were more likely to develop delirium. Even in patients who had other high risk factors for developing delirium (e.g. cognitive impairment, abnormal blood pressure or heart failure) the researchers found that decreasing the opiate strength led to an increased chance of delirium.

There are also risks associated with the inadequate relief of chronic pain. In a study that simulated highway driving performance, chronic pain patients who were not taking any analgesic medication were compared to controls (Veldhuijzen et al., 2006).

Patients obtained a higher score on a measure of the amount of 'weaving', which is associated with unsafe driving. In fact, their performance was equivalent to people who had blood alcohol concentrations of 0.08%, which is above the legal limit in most countries and is associated with a threefold increase in the likelihood of causing accidents. Another study demonstrated that chronic pain patients on stable doses of opiates performed at similar levels to control groups (Sabatowske et al., 2003). These results strengthen the argument that any possible cognitive impairment caused by opiates could be less significant than the impairments caused by pain in every day tasks.

Several studies have investigated cognitive effects in more typical laboratory experiments and results have varied with findings suggesting that cognitive performance and memory can be impaired, unaffected or improved due to opiates. Most research in this patient group has investigated the effects of chronic opiate use, once stable doses have been reached. Again the methodological difficulties outlined above need to be taken into account, particularly the presence or absence of pain, as most of these studies compare patients against pain free controls, or use patients taking placebo instead of analgesia.

In a study comparing chronic pain patients with controls, Sjøgren et al. (2000) found that the use of opiates was linked to poorer performance in a task tapping attention (continuous reaction time), a test of psychomotor speed (Finger Tapping Test) and a test tapping working memory (Paced Auditory Serial Addition Task, PASAT). However they also found that enhanced performance on the working memory task was associated with increased levels of subjective pain. They took this to imply that

pain could have an arousal effect, leading to improved performance in some tests. This contrasts with the explanation given by Veldhuijzen et al. (2006) (described above) where untreated pain was postulated to cause cognitive deficits. This could mean that the tests used in Sjogren's task bear no relation to driving performance, or that pain may enhance performance in some domains whilst impairing performance in other domains. Alternatively it seems likely that a small amount of pain may enhance performance, whilst more severe pain would cause impairments.

Sjøgren et al. (2005) went on to test a similar group of patients, but this time included a group of patients who were not on long term opioid treatment. As before, both the patient groups were impaired compared to controls on the same measures of attention, psychomotor speed and working memory, but they also found that within the patient group, those taking opiates were impaired compared to those not on opiates in a test tapping working memory (PASAT). The authors took this to imply that long-term opiate use was associated with a detriment in working memory. However, they previously reported that arousal caused by pain could have an enhancing effect on some measures so the lower test scores in patients taking opiates could also be ascribed to the fact that they were in less pain than patients not taking opiates.

This difficulty was overcome in a study using a within-subjects design, where chronic pain patients were tested before opiate treatment and after dose stabilization (Francis, 2000). When controlling for pain (as pain decreased following opiate treatment) and mood, they found that opiates impaired short-term memory. This study employed a relatively large range of neuropsychological tests, and they could find no other signs of cognitive impairment in measures of delayed verbal recall, visuo-motor tracking,

psychomotor speed and sustained attention. Levels of depression were also found to be an important factor in modulating their abilities. This overcomes some of the methodological difficulties providing more support for the view that long-term opiate use leads to a detriment in short term memory performance.

In contrast, other studies have failed to show impairment. In a similar study to the one by Francis (2000) described above, Lorenz et al. (1997) found that chronic pain patients did not show signs of cognitive decline following dose escalation during morphine treatment initiation and showed some signs of cognitive improvement. However, in this study they only used one task that required participants to respond to auditory tones, using this as a measure of overall "perceptual cognitive status". Using a similar paradigm with more tests of cognitive performance, Haythornthwaite, Menefee, Quatrano-Piacentini & Pappagallo (1998) did not find any sign of cognitive impairment in patients caused by starting opiate treatment. They found that patients showed an improvement in measures of psychomotor speed and sustained attention.

Few studies have measured memory in detail. Whilst two studies above have revealed impairments in short-term memory, no deficits in delayed recall have been found. Overall, the effects of opiates in this patient group appear to be minimal, with mood factors (e.g. depression) and levels of pain being more relevant that the drug treatment.

4.5.2. Cancer Pain

The majority of patients tested in this cohort are elderly, and their disease progression is likely to make their cognitive status more fragile. Thus, impairments due to medication may be easier to detect. However, other general effects of the medications,

such as the sedative effects, could lead to impairment regardless of whether or not it is an opiate. Also, more people in this cohort are likely to have cognitive difficulties regardless of their medication. Indeed, in a study that found neuropsychological impairments including delayed recall deficits in a group of cancer patients receiving opiates (Wood, Ashby, Somogyi & Flemming, 1998) it was not possible to ascertain what the causal factors were, and they found that memory impairment was not affected by the morphine dose. Since tolerance develops to side effects of opiates, it is more worthwhile to investigate the acute-on-chronic effects of morphine.

This was achieved in a study that assessed the cognitive performance of cancer patients following increases in their morphine dose (Bruera et al., 1989). Following a dose increase, patients showed worsening of performance in a decrease in a number of cognitive tasks, including tests tapping motor coordination, brief and sustained attention, verbal information processing and visual memory. These cognitive impairments reduced after the patients had received a stable dose for one week, providing further evidence that the cognitive side effects of opiates are due to the acute administration of the drugs, and that tolerance to the side effects on cognition reduces on repeated use.

Another study investigated the acute effects of morphine administration by assessing cancer patients who were receiving long-acting morphine as well as short acting morphine for periods of increased acute 'breakthrough' pain (Kamboj, Tookman, Jones & Curran, 2005). In this repeated measures design, patients would receive either their regular dose of morphine or a placebo. Ethical difficulties were minimized by giving patients a second drug following testing which contained morphine if they

had received placebo before and vice versa. Intriguingly, patients did not notice a difference in subjective pain and were unable to guess their treatment. The acute-on-chronic administration of morphine did not have an effect on a number of psychomotor and cognitive tests including finger tapping, verbal fluency, digit span and tests of 'everyday' attention. However, there were clear impairments found in a simple test of executive function and in immediate and delayed verbal memory. On the trail making test, acute morphine was associated with increased speed on part A, which is a measure of psychomotor speed, and significantly slower performance on part B which assesses cognitive flexibility or 'set shifting'. This test is widely regarded as simple measure of executive function deficits (Reiten 1955). In immediate and delayed recall of a prose passage, patients were impaired after acute morphine relative to placebo for the story they learned after morphine administration. This demonstrated a clear anterograde amnesic effect of the morphine. Interestingly, morphine was also associated with impaired delayed recall of a story presented before morphine administration showing that morphine also caused a retrograde memory impairment.

The three main possible reasons for retrograde memory impairments are; (1) accelerated forgetting, (2) impaired retrieval and (3) increased susceptibility to interference (Weingartner, Sirocco, Curran, & Wolkowitz, (1995). Kamboj et al. were unable to determine the precise cause of this impairment but the finding is striking as retrograde memory impairments have not been found with any other pharmacological agent.

5. Summary of effects on memory

From the various studies carried out, it is difficult to gain a consistent impression of exactly how opiates affect cognition, with evidence showing both enhancement and impairment of performance due to morphine. Few studies have actually investigated acute effects, and most of those that did focussed on clinical populations, where other factors could be linked to the cognitive performance. Furthermore, few studies have investigated memory in great detail, with most employing one brief memory assessment. The results from the study by Kamboj et al. (2005) show a clear anterograde and retrograde deficit caused by acute morphine administration. However, this effect was found in elderly cancer patients, whose memory abilities and general cognitive resources may have been more fragile so it is uncertain whether morphine would have the same effect in younger, healthy individuals.

Perhaps the most striking finding is that it has been difficult to establish a clear effect, given the anecdotal accounts of cognitive impairment. This discrepancy may be explained by thinking about aspects of a testing scenario. In laboratory conditions, patients are primed and ready to give their best efforts. In everyday tasks, the morphine may have a more subtle effect, so that they are impaired at recalling information that they have not put effort into trying to remember.

6. Linking the effect of opiates on memory to current understanding of normal memory

Evidence from neuropsychological literature, drawing mostly on evidence from individuals with brain damage or from imaging experiments, shows that memory is not a unitary process and comprises of several functionally dissociable components.

This stresses the importance of performing a range of different memory tests, as performance in one domain does not tell us anything about performance in other domains. Whilst there is still debate about the structure of memory processes, there is general agreement that independent processes are responsible for; (1) different stages in memory processing (i.e. storing, encoding and retrieval of information, (2) different modalities of information to be remembered (i.e. verbal or visual), (3) different types of memory storage (i.e. episodic, semantic or implicit).

Patients with amnesia following damage to the brain usually display retrograde amnesia, the inability to recall information learned for a discrete period before the injury. It is also common for patients to demonstrate a degree of anterograde amnesia, the inability to learn and recall information after the injury. However, some famous cases (e.g. patient H.M., Milner, 1972) have demonstrated severe anterograde memory deficits in the absence of any retrograde amnesia. However, patient H.M. did show intact implicit learning, whilst he was unable to recall episodic information.

Previous psychopharmacology studies have highlighted anterograde memory deficits due to a wide range of drugs (e.g. benzodiazepines, scopolamine, alcohol. For review see Curran, 2000). There is also evidence to show that drugs can cause retrograde memory facilitation (Pomara et al., 2006), i.e. people can actually recall more of the information they encoded prior to a drug than if they were given a placebo. The commonly accepted explanation for this is that whilst the drug is taking effect, participants are not able to encode as much new information, meaning that on subsequent tasks assessing recall of the material presented before the drug, there is less interference from items encoded after the drug.

7. Gender Differences in response to opiates

It is well established that a person's weight modulates the effects of any drugs, with heavier people needing a larger dose to produce the same effect as in a lighter person. Another important and often overlooked factor is gender. There is growing evidence from both clinical and preclinical studies that the main effects and the side effects of opiates may be affected by gender.

In a review of sex differences in opioid analgesia, Craft (2003) points out that there are established differences in the analgesic response to opiates, with females showing are stronger response to opiates which work on the μ-opioid receptors such as morphine. There is also a growing evidence base for gender differences in the side effects of opiates, including respiration, body temperature, nausea and vomiting, reinforcement and subjective effects (for review see Craft 2003). These differential effects are mediated by in the differences in brain anatomy, neurochemistry and sex hormones between males and females.

There was a previous view that gender differences could be entirely ascribed to varying levels of sex hormone. However, a recent review by Cahill (2006) demonstrates that there are other important factors involved and one study assessing the response to cocaine in rats showed that oestrus state did not have an effect on the effects of the drug (Fuchs, Evans, Mehta, Case & See, 2005). One difficulty with this area of investigation is that a lack of difference in behavioural response due to gender does not imply that the neural substrates responsible for that behaviour are identical. Indeed, Pfeike, Weiss, Markowitsch and Fink (2005) used functional neuroimaging to show that whilst memory performance was identical on one task, different brain

regions were associated with the task in men and women. Furthermore, De Vries (2004) points out that neuronal sex differences could actually be used to compensate for differences caused by other factors, such as hormones, resulting in the same behavioural outcome.

Given the differences found so far, it is probable that gender differences would also be observed in the cognitive side effects of opiates. Evidence from humans and animals has revealed that there are differences to structure, function and metabolic response in various brain regions associated with learning and memory (Madeira & Lieberman, 1995). Thus, as different structures or functions may be involved in performing the same task, administration of an identical pharmacological agent to males and females is unlikely to have the same response. In particular, Goldstein et al. (2001) showed that the human hippocampi are larger in women than men after adjusting for overall brain size. Furthermore, studies with rats have shown that the receptor affinity of glucocorticoids in the hippocampus is twice as high in males (Turner and Weaver, 1985) and sex differences also exist in long-term potentiation, the mechanism that is widely accepted to underline much of learning and memory in the hippocampus (Maren, De Oca and Fanselow, 1994). There is also evidence that the levels of sex hormones can also modulate the response of hippocampal cells, as oestrogen levels have been shown to alter the excitability of hippocampal cells and augment their NMDA receptor binding.

Given that there are many μ-opioid receptors in the hippocampus, these differences imply that μ-agonist opiates are likely to affect memory in different ways. Gender is often not taken into account when prescribing on an outpatient basis, and when gender

is taken into account, this is to establish the optimum analgesic effects. It is possible that for a given level of anaesthesia, the cognitive effects could be much different. This could mean that doses would need to be adjusted accordingly, or different classes of opiates, (for example those opiates with κ or δ agonist activity) may be more suitable.

8. Clinical Implications

The Kamboj et al. (2005) study provides one of the most robust pieces of evidence showing that acute-on-chronic opiate administration can impair performance a prose recall test. Prose recall tests are regarded to be the best predictor of everyday memory performance (Sunderland Harris & Baddeley, 1983). Detriments to memory functioning have detrimental effects on a person's functional abilities as well as their quality of life. It would therefore be vital to attempt to minimise any potential memory impairments whilst still providing the necessary analgesia. It would be useful to establish whether a different opiate causes less memory impairment at the same analgesic dose.

Morphine and oxycodone are now widely used in hospital as analgesia for operations. If the drug is causing a retrograde amnesic effect, this has the potential to affect how well a patient can recall information given that is presented before the operation. Thus, when clinicians provide important information such as post operative procedures that the patient should follow after they leave hospital, the timing is important. Patients are often given information prior to operations, as they are likely to have difficulty recalling information after general anaesthetic. However, this new evidence suggests

that whilst patients can understand and learn information well, a subsequent dose of morphine may prevent them being able to recall that information in the future.

Furthermore, the gender differences are a relatively under researched area. As differences may exist to the amnesic effects further research should be done in this area to see whether the differences represent clinically significant effects that clinicians should keep in mind when prescribing opiates.

9. Future Research

Following the suggestion that opiates can cause significant impairment to memory abilities, it is would be crucial to attempt to replicate the findings of Kamboj et al. with a different cohort. If possible, a larger range of memory tests should be employed, in order to improve our understanding of which memory mechanisms are being affected by morphine. It would be useful to assess visual memory as well, as this would indicate whether there was any lateralisation of the effect. As there seem to be flaws in any type of design when testing opiates, it would be useful to test the effects in healthy adults, as well as adults requiring opiates for pain (for example after minor surgery, or for chronic pain). This would provide more evidence for whether pain modulates the cognitive effects of opiates. Furthermore, given the difference in brain structure and function between men and women, it would be essential to test a large enough sample to look for gender differences. If testing only one gender, then generalising findings to the other gender would have to be done cautiously.

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Part 2

Empirical Paper

"The effects of morphine and oxycodone on memory in humans"

Abstract

Unwanted side effects, including cognitive impairment, have in the past been a barrier to prescribing opiates for pain management. A recent study (Kamboj et al., 2005) found both anterograde and retrograde amnesic effects following acute-on-chronic morphine in cancer patients. This study aimed to replicate this effect in healthy volunteers and to explore the effect in more depth by using a greater range of memory assessments. Oxycodone was used as well as morphine, as relatively less is known about this newer and increasingly widely used opiate. Gender differences in response to opiates were also evaluated. A randomised, placebo-controlled, within-subjects design was used with 18 participants (9 males, 9 females) who were administered matched capsules containing 10mg morphine, 5mg oxycodone or placebo. There was no effect of drug on most of the memory tests. However, there was a subtle effect on a test of working memory and a test tapping episodic memory. Furthermore, there were several subtle interactions with gender and weight. These findings show that giving healthy participants these clinically relevant doses does not lead to significant memory impairments. However, the differential effects due to weight and gender highlight the importance of considering these issues when clinicians prescribe on an outpatient basis.

Introduction

Morphine and other opiates are commonly used in the management of both acute and chronic pain. Anecdotal reports indicate that opiates cause cognitive impairment, but there has been a surprising lack of research in this area (for review, see Zacny, 1995). Oxycodone is a relatively new opiate derivative which has been shown to produce a longer-lasting analgesic effect with less side effects compared with morphine (Kalso, 2003). Recently, its use has increased, both clinically and recreationally, and even less is known about the cognitive effects of this drug.

Whilst opiates have been used extensively for the management of cancer related pain for many years, there has been a reluctance to use opiates for chronic (non-cancer) pain. Concerns about the risk of addiction and tolerance are more pertinent for patients without terminal diseases. Furthermore, cancer patients may experience cognitive impairment due to other factors, such as their illness or treatment, whereas patients with chronic pain are more likely to be cognitively intact, younger and have more vocational and family responsibilities. Hence, any disruption to cognitive abilities could have a greater impact on a chronic pain patient's quality of life.

Recent evidence has indicated that risks of addiction and tolerance in patients with chronic pain may be less than expected (Houde, 1985; Melzack, 1992) and that undertreated pain may cause more significant cognitive impairments and detriments to quality of life than the side effects of opiates. This has led the American Academy of Pain and the American Pain Society to endorse opiates appropriate treatment for patients with chronic pain (Anonymous, 1997) resulting in more patients in the community taking opiates.

As well as this increase in the clinical use of opiates, the recreational use of prescription pain killers is also on the increase, with similar number of first time pain killer users as there are cannabis users (Centre for Substance Abuse Research [CESAR], 2004). Of these, oxycodone has become a popular drug of abuse (Substance Abuse and Mental Health Services Administration [SAMHSA], 2002a). Given this recent increase prevalence of both clinical and recreational opiate use, it is vital to further our understanding of how it affects cognition.

Neuropsychology

Research with animals has demonstrated that morphine exerts its amnesic effect by disrupting activity in the hippocampus (McNay, Canal, Sherwin & Gold, 2006), and more specifically via the mu-opioid receptors of the CA3 field. These areas are also vital to human memory, as demonstrated by patients with brain damage (e.g. Cermak & O'Connor, 1983) and from structural and functional brain imaging studies (eg. Kopelman, Stanhope and Kingsley, 1999; Maguire & Mummery, 1999) so it is probable that a similar basic mode of action is employed in humans. Furthermore, opiates produce a retrograde amnesic effect (i.e. disruption of information learned before opiate administration) in mice and rats (Castellano, 1975; Izquuiero, 1979) which has been ascribed to its effects on the memory consolidation process.

Humans

Methodological difficulties

The presence or absence of pain can confound research in this area, as pain has been shown to have an enhancing effect on cognitive performance (Sjøgren, Thomsen &

Olsen, 2000), presumably via its general arousal effects. However, pain can have an impairing effect on some areas of cognition (Veldhuijzen et al., 2006). Also, the presence of pain modulates the effects of pharmacological effects of opiates (Hanks & Twycross, 1984) which causes different physical (Borgberg, Neilson & Franks, 1996) and subjective side effects (Colney, Toledano, Apfelbaum & Zacny, 1997) depending on whether or not the person is experiencing pain. Hence it is probable that pain can modulate how opiates affect cognitive processes. Thus, difficulties can arise when using within-group designs on patients as untreated pain during the placebo condition can affect cognitive performance as well as raising ethical concerns. In non-patient groups, the absence of pain will modulate the cognitive effects of the opiate, rendering the findings less clinically relevant. Using between-subject designs is subject to similar problems, as having a patient control group raises ethical issues about withholding necessary analgesia and problems caused by the presence of pain. Evidence also demonstrates that tolerance to the side effects of opiates develops due to repeated use so tests on opiate naive participants are likely to yield different results to tests on participants receiving stable opiate doses.

Current understanding of opiate effects on memory and other aspects of cognition

Some inconsistencies in previous research can reflect the different designs used, as well as different types of opiates. In a comprehensive review of the cognitive and psychomotor effects of opiates, Zacny (1995) found that opiate naive participants were likely to experience more significant cognitive decrements due to opiates than either patients on stable opiate doses or opiate abusers. Using relatively high doses, Kerr et al. (1991) showed that opiate naive healthy volunteers were impaired at delayed recall following morphine, and Bruera, Macmillan, Hanson & MacDonald,

(1989) showed that cancer patients receiving an escalating morphine dose were impaired at tests of immediate free recall. In Zacny's (1995) review, none of the studies demonstrated any memory impairments following oxycodone in any participant group, although at that time there were relatively few studies.

In the past ten years there has been more research in this area. In healthy volunteers, O'Neill (2000) showed that 10mg of oral morphine did not cause decrements to performance on tests of memory, however they used a relatively simple and insensitive battery of tests. In a test by Curran, Kleckham, Bearn, Strang and Wanigaratne (2001) on former recreational opiate users currently on methadone treatment programmes, a dose escalation paradigm was modelled by giving participants their full daily methadone dose at one time point, compared with when it was divided into two daily doses as they were used to. Whilst participants were unable to notice the difference in doses, the highest dose led to a decrement in performance on the delayed prose recall task. Chronic methadone use has also been shown to be linked to deficits in tests of processing speed, working memory, decision making and executive function but not verbal recall or recognition (Mintzer, Copersine & Stitzer, 2005).

Patients receiving opiates for chronic pain often complain of difficulties with short-term memory, concentration and attention (McCraken & Iverson, 2001) and this generally held view has often led clinicians to withhold or reduce doses of opiates. However, untreated pain is associated with higher levels of post-operative delirium (Morrison et al. 2003) and with poorer driving performance (Veldhuijzen et al., 2006). There has been little evidence to suggest that opiate use in chronic non-malignant pain

patients actually causes cognitive impairments. Long term opiate use has been linked to information processing and working memory difficulties (Sjogren et al., 2000). However, cognitive impairment was not found in chronic pain patients following opiate treatment initiation (Haythornthwaite, Menefee, Quatrano-Piacentini & Pappagallo, 1998) or dose escalation (Lorenz, Beck & Bromm, 1997).

A recent study investigated the acute-on-chronic effects of opiates in cancer patients who were receiving a stable dose of slow-release morphine as well as immediate-release morphine for breakthrough pain (Kamboj, Tookman, Jones & Curran, 2005). The researchers found that acute morphine administration was associated with intact performance on tests of everyday attention and working memory, but impaired performance on a test of executive function (Trail Making Test, Reiten, 1955) and episodic verbal memory. Both immediate and delayed recall of the Prose Recall story was impaired relative to placebo for the story presented after the drug (anterograde amnesia) and delayed recall was impaired in the story presented before the drug (retrograde amnesia).

Delayed recall of verbal material relies on the episodic memory system. Impairments to episodic memory are usually observed clinically following head injury or strokes causing damage to the medial temporal lobes with the capacity to recall new information being reduced (anterograde amnesia). Anterograde amnesia is often accompanied by a period of retrograde amnesia, with patients not being able to recall information they had learned prior to their injury. This anterograde amnesia can be induced by other drugs such as benzodiazepines and scopolamine (Curran, 2000),

however, no other centrally acting drug has been shown to produce a retrograde amnesic effect.

In order to understand the processes behind this retrograde memory impairment, it is useful to conceptualise memory using Tulving's (2002) multiple stages of memory model, where the functionally dissociable processes of arousal, attention, encoding, consolidation and retrieval are all necessary for intact memory abilities. In the Kamboj et al. (2005) paper, measures of sedation and attention were unaffected by morphine. Also, as the drug was administered after the information was encoded, then the impairment must have been due to either consolidation or retrieval difficulties. They concluded that the impairment is due to impaired retrieval processes, increased forgetting, or increased susceptibility to interference.

Clinical Relevance

These amnesic effects have serious implications for patients' quality of life, and their ability to recall vital information relating to surgery. Prose Recall provides a good measure of verbal episodic abilities, and impairments in this domain are associated with impaired activities of daily living (Lezak, 1995) and lower quality of life (Sunderland, Harris and Baddeley, 1983). Given the increased use of opiates in chronic non-cancer pain patients, who tend to be younger, more active and are more likely to be in employment, any possible effects on episodic memory need to be clearly understood. Furthermore, the retrograde amnesic effect could have strong implications for patients undergoing surgery. Often patients are given important information (e.g. procedures to follow after surgery) just prior to analgesia, on the assumption that patients' memory may not be suitably intact to learn this information

later on when taking opiates. If this retrograde effect also occurs in healthy volunteers, then clinicians would need to modify their procedures.

Another important clinical area to explore is the differential effects opiates can have on the different genders. Most healthy volunteer research has been carried out on young adult males, mostly due to justifiable concerns about experimental drugs affecting fertility. However, males and females differ in their response to drugs for a variety of reasons, including structural brain differences, different concentrations of receptors, different (and fluctuating) levels of sex hormones and a different ratio of body fat to muscle. In a recent review, Croft (2003) highlighted that the gender differences in basic brain neurochemistry are greater than has been previously thought, and several studies show differences in opiates' analgesic effects.

Theoretical Relevance

Since no other centrally acting drug has been shown to produce retrograde amnesia, it will be important to replicate Kamboj et al.'s finding in healthy volunteers, to investigate whether other confounding variables (such as age and illness) contribute to the effect. Furthermore it would be useful to perform further tests in order to attempt to tease out what aspect of memory is responsible for the effect, and whether the effect is limited to the verbal domain.

Rationale For Current Study Protocol

The current study therefore aims to explore the effects of morphine and oxycodone in healthy volunteers. Given the finding of both anterograde and retrograde amnesia following morphine in cancer patients, the study will investigate whether similar

impairments are also observed in healthy volunteers. A more comprehensive battery of memory assessments will be used to investigate whether the deficit is restricted to the verbal domain, and to attempt to establish more precisely which memory processes are involved.

Episodic Memory

In order to replicate the paradigm used by Kamboj et al. (2005), six versions of the Prose Recall test from the Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn & Baddeley, 1985) were used. Also, this test was specifically designed to test performance on everyday memory tasks as it uses prose passages that resemble news stories. Furthermore, Curran et al. (2001) demonstrated that this task is sensitive to opioid induced recall impairments. The test provides a measure of verbal recall after no delay (immediate) and after a delay. Several processes are required to perform this task, including arousal and attention, as well the necessary stages of episodic memory, encoding, consolidation and retrieval (Tulving, 2002). Other tests in the battery including Finger Tapping and Trail Making (described below) are also sensitive to changes in arousal and attention, so provided performance on these tasks is unaffected, one can presume that any impairment found in the prose recall task is due to episodic memory processes. By repeating the paradigm used by Kamboj et al. (2005), any retrograde memory impairment found (i.e. impaired recall of the story presented before the drug administration) would be not be due to encoding difficulties, indicating that morphine was affecting consolidation or retrieval processes.

Extra memory tests were added in order to investigate the amnesic properties of opiates in more detail. Firstly, a visual memory recall test was added to find out whether the effect is also present in the visual domain. Investigating visual recall is

difficult as many apparently visual tasks can actually be achieved using verbal memory strategies. For example, if participants are shown an array of meaningful pictures and later asked to recall them then most people would also use their memory for the name of each picture. In attempt to avoid this, a complex figure recall task was used where participants are asked to draw an abstract drawing from memory. It is appreciated that verbal strategies can still be used to complete this task, as a participant may verbalise different aspects of the picture (e.g. "a large rectangle with a cross below and a triangle to the right..."), however it seems that this problem would be inherent in all visual memory tasks and it is hoped that the task used minimises the use of verbal strategies.

Another advantage of using the complex figure test is that it has been standardised to test both immediate and delayed recall. Thus, the same paradigm can be used as in used in the verbal recall task allowing clearer comparison of verbal and visual memory performance. Performing this task also requires a number of cognitive processes, including, visual perception, visuospatial organisation, motor functioning and memory. By including a copy, immediate recall and delayed recall stages, then the involvement of memory alone can be factored out and by comparing immediate recall with delayed recall disruptions to storage, consolidation and recall can be shown. Performance on this test has been shown to be sensative to a variety of mild neuropsychological impairments including head injury and dementia (Spreen and Strauss, 1998). Furthermore, Heyer et al. (2000) found that the magnitude of severe post operative pain was associated with poorer performance on the recall component. In particular, patients with right hemisphere damage tend to forget more elements of the figure from the immediate to the delayed tests (Lezak, 1995).

The testing paradigm used for the verbal and visual immediate and delayed recall tests followed the paradigm used by Kamboj et al., (2005). The delayed recall for information presented before the drug was assessed at the same time as the delayed recall for information presented after drug administration. This means that the delay for pre-drug information was approximately 95 minutes, whilst the delay for the post-drug information was approximately 30 minutes. Whilst the difference in timing is not ideal, it was thought to be important to replicate the paradigm used previously. It is likely that performance with a longer delay, recall performance will be poorer than after a shorter delay. However, recall after a long delay is compared with recall after the same delay under the three drug conditions, and is not compared with recall after a short delay. Thus, the difference in delay does not impede the investigation of possible anterograde or retrograde amnesic effects of the opiates.

The third test of episodic memory chosen was the Source Memory Test (Wilding and Rugg, 1996) as it provides a good measure of episodic memory ability, requiring participants to recall the context in which a word was encoded. Two tests are carried out., The first tests recognition while the second requires the participant to recal the gender of the voice (context) that the word was spoken in. Poor performance on this test has been linked with underactivity of the hippocampus (Wheeler, Stuss and Tulving 1997), and impairments have been induced following Ketamine administration (Morgan, Mofeez, Brandner, Bromley and Curran, 2004). This test was chosen in order to assess whether recognition is affected as well as recall, and to assess whether opiates affect contextual information about the acquired knowledge.

Working memory

The digit span (Lezak, 1995) was used as a measure of attention working memory. In the study by Kamboj et al. (2005) participants did not display any impaired performance on this task, providing further support that the impaired performance was due to episodic memory per se. Likewise, in the current study, this test will is used so that any impairments found can be separated from the effects of opiates on attention and working memory.

Other tests

More aspects of the Kamboj et al., (2005) that were replicated were the Mood Rating Scale (Bond and Lader, 1975) and the Finger Tapping test (used as a measure of psychomotor sedation). Furthermore, Kamboj et al., (2005) found that morphine was associated with poorer performance on the trail making test (Reitan, 1955). This test assesses set shifting and cognitive flexibility and poor performance is associated with frontal lobe deficits (Speen and Strauss, 1998). Furthermore, retrograde amnesia has been associated with frontal lobe damage, (Kopelman, 2002), so it will be useful to look for correlations in performance on this test with retrograde memory performance.

In addition to the tests carried out by Kamboj et al. (2005) other tests were added. Participants had their pulse taken before and after drug administration, in order to look for any changes in arousal. Also, a Somatic Effects Scale was created. This was similar to the Mood Rating Scale already described, but included somatic effects that were found to be sensitive to morphine or oxycodone in a previous study (Zacny and Gutierrez, 2003). These included items such as numbness and itchy skin (see appendix F). Nausea was not included in the scale as the participants in the Zacny and

Gutierrez (2003) study only felt nausea after 30 mg of oral oxycodone (six times stronger than the dose used in this study) and no nausea was associated with 20mg oxycodone or 40 mg morphine.

The current study differs from Kamboj et al. (2005) as it included extra tests and also it does not include a measure of pain (as it was assumed that healthy volunteers were not experiencing pain) and the tests of "Everyday" Attention and Word Fluency were omitted as morphine was not found to have any effect on these.

Two tests of decision making were added to the battery. Data from these tests are not reported in this paper as they were used by the other researcher (CP) investigating the abuse potential of opiates as well as their effects on mood and decision making. These are the "Go-No go test" and Roger's gambling task. Furthermore, another visual analogue scale measuring impulsivity was included for this part of the research.

Method

Power Calculation

The power calculations were based on the results reported by Kamboj et al., (2005) regarding the differences in performance between the placebo and morphine condition on the prose recall task. The number of participants needed to achieve power of 0.80 for delayed recall of both the pre-drug story and the post-drug story were calculated. The power calculations were performed using the Zumastat 2.3 software. For delayed recall of the post-drug story (i.e. looking for anterograde memory effects) the standard deviation in the morphine condition was 2.8 and the standard deviation in the placebo

condition was 2.9. The population correlation between the scores in the two conditions was 0.629. Given the above data, 11 participants would be needed in order to achieve a power level of 0.80 when there is a mean difference of 2.4 between the two drug conditions when alpha=0.05 level of significance. For delayed recall of the pre-drug story (i.e. looking for retrograde memory effects) the standard deviation in the morphine condition was 2.0 and the standard deviation in the placebo condition was 2.5. The population correlation between the scores in the two conditions was 0.608. Given the above data, 19 participants would be needed in order to achieve a power level of 0.81 (and 18 would be needed to achieve power of 0.78) when there is a mean difference of 1.4 between the two conditions at alpha=0.5 level of significance.

Participants

The study was approved by the institutional ethics committee (UCLH COREC). Participants were recruited through advertisement, or by contacting people who had taken part in previous psychology research and who expressed an interest in participating in further trials. All participants gave written, witnessed, informed consent.

The inclusion criteria were that participants were aged between 18 and 35 years and could speak English fluently. Participants were screened using a questionnaire (conducted over the telephone or in person by JF or CP) to exclude those with (i) current psychotropic medication or recreational drug use (moderate alcohol intake allowed); (ii) history of opiate or other psychotropic drug abuse; (iii) hyper/hypo tension and hyper/hypothyroidism, (iv) known allergy to opiates, (v) pregnant or breast feeding, (vi) participation in other recent CNS drug studies. Participants also

agreed not to drink alcohol for 24 hours before each test day and not to drive a vehicle for the remainder of the day after testing. Female participants agreed to give a urine sample for pregnancy testing on each visit.

Participants with current psychiatric problems were also excluded based on their scores on the Beck Depression Inventory II (BDI II, Beck, Steer & Brown, 1996) and the Beck Anxiety Inventory (BAI, Beck, Epstein, Brown & Steer, 1987), administered before the first testing session. At the first session, an estimate of premorbid intelligence was obtained using the Weschler Test of Adult Reading (WTAR, The Psychological Corporation, 2001).

A total of 21 people expressed interest. Of these, one failed screening due to participation in a recent similar CNS drug study. Two participants decided not to participate due to the time commitment. In all, 18 participants took part in the study (9 male, 9 female with a mean age of 24.8 years (range 18 to 35 years). All participants completed all three testing sessions.

Design

A three-way cross-over design was used to compare the effects of a single dose of short-acting oral morphine (10mg) with oxycodone (5mg) and with placebo. Treatment order was balanced using a Latin square. Versions of the tests used were counter-balanced within drug treatments. Drugs were administered orally in an opaque gelatine capsule. These were prepared individually by the hospital pharmacy department, and both researchers and participants were blind to treatment order. Testing occasions were separated by a minimum 7 day 'washout' period.

Participants were asked to fast for 4 hours prior to testing, unless testing was in the morning when they were allowed a light non-fatty breakfast. Testing took place in an office in the anaesthesiology wing of UCLH and sessions started between 9:30 a.m. and 3:00pm. Most participants were tested at a similar time on each of their visits. Participants were first assessed with the pre-drug battery for 15 minutes and female participants then had a urine pregnancy test. They were then given the drug capsule to swallow followed by a 60 minute wait for the drug to be absorbed. During this time participants engaged in sedentary activities (reading, talking etc). After 60 minutes, participants were given the post drug battery, which lasted approximately 70 minutes.

Assessments

Tests were selected to assess memory, attention, physiological and psychomotor effects of the drugs. Memory tests assessed immediate and delayed verbal and visual recall, verbal recognition and episodic memory and working memory. Further subjective ratings and decision-making tests were administered, the results of which are reported elsewhere (Phillips et al. in preparation). The order of test administration is shown in Table 1.

Table 1. Order and Timing of test administration

Time after drug (mins)	Test
-15	VAS Scales
-9	Pulse
-8	Prose Recall Story A immediate
-4	Complex Figure A copy & immediate
0	**Drug administration**
60	Prose Recall Story B immediate
63	Complex figure B copy & immediate
66	Pulse
67	Finger Tapping
69	Trail Making
71	VAS Scales
76	*Go - No Go**
82	Digit Span
87	Prose Recall Story A & B delayed
92	Complex figure A & B Delayed
96	Source Memory Presentation
106	*Roger's Gambling Task**
118	Source Memory Test
121	Subjective Drug Effects Scale

* *Tasks in italics are reported elsewhere*

Cognitive Assessments

Prose Recall

Six versions of the prose recall subtest of the Rivermead Behavioural Memory Test (RBMT: Wilson et al., 1985) were used. Participants listened to two different 30 second long prose passages, one before taking the drug, and one after the drug. Immediately afterwards they were asked to recall it by writing it down in both the pre-treatment and the post-treatment sessions. Later in the post treatment session participants were asked to write down as much as they could recall from both the pre-treatment story and the post-treatment story. The delay between immediate and delayed recall was 95 minutes for the story presented in the pre-treatment session and 30 minutes for the story presented in the post-treatment session. Scoring was standardised and each story was broken down into 21 story units. Participants scored

1 point for perfect recall of a unit or use of an exact synonym; ½ points were awarded for partial recall of a unit or a similar synonym. Recall ability in these tests has previously been shown to be affected by opiates (Curran et al., 2001).

Complex Figure Recall

Visual immediate and delayed recall was assessed using the protocol from the Rey-Ostereith Complex Figure Task (Osterrieth, 1944). Six comparable versions were used, and these were the original Rey-Ostereith Complex Figure, the Modified Taylor Complex Figure (Hubley and Tremblay, 2002) and the four figures from the Medical College of Georgia (MCG) Complex Figures (Meador, Taylor & Loring, 1990).

In order to investigate both anterograde and retrograde memory deficits, the testing paradigm used for the prose recall was recreated. Participants were presented with a figure in both the pre-treatment and the post-treatment test batteries. They were asked to draw a copy of the figure then both the original figure and their copy were removed and they were asked to draw it again from memory (immediate recall). Later in the post-treatment session, participants were asked to reconstruct both figures from memory (delayed recall). The delay between immediate recall and delayed recall was 95 minutes for the pre-treatment figure and 30 minutes for the post treatment figure. The author was unable to find any other study that used two complex figure recalls in the same test battery. Pilot testing was carried out on seven volunteers to make sure that the task was achievable, and that people would be able to differentiate the two figures when it came to delayed recall. In the pilot testing, the mean delayed recall score was 24.3/36, Indicating that the task was both achievable and also difficult enough to avoid ceiling effects. Furthermore, people were generally able to

differentiate between the two figures on delayed recall, and the maximum number of figure elements drawn in the wrong figure (substitution errors) was 3.

Scores on the Rey Ostereith Complex Figure and the Modified Taylor have been shown to be equivalent (Hubley and Tremblay, 2002). However, whilst healthy volunteer performance on each of the MCG figures have been shown to be equivalent (Spreen and Strauss, 1998), average scores are 2 points higher than on the Rey Ostereith and Modified Taylor figures. The researcher was unable to find six equivalent standardised complex figures. In order to look for comparable differences between pre- and post-treatment figures, the Rey and Taylor figures were used in the same session, as the other sessions used two of the four MCG figures each. Scoring was done according to criteria in Spreen and Strauss (1998). Each figure was divided into 18 elements, and participants scored two points for accurately reproducing an element, 1 point for a distorted element in the correct place or an accurate element in the wrong place, and half a point for a distorted element in the wrong place.

Episodic Memory

The Source Memory Test (Wilding and Rugg, 1996) was used as a measure of episodic memory as participants were required to recall the contextual information about the stimuli they had recalled as well as simply recognising it. The test consisted of 240 low frequency words that were randomly assigned to six study lists of 40 words. The word lists were pre-recorded, with half the words being read by a male voice and half being read by a female voice (the order of male and female words was random, with no more than three consecutive words being read by the same gender.)

During the study phase, participants listened to the words on headphones. They were asked to repeat the word and then to decide if the word was pleasant or unpleasant if it was read by a male voice, or abstract or concrete if the word was read by a female voice. There was an eight second interval between words and the list lasted for approximately 6 minutes. After hearing the list there was a delay of 10 minutes, during which time participants were engaged in a non-verbal decision making task. A recognition list was created by adding another study list of 40 words to the original and randomising word order. The words were presented individually on a computer screen. Participants had to respond verbally stating whether they had heard the word before, and if so, whether it had been said in a male or female voice. Word recognition responses were recorded as correct hits, false alarms, correct rejections and misses. Source errors were also recorded.

Digit Span

Working memory was assessed using three alternative forms of the digit span (Lezak 1995). Participants were asked to repeat a string of numbers that had been read out loud either forwards or backwards and were given a score of the maximum number of digits they could recall in both the forwards and backwards conditions.

Trail Making (Reitan, 1958)

In the first part of this test participants were required to draw a line connecting 25 numbered circles in numerical order as quickly and accurately as possible. This gives a measure of psychomotor speed. In part B, half of the circles contain letters instead of numbers. Participants were again asked to connect the circles as quickly and accurately as possible, but this time they had to alternate between numbers and letters

(I.e. 1-A-2-B-3-C etc.). Subtracting the time taken to complete part A from the time taken to complete part B this gave a measure of executive function that controlled for simple psychomotor speed. Errors were also recorded.

Subjective Ratings - Visual Analogue Scales

Visual Analogue Scales (VAS) were used to tap subjective effects. These consisted of the Mood Rating Scale (MRS) (Bond & Lader, 1974) and two tests devised by ourselves, the Somatic Effects Scale (SES) (Appendix E) which were given before and after taking the drug, and the Drug Effects Scale (DES) (Appendix F) which was administered at the end of testing. On each test, participants were presented with a series of 100mm horizontal lines with opposing words at either end (e.g. "No Dizziness - Extreme Dizziness"). They were asked to indicate how they were feeling 'at the moment' in relation to those words by marking on the line. In the DES, the pay scale participants were asked to indicate how much they would pay for the same capsule again by marking on the line somewhere between £0 and £10. Also, in the DES, when subjects were asked to rate their own performance in various domains, the line was labelled with "0% of best abilities" at one end and "100% of best abilities" at the other. The lines were partitioned so that participants' marks could obtain a score of between 0 and 10, in 0.5 increments.

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS Version 11.0). Effects of drug were tested using a Repeated Measures ANOVA where the within subject factor was 'drug' with three levels (morphine, oxycodone and placebo). To analyse scores obtained in both pre- and post- drug sessions,

repeated measures ANOVAs used two factors: drug and time (i.e. pre-drug or post-drug). Gender was a between subjects factor in the analyses. Correlations between specified variables used Pearson and only significant correlations are reported at an adjusted α of 0.01. Due to the number of correlations being administered only bivariate correlations were calculated, to reduce the chance of Type I errors. No non-linear effects were investigated. As weight tended to correlate with several of the variables, this was used as a covariate throughout the analyses.

Results

Demographics

Table 2. Demographic information for the participants

	All (n=18)		*Males (n=9)*		*Females (n=9)*		
	Mean	***SD***	**Mean**	***SD***	**Mean**	***SD***	
Age (years)	24.83	*4.25*	24.56	*5.20*	25.11	*3.33*	
Height (m)	1.71	*0.10*	1.79	*0.07*	1.62	*0.06*	*
Weight (kg)	66.77	*13.3*	77.0	*10.1*	56.5	*6.25*	*
BMI (kg/m^2)	22.73	*2.54*	24.1	*2.1*	21.39	*2.29*	*
Estimated VIQ	109.10	*6.17*	108.90	*5.13*	109.20	*7.38*	
BDI	2.83	*2.83*	2.78	*1.99*	2.89	*3.62*	
BAI	2.33	*2.89*	1.44	*1.74*	3.22	*3.60*	

* = *males differ significantly from females*

One way ANOVA showed that showed that males did not differ from females in age or estimated Verbal IQ, but males were taller ($F_{2,16}$=26.34, p<0.001), heavier ($F_{2,16}$=26.81, p<0.001) and had a higher Body Mass Index ($F_{2,16}$=6.76, p=0.019) than females. 14 of the participants reported their ethnicity to be White British, two Indian, one Malaysian and one Chinese.

Cognitive Tests

Mean scores for all the cognitive tests are shown in Table 3 along with finger tapping and pulse.

Table 3. Mean (S.D.) scores for the cognitive and psychomotor tests.

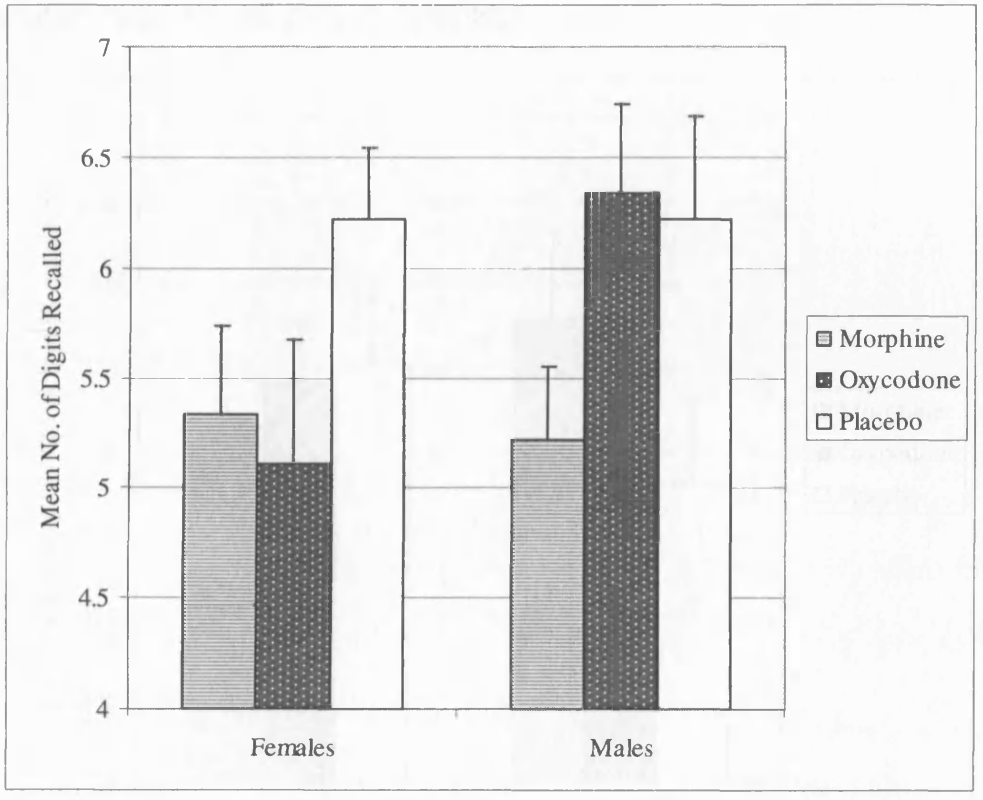
	Morphine		Oxycodone		Placebo		
	Males	Females	Males	Females	Males	Females	
Digit Span							
Forwards	7.7 *(1.4)*	7.3 *(1.1)*	7.7 *(1.0)*	6.8 *(1.5)*	7.7 *(1.1)*	7.2 *(1.6)*	
Backwards	5.2 *(1.0)*	5.3 *(1.2)*	6.3 *(1.2)*	5.1 *(1.7)*	6.2 *(1.4)*	6.2 *(1.0)*	d,a
Prose Recall							
Pre-Drug Story							
Immediate	11.6 *(3.2)*	12.3 *(3.0)*	10.7 *(3.3)*	12.1 *(4.3)*	12.2 *(3.0)*	12.1 *(2.1)*	
Delayed	10.2 *(3.1)*	10.2 *(3.3)*	8.2 *(3.7)*	10.2 *(4.0)*	9.7 *(3.9)*	10.3 *(2.3)*	c
Forgetting	1.4 *(1.8)*	2.2 *(1.4)*	2.6 *(1.9)*	1.9 *(1.5)*	2.5 *(1.9)*	1.8 *(1.5)*	
Retention	0.88 *(0.15)*	0.81 *(0.13)*	0.74 *(0.18)*	0.84 *(0.10)*	0.78 *(0.15)*	0.85 *(0.13)*	a
Post-Drug Story							
Immediate	13.3 *(3.5)*	9.7 *(3.7)*	10.7 *(3.3)*	12.1 *(4.3)*	13.0 *(4.1)*	8.5 *(2.6)*	
Delayed	11.4 *(3.8)*	8.2 *(4.3)*	10.1 *(1.7)*	8.7 *(3.5)*	10.8 *(5.5)*	7.3 *(2.0)*	c
Forgetting	1.9 *(1.9)*	1.6 *(1.3)*	1.3 *(1.8)*	1.5 *(1.4)*	2.3 *(2.5)*	1.2 *(1.4)*	
Retention	0.85 *(0.14)*	0.79 *(0.19)*	0.91 *(0.14)*	0.86 *(0.17)*	0.79 *(0.31)*	0.87 *(0.13)*	
Complex Figure							
Pre-Drug Figure							
Immediate	30.9 *(4.9)*	32.1 *(4.0)*	30.1 *(5.2)*	31.1 *(3.1)*	30.4 *(5.3)*	30.0 *(3.8)*	t
Delayed	22.9 *(8.7)*	20.6 *(6.5)*	21.9 *(8.9)*	20.5 *(6.5)*	20.2 *(11.1)*	19.7 *(5.4)*	
Forgetting	8.0 *(5.8)*	11.5 *(7.1)*	8.2 *(6.7)*	10.6 *(6.1)*	10.2 *(9.7)*	10.3 *(4.9)*	t
Retention	0.73 *(0.21)*	0.65 *(0.19)*	0.72 *(0.22)*	0.66 *(0.20)*	0.66 *(0.30)*	0.66 *(0.16)*	t
Post-Drug Figure							
Immediate	26.3 *(7.5)*	25.1 *(9.4)*	27.3 *(5.9)*	25.5 *(8.3)*	28.1 *(6.0)*	25.7 *(6.4)*	t
Delayed	20.3 *(7.5)*	20.1 *(8.8)*	23.5 *(7.8)*	19.1 *(8.2)*	21.2 *(7.2)*	18.8 *(6.0)*	
Forgetting	5.9 *(3.4)*	5.0 *(4.9)*	3.8 *(4.4)*	6.4 *(4.6)*	6.8 *(3.4)*	6.9 *(6.8)*	t
Retention	0.77 *(0.13)*	0.81 *(0.20)*	0.84 *(0.19)*	0.76 *(0.19)*	0.74 *(0.14)*	0.76 *(0.25)*	t
Source Memory							
Recognition							
Correct Hits	34.4 *(3.5)*	33.3 *(4.5)*	34.2 *(3.0)*	35.1 *(2.4)*	34.3 *(3.9)*	34.8 *(1.9)*	
False Alarms	0.44 *(0.5)*	0.89 *(1.1)*	0.78 *(0.67)*	0.78 *(1.4)*	0.67 *(1.1)*	0.44 *(0.73)*	
Discriminability (d')	3.15 *(0.36)*	2.87 *(0.61)*	2.99 *(0.36)*	3.10 *(0.58)*	3.19 *(0.48)*	3.13 *(0.38)*	
Bias (C)	0.47 *(0.25)*	0.49 *(0.24)*	0.42 *(0.23)*	0.46 *(0.16)*	0.43 *(0.40)*	0.50 *(0.19)*	
Source Identification							
Correct	32.0 *(4.1)*	30.7 *(5.0)*	31.7 *(4.8)*	31.9 *(3.2)*	31.1 *(5.6)*	32.3 *(3.1)*	
Proportion correct	0.93 *(0.08)*	0.92 *(0.05)*	0.92 *(0.08)*	0.91 *(0.05)*	0.90 *(0.10)*	0.93 *(0.06)*	
Errors	2.4 *(3.1)*	2.7 *(1.6)*	2.6 *(2.4)*	3.2 *(1.5)*	3.2 *(3.5)*	2.4 *(2.1)*	d,w,a,b
Trail Making							
Trails A (s)	23.2 *(8.3)*	18.2 *(5.1)*	18.9 *(5.3)*	19.4 *(4.5)*	19.3 *(5.3)*	18.3 *(5.2)*	
Trails B (s)	40.8 *(20.9)*	33.3 *(17.3)*	41.4 *(19.5)*	34.8 *(10.3)*	40.3 *(17.1)*	32.3 *(11.0)*	
Trails B - A (s)	17.6 *(21.8)*	15.1 *(17.9)*	22.5 *(19.3)*	15.4 *(11.3)*	20.9 *(14.2)*	14.0 *(10.7)*	
Tapping	384.6 *(44.2)*	344.6 *(41.9)*	380.4 *(39.8)*	342.6 *(45.4)*	361.7 *(44.3)*	351.3 *(58.4)*	
Pulse							
Before Drug	69.0 *(8.4)*	66.3 *(9.9)*	68.0 *(9.0)*	67.0 *(6.5)*	68.3 *(10.4)*	65.1 *(10.0)*	t
After Drug	67.7 *(10.3)*	62.4 *(10.4)*	64.3 *(8.9)*	59.1 *(4.6)*	63.3 *(8.1)*	57.8 *(7.2)*	t

d = significant main effect of drug; w = significant main effect of weight; t = significant main effect of time; a = significant drug x gender interaction; b =significant drug x weight interaction; c = significant gender x time interaction

Digit span

There was a significant drug x gender interaction on Digit Span backwards ($F_{2,15}$=3.768 p=0.047). As shown in Fig 1, females were equally impaired by morphine and oxycodone compared with placebo whereas males only showed an impairment on morphine. There was also a main effect of drug ($F_{2,16}$=5.90, p=0.012), reflecting higher scores on placebo than on oxycodone and morphine respectively (Table 3). After covarying for weight, this drug x gender effect was no longer significant. There was no effect of drug or gender on Digit Span forwards.

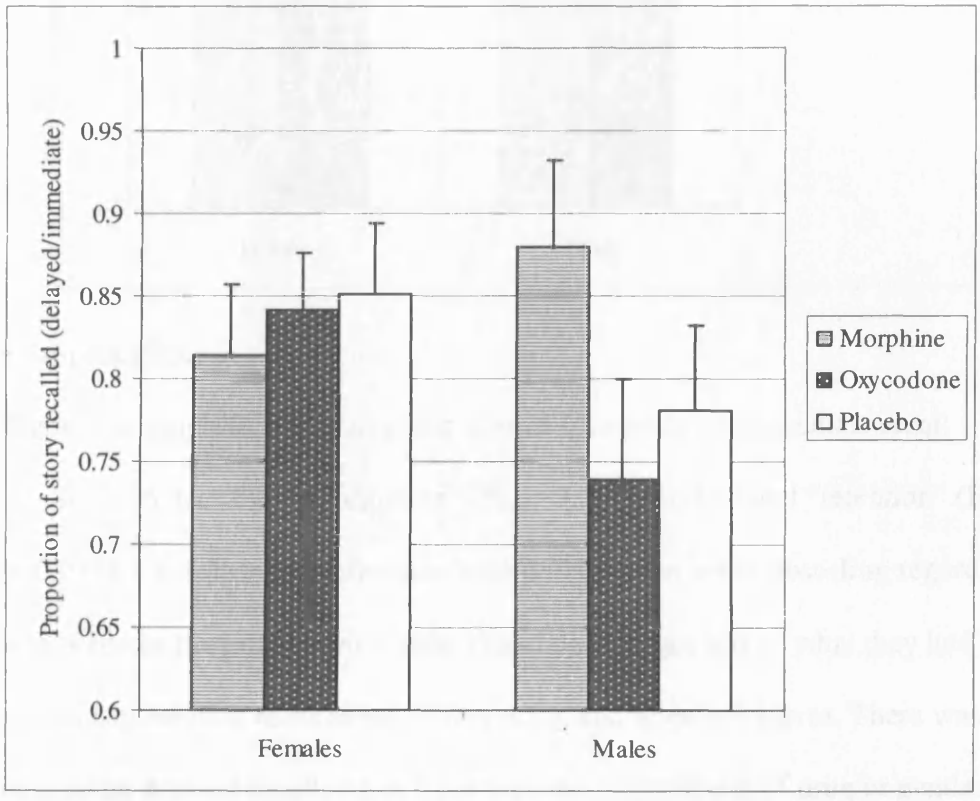
Figure 1. Male and Female mean (+S.E.) no. of digits recalled on the Digit Span backwards



Prose Recall

There was a significant drug x gender interaction on pre-drug story retention ($F_{2,15}$=5.0, p=0.022). As shown in Fig. 2, compared to females, males retained a higher number of story units of the pre-drug story after taking morphine than they did after taking oxycodone or placebo. Again, after covarying for weight, this drug x gender interaction was no longer significant. There was no main effect of drug or gender on the number of correct story units recalled in the immediate or delayed recall of either the pre-drug or the post-drug story. There were no main effects of drug for pre- or post-drug story "forgetting" or "retention" (Table 2).

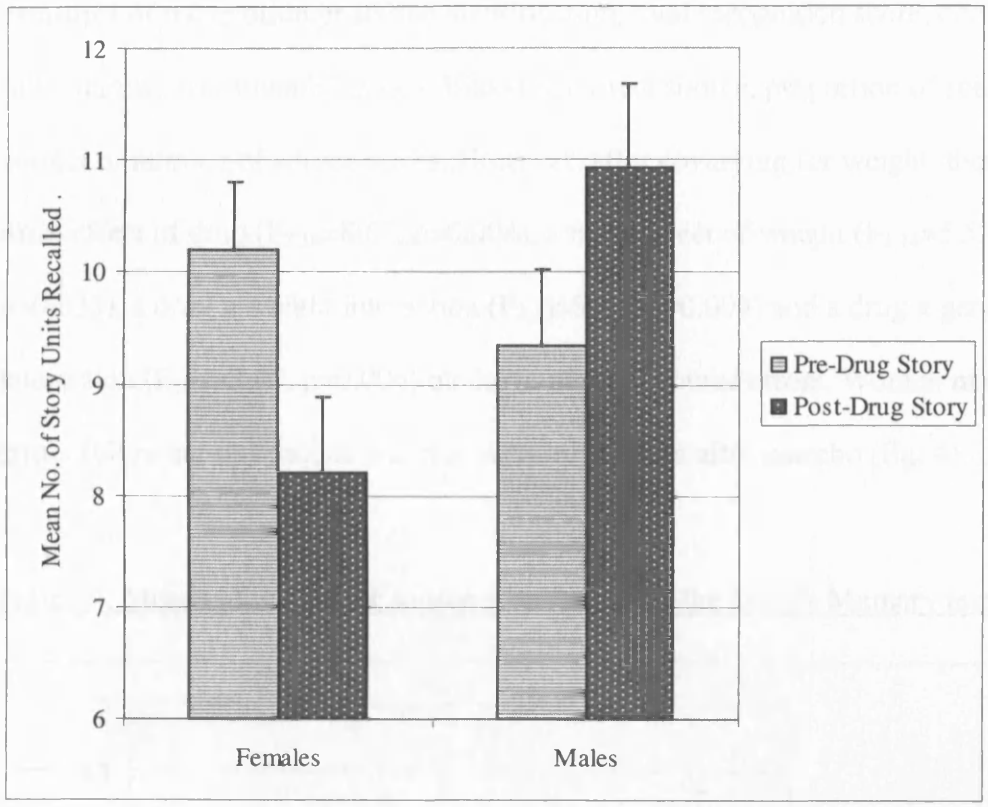
Fig 2. Mean (+S.E.) proportion of pre-drug story units recalled after delay compared with immediate recall (delay/immediate).



There was also a significant gender x time interaction on delayed recall ($F_{2,15}$= 13.474, p=0.002). Females post-drug recall was better than their pre-drug recall in all drug

conditions, and this was reversed in males (Fig. 3). Covarying weight again reduced this gender x time interaction to a trend (p=0.084). There were no main effects of drug or drug x time interactions.

Fig 3. Mean (+S.E.) number of story units recalled during delayed prose recall.



Complex Figure

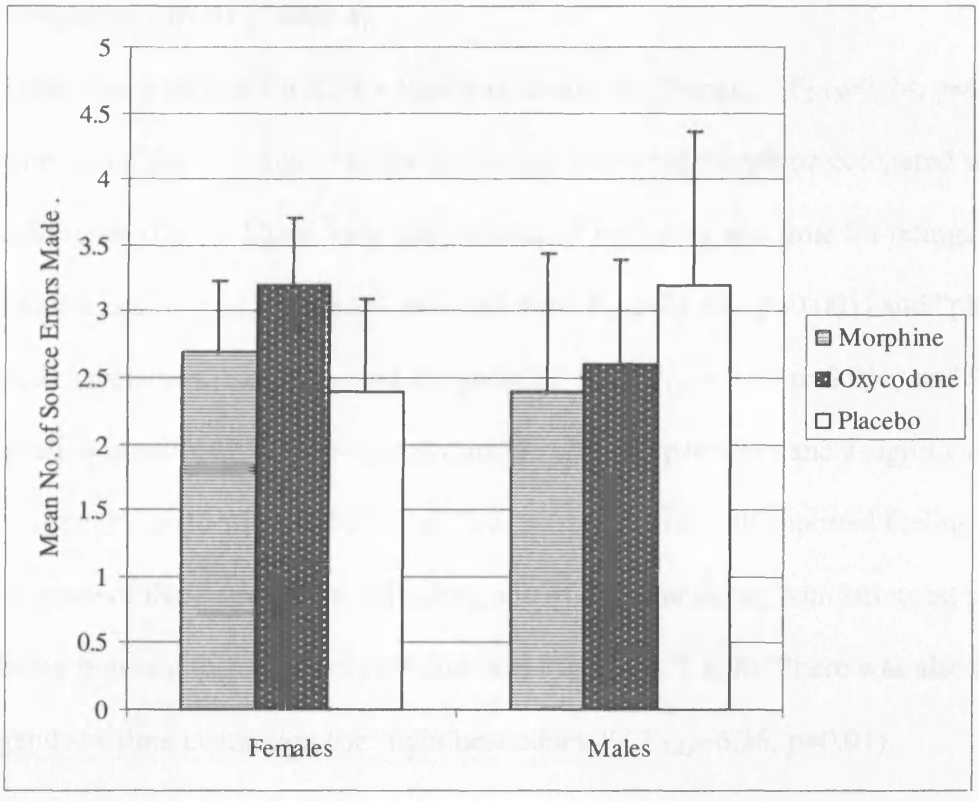
There was a significant main effect of time (pre-post) on immediate recall ($F_{1,17}$=20.06, p<0.001), "forgetting" ($F_{1,17}$=9.16, p=0.002) and "retention" ($F_{1,17}$=6.89, p=0.018). Participants' immediate recall scores were lower post-drug regardless of what capsule they had taken (Table 3) and they forgot less of what they had previously recalled as reflected in forgetting and retention scores. There was no effect of time on delayed recall. Also, there were no main effects of drug or gender on scores for immediate recall, delayed recall, "forgetting" or "retention" for either the

pre-drug figure or the post-drug figure. There was no effect of gender or drug for immediate or delayed recall when time was added as a within subjects factor.

Source Memory

There were no significant main effects of drug or gender on any of the following measures of recognition or source identification; total recognition score, correct hits, false alarms, discriminability (d'), Bias (C), correct source, proportion of source correct or number of source errors. However, after covarying for weight, there was a main effect of drug ($F_{2,14}$=8.67, p=0.004), a main effect of weight ($F_{2,14}$=5.53, p=0.033), a drug x weight interaction ($F_{2,14}$=9.32, p=0.003) and a drug x gender interaction ($F_{2,14}$=7.40, p=0.006) on the number of source errors. Women made more errors following oxycodone whereas men made more after placebo (fig. 4).

Figure 4. Mean (+S.E.) no. of source errors made on the Source Memory test.



Trail Making

There was no effect of drug or gender for the completion time for part A, part B, or for the measure of cognitive flexibility (trails B-trails A).

Finger tapping

There was no effect of drug or gender.

Pulse

There was a significant main effect of time ($F_{1,17}$=20.87, p<0.001). Participants had a lower pulse after taking the capsule, regardless of which treatment it contained. Even though it appeared that the post-drug morphine pulse rates were higher than post-drug oxycodone (Table 3), this effect of drug was not quite significant, ($F_{2,16}$=3.602, p=0.051).

Subjective effects (Table 4)

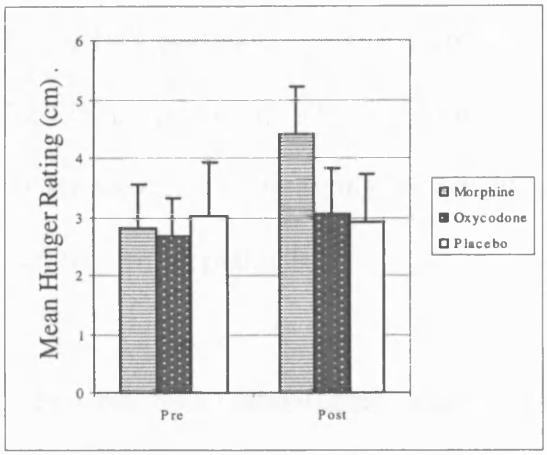
There was a significant drug x time interaction for "hunger" ($F_{2,15}$=3.74, p=0.046), with participants' hunger ratings increasing following morphine compared with other treatments (fig 5). There were main effects of both drug and time for ratings of "light headedness" (drug; $F_{2,15}$=3.99, p=0.039, time $F_{1,16}$=25.59, p<0.001) and "pleasant body sensations" (drug; $F_{2,15}$=4.59, p=0.027, time $F_{1,16}$= 7.08 p=0.016) and there was a nearly significant main effect of drug ($F_{2,15}$=3.61, p=0.051) and a significant effect of time ($F_{1,16}$=12.91, p=0.002) for "dizziness". Participants reported feeling more of all three of these sensations following any of the treatments, with strongest sensations being reported following oxycodone (See Figures 6, 7 & 8). There was also a drug x gender x time interaction for "light headedness" ($F_{2,15}$=6.36, p=0.01).

Table 4. Mean scores (SD) for subjective Visual Analogue Scale ratings from the Somatic Effects Scale (SES), the Mood Ratings Scale (MRS) and the Drug Effects Scale (DES)

	Morphine		Oxycodone		Placebo		
	Pre	Post	Pre	Post	Pre	Post	
SES							
Numb	0.44 *(0.66)*	1.00 *(1.38)*	0.81 *(1.36)*	1.69 *(2.08)*	0.47 *(0.55)*	1.08 *(1.60)*	t
Dry Mouth	1.97 *(2.25)*	2.25 *(2.27)*	2.61 *(2.55)*	2.19 *(2.07)*	1.89 *(2.23)*	1.64 *(2.04)*	
Dizzy	**1.03 *(1.62)***	**1.64 *(2.15)***	**1.42 *(2.18)***	**2.97 *(3.00)***	**0.86 *(1.60)***	**1.58 *(2.24)***	t
Light-headed	**1.14 *(1.44)***	**2.86 *(2.29)***	**1.78 *(2.12)***	**4.06 *(2.98)***	**1.06 *(1.57)***	**2.36 *(2.68)***	d,t
Hungry	**2.81 *(2.20)***	**4.39 *(2.51)***	**2.69 *(1.93)***	**3.06 *(2.34)***	**3.03 *(2.67)***	**2.92 *(2.41)***	e
Tingling	0.39 *(0.65)*	1.25 *(1.97)*	1.00 *(1.83)*	1.61 *(2.39)*	0.53 *(0.58)*	0.78 *(1.18)*	
Flushed/Warm	1.78 *(2.04)*	1.69 *(2.02)*	1.83 *(1.98)*	2.00 *(2.22)*	1.25 *(1.71)*	1.61 *(1.94)*	
Itchy skin	0.83 *(1.01)*	0.69 *(0.77)*	1.14 *(2.00)*	1.33 *(2.26)*	0.86 *(1.36)*	0.92 *(1.43)*	
Depressed	6.08 *(1.97)*	6.31 *(0.96)*	6.28 *(1.46)*	5.94 *(1.07)*	6.31 *(1.39)*	6.28 *(1.10)*	
Euphoric	4.31 *(1.11)*	4.33 *(1.13)*	4.33 *(1.12)*	4.50 *(0.92)*	4.17 *(1.04)*	4.22 *(1.24)*	
Spaced out	6.42 *(1.54)*	4.78 *(1.55)*	6.06 *(2.12)*	4.19 *(1.72)*	6.42 *(1.67)*	5.67 *(2.07)*	
Lost in details	6.89 *(1.72)*	6.22 *(1.93)*	5.89 *(1.95)*	5.44 *(1.88)*	6.58 *(1.66)*	6.28 *(1.74)*	
Heavy/sluggish	5.28 *(1.65)*	4.97 *(1.67)*	5.67 *(2.04)*	5.17 *(1.83)*	5.92 *(1.41)*	5.47 *(1.94)*	
Pleasant body sensations	**1.81 *(2.18)***	**1.92 *(2.00)***	**1.64 *(2.33)***	**2.92 *(2.59)***	**1.28 *(1.94)***	**1.89 *(2.52)***	d,t
MRS							
MF1-sedation	**44.98 *(0.94)***	**45.60 *(1.15)***	**44.52 *(0.86)***	**45.48 *(1.35)***	**44.48 *(0.89)***	**44.94 *(1.17)***	d,t
MF2-discontentedness	56.86 *(1.19)*	57.24 *(1.42)*	56.68 *(1.45)*	56.73 *(1.58)*	56.66 *(1.30)*	56.80 *(1.25)*	
MF3-anxiety	48.31 *(1.87)*	48.21 *(1.73)*	48.03 *(1.83)*	47.90 *(1.95)*	47.42 *(1.42)*	47.96 *(1.75)*	
DES							
Feel drug effect		* 4.25 *(3.42)*		5.19 *(2.98)*		2.78 *(2.78)*	
Like drug effect		4.61 *(2.15)*		4.61 *(1.94)*		4.97 *(0.79)*	
Want more drug		* 5.19 *(2.59)*		* 5.78 *(2.32)*		5.47 *(1.56)*	a
Feel drug high		3.08 *(3.16)*		3.44 *(2.81)*		2.36 *(2.51)*	
Want to take again		2.78 *(2.38)*		3.58 *(2.82)*		3.14 *(2.45)*	
Pay		0.64 *(1.25)*		1.25 *(2.49)*		0.36 *(0.56)*	
Overall performance		5.81 *(1.67)*		5.61 *(1.75)*		6.06 *(1.33)*	
Memory		5.11 *(2.08)*		4.36 *(1.89)*		5.19 *(2.15)*	
Attention		6.33 *(1.72)*		5.97 *(1.93)*		5.81 *(1.83)*	
Decision-making		5.92 *(1.73)*		5.94 *(1.83)*		6.17 *(1.98)*	

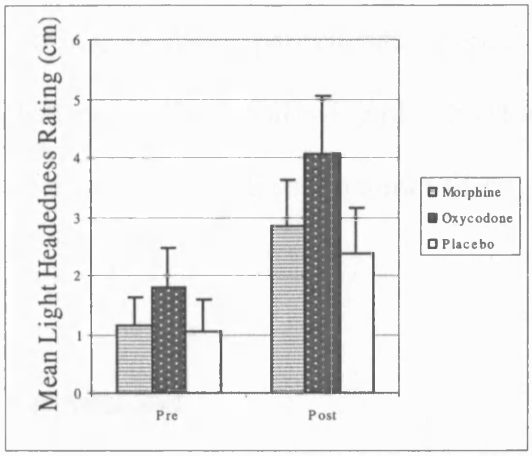
*d = significant effect of drug; t = significant effect of time; e = significant drug x time interaction. a = drug x gender interaction. * = significant difference between male and female scores.*

Figure 5. Mean (+S.E.) VAS rating for hunger



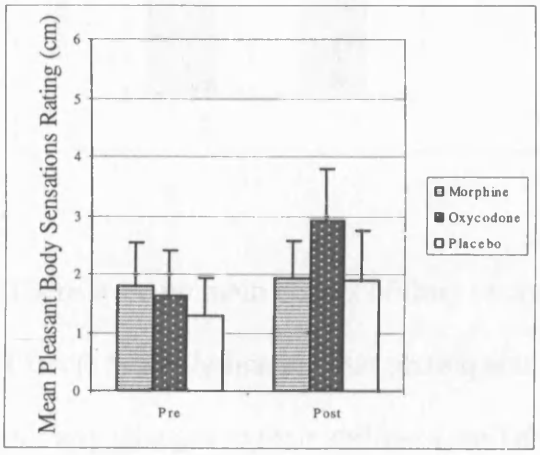
0 = "no hunger"; 10 = "Extreme Hunger"

Figure 6. Mean (+S.E.) VAS rating for Light Headedness



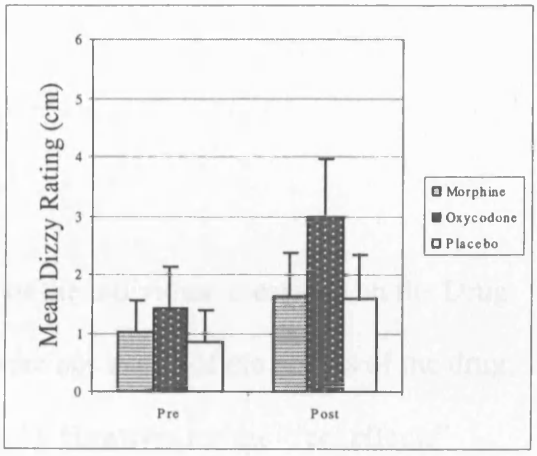
0 = "no light headedness"; 10 = "extreme light headedness"

Figure 7. Mean (+S.E.) VAS rating for Pleasant Body Sensations



0 = "no pleasant body sensations"; 10 = "extremely pleasant body sensations"

Figure 8. Mean (+S.E.) VAS rating for Dizziness

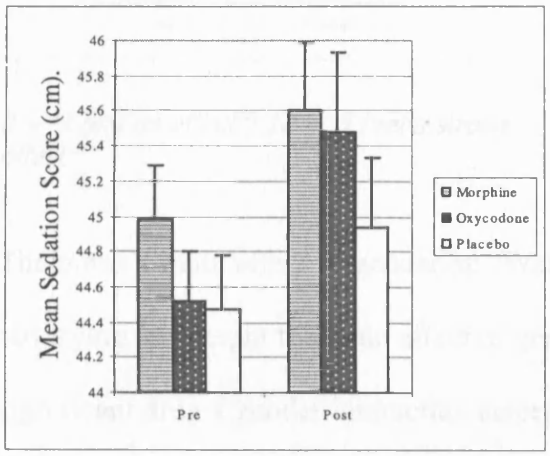


0 = "no dizziness"; 10 = "extreme dizziness"

After covarying for weight, the main effects of drug and time on "light headedness" were no longer significant, but a significant drug x time interaction ($F_{2,15}$=3.88, p=0.044) and a drug x time x weight interaction ($F_{2,15}$=4.192, p=0.036) emerged. For "Pleasant Body Sensations" and "Dizziness", after covarying for weight the main effects of drug and time were no longer significant and there were no interactions.

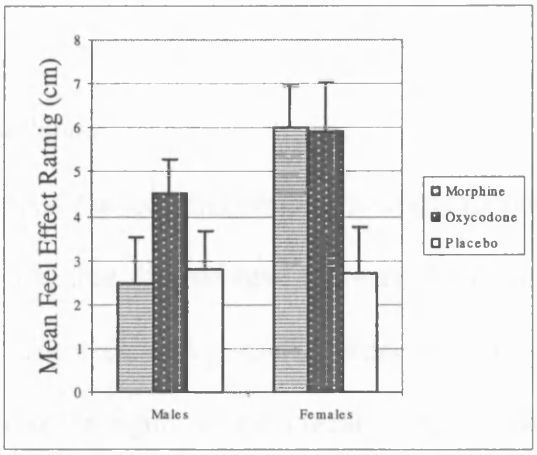
There was also a main effect of both drug and time on sedation (Mood Factor 1) (drug; $F_{2,16}$= 4.45, p=0.029, time; F=$_{2,16}$16.232, p=0.001). As above, participants reported feeling more sedated following either of the active drugs than following placebo (Fig. 9). However, after covarying for weight, these effects were reduced to trends (drug; p=0.079, time; p=0.080).

Figure 9. Mean (+S.E.) Sedation Score calculated from the Mood Rating Scale



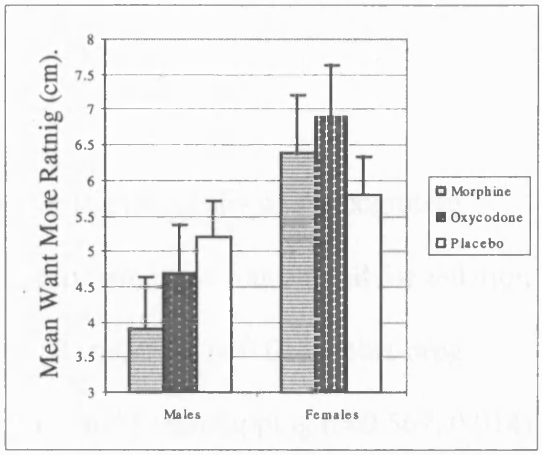
There were no main effects of drug on any of the individual measures on the Drug Effects Scale, indicating that participants were not aware of the effects of the drug, nor any changes to their abilities (see Table 4). However for the "feel effects" measure, there was a main effect of gender ($F_{1,16}$=6.21, p=0.024). Post-hoc simple effects showed that ratings for males and females were significantly different on morphine (p=0.025), with females rating that they felt a stronger effect (Fig. 10). There was a trend towards a linear drug x gender interaction (p=0.068). After covarying for weight, the main effect of gender was no longer significant.

Figure 10. Mean (+S.E.) VAS rating for feeling drug effect



0 = "I feel no effect"; 10 = "I feel a strong effect"

Figure 11. Mean (+S.E.) VAS rating for wanting more /wanting less



0 = "I want more of it"; 10 = "I want less of it"

There was a main effect of gender on "Want more" ($F_{1,16}$=6.93, p=0.018). After covarying for weight the main effect of gender was no longer significant but a significant drug x gender interaction emerged ($F_{2,14}$=4.76, p=0.026). Post-hoc simple effects showed that ratings by males and females were significantly different on morphine (p=0.036) and oxycodone (p=0.038), with females' ratings being closer to the "I want less" end of the scale than males for both of these drug conditions (Fig. 6).

Correlations

Weight

Weight did not correlate with any of the cognitive or subjective ratings on any drugs, but there were several trends. In the morphine condition, there was a trend for weight to correlate positively with Digit Span forwards (r=0.539, p=0.021), finger tapping rate (r=0.492, p=0.038), and negatively with sedation (Mood Factor 1) (r=-0.547, p=0.019), "Feel Effect" (r=-0.516, p=0.028) and "Feel High" (r=-0.495, p=0.037). In

the oxycodone condition there was a trend for weight to correlate with tapping rate (r= 0.527, p=0.025) and "Dislike Effect" (r=0.479, p=0.044).

Sedation

Mood Factor 1 did not correlate significantly ($p<0.01$) with any of the cognitive scores but showed several trends. Following morphine, there was a trend for sedation to correlate with post-drug story immediate recall (r=0.564, p=0.015), post-drug complex figure delayed recall (r=0.505, p=0.033) and finger tapping (r=0.567, 0.014). On oxycodone, there was a trend for sedation to correlate positively with post-drug prose recall retention (r=0.577, p=0.012) and post-drug complex figure immediate recall (r=0.509, p=0.031), and negatively with post drug prose recall forgetting (r=-0.534, p=0.022) and with Digit Span forwards (r=-0.494, p=0.037) and backwards (r=-0.490, p=0.039)

Awareness of drug effects

"Wanting less" of the drug correlated negatively with the amount of post-drug story units forgotten on morphine (r=-0.643, p=0.004) and the delayed recall score for the pre-drug story on oxycodone (r=0.622, p=0.006).

On morphine, participant's subjective "decision making" abilities were correlated positively with post-drug story immediate (r=0.698, p=0.001) and delayed (r=0.640, p=0.004) recall and time to complete part A of the Trail Making Task (r=0.654, p=0.003).

Discussion

The current study used a within subjects design to explore the effects of 10mg oral morphine and 5mg of oral oxycodone on memory and cognition in healthy volunteers. As the volunteers were not taking the medication for pain, the paradigm did not imitate a clinical situation. However, it allowed the use of a double-blind, placebo-controlled design without the ethical difficulty of withholding necessary analgesia. Furthermore, the relatively young and healthy sample was able to tolerate a relatively long battery of cognitive assessments.

The initial hypothesis was that healthy volunteers would display both a retrograde and an anterograde memory impairment. One aim of the study was to investigate whether the effect was also present in the visual domain, and to see if it linked with other episodic memory changes. We found that the drugs did not cause the same transient impairments to anterograde and retrograde memory performance and complex tracking as were found in cancer patients receiving acute-on-chronic doses of oral morphine in a similar study design (Kamboj et al., 2005). The drugs did not cause any significant effect on most of the domains tested. However, there was a significant effect of drug in a test of working memory and a test of episodic memory. Furthermore, there were significant gender differences, and drug with gender interactions, providing valuable evidence that opiates can produce markedly different effects in males and females. Overall, whilst females appear more be more sensitive to the subjective experience of being on the drugs and to the impairing effects of oxycodone on working memory, males show some subtle enhancing effects on tests of episodic memory.

Working memory

On average, participants were able to recall one less digit on the digit span backwards test following morphine compared with placebo. Furthermore there was a drug with gender interaction with females showing the same decrement in performance following oxycodone, while males appeared to be unaffected. Participants were unaffected on digit span forwards, indicating that the morphine only reveals its effect when the task requires the extra cognitive load of holding the digits in memory and reversing them before repeating them. Thus the drug effects were in terms of manipulation rather than maintenance of information in working memory. Impairments to working memory have been linked to difficulties with everyday activities of daily living (Spreen & Staruss, 1998). Performance on this task was not affected by morphine in cancer patients (Kamboj et al., 2005), however these patients were only able to recall an average of 3.6 digits backwards following placebo (compared with 6.2 in our sample) indicating that their performance was already impaired. The extent to which this is due to the effects of chronic slow release opiate treatment, their greater age, effects of their illness per se or a combination of these factors is unknown. If one considers the overall 'resource' model of cognitive abilities, then the above factors would deplete available cognitive resources, leading to a floor effect where subtle effects caused by morphine would be overshadowed. On the other hand, healthy volunteers, with 'spare' cognitive resources would be able to employ compensatory strategies if they noticed an impairment due to a drug.

Other researchers have found mixed results. Performance decrements on different measures of working memory were found in healthy volunteers taking larger doses of morphine (Kerr et al., 1992, Coda et al., 1993). Furthermore, cancer patients

performed worse on the digit span following opiate dose escalation (Bruera et al., 1989). However, some studies have failed to show an effect (e.g. O'Neill et al., 2000), and one has even shown an enhancement in a test of working memory following morphine (Sjogren et al., 2000).

The gender interaction described above disappeared after covarying for weight, indicating that the detriment observed after oxycodone was due to weight differences rather than to other characteristics of being female as all but one of the females in our sample weighed less than the males.

Whilst the score on the test is statistically lower following morphine, a decrement of one digit does not reflect a clinically significant impairment. However, the subtle change produced does provide implications for how other aspects of memory might be affected. Working memory is involved in the normal encoding and storage process associated with long term memory. When encoding and storing meaningful information such as a story, working memory helps by allowing one to hold some words or concepts in mind, whilst listening to more words, in order to gain a cohesive understanding. Manipulating the information into meaningful chunks produces more efficient storage and retrieval. Thus, even a subtle disruption to this ability is likely to have a knock-on affect on other aspects of more long term memory.

Episodic Memory

Prose Recall

There were no effects of drug on the test of verbal and delayed recall. It was hypothesised that participants would experience both an anterograde and a retrograde

amnesic effect following morphine as was found in cancer patients (Kamboj et al., 2005), and this test has also been shown to be sensitive to the amnesic effects of opiates in former heroin users receiving methadone (Curran et al., 2001). The lack of effect found in this robust repeated measures study indicates that clinicians can feel more confident about prescribing this dose of drugs to healthy volunteers without concerns of a loss of function or a detriment to quality of life due to episodic memory difficulties. A plausible explanation for why this cohort differed in its response compared to cancer patients involves the general cognitive 'resource' model described above. For healthy volunteers, if they feel affected by a drug, they may be able to use extra cognitive resources to compensate in order to perform adequately in a task. Cancer patients may not have any extra resources in reserve due to the other factors outlined above (e.g. illness, age, and medications).

A drug with gender interaction on the measure of retention (i.e. proportion of story units recalled relative to immediate recall) for the pre-drug story was observed. Whilst females' scores seem to be relatively unaffected, males showed enhanced performance on morphine compared with oxycodone and placebo. Again, after covarying for weight this effect was no longer significant, showing that the differential effects seen here can again be ascribed to weight.

The enhanced performance in males could indicate that for this specific task, morphine actually aids the process in some way. Perhaps, as seen in studies with benzodiazepines (e.g. Pomara et al., 2006), the enhanced performance may be due to the opiate reducing the amount of material that could be learned after the drug, meaning that when recalling pre-drug information there is less interference from

newer information. The subtle effect of morphine on our measure of working memory did not seem to have any effect on performance on this task. If the impaired performance on this task was due to working memory deficits, then immediate recall scores would be affected and one would not expect the proportion of material retained to be affected. Furthermore, a gender with time interaction was observed, with females performing worse on the post-drug story than the pre-drug story and vice versa in males. Again, after covarying for weight this effect was reduced to a trend once again indicating that the difference is due to weight and not gender per se. This highly significant yet unexpected finding does not provide insights into the effects of opiates, but suggests that, compared to heavier people, lighter people's delayed verbal memory abilities may be worse after a long experimental test battery.

Complex Figure

This is the first study to also investigate visual episodic memory in relation to opiate effects. There were no effects of drugs or interactions with gender observed on these sensitive tests. As visual and verbal memory abilities are not always correlated, this provides valuable evidence that visual episodic memory appears to be unaffected by these doses of morphine and oxycodone and supports the argument that this dose of opiates does not cause an effect on memory generally. The main effects that were observed were due to time rather than to drugs, with immediate recall showing a decrement in the post-drug condition. The author was unable to find any other experiments where the paradigm of using two complex figures was used. The highly significant result here reflects a general feature of running these tasks that after learning one complex figure, learning of a subsequent figure will be impaired. This should be taken into account if running this paradigm in the future.

Source Memory

The drugs exerted a main effect on the number of errors made in identifying what the context in which previous information was learned, which relates to episodic memory abilities. Overall, fewer mistakes were made following morphine, again indicating that it may have an enhancing effect. However, the interaction with gender shows that this relationship is not so straightforward. Women made more errors after oxycodone, indicating that they are more sensitive to the impairing effects of oxycodone than men are. However, men made the most errors following placebo, indicating that both morphine and oxycodone may have had an enhancing effect in men. This was the only cognitive measure where the drug with gender interaction was present after covarying for weight, showing that the differential effects observed here are not merely due to the different weights of the groups of men and women. It is important to note again that whilst these effects were highly significant ($p<0.01$) they are very subtle, with the mean number of errors made varying by less than one across each drug condition and gender.

The increase in source errors made indicate a detriment to the ability to recall contextual information (e.g. how, where, etc.). This uses the same kind of processes needed for storing autobiographical information, and imaging studies have linked deficits in this task performance to over activity in the prefrontal cortex and under activity in the hippocampus (Wheeler, Stuss & Tulving, 1997). Given that opiates restrict activity in the hippocampus, this result is to be expected.

Trail Making Test

There were no effects of drugs on the trail making test or on finger tapping speed. On the trail making test, Kamboj. et al., (2005) observed an improvement following morphine on part A, which assesses visuo-motor tracking speed, and an impairment following morphine on part B which also involves cognitive flexibility. The patients in the Kamboj et al. study performed the task much slower after placebo than our participants with a mean completion time of 64.2 seconds for part A (our participants; 18.8 seconds) and 177.4 seconds for part B (our participants; 36.3). In fact, compared to healthy adults of a similar age, the patients in the Kamboj study were performing on average near the bottom tenth percentiles on both parts of the test, whilst our participants' mean scores were near the ninetieth percentile. Hence it seems likely that our lack of results were due to a ceiling effect. Participants were able to complete the task easily, and any subtle effect caused by the opiate could have been compensated for with other cognitive resources. The patient group were already showing impaired performance at this task, so one would predict that they were already using one hundred percent of their resources in attempting to complete it. Perhaps the enhancement effect shown by Kamboj et al. on digit span forwards only occurs if there is already a significant impairment. This test is one of the most relevant in terms of everyday adaptive functioning (Lezak, 1995) so this lack of effect again strengthens the claim that the doses of morphine and oxycodone used do not have significant effects on activities of daily living in healthy young adults.

Tapping Speed and Pulse

There were no effects of drug on tapping speed, as was also found in cancer patients (Kamboj et al., 2005) implying that there was no decrement to basic psychomotor

performance. The lack of effect on pulse is consistent with previous a finding in healthy controls given much larger oral doses of oxycodone (10-40mg) and morphine (40mg) (Zacny & Gutierrez, 2003).

Subjective Effects

Morphine was associated with an increase in hunger, compared with the other treatments while oxycodone produced an increase in ratings of light headedness, pleasant body sensations and dizziness. Also, both oxycodone and morphine produced a greater increase in ratings of sedation than placebo. There were no main effects of drug on the measures assessing participants' awareness of drug effects but there were interactions with gender. Females tended to feel the effects of both the drugs more than males, and they tended to want less of the drug than males. This discrepancy was greater for morphine than oxycodone.

This pattern of results is different than would be expected following Zacny and Gutierrez's (2003) investigation of the subjective effects of oxycodone and morphine. As the doses used by Zacny and Gutierrez were at least twice as strong for oxycodone and four times as strong for morphine, one would expect them to show greater range and intensity of subjective effects. They found that 10mg oxycodone was associated with an increase in sedation and feeling the drug effect, as was found in our participants after taking 5mg oxycodone. Their participants also experienced higher levels of hunger, feeling high and liking the effect, which was not found in our sample, presumably due to the relatively smaller dose used. However, our participants also experienced higher levels of light headedness, pleasant body sensations and dizziness following 5mg oxycodone, and this effect was only found following 20mg oxycodone

for light headedness and dizziness and 30mg for pleasant body sensations. Furthermore, our participants displayed an increase in hunger and sedation following 10mg morphine, and this was not found after 40mg morphine in the Zacny and Gutierrez (2003) study. It is unclear why we observed these subjective effects while Zacny and Gutierrez did not. The participant groups were comparable in terms of age and body mass index. One could argue that due to the relatively high number of comparisons made the apparent effects were actually due to type I errors. However, Figures 6, 7 and 8 all show a similar pattern for how oxycodone affects light headedness, pleasant body sensations and dizziness, supporting the view that these are actual effects.

Nausea was a notable exception from the items assessed in the Somatic Effects Scale. Several of the participants reported feeling nausea anecdotally, but this was not recorded on a scale. The omission of nausea followed Zacny and Gutierrez' (2003) study where no effects on nausea were found. However, given that several of the subjective effects reported by our participants differed from those found previously, it is clear that nausea should have been included as an item. The inclusion of nausea could have had two main benefits. Firstly, as with other symptoms, the amount of nausea experienced might be directly linked to the strength of the drug effect, so this may have shown some association with memory performance. More importantly, however, a feeling nausea is likely distract participants and prevent them from performing as well as they should in cognitive tasks.

Correlations with weight, sedation and feeling drug effects

There were trends for weight to correlate with some measures as would be expected. Heavier people performed better after morphine on digit span forwards and better on finger tapping after both morphine and oxycodone implying that they were affected less by the drugs. Furthermore, following morphine, heavier people tended to give lower ratings for subjective effects of the drug including sedation and feeling high. These results are to be expected given that we were unable to vary the dose for individual participants' weights. These subtle effects stress the importance of varying dose according to weight in clinical settings.

Whilst sedation did not correlate significantly with any of the cognitive measures there were some trends observed. However, most of these went in the opposite way than would be expected, with higher levels of sedation being associated with better performance in memory tasks. The exception was digit span following oxycodone, where higher levels of sedation were associated with poorer performance, indicating that oxycodone's effect on digit span could be partly mediated by its overall sedative effects.

The correlations with the subjective awareness of drug effects scales are difficult to interpret. Wanting less of the drug was associated with better performance in two aspects of the verbal recall task. Whist some people seemed to want more of the drug (typically males) and others tended to want less, this implies that for those people who don't like the effects, some subtle aspects of verbal recall are actually enhanced.

Throughout the correlation analyses, nonlinear effects were not investigates, as it was thought that due to the large number of correlations being carried out that this would increase the chance of obtaining false positives. However, it seems possible that there may be some non-linear relationships present in the effects of the drugs. For example, sedation may only have an effect on memory once a certain threshold of sedation has been reached. This would mean that only those participants who were adequately sedated would show any performance changes due to the drug. This relationship could easily be masked when only investigating bivariate correlations.

Summary of drug effects

Overall, whilst females appear to be more sensitive the subjective experience of being on the drugs and to the impairing effects of oxycodone on working memory, males show some enhancing effects on tests of episodic memory.

Clinical implications

10mg morphine and 5mg oxycodone are widely prescribed analgesics used routinely on an outpatient basis. This sensitive design failed to reveal any clinically significant effects showing that giving healthy individuals these clinically relevant doses of morphine or oxycodone does not cause significant impairments on a range of memory tests, as would have been predicted following the findings with cancer patients by Kamboj et al. (2005). The only decrements to performance were subtle, and did not reflect clinical impairments. Based on these findings, clinicians should feel confident in prescribing these doses to young healthy adults without fears of causing impairments to activities of daily living or quality of life.

The second important findings concern the involvement of gender and weight in the cognitive effects of opiates. The effects of weight are to be expected, with heavier people being less affected by the same dose of the drug. However, less is known about the effects on gender. Until very recently, the vast majority of research into the effects of drugs has been carried out on males, with the findings being used to guide the drug's use in both sexes. The lack of research on females is understandable given fears that experimental drugs may interfere with fertility in females. However, the differential effects produced by opiates in this study demonstrate that previous assumptions that males and females do not differ much in their pharmacological response are false.

In a review of the sex differences in opioid analgesia, Craft (2003) shows that there is conclusive evidence from both human and animal literature that the analgesic affect of opiates differs between men and women which she ascribes to the differences in genotype and in variable levels of sex hormones. Evidence shows that opiates that work on mu-opioid receptors cause a greater analgesic response in females than in males. However, there has been relatively little research in to this area, with even less exploring gender differences in the side effects of opiates explaining that this could limit their therapeutic use.

The current study reinforces Craft's recommendation that more research should be carried out into the side effects of opiates. Cahill (2006) highlights further differences between the genders in relation to brain function. In particular, the architecture of the hippocampus is different, with females having different concentrations of receptors.

As this is the area where morphine is thought to exert its amnesic effects, it is likely that these differences mediate the differential effects.

In clinical practice, during operations, anaesthetists will calculate the necessary dose of an analgesic based on the patient's weight and gender. However, doses of oral analgesics often prescribed after an operation are not weight or gender adjusted, and tend to be based on the dose needed for the "typical" 70kg male. This study shows that the profile of cognitive and subjective side effects does vary with both weight and gender, so with present prescribing practice, women will be at a disadvantage as they will be more likely to suffer from unwanted side effects due to their relatively lower weights and their gender. To avoid this, these factors should also be taken into account when prescribing oral opiates. However, pharmaceutical companies tend to package drugs in a limited range of doses, so prescribing appropriately for females may not be possible at present. These findings support the notion that drug companies should invest more money in varying the packaging of their drugs otherwise being a woman would be a contraindication to taking the drug as they are more susceptible to the side effects than men. Whilst the effects found here were subtle, it is probable that the differential effects of opiates on men and women would be more significant at higher doses. Furthermore, there has been relatively little research carried out on the differential effects of drugs on different genders for most drugs, and the present study's findings indicate that subtle differences are likely to be found across a range of centrally-acting medicines.

Limitations

This study was carried out on healthy individuals so it did not mimic the clinical situation and therefore has limited generalisability. As outlined above, the presence of pain can mediate the side effects of opiates, so one can not be certain that a similar finding would be found in a cohort of individuals who need opiates for pain relief. However, there are ethical difficulties associated with testing patients in a placebo controlled study, and with subjecting them to a large test battery. Whilst the study has the disadvantage of poor generalisability to clinical situations, the robust nature of the placebo controlled within-subjects design with such an extensive battery of cognitive tests provides clear advantages.

A further limitation is that there were only nine males and nine females, which may not have been enough to detect some gender differences. A power calculation was not carried out to predict how many males and females we would need because no similar studies could be found comparing the effects of cognitive effects of opiates between males and females. Furthermore, the primary goal of the research was to attempt to replicate the retrograde amnesia effect in the whole population. Enough participants were found to do this. Whilst a larger sample size may have illuminated further subtle gender differences, it was not possible in the present study to test more people.

Further Research

Due to the modulating effects of pain, it would be useful to perform a similar study with a more clinically relevant sample of patients needing analgesia for pain. To reduce the confounding variables associated with testing elderly cancer patients, younger patients with few heath problems should be chosen, either following minor

surgery or patients with chronic pain. Another way to improve the clinical relevance of these findings would be to look for anecdotal evidence from patients. Alternatively, giving patients memory tests shortly before receiving analgesia for surgery would help to determine whether people are likely to forget information they learned shortly before receiving an opiate.

In order to try to explore the retrograde amnesic effect in more detail, it would also be useful to increase the dose, either in control or clinical populations. Raising the dose could lead to similar effects found in the Kamboj et al. (2005) study, indicating that the retrograde effect was due to the opiates, rather than other aspects of the cancer patients' condition. If the retrograde amnesic effect was replicated, more detailed research could then provide participants with information to be learned at different time points before taking the drug, to ascertain how far back in time the retrograde amnesic effects of opiates go.

Summary

In summary, this is the first study to look at gender differences in the cognitive effects of opioids. The subtle effects found indicate that further research should be carried out into the differential effects of opiates on men and women, and that doses of oral opiates should be gender and weight adjusted.

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Critical Appraisal

Critical Appraisal

1. Personal Reflection on the research process

1.1 Thought Processes and Expectations

At the start, the rationale for carrying out the research and the hypotheses were clear. Cancer patients receiving morphine had displayed memory impairments following acute-on-chronic morphine administration relative to placebo. One of these effects was an apparent retrograde amnesic effect. As no other centrally acting drug has been shown to produce retrograde memory deficits this unique finding made me curious about how morphine produced the effect, and what the decrement might be able to tell us about the underlying mechanisms of normal memory.

I had gained an interest in this area from my experience as an undergraduate and an assistant psychologist. My undergraduate dissertation investigated the role of the hippocampus in memory in the rat. Following this, I spent time working in the field of dementia. This involved testing patients' memories as part of routine clinical practice and testing patents who were enrolled in clinical drug trials for anti-dementia medication. From working with rats, the relatively simple cortex allowed for relatively clear and interpretable effects from experimental manipulations. Whilst working with patients with Alzheimer's disease, there was also a clear understanding of the structural and neurochemical causes of memory impairment, with cell death and a reduction of the neurotransmitter acetylcholine in the hippocampus being involved. Furthermore, there was a clear rationale for the anti-dementia drug treatments, with acetylcholinesterase inhibitors being used to boost the acetylcholine levels. Acetylcholine is thought to be essential in long-term potentiation, the process which is thought to underlie many aspects of memory, when the post synaptic cell

will show an increased response after repeated incidences when both cells area activated together.

Initially I had hoped that a clear mode of action for morphine would emerge in a similar way and that the retrograde amnesic effect that it produced might be clearly linked to some characteristic of its effects on the brain. However, it soon became apparent from the literature that the effects of opiates were relatively non specific, with diffuse effects over different areas of the brain. Furthermore, opiates are known to produce effects such as sedation and euphoria, so any memory effect could in the past a least, be ascribed to the opiate's effect on sedation, rather than due to a specific mnemonic effect.

However, I felt optimistic that in looking for this effect in healthy volunteers, many of the confounding factors that have been observed in patients could be controlled for, meaning that our findings would add to the understanding of how opiates interact with different memory processes.

Whilst carrying out the testing, although I was blinded to what treatments the participants were receiving, I had observed what I had thought to be relatively impaired performance on some memory tests on some visits, leaving me to believe that I could make a reasonable guess as to whether or not they had taken an opiate. This also maintained my optimism that we would find effects. However, after the testing had finished and we were un-blinded, it became apparent that my guesses on treatment based on memory scores had mostly been wrong. Furthermore, statistical analyses revealed far fewer effects than I had predicted or hoped for, and there was no

effect of drug on either pre- or post-drug story delayed recall. This lack of both retrograde and anterograde amnesic effects that had been found by Kamboj, Tookman, Jones & Curran, (2005) was initially very discouraging especially given the time and effort that went into administering the tests. The testing protocol had included extra memory tests as I had assumed that an effect would be shown and wanted to explore the effect by also assessing visual memory and a different measure of verbal episodic memory.

On reflection, I had been more interested in the theoretical relevance than the clinical relevance while planning and running the experiments. I had not initially grasped the importance of the null result in terms of its clinical implications, that these clinically relevant oral doses of 10mg morphine and 5mg oxycodone can be prescribed without fears of loss of function or a detriment to quality of life due to memory impairments. However, had there been strong amnesic effects caused by these doses of opiates then one clinical implication could be that opiates should be prescribed less on an out patient basis, leading to increased incidence of undertreated pain. In this way my findings are positive in that these widely used doses of analgesics are largely benign in their effects on cognition.

1.2 Practical Issues

Initially, the practicalities seemed straightforward. The choice of tests to use was in part guided by the need to attempt to replicate the finding by Kamboj et al. (2005). Further tests were selected to investigate memory more thoroughly. The initial plan was to test 12 participants twice each, on morphine and placebo. However, another trainee decided to investigate the rewarding properties of these drugs and their effects

on decision making processes. As we would run each others tasks and share data, this meant we could run more subjects and include a second opiate for comparison, so our final design used eighteen participants, who were tested three times each. A major advantage of this was that we could also explore gender differences, a relatively rare accomplishment in psychopharmacology studies. We predicted that we would be able to run two to three tests per day, so we would only need approximately 10 days of testing. We had initially planned to commence testing in early 2005, expecting to finish in the spring with ample time to write up.

However, there were several unforeseen delays. Firstly, our application for ethical approval was initially turned down. Some of the reasons cited seemed like valid concerns, for instance there is an ethical difficulty in giving anyone financial inducement to take part in research as this can be seen as a form of coercion. However, the committee went on to state that "the use of morphine outside of its prescribed form is a criminal activity" and that the study "had neither a scientific validity nor any neuropsychological value". Whilst these strong comments could have dissuaded me from re-applying for ethics, I was also confident that much research was carried out using controlled substances on healthy volunteers, so whilst there are clear ethical issues involved, it was unlikely that there were criminal issues. They did not specify in what way the study failed to have scientific validity, however I would assume that it was the use of healthy controls rather than patients as the rest of the design of the study was robust. As explained in the empirical paper (part 2), I was aware of the limits in generalising to clinical situations as the side effects of opiates are modulated by the presence of pain. However, this does not mean that the study is of no clinical relevance. Furthermore, it was difficult to understand how using a repeated measures

design, and tests which are widely used clinically and for research purposes, could be of no neuropsychological value. Even though I did not think the ethics decision was justified, this was the first time I had been through the ethics application process so I was not confident about the outcome. Fortunately, my supervisor has a great deal of experience in conducting similar psychopharmacology studies also had confidence that the study should meet ethical approval.

A likely explanation for the difficulty with ethics is that the ethics process had recently changed to become much more stringent. This was in response to the recent scandal at Alderhay hospital. It is possible that during this transition phase, ethics committees would have tended to be over cautious. However, this process taught me that if I can see issues that are ethically pertinent but not prohibitive, I should point out why this is in the application, with the citation of other studies employing similar methods.

Finally, about six months after we had planned to start testing, we received ethical approval. By this time, the hospital where we had intended to carry the testing had closed down, so arrangements had to be made for space in the new UCH hospital. Next there were unexpected delays from the pharmacy department in making up the capsules due to a departmental inspection and staff holidays resulting in a further delay of over two months. Fortunately, recruitment went smoothly – the study seemed to be popular among local students.

The testing went mostly without incident and all participants completed all three of the testing sessions. It took slightly longer to complete all the tests than planned.

Many of the participants had jobs, so much of the testing was restricted to weekends. It was not possible to run two participants concurrently, as a researcher needed to be on hand during the one hour wait after the participants took the drug. Also, the test battery usually took about 70 minutes, so we were unable to stagger the testing.

There were some practical issues involved in testing that I would try to avoid or reduce in future. The room where testing was carried out was in the surgery wing of the hospital and we were not allowed key cards to enter. This meant having to wait outside the door until a busy uninterested surgeon rushed through and showing them my identification and letter of permission. Waiting with a participant on the off chance that someone might turn up to let us in made me feel particularly unprofessional, as well as being frustrating, especially if there was another participant booked in later on who would also be delayed. This was particularly problematic during weekends, when one might have to wait for over ten minutes for someone to enter or leave, being aware that this would result in the participant being there for longer than planned and possibly being late starting the next participant. There was also an unpredictable delay from pharmacy who was storing the drugs for us. It was often very busy, with several patients queuing to collect their prescriptions. Staff turnover appeared to be high, as I rarely met the same pharmacist. Some were sceptical about the study, whist others would be unable to find the drugs. This process took up to thirty minutes in busy periods. So, with these unpredictable timings, it was necessary to arrive over thirty minutes before the participant, to allow enough time for setting up the tests.

There were clear advantages to using healthy controls as participants compared to patients. Participants were mostly reliable and engaged well in the testing, with many of them enjoying the tests. The only draw back was that testing commenced in December, when there were many Christmas parties. As participants were not allowed to drink alcohol for twenty-four hours prior to testing, they were often not suitable to be tested at weekends.

1.3 Personal gains

Although I had some prior experience of involvement in clinical drug trials, my involvement was limited to the administration of cognitive tests in a study that was designed and set up by a large drug company and I was not responsible for many of the day-to-day tasks of running the trial. Thus I gained valuable experience of designing and setting up the study from scratch. This included selecting appropriate tests and planning for many of the more practical aspects of research. Also, whilst I had prior experience of administering cognitive tests clinically, the majority of tests I had done had been on patients whose performance was quite slow and impaired. Testing this high functioning group tended to be much faster, and I learned to become more efficient at running individual tests as well as becoming more slick in switching from one test to another.

In terms of writing the paper, this was the longest piece of work I had ever undertaken and I was definitely daunted by it for a long time. This led to a tendency to read more articles instead of writing about what I had already found. Having completed the write-up, I can now look back on the process as a more limited piece of work, instead of the seemingly limitless project it might have seemed like earlier on. If conducting

further research in the future, this will help me to persevere even when it seems that the end is not in sight.

2. Critical Appraisal of the Research

The main findings of the research were that; (i) healthy volunteers appeared to be relatively unimpaired on tests of memory following morphine and oxycodone and (ii) there were subtle interactions between drug and gender and between drug and weight. There are two potential problems with generalisability; whether these results on healthy, pain-free opiate naive participants can be generalised to clinical populations and whether the subtle effects on certain cognitive tests can be generalised to everyday functional abilities.

2.1 Generalising to Clinical Populations

Firstly, as pointed out in chapter 3.1 of the literature review, there are several methodological limitations inherent in testing the effects of opiates. Firstly, the presence of pain can affect cognitive performance when not taking medications, and pain can also modulate both the subjective (Colney, Toledano, Apfelbaum, & Zacny, 1997) and physical (Borgberg, Neilson & Franks, 1996) side effects of opiates. Hence, one needs to be tentative when generalising these findings to people experiencing pain. Secondly, tolerance to both the main effects and side effects builds up over time. Indeed, opiate naive people may experience strong nausea on the first two occasions that they take an opiate, but this side effect can quickly dissipate after a relatively small number of doses. Hence, there are difficulties in generalising these findings to people who are taking opiates for chronic cancer or non-cancer pain and they would

only be relevant for people who have received an opiate for the first time, for example following an accident or following surgery.

Taking a conservative approach, these findings can only strictly be generalised to young, pain-free, opiate naive participants. The only people that would fall into this category would be people taking opiates recreationally for the first time (and people taking part in research trials.) However, I do not think that this means the findings have no relevance to clinical populations. Furthermore, as explained in the literature review, it is very difficult to conduct ethical research in this area which avoids the confounding variables of pain, tolerance or other factors such as illness. Since tolerance reduces the strength of side effects, then the conclusion that these doses of opiates do not cause significant clinical impairments to memory could be generalised to non-opiate naive people. Furthermore, as the absence of pain often increases the side effects of opiates, it would seem safe to conclude that these findings domains where performance was unaffected would also be unaffected if pain was present. This conclusion should, however, carry the caveat that the absence of pain can actually attenuate some of the side effects of opiates.

When attempting to generalise the findings that opiates did have subtle effects, and that there were subtle weight and gender effects, I do not believe one needs to be so conservative. Whilst it is possible that these effects may disappear if pain was present, or after repeated doses of opiates, these results demonstrate that opiates certainly have the potential to create these effects. Furthermore, the fact that gender differences occur at all strongly implies that they would also occur under different conditions (i.e. when participants are in pain.)

In summary, the findings that these doses of morphine and oxycodone had no effect on most measures of memory can be generalised to young and relatively healthy clinical populations with confidence. One has to be more tentative when generalising the subtle cognitive effects, but the gender differences are likely to be present in clinical populations as well.

2.2 Tests Used

The second difficulty with generalisation concerns the tests that were used. In some previous studies, a lack of impairment on one single cognitive test has been generalised to imply that there are no effects on cognition as a whole. Whilst I would be more tentative than this, many of the tests used, including digit span, trail making and prose recall have been used extensively for both clinical and research purposes. They have been shown to be sensitive to pharmacological change previously (e.g. Curran, Kleckham, Bearn, Strang and Wanigaratne, 2001). Furthermore, there were no ceiling effects, so subtle changes should not have been masked. Also, performance on the prose recall tests and the trail making have been linked to levels of everyday functioning, so these tests can provide a fair estimate of how a person may perform outside of the experimental setting.

However, as far as I am aware, the Rey-figure has not previously been used in this way. Thus, whilst our lack of findings in this test seems to indicate that visual memory was unaffected, it may also be true that this particular test is not so susceptible to the effects of opiates. Furthermore, whilst the complex figures used were all abstract, it is likely participants could use verbal strategies to aid their recall.

Indeed, one patient told me he had remembered the "traffic light" in the figure that had a vertical line of three circles within a rectangle in one of the corners. Given this tendency to rely on verbal processes even for seemingly abstract images, it is difficult to think of a test that must be completed using purely visual means.

2.3 Gender Differences

Another criticism is of the second finding, that the subtle interactions with weight and gender were not included in the hypothesis. Whilst we generally expected lighter participants to experience greater effects of the drugs, we did not make any specific predictions about how gender or weight would be involved. Thus, interpretation of our results in this post-hoc fashion needs to be done cautiously. Furthermore, the inconsistent interactions observed led to a rather general interpretation that the opiates affected men and women, or lighter and heavier people differently.

If the study's main aim was to explore gender differences, then it would have been preferable to give people equal doses relative to their bodyweight. Furthermore, as Craft (2003) points out, the differential effects on gender are due to a number of differences including anatomical, physical, neurochemical and hormonal differences. Furthermore, some of the gender differences in the analgesic response are only observed under certain gonadal steroid hormone states. Thus a more robust study would attempt to control for the stage of the oestrous or menstrual cycle.

2.4 Relation to theoretical framework

Due to the lack of effects on anterograde and retrograde memory, this study is unable to provide further understanding of the theoretical framework for retrograde amnesia.

Kamboj et al, (2005) concluded that they were unable to discern whether the retrograde amnesic effect they found was due to accelerated forgetting, impaired retrieval or increased susceptibility to interference. The current study can shed no further light on this question.

2.5 Payment

As described above, there is a clear ethical difficulty with giving someone a financial incentive to take part in a study, especially one that has a risk of unfavourable side effects. To minimise this problem, participants were paid at the standard UCL rate for taking part in psychological research, which was £6.50 per hour. Indeed they would have been paid a far higher hourly rate to stand outside the department in a brightly coloured jacket everyday and accost strangers about giving their money to a charity. There are real risks involved in annoying strangers in central London and I am certain that most of them would not do this without being "coerced" by payment. This is not a research activity though, so the same ethical scrutiny is not present.

3. Further Research

As outlined in the discussion of the empirical paper, I believe it would be valuable to persevere in attempting to replicate this retrograde amnesic effect of opiates. The dose should be increased so that healthy volunteers are given dose strong enough to produce an anterograde memory impairment. If this is accompanied by a retrograde impairment then it would show that the effect was not only limited to cancer patients. It would be useful to conduct a series of pilot studies of different doses before running a whole study again.

Another advantage of raising the doses is that it would tell us more about the gender and weight differences. One hypothesis would be that with increased doses there would be differences observed between the genders for a greater number of cognitive tests and subjective experiences, and that the differences would be different to those that we found. Alternatively, at higher doses, the subtle differential effects on gender may be overshadowed by other more global effects of the drugs.

4. Future Directions

Having undertaken the various stages necessary to run a project from start to finish, I would now feel more confident about running research studies in my work as a clinical psychologist. I think that the field of psychopharmacology is highly relevant to clinical psychology. A substantial proportion of patients take psychotropic medication (e.g. antidepressants, antipsychotics) and as far as I am aware little is known about the differential effects of these drugs on men and women, nor about cognitive side effects. Whilst completing this study, I was also working clinically with patients with severe psychosis. Almost all of them would repeatedly refer to how their medication affected their cognitive abilities, and this was particularly apparent on neuropsychological testing. Clinicians in this field are often unsure as to what whether apparent cognitive deterioration relates to chronic or acute antipsychotic use, the presence of illness or other aspects of their lifestyle such as past substance misuse. This seems similar to some of the difficulties clinicians have in discerning what is causing cognitive impairment in pain patients. Attempting to differentiate illness effects from medication side effects would be vital in attempting to maximise a person's potential activities of daily living or quality of life.

References

Borgberg, F. M., Neilson, K. & Franks, J. (1996). Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: a controlled study in human volunteers. *Pain, 64,* 123-128.

Colney, K. M., Toledano, A. Y., Apfelbaum , J. L. & Zacny, J. P. (1997). Modulating the effects of a cold water stimulus on opioid effects in volunteers. *Psychopharmacology, 131,* 313-320.

Craft, R. M., (2003). Sex differences in opioid analgesia: "From mouse to man". *The Clinical Journal of Pain, 19,* 175-186.

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Kamboj, S. K., Tookman, A., Jones, J. H. & Curran, H. V. (2005). The effects of immediate-release morphine on cognitive functioning in patients receiving chronic opioid therapy in palliative care. *Pain, 117,* 388-395.

Morrison, R. S., Magaziner, J., Gilbert, M, Koval, K. J., McLaughlin, M. A., Orosz, G., Strauss, E. & Siu, A. L. (2003). Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *Journal of Gerontology: MEDICAL SCIENCES, 58A(1),* 76-81.

Appendix A: Study protocol and explanation of joint working.

This project was carried out in collaboration with another researcher, (CP). Her study focussed on the abuse potential of these opiates and included three tests which were not used as part of my analysis. Both of us were allocated half of the participants (nine each) to test on each of their three testing sessions. Both of us conducted each others tests during the test battery. After data collection the entire data set was pooled. For the purposes of this thesis, data from three of the tests was not included (Impulsivity Rating Scale, Go – No Go, and Roger's Gambling task). Likewise, the data used by CP for her analysis did not include the memory assessments (except for digit span). Apart from this, several of the tests were used by both of us, including the SES, MRS, Trail Making, Digit Span, Pulse, and Finger Tapping. All other aspects of the work, including recruitment were shared between us.

The table below (also shown on P.53) shows the order and timing of test administration. Tests marked with "*" were only used as part of CP's research. Those marked with a "#" were used by both of us.

Time after drug (mins)		Test
-15	#	VAS Scales
-9	#	Pulse
-8		Prose Recall Story A immediate
-4		Complex Figure A copy & immediate
0		**Drug administration**
60		Prose Recall Story B immediate
63		Complex figure B copy & immediate
66	#	Pulse
67	#	Finger Tapping
69	#	Trail Making
71	#	VAS Scales
76	*	*Go - No Go**
82	#	Digit Span
87		Prose Recall Story A & B delayed
92		Complex figure A & B Delayed
96		Source Memory Presentation
106	*	*Roger's Gambling Task**
118		Source Memory Test
121	#	Subjective Drug Effects Scale

Appendix B: Official Letter of Ethical Approval

The Joint UCL/UCLH Committees on the Ethics of Human Research (Committee Alpha)
Research and Development

Our Ref: PO/vlh/05AL297

09 September 2005

Prof. H Valerie Curran
Professor of Psychopharmacology
University College London
Clinical Health Psychology
University College London

Dear Prof. Curran

Full title of study:	**The cognitive effects of a single dose of morphine and oxycodone in healthy volunteers.**
REC reference number:	**05/Q0502/52**

Thank you for your letter of 21 July 2005, responding to the Committee's request for further information on the above research.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*

Participant Information Sheet	2	18 April 2005
Participant Consent Form	2	18 April 2005
Response to Request for Further Information		21 July 2005
Sample record book page		21 July 2005

Management approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final management approval from the R&D Department for the relevant NHS care organisation.

Membership of the Committee

The member of the Ethics Committee who was present at the meeting is listed :

- Chairman

Notification of other bodies

The Committee Administrator will notify the research sponsor and the R&D Department for NHS care organisation(s) that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/Q0502/52	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project,

Yours sincerely

Chair

Email:

Enclosures: Standard approval conditions
Site approval form (SF1)

Copy to: , R&D Department for NHS care organisations(s)

Appendix C: Advert for study

Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE LONDON
GOWER STREET LONDON WC1E 6BT

H. Valerie Curran
Professor of Psychopharmacology

VOLUNTEERS NEEDED!!

STUDY OF THE EFFECTS OF PAINKILLERS ON THINKING AND MOOD

We would like to invite you to take part in our research project at The Middlesex Hospital. We are investigating the effects of single doses of 2 different painkillers. We are looking for healthy volunteers who are aged between 18 and 35 years.

The study involves 3 separate sessions, each about 2 hours. Most people find the tests simple and fun to do!

For further information, please contact:

James on

or

Appendix D: **Consent Form**

Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE LONDON
GOWER STREET LONDON WC1E 6BT

H. Valerie Curran
Professor of Psychopharmacology

"The effects of Morphine and Oxycodone on Cognition and Mood in Healthy volunteers" (V2)

Consent form – 18th April 2005

I feel that I have been sufficiently informed about this study and I would like to participate. ☐

I understand that I can withdraw my consent at any time without giving reasons. ☐

I understand that my data will be stored electronically in an anonymised form and that it may be accessed both by researchers in this project and by supervisors/research auditors. ☐

I agree not to drive any vehicle on the testing day. ☐

I agree not to drink alcohol 24 hours before testing. ☐

I agree that I will attend 3 separate sessions each at least a week apart ☐

Signed

.....	.....	.....
Date	Name of participant	Signature of participant
.....	.....	.....
Date	Name of person taking consent	Signature of person taking consent.

Appendix E: Participant Information Sheet

Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE LONDON
GOWER STREET LONDON WC1E 6BT

H. Valerie Curran
Professor of Psychopharmacology

"The cognitive effects of a single dose of morphine and oxycodone in healthy volunteers"
Research participant information sheet – V2, 18th April 2005

You are invited to participate in a research study. This study aims to increase our understanding of the effects of morphine and oxycodone. These are drugs commonly used to relieve pain.

This study is being conducted by doctors form the Anaesthetic Department at University College Hospital together with researchers from the Clinical Psychopharmacology Unit at University College London.

Before we describe the study and its purpose to you we would like to make it clear this is a completely voluntary study and that you will be free to pull out at any time.

Why are we doing this study?
Although morphine and oxycodone are two of the most widely used painkillers, we know very little about how they affect 'cognition' (i.e. thought processes) and mood. As these drugs are now increasingly being used for patients who wish to continue their normal, daily activities, it is important that they be informed of how their treatment may affect their daily function. It would alert us to what tasks patients might have difficulty with whilst they are taking these drugs. Knowledge of these effects may also help develop more effective communication between medical staff and patients who are given these drugs in a hospital setting.

What will I have to do?
You will need to come to the Middlesex Hospital for three separate testing sessions that will be at least one week apart. Each session will last for approximately two hours. On each of the three test days, you will be given a capsule containing the study drug. The capsule will contain either morphine (15mg), oxycodone (5mg) or 'placebo' (milk powder). The tests will be done both before and after taking the capsule. Some of the tests are done on a computer and others are paper and pencil tests. Most people find the tests quite simple and fun to do. You will be asked to fill in questionnaires about how you are feeling.

Neither you nor the researchers will know which drug you have been given on which session. However, there will always be a doctor on hand with access to information about which drug you have taken in case they need to know.

Participants will be asked to not drink alcohol 24 hours before a testing session. Following the session, participants must not drive a vehicle, ride a bike or make any important decisions for the remainder of the day. It is also recommended that you do not drink alcohol for the remainder of the day.

Who can participate in this study?
Any healthy person aged between 18 and 35 years with no history of opiate abuse, no history or current abuse of any drug and no history of adverse reactions to opiates. Participants must have good spoken English and basic literacy skills, as well as good vision. Women may not participate if they are pregnant and all women will be given a urine test on each test day to verify that they are not pregnant. Any one with hypotension or hypothyroidism should not take part.

What are the potential side effects of these medications?
Side effects of these drugs can include drowsiness, nausea, itchy skin and dizziness. It would be unusual to experience any severe effects with the doses being used. You will be able to discuss any side-effects you experience with the doctor. There is the possibility that a drug used in this study, if used outside of a medical or laboratory setting for an extended period of time, can have addictive properties. There is a minimal risk of abuse of the study drug. We consider the risk of subjects in the present study becoming addicted to the study drugs to be low for the following reasons 1) the controlled setting in which the drug is given, 2) the limited number of times you will be exposed to the study drugs and the time between drug administration [at least 7 days], 3) the difficulty in obtaining the study drugs outside of the medical setting, 4) the fact that there is no evidence to suggest that administration of a drug in a medical setting (for medication or research purposes) leads to abuse of that drug in non-medical settings.

How will I receive compensation for giving my time?
You will be given £7.50 per hour that you take part in the 3 main test sessions. On completing all 3 sessions, study you will receive £50.

How will we keep your data?
Your data from this study will be stored electronically in an anonymised form. Only researchers directly involved in the study will have access to the data.

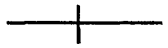
Who do I contact for if I have further questions?
If you have any further questions about the study please contact:

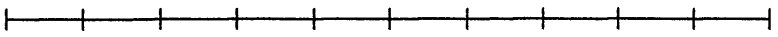
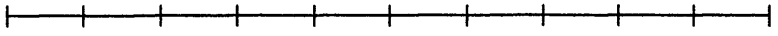
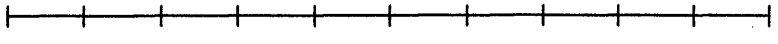
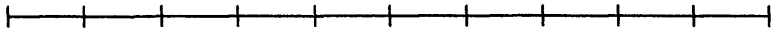
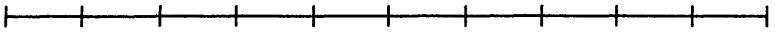
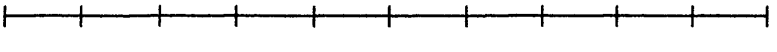
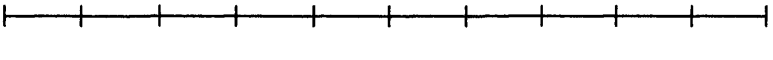
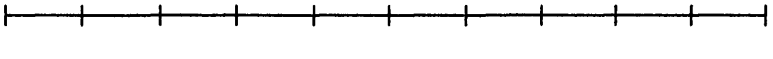
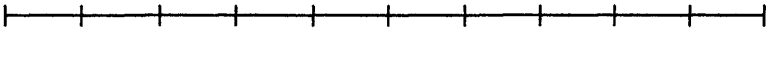
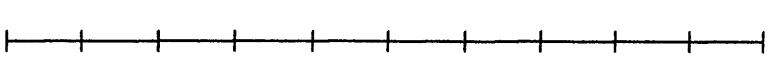
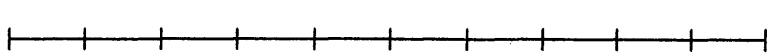
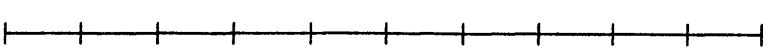
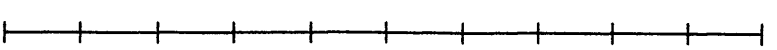
James Friswell
Caroline Phillips
Prof Val Curran

All research projects are reviewed by an ethics committee. This proposal was reviewed and approved by the UCH Ethics Committee.

Appendix F: Somatic Effects Scale (SES) Questionnaire

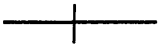
SES SUBJECT NUMBER [ ] DATE [ ] OCC [ ] **PRE**

a. Please rate the way you feel in terms of the dimensions given below.
b. Regard the line as representing the full range of each dimension.
c. Mark clearly and perpendicularly across each line, i.e. 
d. Rate your feelings as they are **AT THE MOMENT**.

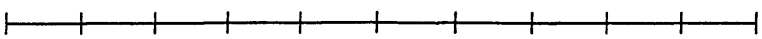
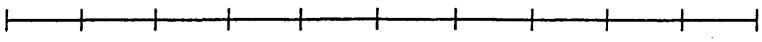
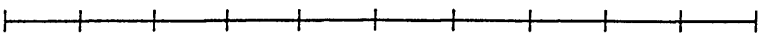
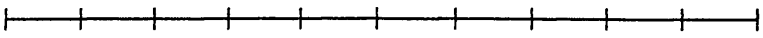
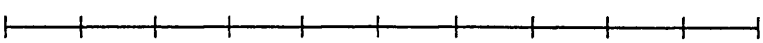
No numbness		Extreme numbness
No dry mouth		Extreme dry mouth
No dizziness		Extreme dizziness
No light-headedness		Extreme light-headedness
No hunger		Extreme hunger
No tingling sensation		Extreme tingling sensation
Not feeling flushed or warm		Feeling extremely flushed or warm
No itchy skin		Extremely itchy skin
No pleasant body sensations		Extremely pleasant body sensations
No difficulty concentrating		Extreme difficulty concentrating
No memory problem		Extreme memory problem
Inhibited		Impulsive
Shy		Confident
Depressed		Elated
Euphoric		Despairing
Very spaced out		Very focused
Lost in details		Able to see the big picture
Heavy/sluggish		Light/energetic
Angry		Peaceful
Aggressive		Cool Headed

Appendix G: Drug Effects Scale (DES) Questionnaire

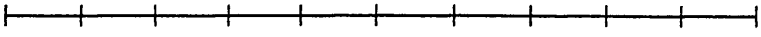
DES SUBJECT NUMBER [ ] DATE [ ] OCC [ ]

a. Please rate the way you feel in terms of the dimensions given below.
b. Regard the line as representing the full range of each dimension.
c. Mark clearly and perpendicularly across each line, i.e. 
d. Rate your feelings as they are **AT THE MOMENT**.

Effects of the drug (capsule):

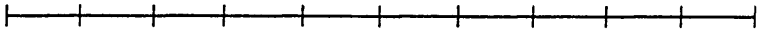
I feel no effect		I feel a strong effect
I dislike the effects a lot		I like the effects a lot
I want more of it		I want less of it
I feel no drug 'high'		I feel a strong drug 'high'
Definitely would not want to take it again for pleasure		Definitely would want to take it again for pleasure

How much would you pay for the capsule to experience its effects again?



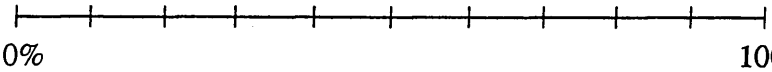
£0 £10

How would you rate your performance today in the following areas:

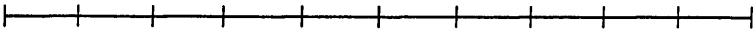
Overall performance 

0% 100%

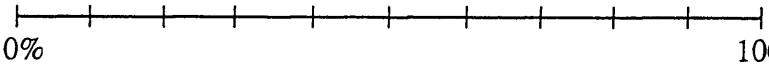
(worst performance) (absolute best performance)

Memory 

0% 100%

Attention/concentration 

0% 100%

Decision making 

0% 100%