Opioids, Decision-making and Sex: A Cross-over Trial of the Abuse-related Effects of Oxycodone and Morphine

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Overview

Part 1 of this thesis comprises a review of the literature. It provides an introduction to prescription opioids, their medical use and non-medical use and abuse. It reviews current understanding of drug dependency and psychological models of addiction. Studies that have assessed cognitive impairments associated with drug abuse, in particular deficits in decision-making, are discussed in terms of these models. The review highlights gaps in the literature concerning the acute effects and abuse-liability of oxycodone. It concludes with suggestions for further research and rationale for the present study.

Part 2 of this thesis is an empirical paper describing the study which investigates the acute effects and abuse-liability of oxycodone and morphine in non-drug abusing healthy volunteers. It reviews the literature and asks whether oxycodone and morphine will produce different subjective and cognitive effects. A detailed description is provided of the study’s methods and design. Results show that under the influence of opioids, gender differences are observed in decision-making and on subjective measures. The findings are discussed with reference to abuse-liability and gender differences in psychopharmacological research.

Part 3 consists of a critical appraisal of the study. It begins with a personal reflection on the process of the research. Following this is a critique of the study, considering issues such as design, measures and methodology. The appraisal concludes with ideas for future research and thoughts about research and clinical psychology in general.
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Part 1: Prescription Opioids, Drug Addiction and Decision-making: A Review of the Literature
Abstract

In the following paper I aim to provide a review of the literature relevant to this research topic. I begin with a summary of prescription opioids and their use in treatment for pain. I follow with a discussion about opioid misuse and abuse and recent epidemiological research. I review current knowledge about addiction and drug dependency, including recent psychological theories and models of addiction. I also provide an examination of studies which have investigated cognitive impairments associated with drug use, with particular emphasis on deficits in decision-making. Following this, I consider differences in abuse potential between drugs, particularly in light of recent concerns about increases in oxycodone abuse. I highlight gaps in the literature regarding the acute rewarding properties of opioids in non-drug abusing humans. I conclude the review with a rationale for the present study investigating the acute effects and abuse-liability of oxycodone compared to morphine in non-drug abusing healthy volunteers.

1. Introduction

Opioids are the most potent and effective analgesics available and are widely used in treatment for both acute and chronic pain (Collett, 2001). However, there is growing concern regarding their usage due to fears about cognitive impairment, decreasing efficacy due to tolerance, and the development of drug dependency. Opiates are increasingly being given for pain relief on an outpatient basis where these concerns are more pertinent. Furthermore, a number of studies in the United States indicate that non-medical use and abuse of prescription opioids, in particular oxycodone, is on the rise
(e.g. Substance Abuse and Mental Health Services Administration (SAMHSA), 2002a & 2002b). Researchers have made significant advances over the last decade in understanding general processes of drug addiction (e.g. Volkow, Fowler, & Wang, 2003). However, rather less is known about individual drugs and their specific reinforcing effects. There are many commonly held misconceptions of the abuse potential for substances such as oxycodone, because they can be obtained legally and have legitimate medical use. Such prescription drugs are becoming primary drugs of abuse in the United States and throughout the world. Therefore, more research is needed to help resolve the on-going debate concerning their abuse potential.

2. Opioids and Pain

The primary effect of opioids when appropriately prescribed is pain relief. However, an improvement in physical, psychological and social function and sleep may also occur secondary to pain relief (Pain Society, 2004). There are two major classes of opioid agonists. Morphine-like agonists (e.g. morphine, heroin, methadone), and opioids producing mixed actions, which consist of agonist-antagonists (e.g. buprenorphine) and partial agonists (e.g. codeine and its derivatives, oxycodone and dihydrocodeine). Opioids are also classified as weak (e.g. dihydrocodeine, codeine) or strong (e.g. morphine, oxycodone). However the distinction between these groups is not always clear and may depend on the dose (Pain Society, 2004). Whereas morphine-like opioids are given to inpatients for analgesia during or after medical procedures to alleviate severe pain, partial opioid agonists, such as oxycodone are commonly prescribed for pain relief after outpatient surgery or for chronic pain (such as moderate to severe pain
in patients with cancer). Codeine, because it is less efficacious than morphine, is used for milder pain.

Opioids work by binding to specific proteins called opioid receptors, which are found in the brain, spinal cord, and gastrointestinal tract. By attaching to these receptors, they can block the transmission of pain messages to the brain. Opioids can potentially provide up to four times the relief of a non-opioid analgesic, so even the most severe degree of pain can be managed. Opioid agonists have an increasing analgesic effect with increased doses, therefore the more a patient takes, the less pain they feel. In addition to pain relief, opioids can produce a variety of other physiological responses. These include nausea, headaches, dry mouth, sweating, constipation, drowsiness, and mood changes (Joint Formulary Committee, 2006). Opioid drugs can also cause euphoria by affecting the brain regions that mediate what we perceive as pleasure. However, high doses can cause slowed breathing and hypotension; and taking a large single dose of an opioid could result in severe respiratory depression that can cause death. Particular care is recommended for women of childbearing age, as opioids can have effects on neonatal wellbeing (Pain Society, 2004).

Chronic use of opioids can result in tolerance, that is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time (Pain Society, 2004). This means that users need to take higher doses to achieve the same initial effects. Long-term use can also lead to physical dependence, where the body adapts to the presence of the drug, and withdrawal symptoms occur if use is reduced or stopped (Pain Society, 2004). Symptoms of
withdrawal include restlessness, muscle and bone pain, insomnia, diarrhoea, vomiting, cold sweats with goose bumps ("cold turkey"), and involuntary leg movements. However, withdrawal usually occurs when opioids are stopped suddenly and can be avoided by gradual reduction of opioid dose (Pain Society, 2004).

3. Opioid Misuse and Abuse

Substance misuse describes (i) the use of any illicit drugs, (ii) the use of prescribed drugs for non-medical purposes or (iii) the use of a drug in particular contexts (e.g. drinking and driving). Opioid misuse therefore, tends to be seen when the drugs are taken not for pain relief but for effects on mood and thinking (Pain Society, 2004). Substance abuse is a pattern of substance use leading to significant impairment or distress and including recurrent use (DSM-IV; American Psychiatric Association (APA), 1994). In addition, substance abuse refers to a use leading to at least one of the following: failure to fulfil important obligations, physical hazards, repeated legal problems, and continued use despite social/interpersonal problems (DSM-IV; APA, 1994).

The primary opioid used for non-medical purposes is the morphine-like agonist heroin (Zacny, 1995). However, a number of epidemiological studies in the United States indicate that non-medical use and abuse of prescription opioids is on the rise (e.g., SAMHSA, 2001; 2002a & 2002b). According to data from the National Survey on Drug Use and Health (NSDUH), the misuse of prescription pain relievers by U.S. youths has increased dramatically during the last decade (Centre for Substance and Abuse
Research, (CESAR), 2005). In 2004, 11.4% of youths aged 12 to 17 reported ever misusing prescription pain relievers, compared to 1.2% in 1989 (CESAR, 2005). In 2002, it was estimated that the number of first time non-medical users (U.S. residents aged 12 and older) of prescription pain relievers was nearly equal to that of new marijuana users (CESAR, 2004). These findings support other indicators of increased non-medical use of prescription pain relievers in the United States.

In particular, oxycodone has gained a substantial amount of attention from clinicians and the general public because of reports of illicit use disrupting its controlled-release nature (Zacny & Gutierrez, 2003). Indeed, the increase in rates of lifetime non-medical oxycodone use, from 1999 to 2000 and from 2000 to 2001, were found to be statistically significant (SAMHSA, 2002c & 2002d).

Oxycodone is usually administered by mouth, as a pill designed to be swallowed whole. Recommended doses are 5 mg every 4–6 hours, which can be increased if necessary according to severity of pain. The usual maximum dose is 40 mg daily, although some patients may require higher doses (Joint Formulary Committee, 2006). Oxycodone can also be administered intravenously and/or subcutaneously. According to the BNF, it is not recommended for children under 18 years old. Rather than ingesting the pill as indicated, people who abuse oxycodone use other methods of administering the drug. To avoid the controlled-release mechanism, oxycodone abusers often chew, snort or inject the medication. These methods lead to the rapid release and absorption of oxycodone providing an instant and intense "high".

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OxyContin (a controlled-release form of oxycodone hydrochloride) is designed to provide the delivery of oxycodone over a 12-hour period and is indicted for the management of moderate to severe pain (Purdue Pharma, 2001, cited in Hays, 2004). OxyContin is a particularly potent drug, containing a much larger amount of the active ingredient, oxycodone, than other prescription opioid pain relievers (Clark, 2001). Although all prescription opioids have the potential for abuse, some have called the recent surge in OxyContin abuse an epidemic in particular areas of the United States (Baumrucker, 2001; Hays, 2004; Young, 2001). An 18-month retrospective chart review at a private freestanding psychiatric facility in the U.S. revealed that 298 of the admissions (51.3%) were for treatment of opioid abuse or dependence. 187 (62.8%) of these individuals were dependent on OxyContin and 111 (37.2%) were dependent on other opioids including Lortabs (30%), Methadone (11%), and Morphine (6%). A survey of high school students found that 98% had heard of OxyContin and 72% indicated that it was not difficult to obtain. In addition, 9.5% of students claimed to have tried OxyContin at least once in their lifetime (Holstege, Kell, Baer & Fatovitch, 2002). Indeed, some clinicians report that they have “never seen a drug proliferate like OxyContin” (Drug Rehab, no date).

All opioids have a street value and may be traded or sold. This includes both weak and strong opioids, and those with long-acting as well as short-acting formulations (Collett, 2001). Both oxycodone and heroin have similar physiological effects; therefore, it is likely that both drugs are attractive to the same abuser population. Oxycodone has sometimes been referred to as "poor man's heroin" or “hillbilly heroin”, even though it demands a high price on the street. In the US, a 40 mg tablet of oxycodone by
prescription costs approximately $4, or $400 for a 100-tablet bottle in a chemist. Street prices vary depending on geographic location, but typically, a 40mg pill sells for $40 on the street ($1 per milligram) (Hays, 2004). Therefore, the cost of a 100-tablet bottle purchased in a chemist can sell for $2,000 to $4,000 on the street. This has led to crime involving robbing pharmacies and writing false prescriptions (Clark, 2001).

4. Addiction and drug dependency

Addiction is more than just drug use or abuse. It is described specifically as a compulsive pattern of drug-seeking and drug-taking behaviour that takes place at the expense of most other activities (Robinson & Berridge, 2003). Substance dependence has been defined as continuing drug use despite awareness of the long-term negative consequences, repeated attempts to cut back or quit substance use, and a gradual exacerbation of drug intake over time (DSM-IV; APA, 1994).

Over the last 20 years, addiction problems have increased in the UK. Drug abuse is at its highest level ever and alcohol misuse at its highest point in 50 years (Curran & Drummond, 2005). This increase has been accompanied by huge financial disadvantage to society, with one estimate putting the cost at £12 billion per annum (Godfrey, Eaton, McDougall, & Culyer, 2002). Substance misuse often has an impact on several areas of a person’s life, such as employment, relationships, criminality, physical health and health risks of HIV and hepatitis (Curran & Drummond, 2005). Although good quality drug treatment can be highly effective (Gossop, Marsden, Stewart & Kidd, 2003), it is well recognised that addiction is characterised by a long-lasting risk of relapse. Indeed,
the high risk of relapse to drug use that persists even in abstinent addicts long after the cessation of withdrawal symptoms has led some to consider addiction as a chronic medical illness (McLellan, Lewis, O'Brien & Kleber, 2000).

Addiction to opioids consists of their compulsive use to the detriment of the user’s physical and/or psychological health and/or social function. Signs of compulsive use include preoccupation with obtaining and taking opioids, impaired control over their use, and reports of craving (Pain Society, 2004). Some argue that the use of opioids prescribed for pain relief only rarely results in addiction (Pain Society, 2004). Indeed, estimates from North America indicate that 3-19% of chronic pain patients have an addictive disorder, which parallels the lifetime prevalence rates of addictive disease in the general population (Fishbain, Rosomoff, & Rosomoff, 1992). However, the exact risk is not known and some studies have found a link between prescription for pain and addiction. For example, according to a web-based survey of a random sample of undergraduate students in the U.S., those who were previously prescribed pain medication were more likely to report illicit use of such medication (CESAR, 2006). Hays (2004) found that 45.9% of OxyContin addicted patients reported having a pain problem at some time during their OxyContin use, and nearly a quarter of them stated that they were no longer experiencing pain.

(i) Psychological theories of drug addiction

Substance dependence is a disorder involving complex interactions between, biological, psychological, and environmental/social variables. Although recreational drug use
usually begins because of a drug's beneficial effects on mood or cognition, the defining characteristic of addiction is loss of control of behaviour resulting in compulsive drug use. There exist a number of psychological theories, which have been particularly useful in informing clinicians about the development of addiction and guiding interventions. The main theories can be grouped into behavioural, cognitive, and motivational theories.

Behavioural theories view addiction as a set of learned or 'conditioned' behaviours. There are two main behavioural theories: 'classical conditioning' and 'operant conditioning'. Classical conditioning proposes that an individual’s drug use (e.g. heroin) is paired with particular objects (e.g. syringes) or people (heroin using friends) or feelings (e.g. bored or lonely). Frequent pairings of these stimuli with the drug, means they become conditioned or associated with heroin use (see Drummond, Cooper & Glahtier, 1990, conditioning model for craving alcohol for an example). Operant conditioning on the other hand, builds on the fact that an action that leads to a reward is more likely to be repeated than one that leads to no reward or to a punishment. Drugs can be very strong rewards as they activate the brain's natural pleasure pathways and are therefore more likely to be repeated. An alternative behavioural theory is 'social learning theory' which is based on the finding that people also learn behaviours by watching and/or imitating other people.

Cognitive models emphasise the role of cognitions (thoughts and beliefs) in behaviour and emotions (e.g. Beck, Wright, Newman & Liese, 1993). Beck et al. propose that cues (internal or external) activate beliefs (e.g., “I’m a hopeless addict”), which lead to
automatic thoughts (e.g., “I can’t cope with this unless I’ve had a drink/drugs”). These thoughts result in cravings for the drug and in turn drug use.

Motivational theories propose that there exist ‘stages’ involved in changing drug behaviour (Prochaska & DiClemente, 1983). Initially an individual may not perceive a problem with their drug use and this is referred to as the ‘precontemplation’ stage. Then the individual may be concerned about their drug use but may not want to change it—the ‘contemplation’ stage. Following this, they may reach a stage where they make a commitment to change in the near future (‘determination’ stage). After this, there may be a change in behaviour (‘action’ stage), followed by attempts in trying to stick to it (‘maintenance’ stage).

(ii) Models of drug addiction

Scientists’ understanding about the process of drug addiction (and the reinforcing effects of psychoactive substances) has been greatly informed by advances in the areas of neuroscience and experimental neuropsychology. For example, research using imaging techniques has highlighted which brain areas and circuits are involved in reacting to drugs and which parts of the brain (anatomy and chemicals) make up its reward system. There have also been advances in understanding the psychological consequences of drug dependency both in terms of how drugs may affect an individual’s cognitive ability and their sensitivity to differing rewards.
Robinson and Berridge's (2003) Incentive Sensitization model of addiction proposes that repeated drug use sensitises/enhances the reactivity of the brain’s reward system causing drug related stimuli to evoke stronger reactions ‘grabbing the individual’s attention’ and becoming more salient than natural rewards. This results in cravings, which compounded with poor response inhibition, lead to increasingly compulsive substance use (Jentsch & Taylor, 1999). This is consistent with experimental studies which have shown that substance users’ attention is grabbed by drug related cues more than other types of stimuli (Bradley, Mogg, Wright, & Field, 2003; Field, Mogg & Bradley, 2004). For example, Cox, Hogan, Kristian & Race (2002) demonstrated that after a four-week alcohol-detoxification programme, an increase in bias towards alcohol was found in individuals who relapsed back to drinking 3 months later, whereas individuals who had managed to stay abstinent showed a slight decrease in bias.

In the last decade or so brain imaging technologies, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have contributed significantly to our understanding of drug addiction and the mechanisms involved in its effects on the brain.

Psychoactive substances exert their effects by affecting the regulation of neurotransmitters or stimulating actions at their receptors, and subsequently within the nerve cell itself, often in highly specific ways (Robbins et al., 2005). Although other systems are likely to be involved as well, most imaging studies have focused on the brain dopamine (DA) neurotransmitter system because this is the system through which most drugs of abuse are believed to exert their reinforcing effects (Koob & Bloom,
1998; Di Chiara, 1999). This system, which projects from the ventral tegmental area to the nucleus accumbens and onto extensive areas of the prefrontal cortex (PFC) as well as the amygdala (Thierry, Blanc, Sobel, Stinus, & Glowinski, 1973) has been shown to be involved in reward, memory, motivation and control (Volkow et al., 2003). Indeed, neurochemical studies have shown that large and fast increases in DA are associated with the reinforcing effects of drugs of abuse. For example, participants who have greatest increases in DA are those who experience the most intense drug effects such as “high”; “rush”; “euphoria” (Volkow, Fowler & Wang, 2002). DA function mediates the reinforcing effects of natural reinforcers, such as food and sex, as well as drugs. However, drugs of abuse are considered to be much stronger reinforcers than natural reinforcers (Wightman & Robinson, 2002).

Volkow et al. (2003) developed these ideas and integrated the findings of neurochemical and imaging studies into their own model of drug addiction (see Figure 1). The model integrates several psychological indices mapped onto four neural networks. Each of these networks is modulated by drugs of abuse and proposed to be instrumental in drug abuse and addiction. Volkow et al. (2003) describe acute drug administration as resulting in a complex and dynamic pattern of activation and deactivation involving regions in the brain that are neuroanatomically connected with the DA system. Specifically, they propose that an individual’s ability to make a decision between behavioural alternatives depends on a DA-regulated reward network consisting of four circuits: (1) reward, located in the nucleus accumbens (Nac) and the ventral pallidum; (2) motivation, located in the orbitofrontal cortex (OFC) and the subcallosal cortex; (3)
memory and learning, located in the hippocampus and the amygdala; and (4) control, located in the prefrontal cortex (PFC) and anterior cingulate gyrus (CG).

The model proposes that the response to a stimulus is affected by its expected reward or predicted value (processed in part by DA neurons projecting into the Nac). This can be affected by memory and/or context. For example, if the individual has been previously exposed to the stimulus, memories (stored as associations between the stimulus and previously memorised experiences) are facilitated via DA activation (processed in part by the amygdala and hippocampus). The value of the stimulus is also weighted against other stimuli and changes as a function of the internal needs of the individual (processed in part by the OFC). For example, the value of food is increased by hunger, but decreased by satiety. The stronger the expected reward for a stimulus, the greater the activation of the motivational circuit and the stronger the drive to obtain it. The decision to act or not is processed in part by the PFC and the CG. In the non-addicted brain, the circuit is balanced by positive and negative feedback loops, and inhibitory control from the PFC.

Thus, Volkow et al.'s (2003) model views addiction as a state arising initially from the reward provided by a drug. The reward value triggers a series of adaptations in the reward, memory, and motivation circuits causing the value of the drug and drug related stimuli to be enhanced. The authors suggest that this enhanced saliency value occurs during intoxication due to qualitative differences in activity in the DA-regulated reward circuit caused by the drugs. For example, the increases in DA induced by drugs are 3-5 times higher and result in greater and longer lasting activation than natural reinforcers.
(Wise, 2002). This results in an over-activation of the motivation/drive and memory circuits which overcome the inhibitory control exerted by the PFC. Without the inhibitory control, a positive-feedback loop resides which results in drug consumption. This, in turn, re-activates the network, strengthening the motivation/drive and memory circuits, further strengthening the saliency value of the drug, and thereby perpetuates drug use.

**Figure 1.** Volkow et al.'s (2003) model proposing four circuits involved with addiction: reward, motivation/drive, memory and control.

This enhanced saliency value of the drug is at the expense of other reinforcers, which are significantly decreased. It is suggested that the high reward value of drugs results in a resetting of reward thresholds, which further causes decreased sensitivity to the reinforcing properties of natural reinforcers (Volkow et al., 2003). There is also less habituation with drugs compared to natural reinforcers. Ultimately, the value of the drug
becomes significantly greater than any natural reinforcer, which can no long compete as a viable choice.

Volkow et al.’s (2003) model supports interventions that address multiple aspects of drug dependence. In particular: decreasing the rewarding effects of the drug; increasing the value of other reinforcers; weakening learned drug responses; and strengthening inhibitory control. They suggest a combination of cognitive, behavioural and pharmacological treatments to target these strategies (Volkow et al., 2003). Indeed, many psychosocial approaches broadly address multiple components within this model.

Imaging studies have also uncovered the brain areas and circuits involved in various stages of the drug addiction process (e.g. intoxication, withdrawal and craving). For example, after chronic drug abuse and during withdrawal, DA function is significantly reduced. Related to this, is the finding that the orbitofrontal cortex is under-active in drug-addicted volunteers tested during withdrawal, perhaps as a result of the lack of brain stimulation by salient stimuli during detoxification (Volkow et al. 2003). In contrast, in active cocaine abusers, the orbitofrontal cortex has been shown to be overactive – in proportion to the intensity of the craving experienced by the volunteers (Volkow et al. 1991).

One question that continues to puzzle researchers is why only certain people exposed to drugs go on to become addicted. However, recent findings in neuroscience may have begun to uncover some of the answers. Euphoria proceeded by drugs such as cocaine may depend on initially low levels of striatal dopamine (D2) receptors, as revealed by
PET which may be indicative of low basal mood states (reviewed in Volkow et al., 2002). For example, Volkow et al. found that non drug abusing individuals who have naturally lower levels of D2 receptors found the stimulant (methylphenidate) more enjoyable than individuals with high levels of these receptors. Furthermore, people who become addicted to alcohol, cocaine or heroin, show decreased densities of dopamine D2 receptors (Volkow et al., 2002). Thus, one of the variables influencing vulnerability to substance misuse could be the inherited variability of D2 receptors.

**5. Cognitive impairments and drug use**

One of the most consistent findings from imaging studies is that drug addicts display abnormalities in the prefrontal cortex (PFC), including the anterior cingulate gyrus (Goldstein & Volkow, 2002). Related to this, research has shown that drug dependent clients have significant neurocognitive impairments of the executive processes mediated by the prefrontal cortex, and drug-induced disruptions to the DA system are related to dysfunction of prefrontal regions. This has been demonstrated in research involving neurological patients and supports brain-imaging studies, which indicate impairments to the frontostriatal neural networks known to support executive processes (Bechara, Tranel, Damasio, & Damasio, 1996; Bechara, A., Damasio, H., Tranel, D., Anderson, 1998; Damasio, 1994, cited in Rogers et al., 1999). Executive functions are involved in attention and planning, decision-making, and inhibitory control of behaviour. These processes are crucial for the successful performance of many everyday procedures like prioritising tasks and remembering important information while performing an action (Stuss & Levine, 2002). They allow for people to plan for the future by permitting the
regulation of behaviour in the service of a goal (George, Rogers & Duka, 2005). Therefore, this has significant implications for clinicians and their patients who are taking these drugs.

In particular, the PFC is involved in decision-making and the ability to delay or inhibit responses (Royall et al., 2002). Therefore, its disruption could lead to inadequate decisions that favour immediate rewards over delayed but more favourable responses. Indeed, disruptions of self-monitoring and decision-making have been seen in drug-addicted subjects (Bechara & Damasio, 2002; Ernst et al., 2003, cited in Volkow et al., 2003; Rogers et al., 1999). It has been suggested that this could account for impaired control over the intake of the drug, even when the addict expresses a desire to refrain from taking the drug (Goldstein & Volkow, 2002). Certainly, substance dependence does appear to be characterised by a significant loss of control over behaviour. Drug-dependent individuals appear unable to exert sufficient control over their drug urges and their drug-seeking and drug-taking behaviours, despite their best efforts and expressed preferences. This suggests that cognitive processes involved in controlling human behaviour may be compromised in drug-dependent individuals and that such processes should be investigated in order to fully understand drug abuse (Garavan et al. 2005).

As mentioned above, neuropsychological tasks particularly sensitive to changes in dopaminergic function and PFC abnormalities tap executive functions. Successive discrimination tasks can be used to measure impulsivity. For example, using a Go/No-Go task, Finn et al. (1999) found support for the theory that alcohol causes increases in impulsivity. Decision-making tasks have also been used to indicate executive
dysfunction. For example, Bechara et al. (2001) found that the decision-making of approximately 75% of people with substance misuse disorders was significantly impaired with drug-addicted subjects appearing to be influenced by short-term rather than long-term outcomes (Bechara et al., 2001).

(i) Deficits in decision-making

The capacity to make effective everyday decisions (involving choice between actions leading to uncertain outcomes) has been shown to depend on the orbitofrontal cortex, its interconnected neural activity and associated striatal structures (Rogers et al., 1999). It has been proposed that the decision-making of normal, healthy individuals involves the interaction of two separate sources of information. One source of “declarative knowledge”, regarding the properties of the situation in hand, is supplemented by a second source of “dispositional knowledge”, regarding the previous emotional states resulting from a response or action (Bechara, Damasio, Tranel & Damasio, 1997). The latter, affective information, relating to visceral, somatic states connected with appetitive and aversive outcomes is used to influence the reasoning processes that result in decisions in favour of more advantageous or adaptive responses. Bechara et al. (1996) suggest that the neural circuitry of the orbital PFC is well matched for this purpose.

Research into decision-making has provided detailed information about the factors which may affect the selection of responses in cognitively demanding tasks. Of particular significance are studies that have utilised tasks involving uncertain rewards and punishments, as they have linked drug abuse with a greater likelihood for making
poor decisions. These findings could be applicable to real life decision making of drug and alcohol abusers. For example, addicted individuals frequently choose the short-term rewards of drug taking over the longer-term negative impact on physical health and social and financial circumstances (Rahman, Sahakia, Cardinal, Rogers & Robbins, 2001).

Bechara and colleagues developed a paradigm to investigate decision-making in patients with PFC damage (Bechara et al., 1996; 1998). The task required participants to select cards from four decks, and after each choice they would receive a monetary reward. However, the participants were not aware that for the two decks that produced large rewards, occasional larger penalties were incurred; and for the other two packs that had small rewards, there was an overall net gain (although occasional smaller penalties were incurred). This meant that over the course of the task, subjects would maximise their rewards by selecting cards consistently from the more conservative decks. The researchers found that patients with damage to the ventromedial PFC consistently chose cards from the high reward decks despite the ultimately punishing consequences of the decision. Bechara and Damasio (2002) found that drug abusers also made unfavourable decisions, failing to respond appropriately to large penalties. At the same time they were found to produce the normal anticipatory skin conductance responses (SCR) (thought to indicate knowledge that the decision could result in high punishment) prior to selection from the 'risky' decks. Bechara et al.'s studies model an important aspect of real-life decisions where underlying contingencies relating actions to relevant outcomes remain hidden. However, where contingencies are not well-defined and openly presented, it is
difficult to assess the precise behavioural character of the impaired decision-making
(Rogers et al., 1999).

In order to overcome this Rogers et al. (1999) designed a task which requires subjects to
make choices between contingences that are presented in a readily comprehensible
visual format. They argue that this allows them to assess the degree to which individuals
are sensitive to the quality of information available (e.g. information about the likely
identity of the rewarded choice). Therefore, decision-making was examined by
presenting participants with two gambles, each consisting of a given probability of
winning or losing a certain outcome. For example, consider a choice between a 25% chance
to win $100 and a 75% chance of losing $20 vs a 25% chance to win $240 and
75% chance to lose $60 (Rogers et al., 2003). The ‘expected value’ of a gamble is the
sum of its component values (gains and losses), each weighted by its probability of
occurrence (Goldstein & Hogarth, 1997). Therefore, the expected value of the above two
gambles is \((0.25 \times 100) + (0.75 \times -20) = 10\) and \((0.25 \times 240) + (0.75 \times -60) = 15\).
Therefore the normatively rational choice for maximising value is the second gamble
(Rogers et al., 2003).

There exists a wealth of research looking at variation in people’s preferences
(determined by differences between magnitudes of gains and losses in each gamble as
well as their respective probabilities) to assess the extent to which human choice
conforms to, or departs from, what would be normatively rational in terms of choices
maximising some positive outcome or expected value over the longer term (Kahneman
& Tversky, 1979). Two well-known examples of violations of normative decision-
making include risk-averse choices, when choosing between gains, and risk-seeking choices, when choosing between losses. For example, most people would choose a 100% chance of a gain of $40 over a 50% chance of $80 and a 50% chance of nothing (risk-aversion for gains), but they would choose a 50% chance of an $80 loss and a 50% chance of no loss over a 100% chance of a loss of $40 (indicating risk-seeking for losses) ('reflection effect'; Kahneman & Tversky, 1979). However, the expected value of each of these gambles is equal, implying that people should be indifferent to the options (Kahneman & Tversky, 1979).

Rogers et al.'s (1999) decision-making task was designed to assess how an individual's pattern of choices might alter given a range of contingencies representing more or less favourable opportunities to earn rewards. They proposed that the task - offering bets in both an ascending and a descending order - also allowed them to separate disinhibition and disrupted impulse control (behavioural changes also associated with orbitofrontal damage) from genuine risk-seeking. They used this task to compare the decision-making ability of both drug addicted subjects and neurological patients. Measures included speed of decision-making, quality of decision-making and willingness of subjects to gamble their already accumulated reward in the hope of earning more reward. The researchers found significant similarities between chronic amphetamine abusers, chronic opiate abusers and patients with focal lesions in orbito and superior regions of the PFC, all of whom deliberated for significantly longer before making their choices. In addition, both chronic amphetamine abusers and patients with focal lesions of the PFC showed impairments in the quality of their decisions (choosing the least optimal of available responses) as well as reduced speed. This finding was more prevalent in subjects with
longer histories of abuse, suggesting a cumulative process of disrupted neuromodulation associated with chronic stimulant abuse. They argue that increased deliberation times shown by chronic drug abusers is consistent with altered neuromodulation of the circuitry incorporating ventral areas of the PFC, ventral striatum, and amygdala. These findings also suggest that deficits were not associated with increased “impulsivity” but were indicative of difficulties in resolving competing response options, demonstrating genuine risk-taking behaviours (Rogers et al., 1999).

Rogers' et al. (2003) adopted these techniques in a follow up study designed to allow for examination of the mechanisms that might have produced these results. In addition to measuring time taken to make a decision, this task assessed the quality of the decision itself. Rogers' et al. (2003) 'Gambling Task' is sensitive to separable factors known to determine human choice; specifically, the magnitude of expected gains (or reward), the magnitude of expected losses (or punishment) and the probabilities with which these outcomes are delivered (Goldstein & Hogarth, 1997). The task also contained two gambles designed to test risk aversion when choosing between options involving a certain gain and risk-seeking behaviour when choosing between options involving certain losses ('reflection effect'; Kahneman & Tverksy, 1979).

(ii) Acute vs. chronic drug effects

One difficulty for studies attempting to link cognitive deficits and underlying changes in neuromodulatory function associated with chronic substance abuse is the problem of establishing the direction of causation. For example, although it may seem plausible to
assume that chronic drug abuse causes changes in the neuromodulation of ventral PFC, leading to changes in decision making, it is important to acknowledge that the true causal relationship might be the reverse; that is, altered neuromodulation of ventral PFC pre-dates and serves as vulnerability factor for individuals to substance abuse. Indeed, while some researchers have proposed that undercontrolled or impulsive behaviours predict drug abuse (Cloninger, Sigvardsson & Bohman, 1988), others have found there is increasing evidence indicating that the reverse may be true (Steele & Southwick, 1985). Block, Erwin, and Ghoneim (2002) attempted to resolve this in a study where they traced back school achievement records of people in treatment for substance abuse. They found that compared to controls, substance misusers were significantly impaired on cognitive tests aged 12, and before they started using drugs. However, even allowing for this, they found additional impairments in their current functioning, suggesting that pre-existing deficits are confounded by impairments subsequent to using drugs (Block et al., 2002).

However, an alternative method for investigating the direction of causation between cognitive deficits and drug abuse is to study acute effects of the drugs themselves, in addition to looking at the long-term effects. Although research suggests that chronic drug abuse is necessary to observe long-term functional changes associated with the DA system and PFC, similar changes have been observed in non-drug addicted subjects. For example, imaging studies have shown that during intoxication, increases in the extracellular concentration of DA occur in both addicted drug abusers and non-drug abusers (Goldstein & Volkow, 2002). Since increases in DA concentration are seen in both drug naïve and addicted subjects, Volkow et al. (2003) suggest that addiction and

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the resulting disruption of the reward circuit occurs from chronic drug administration and repeated perturbation of the reward circuits. However, it is possible that increases in DA concentration in non-addicted subjects cause temporary disruptions to the PFC, similar to those seen in drug-addicted subjects. This disruption could be observed by impaired decision-making and judgement, exacerbated by loss of inhibitory control that the PFC exerts over the amygdala. Therefore, it would also be important to study possible adverse effects of acute drug use on executive cognitive function in healthy volunteers.

6. Individual drug differences in reward

The models discussed in the previous section refer to drug dependence; however there appears to be less research regarding theories about patterns for drug misuse. Although considerable advances have been made regarding our understanding of the processes involved in drug addiction, rather less is known about individual drugs and their specific reinforcing effects. Recreational drug use usually begins because of a drug’s beneficial effects on mood or cognition; and addiction has been viewed as a state arising initially from the reward provided by a drug (Volkow et al., 2003). Indeed, a further variability that requires investigating is the addictiveness of the drugs themselves. For example, what drug characteristics make one drug a preferred reward over another drug?

It appears that some drugs (e.g. heroin) may be more addictive than others, however the question of how to measure this remains. The effect of a drug depends on a number of complex interactions, including individual genetics and development, drug
pharmacology and method of administration (Garavan et al., 2005). For example, the kinetics of drug use (how the drug is delivered) will contribute to the measured effect of the drug and its reinforcing effects (Garavan et al., 2005). The faster a drug reaches the brain, the greater the 'rush' and the potential for reinforcement. For example, drugs which are injected intravenously, leading to a fast intake in the brain and therefore fast changes in DA concentration, are experienced as more reinforcing than drugs taken orally, resulting in slower brain uptake (Volkow et al., 2002). Furthermore, the uptake of intravenous methylphenidate is very fast and has been shown to be associated with subjective ratings of 'high' in healthy volunteers. This is thought to be similar to cocaine (Volkow et al., 2002).

Originally there was an assumption that all the strong opioids were largely interchangeable with respect to abuse liability, and that specific product formulations have little relevance to abuse liability. However, recent research investigating prescription opioid abuse (discussed earlier in this review) raises the question of whether these assumptions are correct. Furthermore, while heroin is known to be highly addictive, less seems to be known about the reinforcing effects of prescription opioids, such as oxycodone. To answer this question it would seem necessary to carry out systematic abuse liability assessment studies that compare the different opioids, evaluate the influence of the various additive agents with which opioids are often combined, compare routes of administration, and evaluate and compare effects when taken as directed versus in various manners of likely tampering or misuse (Zacny et al., 2003).
There is relatively little published data regarding the effects of specific opioids on cognition and mood. Zacny (1995) provided a review of the literature investigating the effects of opioids on psychomotor and cognitive functioning in humans. The review indicated that opioids do affect performance. However, most of the studies used limited measures and none provided a comprehensive profile of their effects. A number of further studies were recommended to fill gaps in past research. In particular, the review showed that little attention had been given to codeine derivatives (e.g. oxycodone) or to how processes of risk-taking and decision-making (skills and behaviours which are part of everyday life) are affected by opioids. Given the current public and professional concerns about oxycodone abuse, it would be important to know about the acute effects of these drugs, particularly as they are frequently given to patients following outpatient surgery.

7. Abuse-liability of Oxycodone

There have been a number of pre-clinical animal studies investigating the abuse potential of oxycodone. The results suggest that oxycodone is a full mu agonist with abuse liability of the morphine type (e.g. Swain, Fly & Severs, 1977; Aceto, Kipps, Harris & Bowman, 2002; Woods, Ko, Winger, France & Traynor, 2003). In regard to humans, Hays' (2004) retrospective chart review produced interesting results with regard to the profile of OxyContin addicts. OxyContin addicts were younger than those addicted to other opioids and were more likely to be from a rural area. Furthermore, individuals dependent on OxyContin described subjective effects from the drug as a sense of increased energy and euphoria as well as invincibility. However, there has been
little psychological research investigating the abuse liability of oral oxycondone in non-drug abusing humans. Indeed, at the time of writing this review, only one study could be found investigating abuse liability and behavioural toxicity of oxycodone in healthy volunteers.

Zacny and Gutierrez (2003) set out to investigate the subjective, psychomotor and physiological effects of oxycodone in non-drug-abusing humans. They aimed to assess whether fairly high doses of oxycodone (10-30 mg) produce abuse-liability subjective effects and to what extent its behavioural toxicity was comparable to other opioid agonists (morphine, 40 mg) and to the benzodiazepine, lorazepam (2 mg, a dosage known to produce clinically significant cognitive impairments). In this study “abuse liability-related subjective effects” were defined as “those measures that are considered pleasant in nature and have apparent face validity in predicting abuse liability” (p.243, Zacny & Gutierrez, 2003). Questionnaires employed to measure the subjective effects were the short form of the Addiction Research Centre Inventory (ARCI; Martin, Sloan, Sapira, & Jasinski, 1971); an adjective rating scale sensitive to the somatic and subjective effects of opioids (Fraser, van Horn, Martin, Wolbach & Isabell, 1961); and visual analogue scales (VAS) (including ratings such as “coasting”; “dreamy”; “light-headed” and assessing drug effect/drug like/take again). A post-session sequelae questionnaire assessed symptoms 24hr after the session.

The results from the subjective measures showed that higher doses of oxycodone (20-30 mg) produced a number of subjective effects that could be considered as abuse liability-related in nature. In particular, the researchers noted an increase on a sub-scale of the
ARCI, believed to measure euphoria; “carefree” from the adjective rating scale; and VAS ratings of “elated”; “having pleasant bodily sensations”; “having pleasant thoughts” and “dreamy”. The lower dose of oxycodone (10 mg) also increased subjective ratings of “high” and “sedated (calm, tranquil)”. Drug liking and “want to take drug again” ratings were increased by all three dose of oxycodone (Zacny & Gutierrez, 2003).

Behavioural toxicity was assessed via psychomotor and cognitive performance. On an eye-hand coordination task, oxycodone (30 mg) impaired performance to the same degree as 2mg of lorazepam. Impairments were also observed with oxycodone (20 & 30 mg), using the digit symbol substitution test (DSST; Weschler, 1958) and a logical reasoning task (Baddeley, 1986). However, neither oxycodone nor morphine were found to affect memory. In general, although some psychomotor and cognitive impairment was noted with higher doses of oxycodone, in most cases the degree of impairment was not approaching that observed with lorazepam (Zacny & Gutierrez, 2003).

The researchers concluded that the subjective and physiological effects of oxycodone resembled those of other mu-opioid agonists (Zacny & Gutierrez, 2003). However, findings regarding abuse-liability were not clear-cut. Although oxycodone produced a profile of subjective effects that could be considered abuse-liability related (pleasant), higher doses of the drug also produced effects that could be considered unpleasant in nature (e.g. itchy skin; nausea; drug disliking). Furthermore, overall ratings of drug liking and wanting 24 hours after the session were no different from placebo; and drug-liking during the session was not necessarily predictive of drug liking 24 hours later.
There was further variability as some participants reported both liking and disliking drug effects, while others reported neither liking nor disliking drug effects.

One difficulty with this and other studies investigating drug reinforcing effects is that the measures used are often limited and do not provide quantitative results. Although subjective measures can provide considerable useful information, their reliability and validity can be questioned. For example, one cannot be certain about how different individuals experience effects. What one individual considers a pleasant effect will be considered as unpleasant for another individual. Therefore, it would be advantageous to investigate alternative ways of assessing abuse potential, not relying solely on subjective measures of assessment.

8. Present study

The present study aims to investigate the abuse liability of oxycodone compared with morphine. It intends to repeat some of the interesting work presented by Zacny and Gutierrez (2003) by using similar subjective measures to assess whether or to what degree these opioids produce abuse liability subjective effects (e.g. pleasant effects). A subjective effects scale (SES), included somatic and subjective experiences previously shown to be sensitive to the effects of opioids (e.g. numbness, dizziness, pleasant body sensations, euphoria) (Zacny & Gutierrez, 2003). The Mood Rating Scale (MRS, Bond & Lader, 1974) assessed sedation, discontentedness and anxiety; and self-ratings of impulsivity were taken with the Impulsivity Self Rating Scale (ISRS, Bond & Lader, 1974). In addition, a drug effects scale (DES) was developed to assess drug liking and
awareness of drug effects on cognition. However, this study intends to further investigate abuse potential by assessing the acute effects of these opioids by using a more objective method of assessment; namely decision-making and inhibition.

One of the major strengths of experimental psychology is that it provides objective, precise, and testable explanations of behaviour by systematically deconstructing complex human behaviours such as drug addiction and eliminating the extraneous uncontrolled factors that are found in more naturalistic observations (Duka et al., 2005). The finding that executive functions, such as decision-making and inhibitory control, are closely associated with changes in the reward centres in the limbic system and related areas of the brain makes them ideal behaviours to monitor effects on reward. By monitoring these, it may be possible to investigate whether oxycodone has a more significant effect on the DA system than morphine.

In the present study, Rogers' et al. (2003) computerised gambling task was used to study acute effects of oxycodone and morphine on decision-making. The task involves presenting participants with two gambles, each consisting of a given probability of winning a certain amount and losing a certain amount and allows an analysis of the extent to which an individual attends to probabilistic, reward or punishment information. In addition, there are separate conditions which test the effects of a drug on choices between gambles driven by risk-aversive (gains) and risk-seeking (losses) biases (Rogers et al., 2003). In the present study the impact of opioids on such decisions was investigated by comparing participants receiving a typical clinical dose oxycodone, or morphine or placebo.
In addition to the gambling task, impulsivity was further assessed using Go/No-Go, a successive discrimination task which instructs participants to respond to certain cues and inhibit others. This required participants to monitor and inhibit activated responses, and scores are recorded in terms of commission (response inhibition) errors, omission errors (on reversal trials) and reaction times.

The present study also involved an equal number of males and females so that analyses could be carried out to detect whether there were gender differences. Increasingly, evidence suggests that there are important gender influences on brain anatomy, chemistry and function (Cahill, 2006). Indeed, Zacny and Gutierrez (2003) found that with oxycodone (30 mg), males but not females showed significant increases on VAS ratings of "heavy or sluggish" and "sleep", although other subjective effects did not differ as a function of sex. Many studies indicate that females may be more sensitive to rewarding effects (e.g. Lynch, Roth & Carroll, 2002); and this difference is often discussed with reference to the modulatory influence of hormones. In a recent review about gender differences in neuroscience, Cahill (2006) highlights some of the more important findings and their implications. Of particular relevance to this study are the inconsistencies in the literature connecting the PFC to decision-making. Indeed, evidence has been found for gender differences in the relationship between PFC function and decision-making ability (Tranel, Damasio, Denburg & Bechara, 2005; Bolla, Eldreth, Matochik & Cadet, 2004). Cahill concludes that research into gender influences is important and can help to explain apparent contradictions in research; while ignoring the influence of gender will only hinder progress. Despite this, there is little
psychopharmacological research investigating potential gender differences. The vast amount of research has been carried out on males, and where participants are mixed there are often not enough numbers to compare across genders. Therefore, as gender differences in subjective effects, decision-making and impulsivity may occur in response to opioid agonists, it was considered important to investigate this possibility.

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Part 2: Opioids, Decision-making and Sex: A Cross-over Trial of the Abuse-related Effects of Oxycodone and Morphine
Abstract: Rationale: Opioids are widely used in treatment for both acute and chronic pain although there is growing concern about increasing prescription opioid abuse. There has been little research investigating the acute rewarding properties of opioids in non-drug abusing humans. Aim: The present study therefore investigated the acute effects and abuse-liability of oxycodone compared to morphine in non-drug abusing healthy volunteers. Methods: Eighteen healthy volunteers (9 women) participated in a crossover, randomised, double blind placebo-controlled design, in which they received placebo (10mg), oxycodone (5mg) and morphine (10mg). Assessments were administered before and 60 minutes after drug administration. Both cognitive (decision making/gambling and impulsivity) and subjective measures were used to assess executive functions and abuse-liability. Results: Under the influence of opioids, males were more likely to choose the experimental gamble than females when gains were large and losses were small. Females chose the experimental gamble significantly more on morphine than on oxycodone. Females also took longer to decide on morphine. Morphine and oxycodone produced similar subjective effects. However females rated themselves more light-headed on morphine, whereas males rated themselves more light-headed on oxycodone; on morphine, females rated larger ‘feel drug’ effects than males; and females rated wanting less morphine and oxycodone than males. Measures of impulsivity were not affected by drug or gender. Conclusions: Opioids, at a dose typically given in outpatient settings, produce subtle, gender specific changes in both cognitive and subjective measures.

Keywords: Opioids; Oxycodone; Morphine; Abuse liability; Subjective Impulsivity; Decision-making; Gender.
Introduction

Opioids are the most potent and effective analgesics available and are widely used in treatment for both acute and chronic pain (Collett, 2001). However, there is growing concern regarding their usage due to fears about cognitive impairment, decreasing efficacy due to tolerance, and the development of drug dependency.

A number of epidemiological studies in the United States indicate that non-medical use and abuse of prescription opioids is on the rise (e.g., Substance Abuse and Mental Health Services Administration (SAMHSA), 2001; 2002a & 2002b). These findings support other indicators of increased non-medical use of prescription pain relievers in the United States (e.g. Centre for Substance and Abuse Research (CESAR), 2004, 2005). In particular, oxycodone has gained a substantial amount of attention from clinicians and the general public because of reports of illicit use disrupting its controlled-release mechanism (Zacny et al., 2003). Research has shown significant increases in rates of lifetime non-medical oxycodone use (e.g. SAMHSA, 2002c & 2002d). OxyContin, a particularly potent drug containing a much larger amount of oxycodone (Clark, 2001), has caused considerable concern with some describing the recent surge in abuse as an epidemic in particular areas of the country (Hays, 2004; Baumrucker, 2001; Young, 2001). Anecdotal reports from individuals dependent on OxyContin describe subjective effects from the drug as a sense of increased energy as well as invincibility (Hays, 2004). Sometimes referred to as "poor man’s heroin", oxycodone commands a high price at street level (a 40 mg tablet typically sells for $40) (Hays, 2004) and this has led to crime involving robbing pharmacies and writing false prescriptions (Clark, 2001).
Researchers have made significant advances over the last decade in understanding processes of drug addiction, both in terms of how drugs affect an individual’s cognitive ability and their sensitivity to differing rewards (e.g. Robinson & Berridge, 2003; Volkow, Fowler, & Wang, 2003). It is believed that opiates exert their reinforcing effects via their action on the mesolimbic dopamine (DA) system (e.g. Koob & Bloom, 1988; Di Chiara, 1999). This system, which projects from the ventral tegmental area to the nucleus accumbens and on to extensive areas of the prefrontal cortex (PFC) as well as the amygdala (Thierry, Blanc, Sobel, Stinus & Glowinski, 1973), has been shown to be involved in reward, motivation, memory and control (Volkow et al., 2003). Imaging studies indicate that drug addicted people have abnormalities in the PFC; further, drug intoxication increases DA concentrations in naïve as well as addicted subjects (Goldstein & Volkow, 2002). The DA system has also been shown to provide an important modulatory influence on the cognitive functions supported by the PFC and its interconnected neural circuitry (Bechara, Tranel, Damasio, & Damasio 1996; Bechara & Damasio, 2002; Rogers et al., 1999).

Neuropsychological tasks particularly sensitive to abnormalities in the PFC and changes in dopaminergic function are executive function in nature, in particular decision-making and inhibitory control of behaviour (Royall et al, 2002). Indeed, disruptions of self-monitoring and decision-making have been shown in drug-addicted subjects (Bechara et al., 2001; Bechara & Damasio, 2002; Ernst et al., 2003; Finn, Justus, Mazas & Steinmetz, 1999; Rogers et al., 1999). It has been suggested that this could account for
impaired control over the intake of the drug, even when the addict expresses a desire to refrain from taking the drug (Goldstein & Volkow, 2002).

Recreational drug use usually begins because of a drug's beneficial effects on mood or cognition. However, rather less is known about individual drugs and their specific reinforcing effects. A drug's "abuse liability" can be defined as "the proactive drug-seeking and drug discrimination which occur as antecedents to habitual drug use together with the adverse effects of such use (i.e. a combination of the drug's reinforcing properties and its toxicity)" (National Institute of Drug Abuse (NIDA), 1984). It is important to consider this independently of "physical dependence potential" which is instead concerned with tolerance and withdrawal (and primarily the reactive biochemical, physiological, and behavioural consequences of drug administration). The relevance and importance of this distinction between "physical dependence potential" and "abuse liability," for drug evaluation purposes, resides in the fact that while both these processes are of obvious public health concern, their defining properties are not coextensive and they do not invariably occur together (NIDA, 1986). Assessing a drug's abuse liability therefore refers to the attempts to predict drug-seeking and drug self-administration. This is particularly important since increasingly the evidence supports the view that the problems of human drug dependence are more closely related to the abuse liability of a drug than to its physical dependence potential.

In terms of abuse liability, it was originally believed that there was little difference between the strong opioids. However, the recent surge in oxycodone as the drug of choice suggests otherwise (Hays, 2004). Furthermore, while some fear that medical
prescription can induce addiction and will lead to an increase in non-medical use in society (Hays, 2004; Zacny, 1995), others argue that opioids prescribed for pain relief only rarely result in addiction (e.g. Pain Society, 2004). Given the current public and professional concerns, there is relatively little published data regarding the effects of opioid analgesics on cognition and mood, and codeine derivatives (e.g. oxycodone) in particular have been neglected (see Zacny for a review, 1995). Furthermore, opiates are increasingly being given for pain relief on an outpatient basis where these concerns are more pertinent.

Pre-clinical studies researching the abuse potential of oxycodone, suggest that it is a full mu agonist with abuse liability of the morphine type (e.g. Swain, Fly & Seevers, 1977; Aceto, Kipps, Harris & Bowman, 2002; Woods, Ko, Winger, France & Traynor, 2003). However, at the time of writing this paper, the author could only find one study investigating the abuse liability and cognitive effects of oral oxycodone in non-drug abusing humans/healthy volunteers. Zacny and Gutierrez (2003) investigated whether oxycodone (10-30 mg) produces abuse-liability subjective effects and to what extent its behavioural toxicity was comparable to other opioid agonists (morphine 40 mg), as well as a known cognitive-impairing drug (lorazepam 2 mg). Subjective measures showed that oxycodone produced a number of subjective effects they considered as abuse liability-related in nature, including rating such as: “carefree”; “elated”; “having pleasant bodily sensations”; and “sedated (calm, tranquil)”. Cognitive and psychomotor impairment was observed with higher doses of oxycodone (20 mg; 30 mg), but to a much lesser degree than with lorazepam. Overall oxycodone was seen to produce effects resembling those of other mu-opioid agonists (Zacny & Gutierrez, 2003). However,
findings regarding abuse-liability were not conclusive as oxycodone also produced
effects that could be considered unpleasant in nature (e.g. itchy skin; nausea; drug
disliking), particularly at higher doses. Although the subjective measures used in this
study can provide considerable useful information, their reliability and validity can be
questioned. For example, one cannot be certain about how different individuals
experience effects and that what one individual considers a pleasant effect could be
considered as unpleasant for another individual. Indeed, some participants reported both
liking and disliking drug effects, while others reported neither liking nor disliking drug
effects (Zacny & Gutierrez, 2003).

Further inconsistencies in research are seen with regard to gender differences in
response to drugs of abuse. For example, some studies indicate that females may be
more sensitive to the rewarding effects of drugs of abuse (e.g. Lynch, Roth & Carroll,
2002) and this difference is often linked to the modulatory influence of hormones
(Cahill, 2006). Zacny & Gutierrez (2003) found that males but not females showed
significant increases on VAS ratings of “heavy or sluggish” and “sleep” under the
influence of oxycodone (30 mg). However, further evidence for gender differences has
been found in the relationship between PFC function and decision-making ability
(Tranel, Damasio, Denburg & Bechara, 2005; Bolla, Eldreth, Matychuk & Cadet, 2004).
For example, gender differences have been found using Rogers’ gambling task, with
male volunteers tending to choose the ‘experimental gamble’ slightly less often than
female volunteers and males tending to make choices faster than females (Rogers et al.,
2003). Gender differences have also been observed in a similar decision-making task
(the Iowa Gambling Task) indicating that brain mechanisms engaged by men and
women when solving the same decision-making task are different (Bolla, Eldreth, Matochik, & Cadet, 2004). Increasing evidence suggests that there are important gender influences on brain function (Cahill, 2006); and that sex-related differences contribute to the heterogeneity observed in both normal and abnormal brain functioning. However, there is little psychological research investigating these potential differences. Therefore, it is important to investigate gender differences in response to opioids.

The finding that executive functions, such as decision-making and inhibitory control are closely associated with changes in the reward centres in the brain make them ideal behaviours to monitor the effects drugs have on reward. Moreover, these behaviours provide more objective and precise measures than those used in subjective ratings and more naturalistic observations (Duka, Sahakian & Turner, 2005). Research into decision-making, particularly studies involving uncertain rewards and punishments, has been particularly helpful in linking drug abuse with a greater likelihood for making poor decisions (e.g. Bechara et al. 1996; Bechara & Damasio, 2002; Rogers et al. 1999). For example, in a paradigm that required participants to pick cards from four decks, two of which have small rewards and an overall net gain, and two of which have large rewards but regularly involve incurring large losses, Bechara et al. (1996) found that patients with PFC damage consistently selected from the risky decks despite the ultimately punishing consequences. Bechara and Damasio (2002) also found that drug abusers made unfavourable decisions, failing to respond to the large penalties. Furthermore, using a computerised decision-making task, Rogers at al. (1999) found that chronic opiate abusers deliberated for significantly longer before making their choices, in a similar way to participants with orbital PFC lesions. However, while some have
proposed that cognitive deficits in decision-making and impulsive behaviour predict drug abuse (Cloninger, Sigvardsson & Bohman, 1988), others feel the reverse may be true so that drug abuse leads to cognitive deficits and impulsive behaviour (Steele & Southwick, 1985). Indeed, one suggests both factors interact (Block, Erwin & Ghoneim, 2002). Therefore, it is important to determine whether there are impairments following acute drug use on human decision-making and impulsivity.

The present study was designed to investigate the abuse liability of oxycodone compared to morphine by measuring acute effects of these opioids in male and female healthy volunteers. A randomised, placebo-controlled, double-blind, within-subject (cross-over) design was used to compare the effects of oxycodone and morphine on cognition and mood. Abuse-liability was investigated by measuring both the subjective and objective behavioural effects of the drugs. In particular, tasks which tap decision-making and impulsivity were used as these abilities are linked to the DA system and PFC, shown to be disrupted in both drug addicts and following acute drug administration in drug naïve people (Goldstein & Volkow, 2002; Volkow et al., 2003).

A computerised ‘Gambling task’ developed by Rogers et al (2003) was used to study the drug effects on decision-making. The task involved presenting participants with two ‘gambles’, each consisting of a given probability of winning or losing a certain amount. As well as measuring time taken to make a decision, this task assessed the quality of the decision itself, allowing analysis of the extent to which an individual attends to information about probability, reward and punishment. In addition, the task contains two gambles designed to assess drug effects on choices between gambles driven by risk-
aversive (gains) and risk-seeking (losses) biases (*reflection effect*; Kahneman & Tversky, 1979). Impulsivity was assessed using a successive discrimination task (Go/No-Go task). This task tapped response inhibition and response reversal by requiring participants to monitor and inhibit activated responses. Other executive function tasks thought to be sensitive to changes in the DA system and the PFC were assessed using Reitan’s (1955) trail making task, and digit span (forwards and backwards) which taps attention and working memory. In addition to the cognitive tasks, this study repeated some of the interesting work presented by Zacny and Gutierrez, (2003) by using subjective ratings to assess abuse liability.

**Methods**

**Participants**

Volunteers (9 males and 9 females) were recruited from the undergraduate and postgraduate population of University College London (UCL). Initial contact was made by email when the volunteers were provided with a detailed information sheet explaining the purpose and requirements of the study. This was followed by a telephone conversation where volunteers were screened. Inclusion criteria were as follows: healthy volunteers aged between 18 years and 35yrs, good spoken English and basic literacy, willing and able to give informed consent to participate, willing and agree not to drive a vehicle on each test day, willing and agree not to drink alcohol for 24hours before each test day, and having good vision. Exclusion criteria were: a history of opioid abuse, a history of adverse reactions to opiates, current psychotropic drug abuse (social drinking
excepted), a history of hypotension or hypothyroidism, participation in recent CNS drug studies, and women who were pregnant or breast feeding.

The study was reviewed and approved by the Central Office for Research Ethics Committee (COREC). All volunteers gave written, informed consent.

**Design**

A randomised, placebo-controlled, double-blind within participants (cross-over) design was used to compare the effects of a single dose of oral oxycodone with that of morphine and matched placebo. Identical opaque gelatine capsules containing either oxycodone (5mg) morphine (10mg), or placebo (lactose powder) were prepared by the pharmacy at University College Hospital (UCH). These doses are the typically prescribed outpatient doses and the ratio was based on a study that suggested that the analgesic potency ratio of oral morphine to oxycodone in humans was approximately 2:1 (Zacny & Gutierrez, 2003). Participants were randomly allocated to treatment order which was balanced using a Latin Square. Both the researcher and the participants were blind to treatment order. Testing occasions were separated by a minimum 6-day ‘washout’.

**Procedure**

Prior to the experimental sessions, participants completed the Beck Depression Inventory (BDI; Beck et al., 1961) and the Beck Anxiety Inventory (BAI; Beck, 1987). Verbal intelligence was assessed with the Wechsler Test of Adult Reading (WTAR, Wechsler, 2001). Participants were asked not to eat anything for 2 hours before a session
unless it was in the morning when they were advised to eat a light, non-fatty breakfast. Pregnancy screening was carried out for all female participants prior to the start of each session. Pre-treatment, participants completed mood scales and their pulse was taken. Participants then swallowed the capsules along with water. One hour later, they completed the assessments detailed below. In the hour between testing times, participants were allowed to engage in sedentary recreational activities. On completion of a testing session, approximately one hour later, participants were offered refreshments and remained in the hospital until they felt comfortable to leave. They were instructed not to engage in certain activities (e.g., drinking alcohol, driving a vehicle) for the remainder of the test day.

Assessments

The selection of tests used was guided by an attempt to balance two test-characteristics. Firstly, it was desirable that tests should have 'ecological validity' (i.e. tap or correlate with everyday mental functioning) and secondly have sufficient sensitivity to detect drug effects. Measures tapped a range of cognitive and psychomotor functions, as well as subjective states related to impulsivity, mood, and side effects. Versions of tests used were counterbalanced across participants and design. The entire test session lasted approximately 2 hours. Order of assessments is given in Table 1.
Table 1. Order of test administration

<table>
<thead>
<tr>
<th>Pre-treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse</td>
</tr>
<tr>
<td>VAS (M RS, ISRS, SES)</td>
</tr>
</tbody>
</table>

Post-treatment (beginning 1 hour after ingestion of capsule):

| Pulse                  |
| Finger Tapping         |
| Trail making task      |
| Go/No-Go               |
| Digit forward/backward |
| VAS (MRS, ISRS, SES)   |
| Decision-making task   |
| VAS (DES)              |

Pre-drug assessments

Participants completed brief subjective assessments of mood, impulsivity and somatic effects, before taking the drug. Beginning 1 hour later, they completed these again alongside additional neuropsychological and psychomotor assessments. A measure of each participant’s pulse rate was also taken before and after the treatment.

Subjective ratings: subjective effects, mood and impulsivity

Subjective effects: Pre- and post-treatment was assessed with a subjective effects scale (SES), which was designed to assess the somatic and subjective experiences of opioids. The checklist consisted of 20 items shown to be sensitive to the effects of opioids (e.g. dry mouth, numbness, itchy skin, dizziness) (Zacny & Gutierrez, 2003).

Participants were asked to rate these symptoms on 100mm visual analogue scales (VAS) by placing a vertical mark on each line indicating how they felt at the moment.
**Mood:** pre- and post-treatment was assessed with the Mood Rating Scale (MRS, Bond & Lader, 1974). Principal components analysis of this scale yields three mood factors: sedation, discontentedness and anxiety.

**Impulsivity:** pre- and post-treatment was assessed with the Impulsivity Self Rating Scale (ISRS, Bond & Lader, 1974). Twenty variables make up the ISRS and a mean impulsivity score for each participant can be calculated for subsequent analysis.

**Pulse**

Researchers took participants’ pulse rate before and after the drug to assess effects on heart rate.

**Post-drug assessments**

**Finger tapping**

Tapping speed was used to index psychomotor sedation (Frith, 1967). Participants were asked to press the space bar of a computer keyboard with 2 fingers of their dominant hand as quickly as possible for 60 seconds. The total number of taps was recorded.

**Digit span**

Forwards and backwards digit span was assessed in the standard form (Lezak, 1995) to tap attention and working memory.

**Trail Making Task**

Reitan’s (1955) trail making task is a timed tracking task consisting of two parts: A and B. Part A involves joining numbered circles (1 to 25) while part B required participants to join alternating numbered (1 to 13) and alphabetised (A to L) circles. Mistakes were not pointed out until completion of the test and timing did not stop. Sample sheets for both parts were completed before each test to ensure participants understood the
instructions. Trails B tests complex visual scanning, which requires psychomotor speed and attention (Lezak, 1995). A difference score (B - A) removes the psychomotor speed component and produces a score that correlates highly with mental ability tests (Lezak, 1995).

Go/No-Go

This task tapped response inhibition and response reversal. Participants were instructed to respond to symbols on a computer screen by pressing a designated key on the computer keyboard as quickly as possible. The task consisted of three blocks: a practice block of 25 stimuli and two test blocks of 99 stimuli (Figure 1). Stimuli were 9 symbols organised into three sets of 3. Each symbol appeared for 800ms followed by an inter-stimulus interval (ISI) of 500ms. For the practice block participants were instructed to respond to any symbol. In the first test block (Phase 1) participants were instructed to respond by pressing the same key to all but one of the three symbols (e.g. “*”). This symbol constituted the ‘No-Go’ trials. The proportion of ‘Go’ stimuli was 60% and of ‘No-Go’ stimuli was 30%. Participants were then presented with a second test block (Phase 2) and were instructed not to respond to a different one (e.g. “?”) of the three symbols. This required participants to respond to the symbol for which responses were required to be inhibited in the previous block (e.g. “*”), thus tapping response reversal. Scores were recorded in terms of commission (response inhibition) errors, omission errors (on reversal trials) and reaction times.
**Decision-making task**

This task, designed by Rogers et al. (2003), assessed decision-making. Participants were required to choose between two visually presented gambles, each represented by a histogram on a computer screen (see Figure 2a). The height of each gamble indicated the probability of winning a given number of points. Prospective ‘gains’ (points to be won) were written in green above the histogram. Prospective ‘losses’ (points to be lost) were written in red below the histogram. On each trial, participants chose between playing an ‘experimental’ gamble and a ‘control’ gamble. The control gamble was coloured yellow (white in the figure) and consisted of a 50% probability of winning and a 50% probability of losing 10 points. The ‘experimental’ gamble was coloured blue (grey in the figure) and varied in the probability of winning which was either high or low (66 vs. 30%), the expected gains which were either large or small (80 vs. 40 points), and the expected losses which were either large or small (80 vs. 40 points). A combination of these variables in a crossed design results in 8 trial types (see Table 2).
Figure 2a. One trial from the decision-making task consisting of an experimental gamble with a 33% chance of winning 80 points and a 66% chance of losing 20 points vs. the control gamble with a 50% chance winning 10 points and 50% chance of losing 10 points.

Figure 2b. A 'gains only' trial from the decision-making task consisting of a certain win of 40 points vs. 50% chance of winning 80 or 0 points.

Figure 2c. A 'losses only' trial consisting of a certain loss of 40 points vs. a 50% chance of a loss of 80 or 0 points.
Table 2. The eight types of experimental gamble resulting from the combination, in a completely crossed design of two levels of probability, expected gains and expected losses.

<table>
<thead>
<tr>
<th>Probability</th>
<th>Expected Gains</th>
<th>Expected Losses</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (0.66)</td>
<td>Large (80)</td>
<td>Large (80)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small (40)</td>
</tr>
<tr>
<td>Small (40)</td>
<td>Large (80)</td>
<td>Small (40)</td>
</tr>
<tr>
<td>Low (0.33)</td>
<td>Large (80)</td>
<td>Large (80)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small (40)</td>
</tr>
<tr>
<td>Small (40)</td>
<td>Large (80)</td>
<td>Small (40)</td>
</tr>
</tbody>
</table>

The control gamble and the experimental gamble appeared randomly on the left or right side of the screen. The participant was instructed to press either the '1' or the '2' key on the computer keyboard to indicate choice of the left or right gamble, respectively. The dependent variable was the proportion of choices of the 'experimental' gamble over the control gamble as a function of the combination of probability of winning, the size of possible gains, and the size of the possible losses as well as the mean deliberation times in milliseconds (ms) for all choices.

The task also included two additional trial types that represent choices between gambles known to be subject to the non-normative biases of risk-aversion and risk-seeking behaviour described before (Kahenman & Traversky, 1979). The first type was a 'gains only' trial in which participants were presented with 2 gambles, one which guaranteed a
win of 40 points and another which offered a 50% chance of winning 80 points and a 50% chance of winning nothing. Neither gamble involved any loss (Figure 2b). The second type was a ‘losses only’ trial in which participants were presented simultaneously with a guaranteed loss of 40 points or a 50% chance of losing 80 points and a 50% chance of losing nothing. In this trial, neither option offered any gains (Figure 2c). For these trials, the dependent measure was the number times volunteers chose the guaranteed outcome.

Ten trial types were presented pseudo randomly within four blocks. Participants were given 100 points to begin with and asked to make choices, which would gain them as many points as possible. The computer gave feedback, informing participants whether they had won or lost and the new points total was presented for 2 seconds before the next trial. Across the four blocks there were a total of 80 trials, split into 4 blocks of 20 – eight repetitions of each ‘experimental gamble’ and eight repetitions of the ‘gains only’ and ‘losses only’ trial types. Overall this task lasted approximately 10 minutes.

**Drug effects:** at the end of the post-treatment session on each of three testing days, participants were asked to rate the ‘subjective effects’ of the capsule they had received (morphine/oxycodone/placebo). This required judgements on (1) the amount of effect (I feel no effect - I feel a strong effect; I feel no drug high – I feel a strong drug high), (2) the ‘pleasantness’ of the effect (I like the effect a lot - I dislike the effect a lot), (3) ‘craving’ (I want more of it - I want less of it), and (4) ‘Enjoyment’ of the experience (Definitely would not want to take it again for pleasure – Definitely would want to take it again for pleasure). Participants were also asked to rate how much they would pay for
the capsule to experience its effects again, ranging from 0mm (£0) to 100mm (£10). In order to further assess participants’ awareness of drug effects, they were asked to assess how they thought they performed on the various tasks. This required judgements on overall performance, memory, attention and concentration, and decision-making, ranging from 0% (worst performance) to 100% (best performance). At the end of the testing session, participants were invited to comment on any other experiences they noticed after taking the capsule.

Statistical Analyses

The data was analysed using the Statistical Package for Social Sciences (SPSS, Version 11.0). One-way analyses of variance (ANOVA) were used to compare males and females on demographics and mood. Repeated Measures ANOVAs (RMANOVA) were applied throughout with drug as a within participants factor and gender as a between-participants factor. For measures taken before and after treatment, pre vs. post was also a within-participants factor. For the gambling task, decisions (to play the experimental gamble) were analysed as proportionate choice. Deliberation times were transformed using log transformations. For any significant effects, further analysis was carried out, using weight as a covariance.
Results

Group characteristics

Group characteristics are shown in Table 3. The eighteen healthy volunteers, nine males and nine females, had a mean age of 25 years. There was no difference in age.

However, body mass index (BMI) was significantly higher in males (24.08±2.12) than in females (21.39±2.29) (F(1,16) = 6.76, p = 0.019). Height (p < 0.001) and weight (p < 0.001) were also significantly higher in males than in females. BDI, BAI, and WTAR did not differ as a function of gender.

Table 3. Group characteristics: Mean, Standard deviation (Std.)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>24.83 (4.25)</td>
<td>24.56 (5.20)</td>
<td>25.11 (3.33)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.71 (0.10)</td>
<td>1.79 (0.071)</td>
<td>1.63 (0.059)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.77 (13.31)</td>
<td>77.00 (10.07)</td>
<td>56.54 (6.25)</td>
</tr>
<tr>
<td>BMI</td>
<td>22.73 (2.54)</td>
<td>24.08 (2.11)</td>
<td>21.39 (2.29)</td>
</tr>
<tr>
<td>BDI</td>
<td>2.83 (2.83)</td>
<td>2.78 (1.99)</td>
<td>2.89 (3.62)</td>
</tr>
<tr>
<td>BAI</td>
<td>2.33 (2.89)</td>
<td>1.44 (1.74)</td>
<td>3.22 (3.60)</td>
</tr>
<tr>
<td>WTAR (raw score)</td>
<td>42.83 (5.23)</td>
<td>42.67 (4.24)</td>
<td>43.00 (6.33)</td>
</tr>
</tbody>
</table>
Cognitive Tasks (Table 4)

*Decision-making task (see appendix F)*

*Proportionate choice:* As expected, all participants chose the experimental gamble significantly more often when the probability of winning was high compared to when it was low ($F(1,16) = 140.04, p < 0.001$). Participants also chose the experimental gamble significantly more often when the possible gains were large versus when they were small ($F(1,16) = 57.53, p < 0.001$). They chose the experimental gamble less often when the possible losses were large compared to when they were small ($F(1,16) = 53.59, p < 0.001$).

Analyses revealed a significant four-way interaction between drug, gains, losses and gender ($F(2,14) = 7.15, p = 0.007$). Covariance of weight did not affect this finding. To explore this interaction, analysis of gains (separately for large and small gains) revealed a significant three-way interaction between drug, loss and gender when gains were large ($F(2, 14) = 5.54, p = 0.017$). As seen in Figure 3, males were more likely to choose the experimental gamble than females when gains were large and losses were small, especially on oxycodone ($F(1, 16) = 6.51, p = 0.022$). Post-hoc simple effects showed a significant difference in females between morphine and oxycodone ($p = 0.045$)*. There was no significant interaction when gains were small (see Figure 4).
**Figure 3.** Mean percentage of times experimental gamble was chosen when gains were large and losses were small; bars represent standard errors (s.e.); * indicates a significant difference.

**Figure 4.** Mean (s.e) percentage of times experimental gamble was chosen when losses were large and gains were small.

*Deliberation times:* Participants were significantly faster to make their choices when the probability of winning on the experimental gamble was high compared to when it was low (F(1, 16) =11.70, p=0.004). They also made their decisions significantly faster
when the probability of losing was low compared to when it was high (F(1,16)=9.27, p=0.008). There was no significant effect of drug condition on overall deliberation time and there were no interactions involving drug and probability, gains or losses.

Further analysis revealed a significant three-way interaction between drug condition, loss, and gender (F (2, 14) =4.27, p=0.036). As seen in Figures 5 and 6, compared to males, females were more affected by morphine, making slower decisions overall regardless of the size of loss. Males made their decisions at a similar speed on all drugs when losses were small. However, when losses were large, they appeared slower on oxycodone compared to morphine and placebo. Simple effects analyses did not reveal any significant drug or gender differences across losses.

![Graph showing mean (s.e) deliberation times (logsecs) when losses were small.](image)

**Figure 5.** Mean (s.e) deliberation times (logsecs) when losses were small.
Figure 6. Mean (s.e) deliberation times (logsecs) when losses were large.

‘Gains only' and ‘losses only' trials

Proportionate choice: Participants chose the guaranteed outcome significantly more often on the ‘gains only’ trials (83.10±0.058) than on the losses only trials (20.50±0.049), demonstrating risk aversion when choosing between gains and demonstrating risk-seeking when choosing between losses (F(1,16) =65.95, p<0.001). This pattern of choices did not differ across treatments.

Deliberation times: Participants were significantly faster to make their choices on the ‘gains only’ trials (F (1, 16) =75.89, p<0.001), however this was not affected by drug condition.
Table 4. Mean (Std.) on cognitive performance measures (figures in bold highlight significant drug effects).

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Oxycodone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulse</strong>&lt;sup&gt;b&lt;/sup&gt; (sec/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-pre</td>
<td>67.67 (8.98)</td>
<td>67.50 (7.65)</td>
<td>66.72 (10.03)</td>
</tr>
<tr>
<td>-post</td>
<td>65.06 (10.42)</td>
<td>61.72 (7.38)</td>
<td>60.56 (7.99)</td>
</tr>
<tr>
<td><strong>Finger tapping</strong></td>
<td>364.56 (46.59)</td>
<td>361.5 (45.81)</td>
<td>356.5 (50.54)</td>
</tr>
<tr>
<td><strong>Digit Span</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-forwards</td>
<td>7.50 (1.25)</td>
<td>7.22 (1.31)</td>
<td>7.44 (1.38)</td>
</tr>
<tr>
<td>-<strong>backwards</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>5.28 (1.07)</strong></td>
<td><strong>5.72 (1.56)</strong></td>
<td><strong>6.22 (1.17)</strong></td>
</tr>
<tr>
<td><strong>Trails times (sec)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A time</td>
<td>20.68 (7.18)</td>
<td>19.14 (4.81)</td>
<td>18.83 (5.14)</td>
</tr>
<tr>
<td>B time</td>
<td>37.05 (19.03)</td>
<td>38.10 (15.53)</td>
<td>36.28 (14.51)</td>
</tr>
<tr>
<td>B-A time</td>
<td>16.38 (19.40)</td>
<td>18.97 (15.78)</td>
<td>17.45 (12.70)</td>
</tr>
<tr>
<td><strong>GoNogo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commission errors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part 1</td>
<td>4.28 (2.91)</td>
<td>3.56 (2.68)</td>
<td>4.11 (2.32)</td>
</tr>
<tr>
<td>Part 2</td>
<td>5.56 (3.45)</td>
<td>4.83 (3.29)</td>
<td>5.83 (3.40)</td>
</tr>
<tr>
<td>Omission errors</td>
<td>0.33 (0.59)</td>
<td>0.44 (1.10)</td>
<td>0.50 (0.62)</td>
</tr>
<tr>
<td><strong>Reaction times</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part 1 hits</td>
<td>374.38 (10.44)</td>
<td>368.35 (42.03)</td>
<td>364.37 (41.14)</td>
</tr>
<tr>
<td>Part 2 hits</td>
<td>393.24 (9.13)</td>
<td>391.33 (41.71)</td>
<td>381.42 (36.82)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Drug effect (p≤0.05); <sup>b</sup>Time effect (p≤0.05)

**Digit Span (Table 4)**

For digits span backwards, there was a significant interaction between gender and drug (F(2,15) =3.77, p= 0.047) and a main effect of drug (F(2,16) =5.90, p=0.0142). As seen in Figure 7, both females (5.33±1.23) and males (5.22±0.97) were impaired by

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morphine, but only females were impaired by oxycodone (5.11±1.69). Co-varying for weight rendered the drug by gender interaction non-significant.

**Figure 7.** Mean (s.e) digits backwards score for each of the drug conditions.

*Pulse (Table 4)*

Pulse rate decreased from pre-to post- treatment (F (2,16) =20.87, p<0.001), regardless of drug treatment.

No significant drug or gender effects were found for finger tapping, Trails and Go/No-Go.

Subjective effects

*Subjective Effects Scale and Drug Effects Scale (Table 5)*

From Table 5, it can be seen that few significant effects emerged on subjective ratings.
Light-headedness ratings showed a significant interaction between gender, drug and time (F (2,15) =6.36, p=0.01). As seen in Figure 8, females rated themselves more light-headed on morphine (2.83±2.15) than oxycodone (1.89±2.62) and placebo (1.06±0.56), whereas males rated themselves more light-headed on oxycodone (2.67±2.69) than morphine (0.61; 2.16) and placebo (1.56; 2.74). After co-varying for weight, the drug by gender interaction was no longer significant.

![Graph showing light-headedness ratings by gender and drug condition.](image)

**Figure 8.** Mean difference (post-pre) (s.e) in light-headedness ratings for females and males for each of the drug conditions.
<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
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<tbody>
<tr>
<td><strong>Morphine</strong></td>
<td></td>
<td></td>
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<tr>
<td>Numb³³</td>
<td>0.44 (0.66)</td>
<td>1.00 (1.38)</td>
<td>0.81 (1.36)</td>
<td>1.69 (2.08)</td>
<td>0.47 (0.55)</td>
<td>1.08 (1.60)</td>
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<tr>
<td>Dry Mouth</td>
<td>1.97 (2.25)</td>
<td>2.25 (2.27)</td>
<td>2.61 (2.55)</td>
<td>2.19 (2.07)</td>
<td>1.89 (2.23)</td>
<td>1.64 (2.04)</td>
</tr>
<tr>
<td>Dizzy³³</td>
<td>1.03 (1.62)</td>
<td>1.64 (2.15)</td>
<td>1.42 (2.18)</td>
<td>2.97 (3.00)</td>
<td>0.86 (1.60)</td>
<td>1.58 (2.24)</td>
</tr>
<tr>
<td>Light-headed³³</td>
<td>1.14 (1.44)</td>
<td>2.86 (2.29)</td>
<td>1.78 (2.12)</td>
<td>4.06 (2.98)</td>
<td>1.06 (1.57)</td>
<td>2.36 (2.68)</td>
</tr>
<tr>
<td>Hungry³³</td>
<td>2.81 (2.20)</td>
<td>4.39 (2.51)</td>
<td>2.69 (1.93)</td>
<td>3.06 (2.34)</td>
<td>3.03 (2.67)</td>
<td>2.92 (2.41)</td>
</tr>
<tr>
<td>Tingling</td>
<td>0.39 (0.65)</td>
<td>1.25 (1.97)</td>
<td>1.00 (1.83)</td>
<td>1.61 (2.39)</td>
<td>0.53 (0.58)</td>
<td>0.78 (1.18)</td>
</tr>
<tr>
<td>Flushed/Warm</td>
<td>1.78 (2.04)</td>
<td>1.69 (2.02)</td>
<td>1.83 (1.98)</td>
<td>2.00 (2.22)</td>
<td>1.25 (1.71)</td>
<td>1.61 (1.94)</td>
</tr>
<tr>
<td>Itchy skin</td>
<td>0.83 (1.01)</td>
<td>0.69 (0.77)</td>
<td>1.14 (2.00)</td>
<td>1.33 (2.26)</td>
<td>0.86 (1.36)</td>
<td>0.92 (1.43)</td>
</tr>
<tr>
<td>Pleasant body sensations³³</td>
<td>1.81 (2.18)</td>
<td>1.92 (2.00)</td>
<td>1.64 (2.33)</td>
<td>2.92 (2.59)</td>
<td>1.28 (1.94)</td>
<td>1.89 (2.52)</td>
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<tr>
<td>Difficulty concentrating³³</td>
<td>2.17 (1.99)</td>
<td>2.94 (2.22)</td>
<td>1.64 (1.76)</td>
<td>3.69 (2.32)</td>
<td>1.81 (1.65)</td>
<td>2.47 (2.15)</td>
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<tr>
<td>Memory problems³³</td>
<td>1.81 (1.78)</td>
<td>3.22 (2.46)</td>
<td>1.50 (1.59)</td>
<td>3.83 (2.75)</td>
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<tr>
<td>Inhibited ↔ Impulsive</td>
<td>5.17 (1.39)</td>
<td>4.97 (0.85)</td>
<td>5.03 (1.44)</td>
<td>5.31 (1.20)</td>
<td>5.22 (1.39)</td>
<td>5.03 (1.46)</td>
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<tr>
<td>Shy ↔ Confident</td>
<td>6.11 (2.17)</td>
<td>6.14 (1.58)</td>
<td>6.50 (1.83)</td>
<td>6.53 (1.50)</td>
<td>6.61 (1.53)</td>
<td>6.75 (1.64)</td>
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<td>Depressed ↔ Elated</td>
<td>6.08 (1.97)</td>
<td>6.31 (0.96)</td>
<td>6.28 (1.46)</td>
<td>5.94 (1.07)</td>
<td>6.31 (1.39)</td>
<td>6.28 (1.10)</td>
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<tr>
<td>Despairing ↔ Euphoric</td>
<td>4.31 (1.11)</td>
<td>4.33 (1.13)</td>
<td>4.33 (1.12)</td>
<td>4.50 (0.92)</td>
<td>4.17 (1.04)</td>
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<tr>
<td>Spaced out ↔ Focused³³</td>
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<td>4.78 (1.55)</td>
<td>6.06 (2.12)</td>
<td>4.19 (1.72)</td>
<td>6.42 (1.67)</td>
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<td>Details ↔ big picture</td>
<td>6.89 (1.72)</td>
<td>6.22 (1.93)</td>
<td>5.89 (1.95)</td>
<td>5.44 (1.88)</td>
<td>6.58 (1.66)</td>
<td>6.28 (1.74)</td>
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<td>Heavy/sluggish ↔</td>
<td>5.28 (1.65)</td>
<td>4.97 (1.67)</td>
<td>5.67 (2.04)</td>
<td>5.17 (1.83)</td>
<td>5.92 (1.41)</td>
<td>5.47 (1.94)</td>
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<tr>
<td>Light/energetic</td>
<td>7.14 (1.90)</td>
<td>7.33 (1.58)</td>
<td>7.22 (1.64)</td>
<td>7.36 (1.55)</td>
<td>7.86 (1.35)</td>
<td>7.58 (1.54)</td>
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<tr>
<td>Angry ↔ Peaceful</td>
<td>7.61 (1.59)</td>
<td>7.25 (1.57)</td>
<td>7.42 (1.19)</td>
<td>7.50 (1.50)</td>
<td>7.89 (1.30)</td>
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<td>Aggressive ↔ Cool</td>
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<td>Headed</td>
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<td><strong>Placebo</strong></td>
<td></td>
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</tr>
</tbody>
</table>

*MRS*

| MF1-sedation³³ | 44.98 (0.94) | 45.60 (1.15) | 44.52 (0.86) | 45.48 (1.35) | 44.48 (0.89) | 44.94 (1.17) |
| 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) |

**ISRS**

| Overall mean³³ | 3.30 (1.02) | 3.64 (1.36) | 3.02 (1.14) | 3.56 (1.46) | 2.88 (1.14) | 3.34 (1.17) |

**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) |
| 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) |

*Drug by time interaction (p≤0.05); °Time effect (p≤0.05); ºDrug effect (p≤0.05)
Ratings for "feel drug effect" showed a main effect of gender ($F(1, 16) = 6.21, p=0.024$), with females rating morphine significantly higher than males ($p=0.025$) (see Fig 9). After co-varying for weight the main effect for gender was no longer significant.

![Graph showing 'feel effect' ratings for females and males across different drug conditions.](image)

**Figure 9.** Mean (s.e) "feel drug effect" ratings for females and males for each of the drug conditions.

Ratings for "want more drug" also showed a main effect of gender ($F(1, 16) = 6.93, p=0.018$). After co-varying for weight the main effect for gender was no longer significant; however, a significant drug x gender interaction emerged ($F(2,14) = 4.76, p=0.026$). Post hoc analyses revealed that females rated that they wanted less of both morphine ($p=0.036$) and oxycodone ($p=0.038$) than males (see Fig 10).
Figure 10. Mean (s.e) “want less/more” ratings for females and males for each of the drug conditions.

Hunger ratings showed a significant interaction between drug and time (F (2,16) =3.74, p=0.046), with ratings being higher after morphine than oxycodone or placebo (see Fig 11).

Figure 11. Mean (s.e) hunger ratings pre and post for each of the drug conditions.
Several ratings showed an increase over time: numbness (F (2,16) =11.86, p=0.003); dizziness (F (1, 17) = 12.91, p=0.002); light-headedness (F (1, 17) = 25.59, p<0.001); hunger (F (1,17) =4.80, p=0.043); pleasant body sensations (F (1, 17) = 7.08, p=0.016), difficulty concentrating (F (1,17) = 17.68, p=0.001), memory problems (F (1,17) = 37.61, p<0.001); feeling spaced out (F (1,17) = 28.04, p<0.001).

A number of ratings also showed a main effect of drug: dizziness (F (2,16) =3.61, p=0.051); light-headedness (F (2,16) =3.99, p=0.039); pleasant body sensations (F (2,16) =4.59, p=0.027), with overall ratings being higher for oxycodone than for morphine and placebo. However, there were no other significant interactions between drug and time.

*Mood rating Scale (MRS)* (*Table 4*)

Overall, mood factor 1 (sedation) increased from pre- to post- drug (F (1, 17) =16.34, p=0.001). Although there was also a main effect of drug (F (2,16) =4.45, p=0.029), there was no significant interaction. No significant effects were found on mood factors 2 (discontentedness) and 3 (anxiety).

*Impulsivity (JSRS)* (*Table 3*)

Overall, impulsivity increased over time (F (2,15) =7.48, p= 0.015). However no significant effects of drug were found and there was no significant interaction.
Discussion

A major finding from this study is that there are gender differences in the acute effects of opioids on healthy volunteers. These differences emerged in objective decision-making measures as well as subjective measures.

Overall, participants' pattern of decision-making was typical and consistent with that found in previous research. That is, participants chose to play a gamble more frequently when the probability of winning was high compared to when it was low, when prospective gains were large compared to when they were small, and when the prospective losses were small compared to when they were large (e.g. Rogers et al., 2003; George, Rogers & Duka, 2005).

However, the interaction of these effects was altered across drug condition and gender. Specifically, when the potential gains associated with the experimental gamble were large and the losses were small, males were more likely than females to display typical decision-making behaviour; i.e., choosing to play the gamble. Females on the other hand were more likely to play the gamble when they had taken morphine compared to oxycodone. This difference between treatments could reflect an impairment for females under the influence of oxycodone, as they were less likely to make the ‘normative’ choice under the influence of this drug. Importantly, this finding was independent of body weight, indicating gender differences over and above differences in weight.
Gender differences were also observed for digits span backwards as females and males were impaired by morphine but only females were impaired by oxycodone. This is consistent with the decision-making findings indicating important gender differences in the response to these opioids. However, weight does appear to be an important factor in this case as covariance of weight left no gender differences.

The above findings cannot be explained by an increase in impulsivity under the influence of opioids as there was no evidence to suggest that opioids decreased the time taken to make risky decisions. In fact, compared to males, females' deliberation times increased, particularly under the influence of morphine. Moreover, when the potential losses associated with the experimental gamble were large, males' decisions appeared slower under the influence of oxycodone compared to morphine and placebo. These findings indicate a slowing down of decision-making processes, rather than increased speed and impulsivity. In support of this, the Go/No-Go task and the Impulsivity Self Rating Scale did not reveal an increased level of impulsivity under the influence of either morphine or oxycodone. This is consistent with Rogers et al. (1999) who suggest that increased deliberation times on their decision-making task are consistent with altered neuromodulation of the circuitry associated with abuse of these substances.

Consistent with previous studies which have used the gambling task, on the “gains only” and “losses only” trials (two known examples of non-normative decisions-making, Kahneman & Tversky, 1979), participants displayed typical risk-averse behaviours when choosing between gains and risk-seeking behaviours when choosing between losses
(Rogers et al., 2003; George et al., 2005). This behaviour did not vary according to drug condition.

Although the findings from these tasks do not demonstrate a clear pattern of impairment, the results suggest that decision-making does change on opioids, and especially for females. The finding that opioids affect people’s performance on tasks believed to tap executive functioning, such as decision-making, is consistent with previous research with drug-addicted subjects (e.g. Bechara et al., 2001; Bechara & Damasio, 2002; Ernst et al., 2003; Rogers et al., 1999). It supports the idea that drugs exert their reinforcing effects via the DA system which has been shown to extend to areas of the PFC, known to support functions which are executive in nature (e.g. Goldstein & Volkow, 2002; Volkow et al., 2003). However the findings from this study emphasise the role of decision-making, rather than impulsivity and inhibitory control discussed in Volkow’s model of addiction (Volkow et al., 2003). Furthermore the finding that opioids can induce disruptions to the DA system and therefore dysfunction of these prefrontal regions in healthy, non-addicted participants lends support to the idea that cognitive changes are seen following acute administration (Steele & Southwick, 1985).

Findings from the subjective effects indicate that in general oxycodone and morphine produce a similar profile of subjective effects. However, differences between genders were again observed. Findings from the Subjective Effects Scale (SES) indicated that females rated themselves as more light-headed on morphine, whereas males rated themselves as more light-headed on oxycodone. The Drug Effects Scale (DES) also uncovered gender differences on ratings for “feel drug effect” and “want less/more
drug”. Compared to males, females tended to rate higher “feel effects” for morphine, which is in part consistent with the ratings for light-headedness (as females also rated themselves as more light-headed on morphine). Females also rated that they wanted less of the opioids than the males, and this difference was independent of body weight.

Again, this finding is particularly interesting as it suggests that gender differences exist in response to opioids, independent of body weight. Zacny and Gutierrez (2003) also observed increases in “like drug” and “want drug” ratings with oxycodone (10-30 mg) but no gender effects with these ratings. Zacny and Gutierrez did observe gender effects on VAS ratings of “heavy or sluggish” and “sleep”. However, these were with higher doses. Indeed, their lowest dose of oxycodone was double that used here and their morphine dose fourfold higher. Specifically, they reported that with oxycodone (30 mg), males but not females showed significant increases on VAS ratings of “heavy or sluggish” and “sleep”. However, other subjective effects and psychomotor and physiological effects did not differ as a function of gender, therefore the researchers concluded that oxycodone and morphine effects did not differ as a function of sex (Zacny & Gutierrez, 2003).

Drug differences were observed for hunger ratings, which increased significantly more under the influence of morphine than oxycodone and placebo. This suggests that morphine is more likely to make people feel hungry. Interestingly, this finding is in contrast to Zacny and Gutierrez (2003) who found that ratings of hunger increased with oxycodone (10-30 mg) but not with morphine (40 mg). Drug effects were also observed for subjective ratings of sedation, dizziness, light-headedness, and pleasant body sensations. Although there were no significant interactions and changes were subtle,
overall ratings were higher under the influence of oxycodone than morphine and placebo. The lack of a significant drug x pre-post interaction on each of these 4 measures is probably due to the larger variance of scores post-oxycodone. Clearly, these measures showed greater individual variation in response to oxycodone than to morphine. These findings are broadly consistent with those of Zacny and Gutierrez (2003) who found similar effects, but with much higher doses (10-30 mg oxycodone). For example, they found subjective effects of dizziness and pleasant body sensations increased with oxycodone (20-30 mg) but not with morphine (40 mg). Ratings of sedation increased with oxycodone (10mg & 30 mg) but not with morphine (40 mg) and ratings of light-headedness increased with both oxycodone (20-30 mg) and morphine (40 mg) (Zacny & Gutierrez, 2003). A number of female participants also reported feelings of nausea. However, subjective ratings for this symptom were not included in the measures in this study as both the SES and the DES scales were designed to include only those significant effects observed by Zacny and Gutierrez (2003) with their lowest dose of painkiller (oxycodone, 10 mg) (nausea was only noted at higher doses (20-30 mg)). However, feelings of nausea are commonly observed with opiate use (Joint Formulary Committee, 2006) and it is important to consider that this omission could have ignored effects which may have had consequences for participants’ performance. Other changes in subjective ratings which Zacny and Gutierrez observed, e.g. carefree, itchy skin, elated, tingling, were not observed in this study. The subjective effects seen in this study appear to be typical of mu-opioid agonists (Joint Formulary Committee, 2006). The results are broadly consistent with other studies involving animals (e.g. Aceto. et al., 2002) and human non-drug abusing volunteers (Zacny & Gutierrez, 2003).
Clearly, we might well have observed many more significant effects had a higher doses of opioids been used. For example, Zacny and Gutierrez found more significant subjective effects using much higher doses of oxycodone (20 mg and 30mg) and morphine (40 mg). However, the findings from that research remained inconclusive with regard to abuse-liability, even with such high doses. As this study aimed to investigate subtle cognitive changes, the typical clinical dose of 5 mg oxycodone and 10 mg morphine was deemed appropriate. Furthermore, it was considered important to measure effects of doses typically given at outpatients.

Prescription opioid abuse is reportedly increasing (e.g., SAMHSA, 2001; 2002a & 2002b; CESAR, 2004, 2005), and increases in the non-medical use of oxycodone in particular is causing concern (Hays, 2004; Young, 2001). However, the only subjective effects produced by oxycodone and morphine that could be considered abuse liability-related (i.e. pleasant in nature) were “pleasant body sensations”. As mentioned above, ratings for this effect was higher for oxycodone than for morphine. However, there was no other evidence from the subjective effects to suggest that at these doses, oxycodone could have greater abuse potential than morphine. The finding that women’s decision-making may be more affected with oxycodone than morphine could suggest that with this opioid, more significant changes are occurring in the DA activated reward system in the female brain. This would be consistent with studies which suggest that females may be more susceptible to the rewarding effects of certain drugs (Lynch et al., 2002; Carroll et al., 2004). However, these findings are not clear-cut as females also had higher ratings than males for “want less drug” on both morphine and oxycodone.
The present study examined the effects of oxycodone and morphine when administered acutely to non-drug-abusing healthy volunteers. However, part of the concern with oxycodone is that abusers choose to disrupt the controlled release nature of the drug leading to rapid release and absorption and providing an instant and intense effects. It would also be important to investigate the abuse potential of immediate release oxycodone compared to other mu opioids, in both drug abusers and non-addicted subjects. Studies such as these could help bridge the gap between preclinical studies of abuse liability and epidemiological studies indicating opioid abuse is on the rise.

The gender by drug interactions found in this study clearly indicate that males and females respond differently to opioids. Differences such as these could be as a result of the modulatory influence of hormones and/or fundamental differences in brain organisation (Cahill, 2006). Indeed, the PFC has been shown to have a high concentration of sex hormone receptors, with the highest concentration of oestrogen receptors in the human brain (Bixo, Blackstrom, Winblad & Andersson, 1995). Gender differences have been observed in executive functions believed to depend on the PFC (see Cahill, 2006, for a review). In particular, and related to the findings from this study, deficits in decision-making seen after PFC lesions appear to differ according to gender. For example, Tran et al. (2005) found that left hemisphere PFC lesions impair performance on a decision-making task in females but not in males, whereas right hemisphere lesions impair performance in males but not in females. Gender differences have also been uncovered in neurotransmitter systems (Cahill, 2006). A number of studies have reported gender differences in the analgesic effectiveness of opioid peptides (Craft, 2003). Neuroimaging studies have revealed gender differences in levels of opioid
receptor binding in some brain regions, such as the amygdala and thalamus (Zubieta, Dannaïs & Frost, 1999). Further sex differences have been uncovered in dopamine function and the nature of addiction. For example, Becker (1999) reported sex differences in levels of dopamine in several brain regions in addition to differences in responsiveness of dopamine to stimulation by amphetamine and sex hormones.

It would appear therefore that there is increasing evidence to suggest that biological and physiological differences exist between genders. Women and men differ in their brain anatomy, chemistry and function/organisation and in their response to drugs. Indeed, the results from this study suggest that not adjusting dosage for weight is a major issue, which has potentially deleterious effects on women. Related to this, Simon (2005) reports how the close of the previous decade saw 8 out of the 10 prescription drugs that were withdrawn from the U.S. market were withdrawn because they caused statistically greater health risks for women than men.

Despite this, there is still little psychological research investigating potential gender differences, and potentially a wealth of unpublished data that could reveal sex differences (Simon, 2005). Indeed, the vast amount of research has been carried out on males with the assumption that the “70-kg white male” can serve as representative of the species. However, results from studies such as this one highlight the importance of accounting for possible differences in sex and including them as part of a clinical study design. For example, in order to prevent adverse reactions, it would seem important to analyse pharmacokinetic effects during early phases of drug development in order to determine gender differences in dosage recommendations. Indeed, while adjusting for
weight is always considered with major interventions (e.g. anaesthesia), it is rarely controlled for with oral treatments. It may be that drug companies need to consider manufacturing a greater range of drug dosages. In addition, female specific factors, such as stage of ovarian cycle, use of oral contraceptives, and hormone replacement therapy may influence intervention outcomes and should therefore be considered (Simon, 2005).

Drug companies may argue that conducting trials with enough power to allow for gender-specific analyses are both costly and time-consuming. However, when prescription drugs are withdrawn from the market because they pose greater health risks for women the cost of not doing these analyses is greater. The findings from this study support other research which indicates that the influence of gender is too important to be ignored. Clinical trials need to be carefully designed to include population samples which allow for a valid analysis of both women and other minority populations. Only studies, which consider these differences, will provide findings that are useful and meaningful to the health of both women and men.

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Part 3. Critical Appraisal
1. Reflections on the research process

At the beginning of the research process intentions were clear. There was a paucity of abuse liability testing of prescription opioids, and a noticeable gap in the literature with regard to the abuse potential of oxycodone. Indeed, at the time of beginning the research, only one study could be found investigating the effects of oxycodone on healthy volunteers. The message coming from the Centre for Substance and Abuse Research (CESAR), 2004, 2005) and other epidemiological studies was evident: Abuse of prescription opioids, in particular oxycodone is increasing at an alarming rate and is becoming a significant problem (Substance Abuse and Mental Health Services Administration (SAMHSA), 2001; 2002a, 2002b, 2002c, & 2002d)). News reports and articles talked about “hillbilly heroin” and “the drug of choice”.

"OxyContin can appeal to anyone — teen to senior citizen"

Sgt. Tom McGrath, coordinator of the countywide Drug Abuse Resistance Task Force (DART).

It was exciting to think that the research I was embarking upon was cutting edge, addressing current concerns in both the public and professional lives. Questions
included: Was there something different about oxycodeone? Was it having significantly
different effects on the reward system in the brain? Could this difference be captured
and measured objectively? Thus, we set out with an aim to assess the abuse liability of
oxycodeone in healthy, non-drug abusing volunteers using both subjective ratings and
objective measures of reward-related decision-making and inhibitory control.

Data collection was to be shared with a fellow trainee, with each of us running each
other’s tasks. We developed our protocol early in the research process and the
application to ethics was submitted in good time. It was estimated that each testing
session would take approximately two hours. With 18 participants to test on three
separate occasions, this totalled about 50 hours of testing each. With ethics approval
expected by March 2005, recruitment of participants and data collection was planned
from April to October 2005. We were expecting to complete the research in good time to
analyse data and write up results.

However, in March 2004 we received a letter from the ethics committee stating that they
would not be able to give favourable ethical opinion of the research. Reasons included
corns that: “the study involved providing addictive drugs to students with an
inducement payment of £50” and “the use of morphine outside of its prescribed form is a
criminal activity”. The committee were also worried that it could be some people’s first
experience of drugs, and they felt that no provision had been made for adverse reactions.
They also suggested, “this study of a potentially addictive drug had neither scientific
validity nor any neuropsychological value”. We were invited to submit a new
application and the process of review would take place again. Obviously, this was
viewed as a major setback. The ethics form itself takes considerable time. Alternatively, we could appeal against the decision and the ethics committee would arrange to meet again. Fortunately, we had the knowledge and expertise of our supervisor in this event. A carefully constructed letter, covering all the committee’s original concerns, was written to appeal the decision. The letter further highlighted the need and rationale for this type of research, with references to previous studies. It was particularly important for us to point out that the risk of ‘addiction’ arising from participating in this study was extremely low, and this could be supported by previous research (e.g. Zacny and Guttierrez, 2003). We emphasised how we were considerate and sensitive to issues concerning drug abuse and that we intended to exclude any volunteers with a history of drug abuse. Consideration was given to the ethical dilemma of offering payment, particularly following the concerns raised by the ethics committee. In order to maximise informed consent, the study was fully explained and participants were given time to consider their involvement. We explained that payment was given at the standard rate, not as inducement but as compensation for time, effort and inconvenience of participating. We were also required to inform the committee that in medical research of this kind, prescribing opiates outside the prescribed form is not a criminal offence. We consulted the Clinical Trial Lead Pharmacist at UCH who confirmed this and assured that standard procedures and would be adhered to when dispensing. The committee were also encouraged that, although it was unlikely that any participants would experience adverse effects on such low doses of painkillers, these events were provided for. Indeed, full medical cover was provided throughout the study as it was conducted entirely within the hospital. At the request of the ethics committee, it was planned that all female volunteers would be given pregnancy tests at the beginning of every visit. Finally we
were required to emphasise both the scientific validity and neuropsychological value of the study and the clinical value and theoretical value of the research.

A new date was arranged for the ethics committee meeting which I planned to attend with the consultant anaesthesiologist and a research colleague. We were armed with all the information to appeal our case, but I was quite apprehensive as our major research project now rested on the outcome of this meeting! Thankfully, following our letter they immediately decided that ethical approval would be granted. This was a huge relief. However, gaining approval late in August meant we were 3-4 months behind schedule.

Following ethics approval, we could begin setting up the study with the anaesthesiology department and UCH pharmacy. However, further setbacks were encountered with pharmacy. Making up the drugs was a considerably slower process than anticipated. It was frustrating that again this appeared to be because of regulations and the amount of paperwork required. Certain restrictions are placed on controlled drugs, such as morphine and oxycodone, and this meant that particular care had to be taken to comply with all the necessary regulations.

Fortunately, recruitment was one area with which we did not seem to have any difficulties. Unlike some of our peers whose research involved patients and participants with mental health issues, we did not experience recruitment difficulties. In fact, initially we were inundated with volunteers who were keen to take part. All volunteers arrived on time and at the appointments arranged.
Testing finally commenced in December 2005; some 6 to 8 months later than initially planned. It took place in the brand new University College Hospital. We were excited to have the opportunity to carry out our research in this new environment with quiet, comfortable rooms for testing. However, with these new facilities came heightened security and it soon became apparent that when testing at quieter times (i.e. weekends), both trainees needed to be available to allow us easy access in and out of locked doors. In addition to this, we were required to carry identification and letters explaining and approving our research. Arranging to have prescriptions written for each participant prior to each testing session and coordinating sessions with the pharmacy opening times and with doctors on call seemed difficult and frustrating at the start. At this point, I questioned my choice of research project. So much organisation was required; I wondered if we would ever complete the data collection. However, we were fortunate to have considerable input from a well-organised anaesthetist who coordinated prescriptions for pharmacy and doctors on call.

Following rehearsals with my supervisor and one of the anaesthetists, the testing sessions themselves ran relatively smoothly. However it soon became apparent that the whole testing process, including collection of drugs from pharmacy and setting up test materials, would take most of the morning or afternoon. With the Christmas break looming, we soon realised that to complete testing in good time, we would need to make ourselves available to test participants on weekends as well as weekdays.

During one of the first testing occasions, a participant felt extremely nauseous. At this time, I experienced feelings of both concern (was the dose too high?) and guilt (feeling
responsible for putting someone through what appeared to be a very unpleasant experience). It quickly became obvious how important it was to have a doctor available to check the participant and to reassure. It was also extremely valuable to have frequent available supervision during this time; and being able to raise these concerns with my supervisor reduced my anxieties. Interestingly, I now know that this participant had been given placebo on that testing occasion. For me, this was one of the most striking discoveries during the research process, as I had not considered how strong the placebo effect could be.

One month in, things were running more smoothly and data collection began to feel like a more achievable goal. However, in March 2007, news headlines read: “six men fall seriously ill during a London trial of an anti-inflammatory drug” and all public attention turned to the news that a number of volunteers had suffered severely adverse effects during a clinical trial. At the same time, we lost contact with one of our participants and feared losing data from her final visit. This was a sobering time as we witnessed what can happen when drug trials go drastically wrong. Although a very different study to ours, it was evidence of the powerful effects drugs can have on healthy volunteers. Fortunately, our participant made contact again and we were able to complete our data collection. Her absence was not related to this news. However, we discussed the potential effect it could have had on our study had we been recruiting at the time.

Reflecting upon my own personal experience, I can see how I set out feeling excited and optimistic about the research process and what the results could potentially reveal. However, soon there were moments when I felt both exacerbated and exhausted as I
realised how much organisation was involved setting up the study. It was at these moments that I was very glad to be sharing the responsibility with a fellow trainee, as we were able to support each other through this process. Towards the completion of data collection, I felt some disappointment as it was becoming clear that volunteers were not experiencing dramatically different effects between treatment conditions. We were not discovering anything particularly unusual and I was not going to be the one to uncover an important and striking effect of oxycodone. Data entry was another part of the research for which I had not appreciated how much time would be needed. There was so much data that at times it felt quite overwhelming. However, organising the data into SPSS provided much satisfaction and compared to this, data analysis was a light relief. In many ways, I felt excited to be conducting research in a relatively understudied area. However, reviewing the literature to the neuroscience of drug addiction highlighted my limited knowledge, and the complexity of the area overwhelmed me. Looking back, however, I believe that part of me enjoyed this process and I felt a sense of achievement and satisfaction completing a review of the literature. With regard to the paper, organising the results was the most complex part. However, overall I enjoyed writing up the research. It required me to re-focus on the research question and resulted in the findings and the literature being pulled together in a meaningful and coherent way.

2. Critical appraisal of the research

The main finding from this research indicates that there are interesting gender differences in effects of the acute administration of opioids in healthy volunteers. These differences were seen in both subjective measures and objective measures of decision-
making. This finding is of theoretical value as it supports research which indicates important gender differences on brain anatomy, chemistry and function (see Cahill, 2006, for a review). It also links the opioid system with decision-making and reward. The research is clinically important as it indicates the effects of single doses of these commonly prescribed drugs on processes which affect patients' daily functioning.

Indeed, the overall findings from this study indicate that opioids at the commonly prescribed doses used in this study (morphine -10mg and oxycodone –5mg), in this mode of operation (ingesting a controlled release form of the drug) can be given to healthy volunteers with no significant impairments in decision-making and impulsivity. Furthermore, with the doses and administration in this study, there were no indications for participants' future drug-seeking and drug self-administration for either opioid. This research further highlights the need for clinical trials to conduct research including both men and women (see Simon, 2005).

However, it was more difficult to answer the original research question, as results regarding abuse-liability were not clear-cut. This invited me to consider a number of issues about the design of the study, including specific aspects of the measures and methodology. Thoughts are given below as to how the research may be limited and how future investigations may address these limitations.

Dosage and method of administration

This study is of considerable value as it demonstrates the effects of these commonly prescribed painkillers at doses typically given for management of pain in the outpatient setting. However, it was difficult to draw the results together as they were both subtle
and at times inconsistent. Although clinically relevant, the disadvantage of using such small doses is that it can be difficult to uncover large and consistent differences. Furthermore, normal fluctuations in participants’ responses and individual differences can have more effect on the overall results. Research involving drug-addicted individuals indicates that people who are abusing these drugs are taking much higher doses in order to experience the desired effects on mood and thinking. It is probable that different doses could account for differences in subjective effects. Indeed, Zacny and Gutierrez (2003) found that higher doses of oxycodone produced both pleasant and unpleasant effects. However, this study used half of the lowest dose of oxycodone and a quarter of the dose of morphine than that used in their research. In addition to increasing doses, people who abuse prescription opioids often use alternative methods of administering the drug, such as chewing or injecting, as this results in rapid release and absorption providing an instant and intense "high". This study involved giving participants the controlled-release form of the drug and they were instructed to ingest the pill as is typically indicated for outpatient use. Again, there was good reason for assessing the drug effects in this way, as it was important to establish clinically relevant effects. However, the reinforcing effects of drugs depend on the speed and magnitude of DA release, which is directly affected by route of administration. For example, drugs that are injected intravenously lead to a fast intake in the brain compared to drugs taken orally, which result in slower brain uptake. The faster a drug reaches the brain, the greater the 'rush' and the potential for reinforcement (Volkow et al., 2003). Therefore it would have interesting to compare different does and alternative methods of administration in this study in order to assess the effects of immediate release and rapid absorption of these drugs.
The population sample and individual differences

This study investigated the acute affects of opioids on a sample of healthy non-drug abusing individuals. To determine the effect of a drug most clearly, it is important to study it with people who have ‘clear minds’—no medical problem; not taking any medication; not taking drugs of their own accord (drug abusers). However, given participants who felt strong drug effects did not tend to indicate “wanting more drug”, it made me think more about why the effects are rewarding for addicts. Although similar changes in the DA system and PFC have been observed in drug naïve as in addicted subjects, it is important to note that research suggests the effect of opioids on healthy volunteers differs from those found in drug-abusing populations. For example, cognitive impairment by opioids tends to occur more often in healthy volunteers (who have little or no exposure to the drugs) than in those who have a history of opioid use (Zacny, 1995). It is also important to recognise that in addition to experiencing pleasant and euphoric effects, opioid use and abuse may occur as a way of escaping from unpleasant experiences, such as chronic physical and/or mental pain, unpleasant intrusive thoughts and persecutory delusions. Furthermore, some evidence suggests that unlike opioid abusers who report predominately pleasant effects, non drug-abusing patients do not report euphoria after being administered opioids (Preston & Jasiniski, 1991).

A further reason why healthy volunteers are the appropriate population concerns testing. Patient studies involve tight limits on testing the effects of a drug because testing itself can put demands on patients in pain and during the placebo phase, patients are required to be without painkillers for a period of time. Furthermore, it has been suggested that level of pain may reduce some of the opioid’s euphoric effects. Therefore, investigating
the effects in non-drug abusing participants who are also not in pain is needed. However, pain itself has been shown to impair cognitive function and therefore studies performed to evaluate cognitive effect of opioids in pain-free controls cannot necessarily be extrapolated to patients in pain (Lorenz, Beck & Bromm, 1997).

It is also possible that vulnerability or susceptibility to some actions of psychoactive substances, including cognitive enhancement and dependence, may depend on individual differences based on genetic, environmental, and developmental factors (Robbins et al., 2005). For example, one of the variables thought to influence vulnerability to substance misuse is the inherited variability of striatal dopamine receptors (e.g. Volkow et al. 2003). It is also important to account for the possible coexistence of personality factors that might contribute both to individual difference in performance and vulnerability to substance abuse itself (Rogers et al., 1999). For example, researchers have linked impulsive personality characteristics to substance abuse (McGown, 1990). It would have been interesting to include a character trait questionnaire to investigate potential differences between individuals, which could be linked to risk of addiction.

Including both male and female participants in this research was important, as research indicates that there are gender differences in brain organisation and responses to drugs. Although some findings were no longer significant when body weight was taken into account, it is clear that weight is confounded with gender. Even so, decision-making is impaired even when we covaried for weight. However the question remains: are healthy volunteers valid predictors of how drug abusers react to opioids and how patients in pain react to opioids? If for example, pain attenuates psychomotor and cognitive impairment,
studies on healthy volunteers may overestimate the impairing effects of opioids on patients in pain. Or are opioid induced decrements greater in healthy volunteers than chronic users because of tolerance? Further research is needed to clarify this.

Gambling task

Rogers’ gambling task (Rogers et al., 1999) is a complex task, designed to assess speed of decision-making, quality of decision-making and willingness of subjects to gamble. It aims to separate disinhibition and disrupted impulse control from genuine risk-seeking. Despite clearly presented instructions, some participants appeared to have difficulties understanding the aim of the task; and commented that they really only understood as they began playing the game. Indeed practice effects have been found with this task, and accounting for these effects would be important. However, this was complicated given the cross-over design used in this study. The gambling task was a useful measure of risky decision-making. However, analysis of the data was complex, as the results provided a number to four-way interactions which were particularly difficult to interpret. When using tasks such as this, it is also important to consider statistical significance versus clinical significance. For example, what does impairment on this decision-making task actually mean and what does it tell us little about how people make decisions in the ‘real world’? For example, does it mean that participants shouldn’t drive? Further research may be needed to establish how observed deficits in this task translate to everyday functioning.
Subjective measures

Both the Mood Rating Scale (MRS, Bond and Lader, 1974) and the Impulsivity Self Rating Scale (ISRS, Bond & Lader, 1974) are standardised tests. The Subjective Effects Scale (SES) and the Drug Effects Scale (DES) were designed to include significant effects observed by Zacny and Gutierrez (2003) with their lowest dose of painkiller (oxycodone, 10 mg). As a result, we did not include a subjective rating for nausea as this effect was only noted at higher doses (20-30 mg). In retrospect, I think it would have been useful to include this measure as a number of female participants noted this as an unpleasant effect. As discussed in the literature review (part 1 of this thesis), the reliability and validity of subjective measures can be questioned. We need to be cautious about interpreting the results of subjective measures because we cannot be certain about how different individuals experience effects. For example, what one individual considers a pleasant effect can be considered as unpleasant for another individual. Nevertheless, subjective ratings can provide considerable useful information particularly alongside more objective and precise measures of behaviour, such as those used in this study.

It is important to consider the possibility that positive findings may represent a type 1 error, especially on the individual (SES) ratings. This is unlikely given the conservative analysis and Bonferroni corrections. However, further research should seek to replicate these findings.
3. Future directions for research

Of most significance for me, having completed this research, is how the process has encouraged me to think about research in general. The experience I gained from designing and setting up this study has been particularly valuable. From this, ideas have evolved about a number of other research possibilities in a variety of areas. In the area of drug addiction itself, it seems that more research is needed to evaluate the influence of different opioids. Attention should also be given to routes of administration, and studies should compare effects when taken as directed versus in various manners of likely tampering or misuse. Research also needs to identify those populations most at risk for abusing prescription opioids. Risk taking, impulsivity and decision-making appear to be important and interesting processes that should be assessed.

The British Association for Psychopharmacology guidelines on substance misuse treatment provides a review of treatment research (Lingford-Hughes, Welch & Nutt 2004, cited in Curran & Drummond, 2005) and there have been systematic reviews for treatments for opiate dependency (e.g. Mayet, Farrell, Ferri, Amato & Davoli, 2004, cited in Curran & Drummond, 2005). However, it would seem important to note that although there is more recent recognition that the misuse of prescription drugs is a large problem clinically, little is known about the best psychological treatment for these drugs and there is hardly any research to guide clinical practice (Curran & Drummond, 2005). The findings from this research suggest that at these doses, decision-making rather than impulsivity may be important for clinicians to consider when devising strategies for the prevention of opioid abuse. However, changes in decision-making were small and were
not predictive of subjective abuse liability measures, such as drug-liking and drug-seeking. As a result, it difficult to make more specific recommendations regarding the prevention of opioid abuse. Clinical trials are needed to determine the efficacy of different approaches for the prevention and treatment of prescription opioid abuse. Following this, research needs to focus on the development of appropriately targeted prevention programs.

4. Final thoughts

This learning process has been very important for me. It was a very valuable experience to be involved in a research study using a double-blind, placebo cross-over design, as this is quite often referred to as the internationally accepted gold standard or “Rolls Royce” of research designs. I would like to remain research active in my work as a clinical psychologist. However, having learned of the time demands of this type of research, I wonder how it can be conducted alongside clinical work. Certainly, I have learnt that particular aspects can make a study easier and less time-consuming. For example, beginning the research process early, remaining extremely organised, and developing positive working relationships with co-researchers are all very valuable aspects. I have become aware of the role of good supervision to help keep me focused and reduce anxieties at times of uncertainty. However, it also became clear that working with healthy volunteers, and working outside of clinical settings meant that even more lengthy ethics forms and research and development procedures could be avoided. Sadly, this draws researchers away from clinically relevant and ecologically valid studies. It is disappointing to think that this could encroach on clinicians’ decisions to develop and
conduct research which may fill critical gaps in both our theoretical and clinical knowledge in this area.

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Appendix A: Letter of Ethical Approval
09 September 2005

Prof. H Valerie Curran
Professor of Psychopharmacology
University College London
Clinical Health Psychology
University College London
Gower Street, London
WC1E 6BT

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:
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:

Mrs Patricia Orwell - 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.

Enclosures:
- Standard approval conditions
- Site approval form (SF1)

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

SF1 list of approved sites
Appendix B: Participant Information Sheet
Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE LONDON
GOWER STREET LONDON WC1E 6BT

H. Valerie Curran
Professor of Psychopharmacology
UCL: 020 7679 1898
E-mail:

"The cognitive effects of a single dose of morphine and oxycodone in healthy volunteers"
Research participant information sheet

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 from the Anaesthesiology 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 University College 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 (10g), 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 also 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. They will also be asked not to eat anything for 2 hours before a session; unless it is in the morning when they will be advised to eat a light, non-fatty breakfast. 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. Anyone 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. Therefore, on completing all 3 sessions, 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  
Brigitta Brandner  
Dr James Holding

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*All research projects are reviewed by an ethics committee. This proposal was reviewed and approved by the UCH Ethics Committee.*
Appendix C: Participant Consent Form
"The cognitive effects of a single dose of morphine and oxycodone in Healthy volunteers"

Research Participant consent form

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 D: Sample Subjective Effects Scale (SES)
Please rate the way you feel in terms of the dimensions given below. 

Regard the line as representing the full range of each dimension.

Mark clearly and perpendicularly across each line, i.e. ————

Rate your feelings as they are AT THE MOMENT.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>No numbness</td>
<td>Extremes numbness</td>
<td></td>
</tr>
<tr>
<td>No dry mouth</td>
<td>Extremes dry mouth</td>
<td></td>
</tr>
<tr>
<td>No dizziness</td>
<td>Extremes dizziness</td>
<td></td>
</tr>
<tr>
<td>No light-headedness</td>
<td>Extremes light-headedness</td>
<td></td>
</tr>
<tr>
<td>No hunger</td>
<td>Extremes hunger</td>
<td></td>
</tr>
<tr>
<td>No tingling sensation</td>
<td>Extremes tingling sensation</td>
<td></td>
</tr>
<tr>
<td>Not feeling flushed or warm</td>
<td>Feeling extremely flushed or warm</td>
<td></td>
</tr>
<tr>
<td>No itchy skin</td>
<td>Extremely itchy skin</td>
<td></td>
</tr>
<tr>
<td>No pleasant body sensations</td>
<td>Extremely pleasant body sensations</td>
<td></td>
</tr>
<tr>
<td>No difficulty concentrating</td>
<td>Extreme difficulty concentrating</td>
<td></td>
</tr>
<tr>
<td>No memory problem</td>
<td>Extreme memory problem</td>
<td></td>
</tr>
<tr>
<td>Inhibited</td>
<td>Impulsive</td>
<td></td>
</tr>
<tr>
<td>Shy</td>
<td>Confident</td>
<td></td>
</tr>
<tr>
<td>Depressed</td>
<td>Elated</td>
<td></td>
</tr>
<tr>
<td>Euphoric</td>
<td>Despairing</td>
<td></td>
</tr>
<tr>
<td>Very spaced out</td>
<td>Very focused</td>
<td></td>
</tr>
<tr>
<td>Lost in details</td>
<td>Able to see the big picture</td>
<td></td>
</tr>
<tr>
<td>Heavy/sluggish</td>
<td>Light/energetic</td>
<td></td>
</tr>
<tr>
<td>Angry</td>
<td>Peaceful</td>
<td></td>
</tr>
<tr>
<td>Aggressive</td>
<td>Cool Headed</td>
<td></td>
</tr>
</tbody>
</table>
Appendix E: Sample Drug Effects Scale (DES)
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% (worst performance) ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— 100% (absolute best performance)

Memory

0% ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— 100%

Attention/concentration

0% ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— 100%

Decision making

0% ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— ———— 100%
Appendix F: Table of Results for the Gambling Task
### Table 1. Mean (s.e.) proportion of choices of ‘experimental’ gamble over ‘control’ gamble for male and female participants for each drug condition.

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Morphine Female</th>
<th>Morphine Male</th>
<th>Oxycodone Female</th>
<th>Oxycodone Male</th>
<th>Placebo Female</th>
<th>Placebo Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>High probability</td>
<td>0.65 (0.078)</td>
<td>0.72 (0.073)</td>
<td>0.68 (0.073)</td>
<td>0.72 (0.069)</td>
<td>0.69 (0.061)</td>
<td>0.73 (0.057)</td>
</tr>
<tr>
<td>Low probability</td>
<td>0.21 (0.063)</td>
<td>0.27 (0.059)</td>
<td>0.13 (0.057)</td>
<td>0.31 (0.054)</td>
<td>0.17 (0.054)</td>
<td>0.24 (0.051)</td>
</tr>
<tr>
<td>Large gains</td>
<td>0.53 (0.071)</td>
<td>0.65 (0.067)</td>
<td>0.46 (0.063)</td>
<td>0.68 (0.059)</td>
<td>0.53 (0.062)</td>
<td>0.64 (0.058)</td>
</tr>
<tr>
<td>Small gains</td>
<td>0.33 (0.064)</td>
<td>0.34 (0.06)</td>
<td>0.36 (0.055)</td>
<td>0.35 (0.052)</td>
<td>0.32 (0.045)</td>
<td>0.34 (0.043)</td>
</tr>
<tr>
<td>Large losses</td>
<td>0.29 (0.074)</td>
<td>0.32 (0.07)</td>
<td>0.34 (0.054)</td>
<td>0.35 (0.051)</td>
<td>0.32 (0.055)</td>
<td>0.31 (0.052)</td>
</tr>
<tr>
<td>Small losses</td>
<td>0.56 (0.066)</td>
<td>0.67 (0.062)</td>
<td>0.47 (0.065)</td>
<td>0.68 (0.062)</td>
<td>0.54 (0.60)</td>
<td>0.66 (0.056)</td>
</tr>
</tbody>
</table>

### Table 2. Mean deliberation times (ms) (s.e.) for female and male participants for each drug condition.

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Morphine Female</th>
<th>Morphine Male</th>
<th>Oxycodone Female</th>
<th>Oxycodone Male</th>
<th>Placebo Female</th>
<th>Placebo Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>High probability</td>
<td>2,487 (331)</td>
<td>1,827 (312)</td>
<td>2,176 (242)</td>
<td>1,921 (228)</td>
<td>1,964 (283)</td>
<td>1,844 (267)</td>
</tr>
<tr>
<td>Low probability</td>
<td>2,602 (333)</td>
<td>2,028 (314)</td>
<td>2,132 (250)</td>
<td>2,108 (236)</td>
<td>2,238 (358)</td>
<td>2,072 (337)</td>
</tr>
<tr>
<td>Large gains</td>
<td>2,664 (360)</td>
<td>1,928 (339)</td>
<td>2,220 (260)</td>
<td>2,027 (245)</td>
<td>2,113 (334)</td>
<td>1,988 (315)</td>
</tr>
<tr>
<td>Small gains</td>
<td>2,424 (306)</td>
<td>1,927 (289)</td>
<td>2,088 (225)</td>
<td>2,002 (212)</td>
<td>2,089 (294)</td>
<td>1,927 (277)</td>
</tr>
<tr>
<td>Large losses</td>
<td>2,585 (327)</td>
<td>1,904 (308)</td>
<td>2,085 (229)</td>
<td>2,084 (216)</td>
<td>2,008 (283)</td>
<td>1,914 (267)</td>
</tr>
<tr>
<td>Small losses</td>
<td>2,504 (336)</td>
<td>1,951 (316)</td>
<td>2,223 (253)</td>
<td>1,946 (239)</td>
<td>2,194 (346)</td>
<td>2,002 (326)</td>
</tr>
</tbody>
</table>
Appendix G: Letter of Rejection from Ethics
Dear Prof. Curran

Full title of study: The cognitive effects of morphine and oxycodone in healthy volunteers.

REC reference number: 05/Q0502/21

Protocol number:

EudraCT number:

The Research Ethics Committee reviewed the above application at the meeting held on 10 March 2005. Thank you for attending the meeting to respond to questions from the committee.

Ethical opinion

This study will consider how single doses of morphine and oxycodone affect human memory. It will also consider how single doses of morphine and oxycodone affect decision making and what are the reinforcing effect potentials of the two opiates in healthy volunteers.

The members of the Committee present decided that it was unable to give a favourable ethical opinion of the research, for the following reasons:

- The study involved providing addictive drugs to students with an inducement payment of £50.
- The use of morphine outside of its prescribed form is a criminal activity.
- The committee expressed concern about a study, of a potentially addictive drug, that had neither a scientific validity nor any neuropsychological value.
- There was concern that this could be the first experience of drugs for some participants and no provision had been made for any adverse reactions.
- It was confirmed that the drug would be obtained from the UCH Pharmacy. It should be clarified whether it would be obtained as a prescription or as a clinical trial of a medicinal product. If this is a clinical trial, then it should have been registered with the MHRA.

Continued......
- The consent form does not say that the tests would be carried out on three separate occasions.

- The committee would need more details of the tests that would be carried out to assess drug effects.

- It was noted that pregnant women would be excluded from the study. However, the committee felt that urine tests would be a better safeguard for participants who may have recently conceived.

On the information sheet:

- A description of a psychotropic drug and its addictive potential should be stated on the information sheet.

- The potential side effects of the drug should have been listed.

- There are typographical errors on the information sheet.

On the application form:

- Page 4 - Question A14. Details of previous drug use could be considered a sensitive issue.

- Page 5 - Question A23. The exclusion of participants with hypotension and hypothyroidism should have been stated on the information sheet.

- Page 10 - Question 53. Details of the statistical analysis should have been included.

I regret to inform you that the application is therefore not approved.

Options for further ethical review

You may submit a new application for ethical review, taking into account the Committee's concerns. This would be processed in exactly the same way as any new application. You should enter details of this application at Question A55 on the application form.

Alternatively, you may appeal against the decision of the Committee by seeking a second opinion on this application from another Research Ethics Committee. The appeal would be based on the application form and supporting documentation reviewed by this Committee, without amendment. If you wish to appeal, you should notify the Central Office for Research Ethics Committees (COREC) in writing within 90 days of the date of this letter. If the appeal is allowed, COREC will appoint another REC to give a second opinion within 60 days and will arrange for the second REC to be provided with a copy of the application, together with this letter and other relevant correspondence on the application. You will be notified of the arrangements for the meeting of the second REC and will be able to attend and/or make written representations if you wish to do so.

Continued.........
The relevant COREC contact point is:

Dr. Althea Allison  
Deputy Director of Operations  
Central Office for Research Ethics Committees (COREC)  
2nd Floor, Block A  
50 Eastbourne Terrace  
London W2 6LX  
E-Mail: althea.allison@corec.org.uk

Documents reviewed

The documents reviewed at the meeting were:

<table>
<thead>
<tr>
<th>Document Type</th>
<th>Version:</th>
<th>Dated:</th>
<th>Date Received:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application</td>
<td>07/02/2005</td>
<td>08/02/2005</td>
<td></td>
</tr>
<tr>
<td>Investigator CV</td>
<td>08/02/2005</td>
<td>08/02/2005</td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td>01/02/2005</td>
<td>08/02/2005</td>
<td></td>
</tr>
<tr>
<td>Covering Letter</td>
<td>07/02/2005</td>
<td>08/02/2005</td>
<td></td>
</tr>
<tr>
<td>Copies of Advertisements</td>
<td>01/02/2005</td>
<td>08/02/2005</td>
<td></td>
</tr>
<tr>
<td>Participant Information Sheet</td>
<td>01/02/2005</td>
<td>08/02/2005</td>
<td></td>
</tr>
<tr>
<td>Participant Consent Form</td>
<td>01/02/2005</td>
<td>08/02/2005</td>
<td></td>
</tr>
</tbody>
</table>

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Notification of other bodies

This letter is confidential but we shall notify the research sponsor and the Medicines and Healthcare products Regulatory Agency of the outcome of the review.

It is your responsibility to notify local Principal Investigators of the outcome of the review.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.
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.

| REC Reference Number: 05/Q0502/21 | Please quote this number on all correspondence |

Email:

**Enclosures**  
List of names and professions of members who were present at the meeting and those who submitted written comments
Appendix H. Adverse Events Protocol
Study Ref : 05/Q0502/52

The cognitive effects of a single dose of morphine and oxycodone in healthy volunteers

Adverse events policy

In a dire emergency call 2222 for the cardiac arrest team – ‘Maples Link Corridor’

For other problems contact the anaesthetist on call – who will be somewhere in the building; this is best done via mobile phone or they can be bleeped on 4600 (or 4300) To bleep dial 11 then the bleep no., then the number of your phone followed by the # e.g. 11 4600 73366 #

Unblinding procedure

In case of adverse event, the anaesthetist on call will be contacted by the investigators. The on-call anaesthetist will come and assess the subject.

If the trial needs to be unblinded for any subject the procedure is as follows:

Each subject / visit number has its randomisation to Morphine, Oxycodone or Placebo kept in individual envelopes in the trial master file, which is in the fellows area of the trainee anaesthetists room at UCH. The subject's visit number envelope is opened and the trial unblinded. Alternatively, the pharmacy has a complete randomisation list kept in the pharmacy, which can be accessed at any time.

Information for the anaesthetist on call

The researchers in this trial are trainee clinical psychologists. The subjects in this trial have had an oral trial drug. This will have been either placebo or immediate release morphine 10mg or oxycodone 5mg. The actual drug taken is blinded to patient and investigators but if necessary can be discovered by opening the appropriate coding envelope (subject no., visit no.) which are kept in the trial master file in the Fellows area of the trainees room.

There is a trial emergency bag, also in the Fellows area of the trainees room, containing ambu-bag, naloxone, granisetron etc. Treat the subject as necessary, have a low threshold for admitting via A+E. Call Brigitta Brandner (07855 956 021) or James Holding (07905 327573) with any problems.
REPORTING SERIOUS ADVERSE INCIDENTS IN RESEARCH SUBJECTS: Policy and procedures

The purpose of the flow chart is enable you to understand where to report the incident or event. *When in doubt report to Sponsor*¹ and Trust incident reporting system.

Key to flow diagram reporting incidents, events and reactions to research subjects

(a) All serious incidences in research studies should be reported using the Trust Incident Form. This is available on the Trust intranet website http://uclhweb.

(b) An *Incident* may be a medical or other type of occurrence. Examples of the latter include the failure to obtain consent for any of the research subjects or major deviations from the protocol. For non medical incidents, completion of the Trust Incident form is all that is required.

(c) A *serious medical event* is one which

- results in death, or is life threatening, or
- requires hospitalisation or prolongation of existing hospitalisation, or
- results in significant disability or incapacity or
- is a birth defect or congenital abnormality.

(d) Where a serious adverse medical event occurs to a research subject, the investigator or another delegated member of research team must review all relevant documentation. The event and relevant comments must be recorded in the subject's source data.

(e) If the event is not serious, as defined above, then the investigator should refer to the protocol which should contain information about what types of non serious adverse events should be recorded as part of the secondary outcomes of the study. There is no requirement to report these but there may be a requirement to record them.

(g) If the study does not fall under the trial regulations then there is a requirement to report serious adverse events:

- to the main REC, where it is “considered possible that the event resulted from participation in the research”. For details of reporting to main REC see [www.corec.org.uk/applicants/apply/safety.htm](http://www.corec.org.uk/applicants/apply/safety.htm);
- to the sponsor.

(i) For all studies not sponsored jointly by UCLH/UCL or UCLH only, the sponsor and, where required, the main REC should also be informed as required by the protocol. A Trust incident form must also be completed grading the event as serious.

¹. Prof. Val Curran 0207 679 1898; Dr Brigitta Brandner 07855 956021
REPORTING SERIOUS ADVERSE INCIDENTS AND EVENTS IN RESEARCH SUBJECTS
(see notes for guidance)

Golden rule: When in doubt report (i) to the study sponsor
(ii) through Trust incident policy

1. Serious Untowards Incident
   - Complete Trust Incident Form (a)
   - Medical Incident? (b)
     - Yes
       - Is this medical event defined as serious? (c)
         - Yes
           - Review and record in medical notes (d)
             - Consult sponsor, protocol or SOP for any requirements to report to main REC (g)(i)
             - And inform sponsor
           - Record as required by protocol (e)
         - No
           - No further action
     - No
       - No further action