The Effect of Opioids on Emotional Reactivity

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Abstract

Though opioid users report a decrease in negative emotions after opioid administration, there has been no formal study on the effect of opioids on emotional reactivity. This thesis details a body of work using mood induction procedures on opioid maintenance treatment patients, with the main aim of determining the effect of changing plasma opioid concentrations on emotional reactivity. Secondary aims include determining the relationship between pain sensitivity and depression or anxiety in methadone maintenance patients. In the first study, 21 patients on methadone maintenance and 21 Controls were induced into elated and depressed emotional states using Velten's elation or depression induction procedures respectively. These procedures were administered at times corresponding with trough (0 hour) and peak (3 hours) plasma methadone concentrations. The response to the induction procedures were measured as emotional reactivity, using primary measures (Visual Analogue Scales) and secondary measures (Profile of Mood States scores). At 0 hour, methadone patients and Controls showed similar elation (Methadone 13.2 ± 3.1 [Mean $\pm$ SEM], Controls 14.4 ± 3.7) and depression reactivity (Methadone 23.6 ± 5.0, Controls 25.1 ± 5.0), as measured by Visual Analogue Scales. However at 3 hours, the methadone patients had significantly decreased depression (Methadone 18.5 ± 4.6, Controls 36.7 ± 5.7; p=0.021) and elation reactivity (Methadone 4.4 ± 1.9, Controls 19.0 ± 2.4; p = 0.01) compared to Controls. Methadone patients appeared to be less reactive to mood induction at times of peak plasma methadone concentration than Controls, suggesting that methadone blunts both elative and depressive emotional reactivity. Study 2 compared the effects of methadone and buprenorphine on emotional reactivity in opioid maintenance patients at steady state of dosing. 26 patients on buprenorphine maintenance, 27 patients on methadone maintenance and 27 Controls were induced into elative and depressive emotional states at either 1.5 hours or 3 hours post dose, corresponding with peak plasma buprenorphine and methadone concentrations respectively. The results show significant differences between the three groups in elation and depression reactivity scores, controlling for Beck's Depression Inventory scores. Methadone patients showed a smaller increase in elation reactivity than buprenorphine patients (Methadone 13.3 ± 3.5, Buprenorphine 25.3 ± 3.4; p = 0.015), and a smaller increase in depression reactivity than buprenorphine patients (Methadone 20.3 ± 4.3, Buprenorphine 32.3 ± 4.2; p = 0.044) and Controls (Methadone 20.3 ± 4.3, Controls 35.8 ± 4.4; p = 0.021). This demonstrates that at time of peak plasma opioid concentration, methadone maintained patients are less reactive to mood induction than buprenorphine maintained patients. Therefore only methadone blunted

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elative and depressive emotional reactivity. These results have improved our understanding of the psychotropic effects of opioid maintenance drugs. The results show that methadone blunts both elation and depression emotional reactivity in opioid dependent users and can be added to the range of effects that are observable at the time of peak plasma methadone concentrations. Buprenorphine, a partial μ-opioid agonist, does not blunt emotional reactivity in buprenorphine maintained treatment patients. As emotional reactivity has consequences in social and psychological functioning, consideration of the effect of opioids on emotional processing systems may improve treatment outcome.

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Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree. I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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CHAPTER 1 - INTRODUCTION

1.1   OPIOIDS AND OPIOID MAINTENANCE TREATMENT

1.1.1   A BRIEF HISTORY OF OPIOIDS

Beginning with the cultivation of the opium poppy, opioids have been used for their analgesic and euphorigenic properties for thousands of years (Brownstein 1993). Drugs derived from the opium poppy are strictly classified as 'opiates', but the preferred broader term of 'opioids' encompasses both natural and synthetic compounds with morphine-like properties. By the start of the 1800s, the active ingredient of opium had been isolated and named morphine (Casy and Parfitt 1986) and has since become the standard by which all other opioids are assessed. With the invention of the hypodermic needle later in the 1850s, morphine became widely adopted as an analgesic in the medical field (Brownstein 1993). In the search for a less addictive opioid, heroin was synthesised just prior to the start of the 1900s. However abuse liability studies showed it to be no less addictive (Comer et al. 2008). Further advances in opioid research followed, including the synthesis of the opioid methadone in the 1940s that eventually led to its use in the 1960s as a therapeutic drug to aid the cessation of heroin abuse (Brownstein 1993; McArthur 1999). In Australia this approach is referred to as methadone maintenance treatment. The later discovery of the opioid buprenorphine (Cowan, Lewis, and Macfarlane 1977) led to its approval as an alternative opioid in maintenance treatment in the late 1990s in France (Carrieri et al. 2006), followed by adoption in America, Australia, and other countries around the world.

1.1.2   OPIOID RECEPTORS

The three main subtypes of opioid receptors are the classical opioid receptors: μ, κ and δ (Martin 1979). Though recommended terminology (Dhawan et al. 1996) is MOP, KOP and DOP, other historical nomenclature include mu, kappa and delta (Hughes et al. 1975), or MOR, KOR and DOR (Lord et al. 1977). Radioligand binding and second messenger studies also suggest that each subtype may have variants [μ1, μ2 (Pasternak 2005); δ1, δ2 (Traynor

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and Elliott 1993); κ1, κ2, κ3 (Traynor 1989)]. A fourth receptor with similar structural homology to the three classical opioid receptors is the nociception / orphanin FQ peptide (ORL-1, NOP, NOR) (Henderson and McKnight 1997) but is beyond the scope of this review.

The discovery of the endogenous opioid peptides, including enkephalins, β-endorphins and dynorphins suggested that opioid receptors must be able to perform physiological functions (Hughes et al. 1975; Kosterlitz 1979; Goldstein et al. 1981). Subsequent research showed that agonist activity on the μ-opioid receptor is primarily responsible for the analgesic and euphorigenic properties of opioids (Kieffer 1999). Respiratory depression, pupil constriction, and physical dependence are also attributed to μ-opioid activity (Kieffer 1999). Though μ-opioid receptors are the most important of the opioid subtypes in terms of functional effects (Dhawan et al. 1996), the κ- and δ- opioid receptors also mediate analgesic effects (McDonald and Lambert 2005). The κ-opioid has comparable sedative effects as the μ-opioid receptor and mild effects on pupil constriction, reduced gastrointestinal mobility, and can induce physical dependence (McDonald and Lambert 2005). The κ-opioid receptor is the only opioid receptor showing any strong association with dysphoric effects (McDonald and Lambert 2005). The δ-opioid receptor is associated with respiratory depression and reduced gastrointestinal mobility (McDonald and Lambert 2005), but has few other known effects.

Opioid receptors are distributed through the body, concentrated mainly in the central nervous system and brain stem (McDonald and Lambert 2005). μ-Opioid receptors are found in high concentrations in the dorsal horn of the spinal cord and periaqueductal gray, in the cerebral cortex, amygdala, olfactory bulb and nucleus accumbens, and in the gastrointestinal tract (McDonald and Lambert 2005). δ-Opioid receptors are less widely distributed and are at the highest densities in the olfactory bulb, cerebral cortex, nucleus accumbens and caudate putamen (McDonald and Lambert 2005). κ-Opioid receptors are found primarily in the nucleus raphe magnus (McDonald and Lambert 2005).

The structure of opioid receptors is now well understood. All opioid receptors are G-Protein Coupled receptors (GPCR) (Waldhoer, Bartlett, and Whistler 2004), predominantly inhibitory and mainly found at pre-synaptic sites to control neurotransmitter release. All three receptor subtypes exert their pharmacological effects by inhibiting adenylate cyclase, and by influencing ion flow (Dhawan et al. 1996). In some brain regions (e.g. regions important to

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supraspinal analgesia such as the periaqueductal gray, and regions related to euphoria/reward such as the ventral tegmental area), opioid receptors are excitatory, not through direct action but by inhibiting the release of the inhibitory neurotransmitter GABA (Corbett et al. 2006). Ultra-low dose opioid antagonist research was also instrumental in showing that opioids can produce both inhibitory and exhibitory effects (Crain and Shen 1996), though spinal glia may be a crucial modulator (Mattioli, Milne, and Cahill 2010).

Morphine, morphine analogues such as 6-monoacetylmorphine (an active metabolite of heroin) (Casy and Parfitt 1986), and methadone have an agonistic action at μ-opioid receptors. This action is responsible for the effects commonly attributed to opioids – euphoria, analgesia, pupil constriction, constipation, and respiratory depression (Waldhoer, Bartlett, and Whistler 2004). These effects are typically explained as a function of the receptor type and its anatomical distribution (Corbett et al. 2006). For example, opioid-induced constipation is due to opioid receptor binding in the gastrointestinal tract (Holzer 2009), opioid-induced respiratory depression due to activation of opioid receptors in the brainstem (Pattinson 2008), euphoric experience associated with μ-opioid activation in meso-limbic (Wise 1989) and fronto-limbic (Boecker et al. 2008) brain regions, and analgesia due to μ opioid activation occurring at the supraspinal level, spinally or peripherally (Pleuvry 2003).

Receptor function differs for acute versus chronic administration. With acute administration of an agonist, the opioid receptor inhibits the activity of adenylate cyclase (Nestler 2001). This results in a decrease in Cyclic AMP (cAMP) and a decrease in protein kinase (PKA) activation. Protein kinases control the activity of ion channels (closing Na+ channels), and control some enzymes and transcription factors (CREB). Independent of the cAMP pathway, ion balance is also disrupted – potassium ion (K+) current is increased (resulting in decreased excitability of the cell) and calcium ion (Ca+) influx decreased (decreasing excitability and vesicle release).

1.1.3   ADAPTATION TO OPIOIDS

Chronic opioid administration leads to changes in physiological function and behaviour that include tolerance, withdrawal, and dependence. These effects impact on the clinical and therapeutic use of opioids.

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1.1.3.1 Tolerance

With repeated administration of an opioid agonist, analgesic effect reduces. This diminution of opioid effect is termed tolerance (American Academy of Pain et al 2001). An increase in drug dosage is then needed to overcome the body's tolerance to the drug. It is these adaptive mechanisms occurring with repeated exposure to opioid administration that results in the development of tolerance.

Synaptic, cellular and network changes occur in response to repeated drug administration in an attempt to bring about normal function despite repeated drug use (Williams, Christie, and Manzoni 2001). One aspect of the body's adaptation to the drug is an alteration in the nature of the μ-opioid receptor itself and with long term exposure the μ-opioid receptor becomes desensitised. Multiple mechanisms including receptor desensitisation, receptor down-regulation and particularly cAMP super-activation may be implicated in tolerance development (Waldhoer, Bartlett, and Whistler 2004). cAMP super-activation from cellular adaptation occurs via upregulation of the cAMP pathway with chronic opioid administration (Nestler 2001). Here tolerance develops due to recovery of the previously inhibited cAMP pathway, via increased CREB expression (via a homeostatic mechanism from a CRE site). A gradual increase in adenylate cyclase and protein kinases (PKA) sees an increase in the cAMP pathway, with PKAs activating the Na+ channel (thereby increasing excitability of the cell). These processes oppose the inhibition of adenylate cyclase that resulted from acute opioid administration. These molecular adaptations provide the mechanism explaining the observable effects of chronic opioid administration. As opioid receptors are found in the brain, spinal cord and the peripheral nervous system, molecular tolerance occurs in many regions. Tolerance to the effects of morphine occurs for analgesia, sedation, respiratory depression, cardiovascular, nausea, and euphoria. There are only limited tolerance effects to miosis and constipation (Kreek 1973). As tolerance occurs with the desirable effects of opioids (particularly analgesia and euphoria), increases in dosage and frequency contribute to dependency.

1.1.3.2 Withdrawal

When opioids no longer activate the opioid receptor after a period of chronic administration, a withdrawal syndrome may develop. Dependent on dose and duration, symptoms of opioid withdrawal include diarrhoea, shaking, sweats, piloerection (goose bumps), lacrimation

(tears), rhinorrhoea (runny nose), anxiety, nausea, and muscle pain (Handelsman et al. 1987). Though withdrawal may be severe, it should be noted that opioid withdrawal will rarely lead directly to death (unlike the potential dangers of alcohol withdrawal for example). Withdrawal occurs as the receptor has changed due to repeated activation by an opioid and there is a rebound effect due to an upregulated cAMP pathway when no longer inhibited by opioids. A strong motivator in opioid abuse is the prevention or alleviation of withdrawal symptoms (Gordon and Dahl 2011). However, this is not the sole factor as evident by opioid cravings occurring up to years after chronic opioid use has stopped.

1.1.3.3 Dependence and Addiction

Dependence (or addiction) is characterised by compulsive use of a drug, in spite of its continual harm to the user (American Psychiatric Association 2000), and is a combination of physical and psychological attachment to a drug. Considerable research and public policy is concentrated on the management of those dependent on drugs, with the search for an opioid that provides analgesia without the risk of dependency being a primary goal of opioid drug development (Corbett et al. 2006). Opioids have a high abuse liability due to strong body adaptations and motivators associated with opioid use such as tolerance, withdrawal, physical dependence and euphoria/reward.

Many factors contribute to the development of physical and psychological attachment to drugs and a number of brain systems seem to be involved. The brain stress system (centralised on the amygdala), the hypothalamus, and the cortico-frontal cingulate system (or 'obsessive-compulsive circuitry') are all important in addiction (Everitt, Dickinson, and Robbins 2001; Koob and Le Moal 2001). However, dopaminergic input from the ventral tegmental area to the nucleus accumbens seems to play a central role. This system is referred to as the mesolimbic pathway or 'reward circuitry' and is implicated in the development and maintenance of addiction related behaviours. Opioids, psychostimulants, alcohol and nicotine all activate this pathway though evidence suggests that this pathway is involved in learning cues that predict reward as opposed to mediating hedonic experience directly (Waelti, Dickinson, and Schultz 2001). Long term potentiation of this pathway by opioid (and other drugs of abuse) may be a mediating factor in the development of dependence (Wolf 2003).

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1.1.4   OPIOID MAINTENANCE TREATMENT

In the management of opioid dependence, there are a range of pharmacotherapy treatment options available for patients in a clinical treatment setting. These include the cessation of opioid use with precipitated opioid withdrawal via an opioid antagonist (e.g. naltrexone), medicated withdrawal (typically with buprenorphine), or substitution of an opioid with a more favourable pharmacological profile (opioid maintenance treatment). The preferred treatment option of most health care professionals is opioid maintenance treatment. Methadone was the most widespread opioid used in maintenance treatment in Australia in 2010 (Australian Institute of Health and Welfare 2011), with 69% of the 46,078 opioid maintenance treatment patients on methadone. Buprenorphine maintenance treatment accounted for the remainder. The pharmacological difference between the two opioid drugs is substantial – methadone is a full μ-opioid agonist whilst buprenorphine is considered a partial μ-opioid agonist (Martin 1979).

1.1.4.1 METHADONE

Methadone has been prescribed for opioid substitution for many years in Australia and still is the most commonly prescribed maintenance treatment drug for opioid abusers (Australian Institute of Health and Welfare 2011). Developed in the 1940s, the reason for its popularity as a therapeutic option is its pharmacological profile. When used in treatment, methadone's long half-life enables the patient to avoid the drug cycle of seeking, using, and then seeking again drugs that delay the withdrawal associated with opioid abuse. The aim of treatment is to allow the patient to experience a 'normal life' and hopefully make the changes necessary to encourage and support long-term opioid abstinence. However, some early pioneers in methadone maintenance argued that abstinence from opioids should not necessarily be the long term goal of methadone maintenance. Rather they suggested that the role of methadone was only to stabilise an inherited opioid deficiency (Dole and Nyswander 1967; National Drug and Alcohol Research Centre 1987).

Methadone maintenance treatment has been widely researched and has shown to be effective in promoting a wide variety of positive outcomes for opioid abusers. For example, methadone patients as compared to heroin users have less involvement in criminal activity, are more likely to abstain for opioid drug use, more likely to have positive health outcomes, and less

likely to be depressed or psychopathological (National Drug and Alcohol Research Centre 2012).

Pharmacological profile of methadone

Methadone is a potent μ-opioid agonist and N-Methyl-D-Aspartate (NMDA) receptor antagonist (Inturrisi 2005). As an NMDA receptor antagonist, methadone reduces glutamate activity, thus decreasing central nervous system excitation. Methadone is also a non-competitive nicotinic cholinergic antagonist (Pakkanen et al. 2005) though it has no effect in reducing nicotine consumption in methadone maintained patients (Elkader et al. 2009).

Pharmacokinetics of Methadone

There are many factors that may affect the pharmacokinetics of methadone. Genetic variability, body changes (such as pregnancy), diseases (especially renal and liver related), and interactions with other drugs may all influence the body's effect on methadone. Therefore for a given dose, plasma methadone concentrations may vary considerable between individuals. In general though, bioavailability profiles show that 86% of the methadone consumed orally is absorbed (Dale, Sheffels, and Kharasch 2004). Methadone is metabolised in the liver, with an insignificant first pass metabolism rate. The principle enzyme mediating metabolism is CYP3A4, though CYP2B6 is also implicated (Foster, Somogyi, and Bochner 1999). Methadone distribution in the body is complex, but as it is lipophilic, it leaves the systemic circulation and localises in tissues such as the liver, kidney, brain, and muscle. Excretion of drug and metabolites is via the kidney.

The reported half-life of methadone ranges from 15 - 60 hours (Foster et al. 2004; Inturrisi 2005), averaging around 48 hours. A long half-life facilitates the standard methadone maintenance treatment dosing regimen of once-daily dosing. Methadone peak plasma concentrations occur approximately 3 - 4 hours after acute oral dosing, though with chronic dosing this may reduce to approximately 2.5 hours post dose (Dyer et al. 1999). Peak opioid effects are correspondingly seen approximately 3 hours post administration (Dyer et al. 1999). Figure 1 shows the plasma methadone concentrations after drug administration after chronic dosing to steady-state.

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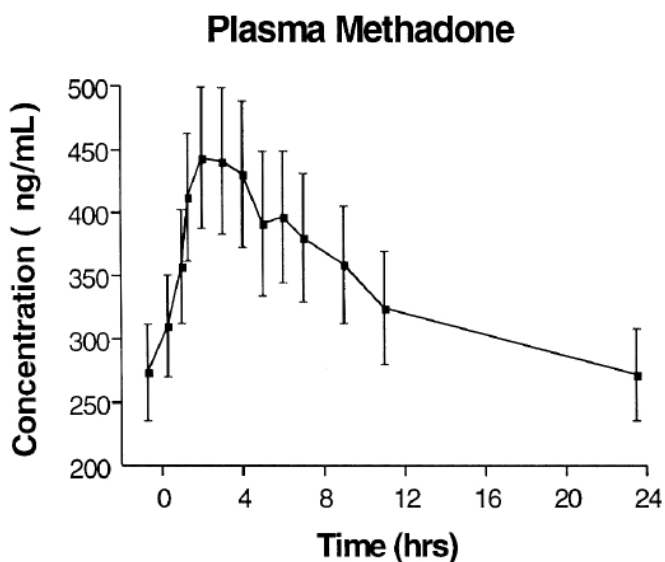
Figure 1: Plasma methadone concentrations over a 24 hour period. The figure shows plasma methadone concentrations in a methadone maintenance treatment cohort. Peak plasma methadone concentrations occurred approximately 3 hours (post dose), with trough concentrations occurring at 0 hour (pre dose). Bars show mean ± standard error. From Dyer et al. (2001).

Pharmacodynamics of methadone

Like other μ-opioid agonists, methadone has a similar pharmacodynamic profile and is euphorigenic and a powerful analgesic. Both pain threshold and pain tolerance increase with methadone administration (though conversely with long term opioid exposure, hyperalgesia may develop) (Doverty et al. 2001). Other typical methadone effects include respiratory depression, pupil constriction, opioid-induced constipation, nausea, and sedation/drowsiness. There is a direct relationship between plasma methadone concentrations (and via proxy, methadone dose administered) and some of these effects (Dyer et al. 1999). Methadone withdrawal may typically result in diarrhoea, nausea, disturbed mood, anxiety, rhinorrhoea, lacrimation, vomiting, and insomnia. The severity of withdrawal depends on the level of physical dependence. Compared to morphine, the onset of withdrawal effects is slower and the effects are less severe (Isbell and Fraser 1950).

Even when methadone dose is considered adequate, symptoms of withdrawal may still be present, especially just prior to the next daily dose. Dyer and White (1997) found that a third of a non-selected sample of methadone maintenance patients at a drug clinic reported regular withdrawal complaints during an inter-dosing interval.

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1.1.4.2 METHADONE MAINTENANCE TREATMENT

Like most opioids, methadone is a regulated drug in Australia. It must be prescribed and access, storage and transportation are restricted and require a licence. For inclusion into a methadone treatment program, an opioid abuser is enrolled in an appropriate drug clinic and then inducted into a methadone maintenance program with the support of a medical and health network. This process may include the expertise of doctors, social workers, psychologists and pharmacists. Methadone may also be prescribed as a treatment option in a general practice setting.

Methadone hydrochloride in Australia is available in either tablet or liquid form. Methadone tablets are available under the brand name Physeptone (Sigma Pharmaceuticals [Australia] Pty Ltd) and are occasionally used in maintenance treatment though this is increasingly rare in Australia. Each Physeptone tablet contains 10 mg methadone hydrochloride. Methadone is also available as a liquid, either as methadone syrup (Sigma Pharmaceuticals [Australia] Pty Ltd) or Biodone Forte (McGaw Biomed Pty Limited). Methadone syrup is a brownish liquid containing 5 mg / ml methadone hydrochloride and including caramel as an excipient. Biodone Forte is a pinkish liquid containing 5 mg / ml methadone hydrochloride but with only Permicol red colouring and purified water as excipients. Methadone is usually administered as a racemic mixture of (R) and (S) enantiomers (Garrido and Trocóniz 1999). The enantiomers are in 1 : 1 ratio and they have different pharmacological profiles, with the R-Methadone having much greater affinity for the µ-opioid receptor. Methadone is almost exclusively administered as a single daily oral dose (though occasionally dose may be a daily split-dose, administered morning and night).

1.1.4.3 BUPRENORPHINE

Buprenorphine is a relatively recent alternative to methadone in the treatment of opioid dependence in Australia, available since 2000. A derivative of the morphine alkaloid thebaine, buprenorphine has unique pharmacological properties that have promoted widespread usage in opioid treatment programs. In particular, a number of studies show the risk of overdose with buprenorphine is considerably lower than methadone (Auriacombe et al. 2004; Borron et al. 2002), with mortality rates of opioid treatment patients in Australia revealing that methadone related deaths were higher than for buprenorphine (Gibson and Degenhardt 2007).

Pharmacological profile of buprenorphine

Buprenorphine is available in Australia in a number of formulations. It is available as a sublingual tablet or film coated tablet (NPS 2012) for use in opioid maintenance therapy. It is also available as a subcutaneous or intramuscular injection, and as a transdermal patch. These forms are typically for the treatment of moderate to severe pain.

As buprenorphine is a partial μ-opioid receptor agonist, it has less intrinsic opioid effects than other full μ-opioid agonists such as methadone. It only partially activates the μ-opioid receptor, so it produces a milder euphoric effect with less respiratory depression and sedation. Though its intrinsic activity at the μ-opioid receptor is low, it is still sufficient to prevent opioid withdrawal in opioid dependent patients and therefore is appropriate for opioid treatment programs. With a high affinity for the μ-opioid receptor, buprenorphine attaches tightly and dissociates slowly with a 2 to 3 day duration of action. As it attaches tightly to the μ-opioid receptor, it competitively displaces other opioids (Schuh, Walsh, and Stitzer 1999) and prevents other opioids from occupying those receptors. Due to this high affinity action, buprenorphine limits the impact of other opioids used once buprenorphine has been administered. As opioids occupying the receptors can be displaced by buprenorphine, administration may trigger / precipitate opioid withdrawal in opioid dependent individuals (Rosado et al. 2007). Buprenorphine is also a κ-opioid antagonist (Cowan, Lewis, and Macfarlane 1977). κ-opioid agonists are implicated with dysphoria and depression. Therefore, buprenorphine may have some antidepressant-like properties due to antagonism at this receptor (Rothman et al. 2000). Buprenorphine is also a full nociception / orphanin FQ peptide (NOP) agonist, though the effect of this is less than clear.

Pharmacokinetics of buprenorphine

Buprenorphine bioavailability is poor in the gastrointestinal tract due to extensive first-pass hepatic metabolism (Brewster, Humphrey, and Mcleavy 1981). Sublingual administration (through the mucous membrane in the mouth) is more effective with bioavailability via sublingual solution at approximately 50% (Kuhlman et al. 1996). Buprenorphine is metabolised in the gastrointestinal tract and liver by CYP3A4 into various metabolites by N-dealkylation, with norbuprenorphine being the main active metabolite (Kobayashi et al. 1998).

Buprenorphine has a long half-life and also disassociates slowly from the μ-opioid receptor, and therefore it has a long duration of action, anywhere from 48 to 72 hours. As such, less-than-daily dosing is possible (with alternate day dosing common) and with three times / weekly dosing plausible (Amass, Kamien, and Mikulich 2001; Schottenfeld et al. 2000). Research shows that less-than-daily dosing is also effective in reducing opioid usage (Caldiero et al. 2006).

Pharmacodynamics of buprenorphine

Buprenorphine has a similar pharmacodynamic profile as other opioids but there are differences due to its low intrinsic activity at the μ-opioid receptor. Buprenorphine is an analgesic when administered via epidural, intrathecal and transdermal routes, as well as the sublingual route (Vadivelu and Hines 2004), and is effective for post-operative and cancer pain (Houde 1979). At low doses, morphine and buprenorphine are similar with an increase in dose resulting in a corresponding increase in analgesia. It is however unclear if there are ceiling effects once a certain dose of buprenorphine is reached, where additional buprenorphine provides little to no further effect (Walsh et al. 1994; Rolley E Johnson, Strain, and Amass 2003). Some research suggests that some effects show a ceiling effect, while others do not. For example, Dahan et al. (2006) showed that intravenous buprenorphine displays a ceiling effect for respiratory depression but not for analgesia. Duration of withdrawal suppression and opioid blockage may also still increase with increasing dose.

Buprenorphine has side effects common to most opioids, including sedation, respiratory depression, constipation and nausea. Buprenorphine's lower impact on respiratory depression increases its safety profile, resulting in less risk of overdose compared with methadone. Many users report that sedation is less problematic with buprenorphine than methadone. Compared to methadone, buprenorphine has some other advantages. It does not prolong the QT interval (Fanoe et al. 2007; Wedam et al. 2007), is less likely to cause erectile dysfunction (Hallinan et al. 2008), and may have less of an impact than methadone on cognition (Pirastu et al. 2006; Rapeli et al. 2007).

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1.1.4.4 BUPRENORPHINE MAINTENANCE TREATMENT

Buprenorphine is increasingly being used as an alternative to methadone in opioid pharmacotherapy. Research has shown that buprenorphine is effective as an opioid substitute in opioid maintenance treatment (Johnson et al. 1995). The aims in the use of buprenorphine as an opioid substitute in maintenance therapy are similar to those for methadone pharmacotherapy – to alleviate symptoms of drug withdrawal, to stop illicit drug use, to stabilise the patient so that underlying factors contributing to drug abuse can be addressed, and to provide a treatment regime that can encourage tapering down of pharmacotherapy drug (Ducharme, Fraser, and Gill 2012). These aims are collectively part of the 'harm reduction' approach for treatment (Dole and Nyswander 1967). The efficacy of buprenorphine compared to methadone in opioid pharmacotherapy is mixed, though a large meta-analysis by Mattick et al. (2008) slightly favoured methadone on the outcome of treatment retention.

Buprenorphine is documented as a drug of abuse (Wish et al. 2012). Due to its partial agonistic action, buprenorphine is considered to have a lower abuse profile than full agonist opioids, with lower rewarding effects that plateau due to ceiling effects (Walsh et al. 1994). Also, though the buprenorphine/naloxone formulation is rated by opioid dependent users as less desirable than buprenorphine alone or other full opioid agonists, it still has abuse potential (albeit at a lower level) (Comer et al. 2010). An Australia study showed that buprenorphine/naloxone maintenance patients were half as likely (13%) to divert their dose for injection, than patients on buprenorphine alone (26%). As a comparison, methadone patients reported recent diversion of their dose for injection at 23% (Larance et al. 2011).

Buprenorphine is available sublingually as Subutex (containing only the active ingredient buprenorphine) or Suboxone (containing the active ingredients buprenorphine and the opioid antagonist naloxone). Suboxone is also available as a sublingual film. Buprenorphine sublingual tablets contain buprenorphine hydrochloride and are available in dosages of 2 mg and 8 mg. For Suboxone, the ratio of buprenorphine hydrochloride to naloxone is 4 : 1. Both Subutex and Suboxone are used interchangeably in opioid pharmacotherapy as they have similar clinical effects when administered sublingually (Stoller et al. 2001), and naloxone has little effect when taken sublingually due to poor oral absorption (Chiang and Hawks 2003). However, when Suboxone is administered intravenously, naloxone will precipitate withdrawal (O'Brien et al. 1978). Suboxone is preferred by clinicians over Subutex when diversion may be of a concern.

1.2   OPIOIDS AND EMOTION

1.2.1   BACKGROUND

Opioids have a long history as analgesics and euphorigenics. Although opioids have been shown to also have anti-depressant like qualities (Berrocoso et al. 2009), these effects have not been sufficiently explored to provide a comprehensive understanding of their possible clinical application. As the concomitant impact that drugs have on affective systems is considered of greater importance, these effects of opioids become more central.

With advances in affective neuroscience, research is confirming that emotion is built from many subcomponents of the brain in a network of cortical and subcortical systems (Davidson 2003; Davidson, Jackson, and Kalin 2000). It is from this network that emotions are produced, modulated, regulated and processed. Affective neuroscience has explored in greater depth the role of different brain areas on emotion. However, at its core remains the notion proposed by MacLean in the 1940s (MacLean 1949) - that the limbic system is central to emotion. Incorporating earlier work, MacLean postulated there were three main emotional brain architectures – an evolutionary ancient 'reptile brain' (stratal complex and basal ganglia) that controls primitive emotions such as fear and aggression, an evolutionary old 'mammalian brain' (thalamus, hypothalamus, hippocampus, cingulate cortex, amygdala, prefrontal cortex) that augments the 'reptile brain' and also regulates the social emotions, and the evolutionary new 'mammalian brain' (neocortex) that interfaces cognition with emotion processes. Animal studies show that both higher and sub-cortical regions are activated with emotional reaction, though higher cortical regions do not necessarily have to be activated. For example, sub-cortical activation such as the periaqueductal gray, hypothalamic and brain stem functions may be sufficient for emotion reactions in animal studies (Bard 1928; Hess 1954; Panksepp 2004). Higher cortical regions may also be involved, such as the insula (Augustine 1996; Cheung and Hachinski 2000) and the amygdala (Armony and LeDoux 1997).

1.2.2   AFFECT

Affect is a term that encompasses emotions, feelings and mood. Scherer (1984) defined human affect as a collection of human states that involves quick 'good-bad' discriminations. Included in this definition of affect are emotions, stress responses, moods, and motivational responses (such as sex, pain, thirst etc.). Other noted researchers however define affect as the conscious component of emotion (Panksepp 2000), the outward expression of emotion, or the experience of feeling and emotion. Velten defined affect as the effect of emotion or mood on other behaviours (Velten 1968). The concept of positive or negative affect is a general and non-specific approach to conceptualising emotions. Positive and negative affect is then typically mapped in two dimensions, composed of an approach-avoidance dimension and an arousal dimension (Lang 1995; Russell 2003), from which categories of specific emotions can be conceptualised.

1.2.3   MOOD

Mood and emotion are closely related, and the consensus is they are differentiable by duration and specificity (Ekman 1994). Moods are defined as longer in duration than emotional experiences, lasting from a few hours to days or weeks. Timeframes are inexact and may overlap with emotions which last from seconds to minutes [to even hours as defined by some authors, though Ekman argues that an emotion lasting for hours may be better conceptualised as a series of emotional episodes summated over a longer time frame. Ekman also suggests that moods that last longer than days may be better identified as an affective disorder]. Moods are also defined as less specific than emotions as emotions are a response to a specific stimulus (whether this stimulus is external or internal). Furthermore, moods and emotions are interdependent, with moods increasing the likelihood of experiencing certain emotions, and emotions predisposing a particular mood. For example, a person in an irritable mood would be more likely to experience an angry emotion if exposed to the appropriate stimulus. Conversely, an individual experiencing bouts of anger over an extended time is more likely to be in an irritable mood. It is unclear then whether moods may actually be low intensity level emotions that are under the threshold of eliciting the typical response pattern of the emotion. The final differentiation between emotion and mood concerns facial expressions, as emotions have unique and 'universally' recognisable facial expressions whilst moods don't exhibit this typicality.

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1.2.4 EMOTION

There are multiple definitions for what is an emotion. Nesse (1990) captures most of the common salient points with his description that emotions are 'specialized modes of operation shaped by natural selection to adjust the physiological, psychological, and behavioural parameters of the organism in ways that increase its capacity and tendency to respond adaptively to the threats and opportunities characteristic of specific kinds of situations'. Emotion is thus a response to stimulus that results in a pattern of changes in the organism, including physiological changes. Broadly, the nature of emotion can be grouped into one of four models – basic emotion models, appraisal models, psychological construction models, and social construction models [for review, see Gross and Barrett (2011)]. Though these models are conceptually separate, some researchers have developed models of emotion that incorporate elements of more than one model.

Basic emotion models assume that emotions represent a discrete number of basic biological states, each having their own mechanism that produces a set of typical responses. Charles Darwin's seminal work on the expression of emotions in humans and animals (Darwin 1872) proposed a basic emotion model that suggests that human emotion is an evolutionary process derived from animal systems, that there are cross-species similarities, and that there exists a basic set of emotions common to man and animals (e.g. anger, fear, sadness). This work influenced the study of animal behaviour to better understand human emotions. Plutchik (2001) expanded on this 'evolutionary biology' approach to emotion, and proposed that drawing on the emotions of other species could provide a functional framework from which to better conceptualise human emotion, their adaptive function, and better understand their interactions and biological basis. This perspective is supported with some researchers arguing that animals have evident emotional reactions, analogous to the human experience (Panksepp 2004). However, other perspectives such as behaviourism argue that it is unnecessary to attribute more complex 'humanistic' emotion states to animal emotional behaviours that may better be ascribed as stimulus-response (Dixon 2001).

Appraisal models of emotion argue that cognition pre-meditates emotion onset, with appraisal of a stimulus determining the contextual meaning and triggering a disposition to respond in a certain physiological manner, from this emotion results. Such a model is Communicative Theory (Oatley and Johnson-Laird 1996) that views emotions as conscious or unconscious cognitive evaluations, producing basic emotions that prime the organism to a particular state

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(that is assumed to be beneficial e.g. directing attention or readying the body for action). However, other authors suggest that without physiological change, there is no emotion (e.g. James-Lange theory). These emotion theorists suggest that the resulting physiological changes (such as a change in heart rate, blood pressure, facial expression) due to the body's response to a stimulus are registered by the organism and the mental state resulting from monitoring these body responses 'is the emotion' (James 1884; Damasio 2001; Prinz 2006; Prinz 2004). Levenson (1994) argues that emotions serve to rapidly organise a set of physiological responses that are appropriate and effective in promoting the survival of the organism, either physically or socially.

Psychological construction models assume there are no unique basic mental states and instead defines all emotions as emerging from an ongoing constructive mental process. Finally social construction models posit that emotions are culture dependent, and depend on social constructs (Ratner 1989).

Numerous researchers have devised lists of what they consider to be basic or fundamental emotions. Some overlap does exist. Most authors would agree that anger, fear, sadness, and happiness are basic emotions. Many authors then add disgust and surprise (Griffiths 1997). Ekman has expanded his list to include: amusement, anger, contempt, contentment, disgust, embarrassment, excitement, fear, guilt, pride in achievement, relief, sadness/distress, satisfaction, sensory pleasure and shame (Ekman and Ekman 2005). Other authors suggest that a more comprehensive list of emotions is unwarranted, arguing that some emotions are either a combination of two or more basic emotions (for example despair can be considered to be composed of the basic emotions of sadness and fear), or a change in emotional intensity (for example annoyance may be a mild form of anger) (Plutchik 1980).

1.2.5 EUPHORIA

Euphoria is not considered to be a basic emotion and is more likely to be a mental or emotional condition. It is attributed as an exaggerated state that encompasses intense happiness and contentment, orgasmic sensation, light-headedness, and exultation. Due to its intensity, euphoria is not considered to be a normal state, rather experienced through sexual orgasm or drug use. A milder form of euphoria may be achieved with intensive exercise. Disease and psychological disorders such as Alzheimer's disease and bipolar disorder may

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also give rise to symptoms of euphoria. There are also reports that euphoria can be experienced via religious and spiritual ceremonies or transcendence (Laski 1961).

1.2.5.1 Mesolimbic dopamine system

Self-injection and conditioned place preference studies suggest that the rewarding effects of addictive and euphoric drugs are mediated by sub-neocortical systems (McBride, Murphy, and Ikemoto 1999), including the ventral tegmental area, the nucleus accumbens, periaqueductal gray and ventral palladium. Sexual orgasm for example has shown to strongly activate the ventral tegmental area and surrounding clusters (Holstege et al. 2003), and the nucleus accumbens (Komisaruk et al. 2004). Recent research suggests that dopamine is involved with the anticipation and 'wanting' aspects of rewards whilst direct evaluation of pleasure is regulated by other brain systems, such as endogenous opioid. For example the pleasurably experience of palatable food suggests opioids play a role in modulating hedonic experience contrasted with dopamine's involvement in only the anticipatory/preparatory aspects (Barbano and Cador 2007).

1.2.6   EMOTIONAL PROCESSING

1.2.6.1 Emotion and emotional reactivity

The emotional experience for humans is complex and emotional functioning involves both neuroanatomical and physiological processes. There are many aspects involved in emotional processing that involve different areas of the brain. Four major aspects are emotional appraisal, emotional understanding, emotional regulation, and emotional reactivity (see Figure 2). Emotional appraisal involves the processing of emotional stimuli and also involves recognising facial expressions. Research shows that the amygdala plays an important role in emotional appraisal (LeDoux 1996; Adolphs and Tranel 2004), with multiple direct pathways to the amygdala facilitating this process. Other areas of the brain are also implicated in emotional appraisal, in particular the anterior cingulate cortex (Phan et al. 2002; Bush, Luu, and Posner 2000). Emotional understanding (empathy) is another aspect of emotional functioning, and involves understanding the emotions of others and the ability to view the emotional perspective of another person. Many brain regions including the amygdala, anterior cingulate cortex, and the anterior insula have been implicated in emotional understanding.

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Emotional regulation is a voluntary component of emotional experience and involves the adjustment of emotion reactions in response to the demands of the situation. There are two typical methods of emotion regulation – emotional reappraisal and emotional down-regulation (Rosen and Levenson 2009). Emotional re-appraisal is a voluntary process where an emotional reaction is modified in-situ. For example, the emotional response of seeing a knife in a kitchen compared to a knife in the hand of a stranger. Emotional down-regulation is the use of techniques to modify emotions, such as deep breathing for relaxation, or controlling facial expressions.

Finally emotional reactivity is the change in emotional state in response to an emotionally salient stimulus. For example, a depressing scene from a film may induce feelings of sadness. Such a change in sadness is a measure of emotional reactivity. Kuo and Linehan (2009) provides a similar definition that emotional reactivity is a 'change in intensity of emotional responding after presentation of an emotionally evocative cue'. A number of brain regions are implicated as central to emotional reactivity, including the thalamus. Though lesion studies have shown that the thalamus is associated with emotional reactivity (Orchinik et al. 1949), it is suggested that the thalamus is important due its connections with other limbic systems in the brain like the hypothalamus, hippocampus, cingulate gyrus, and pre-frontal regions, and thus also involving the Papez circuit (Papez 1995).

Concept of emotion

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                        ┌─────────────┐
                        │   Affect    │
                        └─────────────┘
          ┌───────────────────┼───────────────────┐
┌──────────────────┐ ┌──────────────────┐ ┌──────────────────┐
│      Mood        │ │     Emotion      │ │  Other Affects   │
│Long Acting       │ │ (Emotional State)│ │eg stress, pain,  │
│Response          │ │Short Acting      │ │sex, thirst       │
│                  │ │Response          │ │                  │
└──────────────────┘ └──────────────────┘ └──────────────────┘
                              │
                     ┌──────────────────┐
                     │Emotional Processing│
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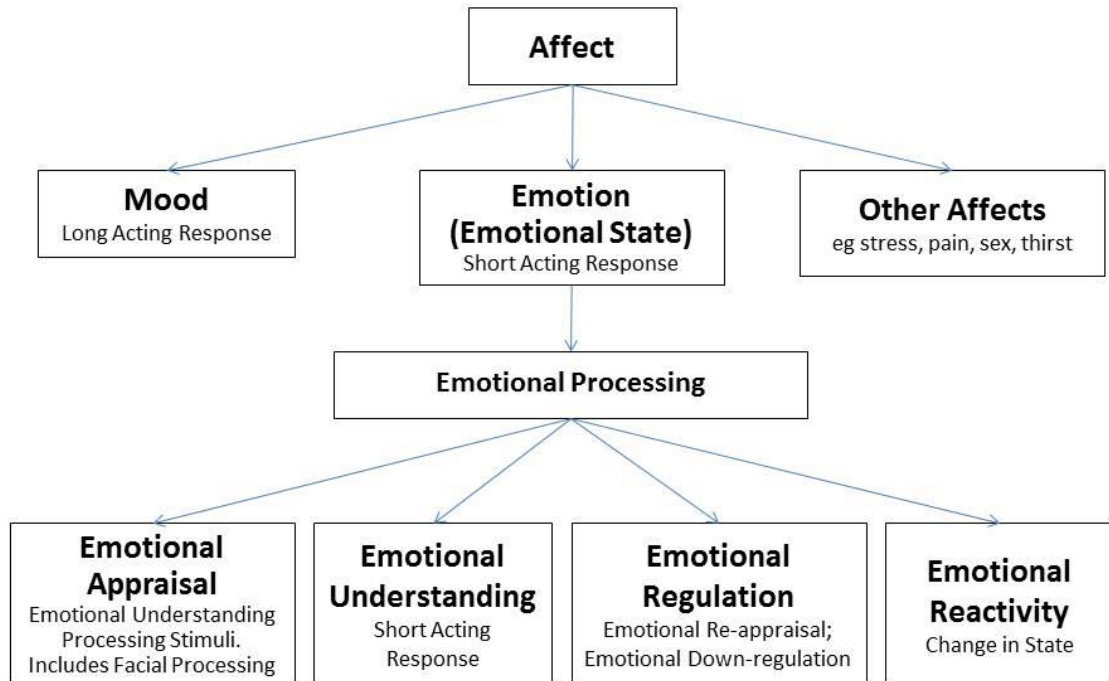
Figure 2: Concept of Emotion: Emotion is a short acting response, differentiable to mood and other affects. Note that emotion (emotional state) and emotional processing systems are not the same.

1.2.7   DRUG EFFECTS ON EMOTIONAL SYSTEMS

Most recreational drugs have an effect on affective states and processes. Alcohol, cannabinoids, opioids, stimulants, nicotine, and hallucinogens all have differing levels of effect on emotions and emotional processing systems. Once a drug has been administered, it may have a pharmacological effect on the emotional state of the individual user, even in the absence of any apparent emotionally salient experience. In contrast, emotional reactivity in this context is the change in emotional state due to an emotionally charged experience, whilst under the effect of a drug.

1.2.7.1 Opioid effects on emotions

Opioids have been implicated in changing both emotional states and in modifying emotional reactivity. Animal behaviour studies suggest that all 3 major opioid subtypes (μ-, δ- and κ-)

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regulate emotional reactivity, though μ-opioids are primarily associated with euphoric effects. Clinical studies also show that μ-opioids in particular can influence emotional states.

Animal research has shown that opioids play a role in the regulation of behaviour analogous to emotional reactivity. In particular, learned helplessness models of depression in rats suggest that both μ- and δ- opioid agonists have an anti-depressant-like effect. For example, methadone significantly reduced the number of escape failures to shock stimuli as compared to saline placebo (Rojas-Corrales et al. 2002a). Opioids also mediate animal activity in the forced swim test, another model used to test anti-depressant-like activity. μ-opioid agonists (Fichna et al. 2007), δ-opioid agonists (Broom et al. 2002; Torregrossa et al. 2006) and κ-opioid antagonists (Mague et al. 2003) have been shown to produce anti-depressant-like effects in rats in forced swim models. Other lines of animal research support the evidence that opioids play a role in emotional reactivity. Social separation models have shown that opioids reduce distress in animals. For example, DAMGO, a μ-opioid agonist, reduced the number of vocalisations (a measure of distress) in rooster chicks when socially isolated (Warnick, McCurdy, and Sufka 2005; Panksepp et al. 1980). Furthermore, the reduction in vocalisations in this high stress environment when administered a μ-opioid was comparable to the number of vocalisations in a low stress environment with no opioid on-board.

While animal research has focused on the effect of opioids on emotional reactivity, human research has focused on the role of opioids on emotional states. Opioids have been shown to have mood enhancing properties and to reduce mood disturbance, and have a long history of recreational abuse due to these euphoric inducing effects. Historically, μ-opioids such as heroin and morphine were occasionally prescribed to play a similar role as anti-depressants.

As a μ-opioid receptor agonist, methadone has also been shown to have mood-enhancing properties. Methadone has been shown to have similar euphoric properties compared with morphine and heroin. Research comparing these 3 drugs and their euphoric effects suggests that subjects cannot distinguish between the 3 drugs. The relative measures of these drugs over the initial 5 hours of effect were constant over all opioid-like effects, including euphoria (Jasinski and Preston 1986). Dyer et al. (2001) showed that methadone administration in long-term methadone maintained patients reduced feelings of depression (Figure 3) and diminished total disturbance as indexed by depression, anger, tension, fatigue, confusion, and inactivity (Figure 4). These reductions in negative mood disturbance correlated with increasing plasma methadone concentrations, with greatest reductions in negative mood corresponding with

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peak plasma methadone concentrations at 3 hours post dose. However, mood scores of methadone maintenance patients were significantly more disturbed than controls on a number of mood dimensions. This shows that the opioid-dependent person rates higher on such measures as anxiety, anger, depression, fatigue and confusion. The administration of methadone alleviated feelings of depression and total mood disturbance scores but not sufficiently to return them to health control levels. Supporting this conclusion is the observation that methadone maintenance patients are typically more depressed than controls (De Leon, Skodol, and Rosenthal 1973).
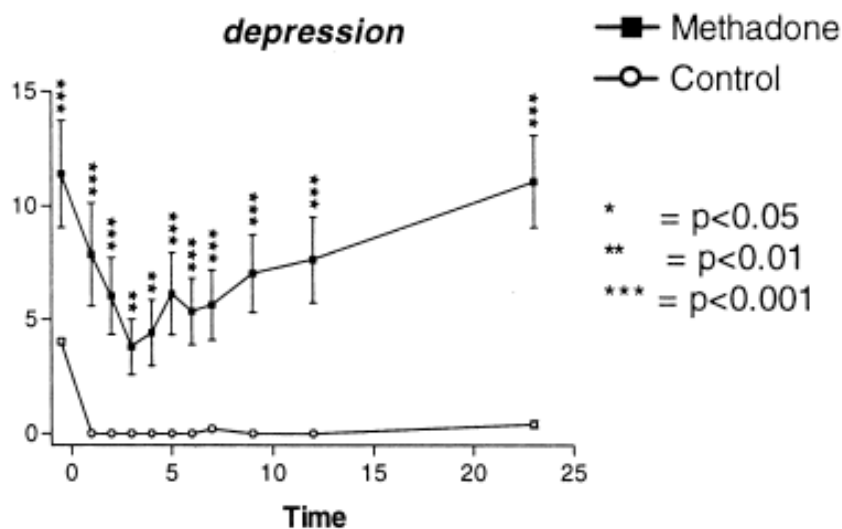
Figure 3: POMS-Depression score during a 24-hour inter-dosing interval. Over a 24 hour period, POMS-Depression scores were measured in methadone maintenance treatment patients and controls. Methadone dosing occurred just prior to 0 hour. The methadone group showed more depression than controls (all points significant, $p < 0.001$). Improvements in depression score in the methadone group corresponded with approximately the 3 hour time point. Bars show mean ± standard error. From Dyer et al. (2001).

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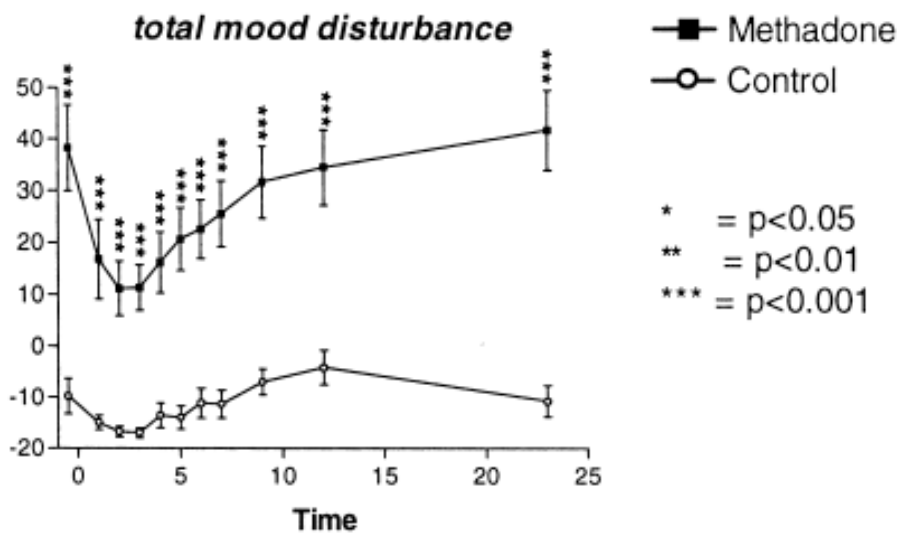
Figure 4: POMS total mood disturbance scores during a 24-hour inter-dosing interval. Over a 24 hour period, POMS-Total mood disturbance scores were measured in methadone maintenance treatment patients and controls. Methadone dosing occurred just prior to 0 hour. The methadone group showed greater global mood disturbance than controls (all points significant, $p < 0.001$). Improvements in mood disturbance in the methadone group corresponded with approximately the 3 hour time point. Bars show mean ± standard error. From Dyer et al. (2001).

1.2.7.2 Opioid effects on euphoria

Drugs may induce a euphoric state. Alcohol induces euphoria shortly after ingestion (Morgan and Badawy 2001) and increases positive mood (Ray et al. 2009). Cannabis has been shown to have both sedative and euphorigenic properties (Ashton 2001). Amphetamines (and many other stimulants) are also euphorigenic, with research showing that users administered amphetamine report an increased score on the Morphine-Benzedrine Group (MBG) and liking scales, a scale that measures euphoria (Jasinski and Preston 1986). This study also showed that the combination of morphine and amphetamine increased euphoria scores greater than either drug alone. MDMA and its analogs are shown to be powerful euphorigenics and to diminish anxiety (Greer and Tolbert 1986). MDMA also increases feelings of 'loving' and 'friendly' compared with placebo (Bedi, Hyman, and de Wit 2010). Cocaine, both a CNS stimulant and local anaesthetic, also has euphorigenic properties.

Opioid users typically do not experience euphoria with initial use, instead reporting a predominantly unpleasant experience that is sometimes accompanied with nausea and vomiting. However with repeated administration, euphoria is experienced and can promote continual use (Haertzen 1966; Ribeiro et al. 2005). For example, abuse liability studies on ex-addicts (Preston and Jasinski 1991) show that heroin/morphine administration increases

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euphoria on MBG scales. A more recent study (Webster et al. 2011) directly testing the euphoric properties of morphine has shown that non-dependent experienced male opioid users rated morphine significantly higher ($p < 0.0001$) on the Cole / ARCI stimulation-euphoria subscale (27.8 ± 11.2 [mean $\pm$ sd]) compared with users administered placebo (1.3 ± 3.1). Opioids have also been shown to be associated with the euphoria experienced by intensive exercise such as long distance running (Boecker et al. 2008). Here euphoria ratings were associated with increased endogenous endorphin levels in the prefrontal and limbic brain areas, particularly the anterior cingulate cortex, the bilateral insular, para-insular cortex and tempero-parietal regions (Boecker et al. 2008).

The mesolimbic dopamine system is implicated in inducing euphoria with drug administration. Dopamine neurons in the ventral tegmental area (VTA) are associated with euphoria and natural reward (Bayer and Glimcher 2005), motivating behavior (Wang and Tsien 2011), and drug addiction (Ikemoto and Wise 2004). μ-Opioid agonists induce euphoria by indirectly enhancing dopamine release in the nucleus accumbens (Wise 1989). They do this primarily by inhibiting GABA release from interneurons within the ventral tegmental area, thus disinhibiting the dopaminergic VTA neurons that project to the nucleus accumbens (the 'opioid disinhibition' hypothesis) (S. W. Johnson and North 1992). On the other hand, κ-agonists are dysphoric because they directly inhibit dopamine release from nerve terminals in the nucleus accumbens.

Opioid-induced euphoria may also be independent of dopamine systems. There is considerable evidence that euphoria is mediated directly by opioid systems. The euphoria from strenuous exercise has been associated with endogenous opioid release in the fronto-limbic system (anterior cingulate cortex, orbito-frontal cortex and insular cortex) (Boecker et al. 2008), a region important in emotion processing. However the nucleus accumbens showed no opioidergic activity, a key structure in opioid-dopamine interactions.

Research shows a number of factors in opioid administration may influence the effects of euphoria. In particularly, the rate of administration plays a significant factor in the level of euphoria experienced, with faster rates of administration increasing the euphoric effect experienced (Marsch et al. 2001). Consequently, intravenous opioid use generally provides greater euphoric experience than intramuscular or subcutaneous administration. Oral opioid use produces weaker effects again. Another key factor is plasma opioid concentrations

relative to opioid tolerance levels. As an opioid user's tolerance to the drug increases, the euphoria experienced decreases.

1.2.7.3 Modification of affective disorders by opioids

β-Endorphin has been shown to have anti-depressant-like effects when administered to depressed patients (Kline et al. 1977). Furthermore, naltrexone has been shown to induce depressive effects in non-opioid dependent subjects (Hollister et al. 1981). Numerous studies have shown that opioid maintenance treatment reduces depressive symptoms in opioid-dependent populations (Strain, Stitzer, and Bigelow 1991; Kosten, Morgan, and Kosten 1990), suggesting that opioids have antidepressant and anxiolytic properties when administered. The mechanisms of action are complex and can involve dopamine in the mesolimbic system (dopamine), serotonin or epinephrine/norepinephrine availability via re-uptake inhibition, adjusting cortisol serum levels, neurotransmitter availability via MAO inhibition or NMDA receptor antagonism (Tenore 2008).

Opioids alleviate depressant-like symptoms by interacting with dopamine systems through the mesolimbic reward pathways in the brain. In a non-depressed brain, endorphins bind to μ-endorphin receptors on dopaminergic neurons in the ventral tegmental area. Research has shown a relative endorphin deficiency in depressed brains, with an increase in endorphin receptors on dopaminergic neurons, but without corresponding increase in endorphin levels (Gross-Isseroff et al. 1990; Naber et al. 1981). As such there is lower endorphin stimulation and lower dopamine levels resulting in anhedonia, a symptom of depression. Studies have shown that buprenorphine (Emrich, Vogt, and Herz 1982; Maremmani, Pacini, and Pani 2006) and methadone (Dean et al. 2004) are effective in relieving depressive symptoms in depressed patients (whom are often resistant to Selective Serotonin Reuptake Inhibitor medication [SSRI]).

Opioids also play a role in other areas in the brain important for mood regulation, and have been shown to have an impact on systems related to catecholamines such as adrenaline and serotonin, and MAO inhibitors, and cortisol. Opioids have been shown to block the reuptake of adrenaline and noradrenaline, resulting in more available or free adrenaline, improving mood and relieving depressive-like symptoms. Methadone has been shown to have an affinity for noradrenaline reuptake sites (De Montis, Devoto, and Tagliamonte 1982). Methadone has also been shown to regulate serotonin availability (169), albeit weakly (Codd et al. 1995).

Serotonin plays a primary role in depression psychopathology, and it has been shown that both the number of serotonin receptors (Drevets et al. 1999) and the amount of serotonin synthesised are decreased in depressed brains (Rosa-Neto et al. 2004). Animal models have shown that methadone binds with serotonin transporters, limiting serotonin reuptake by acting like a SSRI, and resulting in anti-depressant-like effects (Ciofalo 1974). Methadone has also been found to impact NMDA receptor activity, with the NMDA system playing a role in mood regulation (Paul and Skolnick 2003). When NMDA receptors located on serotonin neurons are activated by glutamate, they inhibit serotonin synthesis and release, thus having a depressant-like effect. Methadone has been shown to have NMDA antagonist properties in animals (Callahan et al. 2004).

Though the effect of opioids on emotional states has been studied clinically, the effect of opioids on emotional reactivity in humans is lacking. Related research has shown a dysregulation of emotion processing when opioid users were shown pleasant or unpleasant stimuli (Aguilar de Arcos et al. 2008). As subjects were not required to actively react to this stimulus, the study strictly did not measure emotional reactivity but rather emotional appraisal. A number of studies have investigated opioid effects on emotional appraisal, typically by using affective picture sets and then measuring response. However the effect of opioids on the other three major aspects of emotional processing (emotional understanding, emotional regulation and emotional reactivity) have received insufficient attention. Thorough investigation of the effect of opioids on emotional processing will enhance understanding of the impact of opioid substance abuse and opioid maintenance treatment. The numerous studies that show euphoric or positive affective response with opioid administration measured the effect of opioids on emotional state, not emotional reactivity. There has been little investigation on how reactive individuals are to mood stimuli whilst on opioid agonists.

1.2.7.4 Summary of Opioid effects on emotions

Like other recreational drug classes, opioids have an impact on emotional state and emotional processing systems. Considerably research has showed that opioids reduce behaviours indicative of negative affective/emotive reactions in animals when using learned helplessness, forced swim tests and social separation models. In humans, opioids have been shown to be euphorigenic, enhancing emotion or mood state. Some evidence has suggested that opioids also have anti-depressant properties, via a number of possible receptor mechanisms. Though

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research has shown the effect of opioids on some emotion processing systems (such as emotional appraisal), opioids' effect on other processes like emotional reactivity is unknown.

1.2.8   CHALLENGES IN RESEARCHING EMOTION AND MOOD

Research in emotion is difficult for a number of reasons. The distinction between emotion, mood, and affect is imprecise and less well-defined. Everyday language also creates ambiguity and confusion. For example, though anger is typically defined as an emotion, it is also associated with mood in everyday parlance (i.e. 'being in an angry mood'). Therefore caution needs to be exercised in deciphering how a person explains their emotional state or mood, versus labelling it appropriately for research purposes. This difference between scientific definition and common language means that it can be more difficult to accurately measure emotion and mood changes in subjects. Techniques to measure subjects' mood changes include independent observation, recording physiological changes, or self-report, each with their own limitations. For example, many studies rely on self-report to gauge the impact that an intervention or drug or stimulus has on affective systems. However, Davidson (2003) argues that emotion may also be generated non-consciously, limiting self-report measures. Another major hurdle is that it is difficult to induce mood and emotion. All current methodologies have drawbacks, either in efficacy or in specificity.

Furthermore, the assumption (implicit or not) that research on affective behaviours in animals is directly translatable to humans needs caution. That animals such as rodents have emotions is controversial. Panksepp (2004) argues strongly that animals have affective experiences more complicated than previously acknowledged. Animal data has progressed affective research considerably, but it is also true that there are fundamental anatomical differences in the brain regions identified as being involved in affective systems. For example, there are differences in the organisation and connectivity of the amygdala (Amaral et al. 1992) and anterior cingulate cortex (Bush, Luu, and Posner 2000), and the anatomy of the prefrontal cortex (Goldman-Rakic 1987), all central to affective processes.

Studies that test emotional regulation include showing pleasant and unpleasant pictures from the International Affective Picture System (IAPS) and asking subjects to enhance or suppress their emotional response regardless of the valency of the picture (Jackson et al. 2000). A widely used objective index called the startle reflex is then used to measure any change in emotional response. Startle reflex tests measure the time to blink when exposed to white noise

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audio. Results show that startle reflex is reduced when subjects are instructed to suppress negative emotions upon seeing an unpleasant picture. Furthermore threat-of-shock paradigms (Grillon et al. 1991) extend these results from the symbolic (IAPS) to real-life application. These test whether emotion suppression would reduce startle response in a real-life situation where an electric shock may be delivered. When instructed to supress emotional response under threat of shock, startle response was reduced (Lissek et al. 2007). Conversely, enhancing emotion response under threat of shock increased startle response.

1.2.8.1 Mood Induction Procedures

Mood induction procedures are techniques that can be used to test emotional reactivity in a clinical setting (Martin 1990). These techniques challenge the subject by introducing emotional stimuli that aims to induce moods and feelings ranging from anger, depression, elation and anxiety. Though mood induction procedures (MIPs) find use in a wide variety of research fields, they are primarily used as models of depression (Goodwin and Williams 1982; Hunt and Forand 2005). That is, depressive mood induction procedures create a depressed state that mimics naturally occurring depressed mood states (Clark 1983). Tests are then performed to further investigate the effect that depressive-like symptoms have on cognitive performance in memory, attention, etc. For example, induced depressed mood state (like its naturally occurring counterpart) results in increased accessibility to negative thoughts (Clark and Teasdale 1985), and an underestimation of probable future success (Teasdale et al. 1984). Mood induction is occasionally used in drug research, though to a much lesser degree. Recently, with the advent of brain imaging techniques such as Positron Emission Technology, mood induction procedures are seeing a resurgence as an aid in studying the relationship between emotional states and brain activity (Koepp et al. 2009b).

There are a number of mood induction procedures that have been developed, including Velten self-statement mood induction (Velten 1968), autobiographic recall of sad events, passive display of emotionally salient stimuli such as the presentation of strongly emotive music, and situational mood induction (such as informing subjects that they will shortly present a public speech). Of these varied procedures, Velten's mood induction has been shown to be a powerful inducer of mood (Teasdale and Fogarty 1979; Frost, Graf, and Becker 1979; Brewer and Doughtie 1980), is amongst the most effective (Gerrards-Hesse et al. 1994), and has been used in diverse research areas such as examining the relationship between mood and pain

tolerance (Zelman et al. 1991), cognitive impairment in depressed individuals, and the effect of nicotine on affective response (Spring et al. 2008; Cook, Spring, and McChargue 2007).

Velten's mood induction was developed in the late 1960s and is a procedure that uses self-suggestion to induce a brief change in mood (Velten 1968). Its original form consisted of two procedures that induced either one of two different mood states – elation or depression. With each of these procedures, subjects were shown a large number (60) of self-referent statements, such as 'My parents never really tried to understand me'. Subjects were asked to reflect briefly on each statement in turn and to 'get into the mood' suggested by each statement. A battery of cards (with each battery focusing on only one mood) is sufficient to induce a change in mood, as shown by self-report questionnaires. See Section 2.3.2.1 in General Materials for a more detailed description of Velten's Mood Induction Procedure.

1.2.8.2 Measuring the effect on affective systems

There are a number of approaches to measure the effect of drugs on emotion systems (Stone 1995). The most common instrument used to measure emotion is adjective checklists. Here a number of adjectives that represent different emotion states are presented to respondents, who indicate whether the presented emotion is reflective of their current state. There are a number of variations to this approach, including different response scales or set of adjectives. Validated scales include Profile of Moods States (POMS) (McNair et al. 1971), Mood Adjective Checklist (MACL) (Nowlis 1965) and Multiple Affect Adjective Checklist (MAACL) (Zuckerman 1960). Other common instruments used are Mood Visual Analogue Scales (Aitken 1969), and the Positive Affect-Negative Affect Schedule (PANAS) (Watson, Clark, and Tellegen 1988). Both these instruments ask the respondent to indicate the severity of their current affective state on a linear scale.

Opioids have experienced a long history from use to abuse due to their euphorigenic properties. They also can reduce depressant-like symptoms. Animal research has shown that opioids reduce emotional distress in models of depression / anxiety, suggesting that opioids impact emotional reactivity. Human research shows that opioids such as methadone change affective state once administered, with increased mood disturbance with repeated long term opioid administration in methadone maintained patients (50). Emotional appraisal studies have also show a dysregulated emotion system in opioid users currently prescribed heroin. Generally though, research on opioid effects on emotional processing systems has not been

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extensively explored. Mood induction techniques can provide a method to determine the effect of opioids on emotional reactivity in humans.

1.3   OPIOIDS AND PAIN

1.3.1   PAIN

Pain is a complex and multifactorial phenomenon (Gatchel and Theodore 2008): it is a subjective experience with sensory and emotional aspects, interpreted by the brain, and expressed through behaviour. Pain is categorised into nociceptive, inflammatory or neuropathic pain: nociceptive pain results from noxious stimuli, inflammatory pain is from tissue injury or immune cell activation, and neuropathic pain is due to disease or damage in the nervous system. Pain is also either acute or chronic, with chronic pain lasting for a prolonged length of time (3+ months) (Shvartzman 2001). Evolutionary models of pain attribute a functional role to acute pain as an adaptive alarm that focusses the organism to attend to the source, motivating action to protect the body. However, chronic pain may or may not be associated with a well-defined disease process and is seen as maladaptive (Nesse and Ellsworth 2009) as the pain is no longer a reliable indicator of tissue damage.

The perception of pain involves both peripheral and central nervous systems (see Figure 5). When the body is subjected to a noxious stimuli, peripheral nociceptors at the site transmit signals along small myelinated A fibres and unmyelinated C fibres to the soma in the dorsal root ganglion. Their axons synapse in the dorsal horn, travelling along the spinothalamic tract of the spinal cord to synapse on neurons in the thalamus and cortex. Nerves from the thalamus then relay the signal to other areas of the brain. This is the principal ascending spinal pain pathway and is referred to as the lateral or spinothalamic pain pathway. There are also other ascending pain pathways such as the spino-parabrachio-amygdaloid and the spino-parabrachio-hypothalamic pathway, and these may play a particular role in the initial affective response of pain (Bernard, Peschanski, and Besson 1989; Bernard and Besson 1990). These ascending pathways are responsible for distributing nociceptive information to areas of the cortex involved in pain perception. However pain perception can be diminished via redirection, conscious thought, and distraction, suggesting that the brain can modify pain perception. These descending pathways originating from the somatosensory cortex and

hypothalamus may therefore modulate the pain signal. Thalamic neurons descending into the midbrain inhibit ascending pain signals at the medulla and spinal cord, partially due to the release of endogenous opioids. The response to noxious stimuli can also be modulated by repeated application. For example, peripheral nociceptors become more responsive with repeated application of the noxious stimuli. Neuronal response in the dorsal horn is biphasic. The initial response to noxious stimuli is brief and localised. The second phase of the response is prolonged and correlates with diffuse pain experience. The second phase is associated with a growing region of hypersensitivity around the point where the noxious stimuli was initially applied. The process where dorsal horn neurons become sensitised by noxious stimuli is called windup or central sensitisation (Woolf 1983).
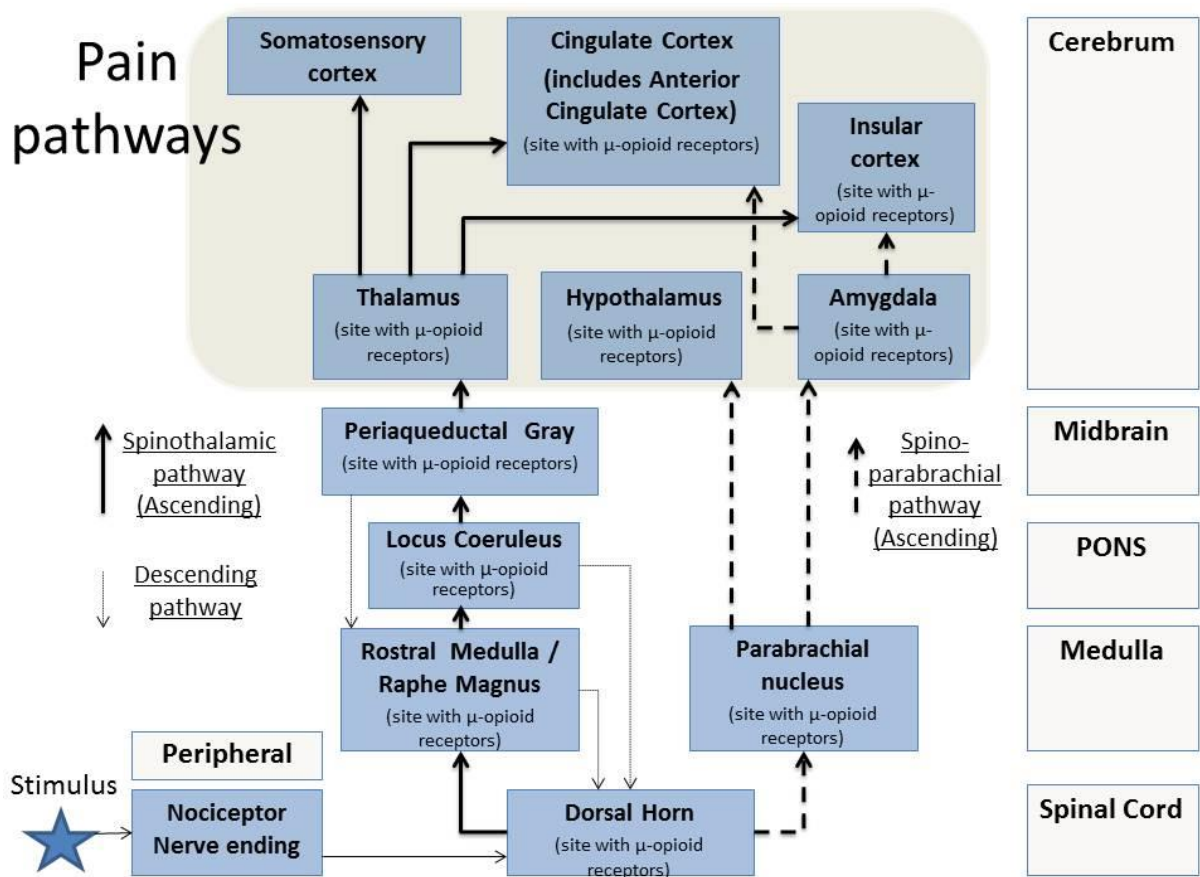
Figure 5: Pain Pathways. The figure shows ascending and descending pain pathways that may be activated on the presentation of a potentially painful stimulus, The spino-thalamic and spino-parabrachial pathways are primary ascending pathways. Midbrain, PONS and Medulla regions play a primary role in descending pain pathways, Most areas involved in pain processing are dense with μ-opioid receptors. Adapted from Purves et al. 2001 and Almeida, Roizenblatt, and Tufik 2004.

Melzack and Casey (1968) argue that pain is composed of three dimensions – a sensory-discrimination dimension, an affective-motivational dimension, and a cognitive-evaluative dimension. The sensory-discrimination dimension identifies the location, timing, extent, and type of injury (e.g. thermal, mechanical, etc.). The lateral pain system is the biological pathway that supports this dimension, with axons that ascend via the spinothalamic tract that synapse neurons in the lateral nuclei of the thalamus which then project to the somatosensory cortex. The affective-motivational dimension is responsible for the negative affect of the injury and associated behavioural responses such as inducing reflex actions or more complex behaviours such as escape and avoidance. The medial pain system supports this dimension with axons that project medially within the spinothalamic tract synapsing within the medial thalamic nuclei and then finally projecting to a number of brain regions including the cingulate cortex and the limbic system, amygdala, hypothalamus, and periaqueductal gray. The amygdala, hypothalamus and periaqueductal gray are sites also central to emotion and are part of a system responsible for pain affect (Vogt and Sikes 2000). Research has shown that these two pain systems play distinct roles (Kulkarni et al. 2005; Ploner, Freund, and Schnitzler 1999). The cognitive-evaluation dimension appraises the meaning and consequence of the injury. It involves the influence of attention, beliefs and attitudes, past experience and cultural values (203).

Chronic pain seems to be mediated by sensitisation, particularly in the medial pain system. Persistent stimulation by pain in peripheral tissue changes neurons in the cingulate cortex (Shyu and Vogt 2009), which may maintain the chronic pain condition (Cao et al. 2009). This 'central sensitisation' (or windup) may enhance pain response to normally pain stimuli (hyperalgesia) or reduce pain threshold to normally non-painful stimuli (allodynia).

1.3.2   OPIOID RECEPTORS AND ANALGESIA

Typically opioids are strong analgesics for injury and inflammation, with only a limited effect on neuropathic pain (Eisenberg, McNicol, and Carr 2006). Analgesic effects are due to μ-opioid receptor activation at supraspinal, spinal and peripheral centres (Pleuvry 2003), with supraspinal activation showing the greatest analgesic effect. Activated δ-opioid receptors have moderate analgesic function predominately only at spinal sites, whilst κ-opioid receptors show virtually no supraspinal analgesic function, mild analgesic function at spinal sites, and moderate analgesic function at peripheral sites (Rang and Dale 2007).

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µ-Opioid agonists have supraspinal analgesic activity by inhibiting descending pain pathways (see Figure 5). For example, morphine injected into the midbrain causes marked analgesia as it agonises µ-opioid receptors densely concentrated in the periaqueductal gray, an area involved in nociceptive transmission. These receptors inhibit glutamate release in the periaqueductal gray, with efferent outflow then inhibiting afferent nociceptive pathways further below in the spinal cord. This pathway is called the descending inhibitory control pathway. Morphine also inhibits the transmission of pain impulses through the dorsal horn. Research also shows that morphine can be injected directly into the peripheral system to provide analgesia, particularly in pain caused by inflammation (Stein and Yassouridis 1997). Research shows that pain has an affective component that if reduced, shows corresponding reductions in pain reporting. µ-opioid agonists are euphorigenic and therefore have a strong affective component. By reducing stress and anxiety at a supraspinal level, opioids reduce reported pain via this mechanism.

Methadone is a strong µ-opioid agonist showing efficacy in both acute and chronic pain. Doverty et al. (2001) showed that methadone patients had significantly higher electrical pain detection and pain tolerance compared to matched controls at a time point corresponding with peak plasma methadone concentrations. At trough plasma methadone concentrations, methadone patients showed similar electrical pain detection and a slightly worsened pain tolerance compared with matched controls.

1.3.3 OPIOID INDUCED HYPERALGESIA

The IASP define hyperalgesia as 'increased pain from a stimulus that normally provokes pain' (International Association for the Study of Pain 2013). Therefore opioid induced hyperalgesia (OIH) is characterised as a worsening of a chronic opioid user's pain sensitivity, not resulting from new injury or the exacerbation of an old injury. This type of pain is often diffuse and of a different quality. Though it seems counter-intuitive that pain relieving opioids may increase pain sensitivity, research consistently shows that chronic opioid administration results in increased sensitivity to some types of pain (Dyer et al. 2001; Doverty et al. 2001; Mitchell et al. 2006). The causes of OIH are unclear, though a number of mechanisms have been proposed that include changes in µ-opioid, glutamate or other excitatory receptors, or changes in the descending pain pathway. There are four main theories as to the exact mechanism

underlying OIH – sensitisation of peripheral nerves, enhancement of pro-nociceptive signals via the descending pain pathway, changes in nociceptive neurotransmitters, and/or sensitisation of second-order neurons to nociceptive neurotransmitters (Tompkins and Campbell 2011). Chemokines have also been suggested as playing a role (White and Wilson 2010). Research suggests that the primary mechanism involved is the central glutaminergic system, which may mediate both sensitisation to pain and pharmacological opioid tolerance (Mao, Price, and Mayer 1995) and and with NMDA receptor disinhibition central to the development of tolerance and hyperalgesia (Trujillo and Akil 1991). Glutamate transport system inhibition may further increase NMDA activation (Mao et al. 2002). However, Hay et al. (2010) found that co-administration of memantine (an NMDA antagonist) did not reduce thermal hyperalgesia in rats chronically administered methadone, though other nociceptive modalities were not tested. More recently, glial activation has been identified as a mechanism that may also be central to OIH (Hutchinson et al. 2007)

In animal models, rats developed less thermal analgesia with co-administration of an opioid and an NMDA antagonist, than compared to the administration of the opioid alone (Minville et al. 2010; Mert et al. 2009). Opioids such as morphine and methadone have been shown to induce hyperalgesia to certain types of pain once chronically administered. For example, prolonged administration of subcutaneous morphine induced hyperalgesia in mice (Vanderah et al. 2001), methadone in rats (Hay et al. 2010) and in rats repeatedly administered heroin instead of morphine (Célèrier et al. 2001). It seems that neurobiological systems involved in the analgesic response with acute opioid administration change with chronic administration, enhancing nociception (Chu, Angst, and Clark 2008).

Clinical studies also report OIH using models that evaluate pain tolerance. Pain tolerance is defined by the IASP as 'the maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation' (International Association for the Study of Pain 2013). Compton et al. (2001) showed that methadone maintained and buprenorphine maintained patients were hyperalgesic to cold pain compared to healthy controls, and that methadone maintained patents were less pain tolerant to cold pain than buprenorphine counterparts (Compton et al. 2000). Other studies reported that chronic pain patients naive to opioids were hyperalgesic to cold pain but not heat pain after morphine treatment (Chu, Clark, and Angst 2006). Doverty et al. (2001) showed that methadone patients were less tolerant to cold pain than controls (Figure 6). With methadone administration, they were more tolerant to cold pain than at 0 hour, but still not at pain tolerance levels exhibited by controls.
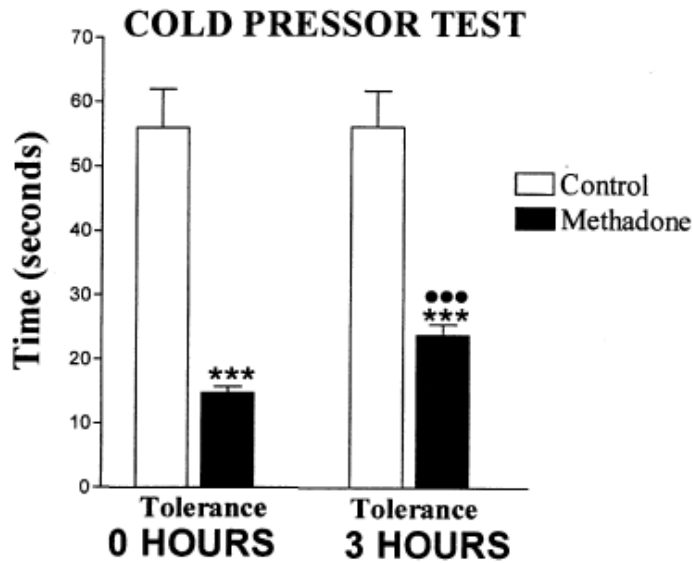
Figure 6: Cold pressor pain tolerance for methadone maintained patients and controls. Methadone patients showed hyperalgesia to cold pain at trough plasma methadone concentrations (0 hour) and at peak plasma methadone concentrations (3 hours), with increased cold pain tolerance at 3 hours. Bars show mean ± standard error. From Doverty et al. (2001).

However, some clinical studies have found little evidence of OIH. A large scale study by Reznikov et al. (2005) evaluated hyperalgesia using a battery of QST methods (including von frey, mechanical and heat tests) found no difference in hyperalgesia between opioid treated and non-opioid treated chronic pain patients. A comprehensive review by Fishbain et al. (2009) found that the strength of evidence of OIH is limited, except opioid infusion studies showing secondary hyperalgesia development in healthy volunteers.

1.3.4   PAIN AND EMOTIONAL STATES

Pain has both a sensory (pain sensation) and affective (pain unpleasantness) dimension. Pain is unpleasant and often the affective component is moment-to-moment, consisting of annoyance, fear and / or distress. Secondary pain affect encompasses long term implications such as suffering. Rainville et al. (1999) illustrated that the sensory and affective components of pain are two distinct dimensions, with pain sensation the cause of pain unpleasantness. In this study, hypnotic suggestion was utilised to modify pain unpleasantness or pain sensation when subjects placed their hand in a painful warm-water bath. Under hypnotic suggestion that modified pain unpleasantness, subjects reported a change only in pain unpleasantness.

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However, when subjects underwent suggestion that modified pain sensation, subjects reported a change in both pain sensation and pain unpleasantness.

The relationship between pain and affect is bi-directional. While it is apparent that pain impacts on emotional state and emotional processing, positive and negative affect also both influence pain. Research suggests that both the valence (positive to negative) and arousal (calming to exciting) determine the impact. Only high arousal emotional states affect pain as low arousal positive and negative affect do not affect pain sensitivity (Rhudy, Bartley, and Williams 2010). Fear and anxiety are both considered highly arousing negative affects yet both have a different impact on modulating pain experience. Fear is elicited by a present or imminent threat to the organism whilst anxiety is the anticipation of threat. Fear has been shown to reduce pain through the activation of the endogenous opioid system, while anxiety has been shown to increase pain (Rhudy and Meagher 2000a). Furthermore, when people expect pain, pain report increases (Benedetti et al. 2007) with increased activity shown in the anterior cingulate cortex.

Positive affect has also been shown to reduce pain experience. Franklin (1998) referred to this as 'affective analgesia', where systems central to reinforcement (such as the dopamine system) reduce the distress associated with pain. Fields (2007) proposed that opioid activation in the mesolimbic dopaminergic pathway plays a role in the reward or positive emotion that is associated with pain analgesia. Activation of this system has been shown to reduce emotional reaction (Kender et al. 2008). Pain reduction during orgasm is also associated with activation of the pain reward system

The dynamic model of affect (Davis, Zautra, and Smith 2004) proposes that the presence of pain may reduce emotional functioning, in particular the ability to differentiate emotional experience. Zautra et al. (2001) found that when under low stress or pain, people can differentiate positive affect from negative affect (mood clarity) and that the two affects are independent. However, when under elevated stress or pain, the ability to differentiate between positive and negative affect is diminished and positive affect is inversely correlated with negative affect. Anger suppression has also been shown to enhance pain experience, reducing pain tolerance and increasing pain ratings in the cold pressor pain test (Burns, Quartana, and Bruehl 2011; Quartana et al. 2010). Other lines of research on social pain also suggest a link between physical pain and emotion. Social pain is described as the painful experience due to the loss of important social bonds. Language used in everyday life is similar to that used in

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describing physical pain. To describe the end of a relationship as a 'broken heart' or to have 'hurt feelings' may reflect an underlying common neural circuitry between pain and emotion.

1.3.5   COMMON PATHWAYS IN PAIN AND MOOD

Positron Emission Tomography (PET) studies have implicated certain brain regions in the modification of pain and mood by opioids. A PET study directly comparing the effects of sustained pain and sustained sadness on the μ-opioid system concluded that pain and emotion share psychological and neurochemical pathways (Zubieta et al. 2002; Zubieta et al. 2003). In particular, both the amygdala and the ventral basal ganglia (both the nucleus accumbens and the ventral pallidum) showed similar effects under both a sustained pain and a sustained sadness challenge. PET studies also show that the endogenous opioid system is significantly activated at a 'higher' level in the pain pathway (Zubieta et al. 2001). Some of these systems that are activated are more typically associated with the intensity and valence of emotions, and reward and reinforcement (Anderson 2003; Koob and Le Moal 2001).

Finally, a significant decrease in the activation of the μ-opioid system in the nucleus accumbens in women was found when challenged with sustained pain (Zubieta et al. 2002). This deactivation was associated with hyperalgesia. The results seem to be conditional on women having low estradiol and progesterone levels. Other research has shown that the endogenous opioid system is also 'deactivated' when challenged with the induction of a sustained sadness state (Zubieta et al. 2003). The deactivation of brain regions under sustained pain and sustained sadness seems to illustrate the bidirectional role of the μ-opioid system under sustained versus acute activation, and that these systems may play a role in the modulation and regulation of emotional responses in both physical and psychological challenges.

1.4   SUMMARY

Opioids have been shown to alter emotional states and emotional processing systems. Building on animal research that shows that opioids modify behaviours indicative of affective change, opioids have been shown to likewise affect emotional states in humans. However the effect of opioids on emotional processing systems has received little research attention, with

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only emotional appraisal systems having been scientifically investigated. As emotional processing is fundamental to psychopathology, additional research in this area seems prudent. This is particularly important for patients using opioids long term, such as methadone or buprenorphine maintenance therapy patients.

Opioids are also powerful analgesics with opioid agonists shown to be effective at a number of points along the pain pathway. However with repeated opioid administration, tolerance develops and can potentially result in opioid induced hyperalgesia. A powerful observation pertinent to this thesis is that methadone maintenance patients are shown to exhibit both hyperalgesia to cold pain and be in a disturbed mood state, despite the euphorigenic and analgesic properties of the opioid.

Emotion and pain processing seem to have considerable overlap in humans, both in how they interact at an organism level and in common brain regions that regulate both systems. This thesis therefore aims to investigate whether opioid maintenance patients (methadone or buprenorphine) that are hyperalgesic to cold pain are also hyper-emotional to emotive stimulus.

CHAPTER 2 - GENERAL METHODS AND PROCEDURES

This thesis consisted of two studies with similar methodologies. Outlined in this chapter are the general aims and methods common to both:

Study 1: tested the effects of methadone on emotional reactivity and cold pain sensitivity in a cohort of methadone-maintained patients and controls. The effect of methadone on emotional reactivity was tested at times corresponding with trough (0 hour) and peak (3 hours) plasma methadone concentrations.

Study 2: was broader in scope, testing the effect of two opioids (methadone and buprenorphine) on emotional reactivity in a more generalizable group of opioid maintained patients and controls. Study 2 tested the effect of these opioids at times only corresponding with peak methadone (3 hours) or buprenorphine (1.5 hours) plasma concentrations. With this methodology the effect of methadone on emotional reactivity could be replicated, whilst a comparison with buprenorphine would provide evidence of how other maintenance opioids impact on emotional processing systems.

2.1   GENERAL AIMS AND HYPOTHESES

Study 1: this was to investigate the effect of methadone on emotional reactivity using mood induction procedures at time points corresponding with trough and peak plasma methadone concentrations. The study first aimed to demonstrate that methadone-maintained patients were more reactive to emotional stimuli than controls, shown by using Velten's mood induction procedure to induce a depressive state. Furthermore greater depression reactivity would be evident at times corresponding with trough plasma methadone concentrations. As methadone maintained patients have been shown to be hypersensitive to cold pain in previous studies (Doverty et al. 2001), this study also aimed to show that methadone patients hyperalgesic to cold pain were also hypersensitive to depression mood tasks. Finally the study would also investigate the effect of Velten's elation inducing tasks on the emotional state of methadone maintained patients. Subjects not using methadone and naïve to opioids were used as a comparison cohort and to control for effects of repeated testing.

Following the methodology and a summary of the demographics of the methadone group and controls, the following hypotheses will be tested in Chapters 3 to 6:

(i) Methadone patients will show a differing relationship of pain sensitivity to psychological components of depression than controls (Chapter 3),

(ii) Methadone patients will show greater depression reactivity than controls, with greatest depression reactivity at times corresponding with trough plasma methadone concentrations. This will be shown on both primary measures (VAS scores; Chapter 4) and secondary measures (POMS scores; Chapter 5).

(iii) Within subjects, increasing plasma methadone concentrations (trough-to-peak) will reduce cold pain sensitivity and reduce depression reactivity in methadone maintained patients, but not to levels exhibited by controls (Chapter 3 and 4),

(iv) Methadone patients will show reduced elation reactivity compared with controls (Chapter 6).

Study 2: this expanded the scope of the research to include buprenorphine maintenance patients. The aim of study 2 was to determine the effect of buprenorphine on emotional reactivity in buprenorphine maintenance patients. The effect of methadone on methadone maintained patients and an opioid naïve control group would be comparison groups. Unlike study 1, subjects were only tested at times corresponding with peak opioid plasma concentration times. The exclusion criteria were relaxed for generalisability of any findings.

The following hypotheses will be tested in Chapter 7:

(v) Buprenorphine patients will show less blunting of emotional reactivity (elation and depression) compared with methadone patients, as measured by VAS (primary measures). Buprenorphine patients will show some blunting of emotional reactivity compared with controls.

(vi) Buprenorphine patients will show less blunting of depression reactivity and total negative reactivity compared with buprenorphine patients, as measured by POMS (secondary measures). Buprenorphine patients will show some blunting of emotional reactivity compared with controls.

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2.2   GENERAL METHODS

This section provides a brief overall of the two studies, including recruitment strategies, screening processes, stimuli and scales used. For further details, see the procedure section in subsequent chapters.

2.2.1   ETHICS

Ethical Approval for study 1 (#060917) and study 2 (#091214) were granted by the Royal Adelaide Hospital, Research Ethics Committee.

2.2.2   RECRUITMENT

In both studies, subjects were recruited at multiple sites. Methadone and buprenorphine maintained subjects were recruited via a variety of means. Staff at a government drug clinic (Drug and Alcohol Services South Australia [DASSA], Warinilla, South Australia) were briefed on the scope of the study and the inclusion and exclusion criterion. They were then instructed to refer eligible subjects to the researcher. Posters were also displayed at the reception and dosing areas of the drug clinic. The researcher also recruited subjects through direct solicitation outside the dosing area of the drug clinic, and via word-of-mouth. For study 1, a metropolitan pharmacy (Midnight pharmacy, Adelaide) with a large methadone patient base was also approached for recruitment purposes. For study 2, both a metropolitan pharmacy (Midnight pharmacy, Adelaide) and a suburban pharmacy (Brad Jackson Pharmacy, Sefton Park) were approached to recruit buprenorphine and methadone patients. Posters were displayed in the dosing area of the pharmacy, and the researcher actively recruited potential subjects on selected days (direct solicitation).

For study 1, healthy controls were successfully recruited primarily from Governmental Welfare Agencies (Centrelink, Australia) in two locations (Marion, Adelaide and Salisbury, Adelaide). Two other Centrelink locations failed to recruit subjects (Norwood, Adelaide and Elizabeth, Adelaide). The researcher actively recruited potential subjects by approaching Centrelink customers as they entered and exited the building (direct solicitation). Healthy controls were recruited in this manner in an attempt to recruit a control group that was similar

on a key number of indicators to the methadone maintained subjects – primarily employment status, education and tobacco smoking status. It should be noted that this study was not a matched-subject design per se, rather that controls were recruited from sites that would minimise between-group variability. Finally, some subjects were also recruited through word-of-mouth.

For study 2, healthy controls were successfully recruited primarily from a contact list of persons who had expressed interest in research at the department of Psychology, University of Adelaide. They were primarily university students or ex-university students. Finally, some subjects were also recruited through word-of-mouth and snow-balling recruitment techniques. It should be noted that the controls recruited for study 2 (students) were demographically different from study 1 (unemployed).

2.2.3   SCREENING

From all the aforementioned sources, potential subjects were identified. All subjects provided informed consent before commencement of the trial. Demographic and background information was collected at screening. A battery of tests was also administered at the clinic to gauge psychological function at screening. These included the state-trait anxiety inventory (STAI-R), the state-trait anger expression inventory (STAIX-R), the Beck Depression Inventory (BDI) and the Hassles and Uplifts Scale (HSUPS). The Visual Analogue Scales–Depression (VAS-D) and Visual Analogue Scales-Elation (VAS-E) were also administered at screening as practice tests for subjects. See Chapter 2.3.1 for more detail on the scales used.

2.2.4   PAYMENT

Subjects received compensation for completing study 1 – methadone patients received $100, controls attending the sessions on the same-day received $100, or $150 for attending over two-days. The difference in the pricing of reimbursement across the control groups reflected the increased time commitment for the subjects randomised to the split-day session. There was no reimbursement for subjects that withdrew from the study prior to completing both stages. Subjects also received a payment for participating in study 2. Payment for completing

the study was \$50 for all subjects. There was no reimbursement for subjects that withdrew from the study (or met exclusion criteria) prior to completing the study.

2.3 GENERAL MATERIALS

2.3.1 SCALES

A number of scales and questionnaires were used at screening and / or during testing. All the scales employed were pen-and-paper tests completed by the subject.

2.3.1.1 Demographic and background information.

Demographic and background information was collected during screening. Information collected included demographic (ethnicity, age, gender, highest level of education completed, relationship status, number of children, work status and field of work, previous 3 year field of work), drug-use history and injecting practices, current illnesses and medications, criminal activity history, legal pressure history, and social functioning. It was completed in approximately 15 minutes.

2.3.1.2 Visual Analogue Scales (VAS-D and VAS-E)

Two Visual Mood Analogue Scales (Aitken 1969) were the primary measures used to determine the effectiveness of Velten's mood induction procedures used in study 1 and 2. The Visual Analogue Scale-Depression (VAS-D) and the Visual Analogue Scale-Depression (VAS-E) were used to measure elation and depression scores before and after each induction procedure. Subjects self-reported the severity by marking a point on a 10cm line bearing a 0-100 line scale appropriately labelled at either end. For VAS-D the end points were labelled 'I do <u>not</u> feel at all depressed' at 0 and 'I feel extremely depressed' at 100. For VAS-E the labelling was 'I do <u>not</u> feel at all elated' at 0 and 'I feel extremely elated' at 100. State rather than trait emotion was rated as the scales were labelled 'At this moment'. VAS-D and VAS-E were administered at screening for practice and throughout testing session (see Figure 7 and Figure 8).

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2.3.1.3 Profile of Mood States (POMS)

Profile of Mood States (POMS) (McNair et al. 1971) measures subject mood states along six dimensions (anger-hostility, depression-dejection, confusion-bewilderment, fatigue-inertia, vigour-activity, tension-anxiety) of a subject at a particular moment in time (when using the 'RIGHT NOW' setting). Secondary measures for study 1 and study 2 were the dimension of depression-dejection (POMS-Depression [POMS-D]), and a composite score of all 6 dimensions that indicated total mood disturbance (POMS-Total Mood Disturbance [POMS-TMD]). POMS is a self-report instrument that takes 5 minutes to complete and has been used by our group previously (Dyer et al. 2001). POMS has been shown to be robust versus gender, with McNair (1971) finding that gender accounted for less than 1% of the variance in POMS scores for college students (McNair et al. 1971). As such, the normative tables generated by McNair combine the scores of males and females. POMS scales have been shown to be sensitive to subject manipulation from emotion-inducing conditions, such as anxiety inducing films (Pillard and Fisher 1967) and anxiety inducing situations (Pillard and Fisher 1970). POMS was administered at screening for practice and throughout testing (see Figure 7 and Figure 8).

2.3.1.4 Subjective Opiate Withdrawal Scale (SOWS)

Any withdrawal experienced by methadone or buprenorphine maintained subjects was measured via self-report using the Subjective Opiate Withdrawal Scale (SOWS) (Handelsman et al. 1987). SOWS is a measure of the severity of withdrawal from opiates that a subject experiences, and is completed in 5 minutes. It consists of 16 items that reflect common symptoms such as rhinorrhoea, piloerection, lacrimation, sedation / sleepiness, yawning, muscle twitches and cramps. SOWS was administered at screening for practice and throughout testing (see Figure 7 and Figure 8).

2.3.1.5 Beck's Depression Inventory (BDI)

Severity of depression was measured using Beck's Depression Inventory II (BDI) (Steer et al. 1999a). BDI is a self-report instrument that can be completed in 5 minutes. It is a scale of 21 items, based on how the subject has felt in the last 2 weeks. The inventory asks questions about frequency of suicidal ideation, lack of interest in sex, changes in appetite or sleep, loss of pleasure, feelings of self-worth, sadness and frequency of crying, etc. Scores from 0-13

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indicate minimal depression ('these ups and downs are considered normal'), 14-19 indicates mild depression, 20-28 indicates moderate depression, and 29-63 indicates severe depression. A derived BDI score was also calculated which excluded 2 questions from the BDI due to their relatedness to typical opioid withdrawal symptoms. Items excluded on the BDI were related to loss of energy (item 15) and tiredness/fatigue (item 20), as they corresponded with items on the SOWS that measured tiredness (item 2 [yawning]).

A three factor model of depression separated BDI depression into cognitive, affective, and somatic components (Buckley, Parker, and Heggie 2001). The cognitive subscale contained 9 items: sadness, pessimism, past failure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal ideation, and worthlessness. The affective subscale contained 4 items: loss of pleasure, crying, loss of interest, and indecisiveness. The somatic subscale consisted of 8 items: agitation, loss of energy, change in sleep patterns, irritability, change in appetite, concentration difficulties, tiredness and/or fatigue, and loss of interest in sex. BDI was administered only once to each subject, at screening.

2.3.1.6 State-Trait Anxiety Inventory (STAI-R)

The State-Trait Anxiety Inventory (STAI-R, Form Y [Spielberger, 1983]) is a test that is sensitive to both the immediate (state) and the long-term disposition (trait) of a subject's experience of anxiety. Both components were used in this study (State-Anxiety, Form Y-1 and Trait-Anxiety, Form Y-2), taking approximately 5 minutes each to complete. Both components are composed of 20 items. Scores range from 20 to 80 with higher scores correlating with higher levels of state or trait anxiety. STAI-R was administered only once, at screening.

2.3.1.7 State-Trait Anger Inventory (STAIX-R)

The State-Trait Anger Expression Inventory (STAIX-R, Form Y [Spielberger 1983]) was also utilised. Both State (STAIXI-Part 1) and Trait (STAIXI-Part 2) was administered. These scales provided pilot data for any future research investigating the impact of opioids on other emotional responses such as anger, as a Velten induction procedure has been developed to induce anger (Engebretson et al. 1999). As this inventory was not used in the analysis of this study, it will not be discussed further. STAIX-R was administered only once, at screening.

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2.3.1.8 Hassles and Uplifts Scale (HSUPS)

The Hassles and Uplifts Scale (HSUPS) (DeLongis et al. 1982) measures the subject's attitude to positive events (uplifts) and negative events (hassles) that are common experiences in daily life. Hassles were described as irritants and events that annoyed the subject. The scale is composed of 117 items. Uplifts were described as things that made one feel good about life, and the uplifts scale contains 135 items. Each scale takes approximately 10 minutes to complete. HSUPS was administered only once, at screening.

2.3.2   STIMULI

Two procedures were used to test subjects. To test the emotional reactivity of subjects in study 1 and 2, Velten's Mood Induction Procedures (MIP) was used (see Figure 7). To test the pain threshold and pain tolerance of subjects in study 1, the cold pressor pain test was utilised (see Figure 8).

2.3.2.1 Velten's Mood Induction Procedure (MIP)

Velten's mood induction procedures were used to induce changes in subjective emotional state by using self-suggestion techniques. Velten's mood induction procedure for elation (MIPE) and Velten's mood induction procedure for depression (MIPD) were used to induce elative (positive) and depressive (negative) emotions respectively. Any changes in emotional state are short lived, with the depression induction procedure inducing a larger and more sustained change than the elation induction. As Velten's neutral mood induction procedure (MIPN) was designed to induce no emotional change, it was administered between other mood inductions to provide sufficient time for any previous mood induction to washout (see Figure 7). Each induction procedure used 50 statements chosen from Velten's original set of 60 statements (Velten 1968), based on ease of understanding for a cohort of limited secondary education. Some statements were further shortened or modified for ease of understanding.

For each induction procedure, the 50 statements were numbered, presented on index cards and placed in front of the subject in numerical order. Each subject was instructed to read each statement out aloud and then try to 'get into the mood' suggested by each card. Each subject

had 15 seconds with each card, before prompted to read the next card. Each induction procedure required approximately 12 mins to complete.

Velten's Mood Induction procedure
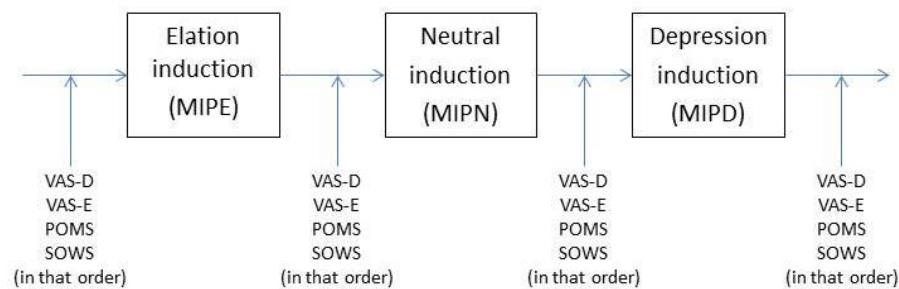
Figure 7: Velten's Mood Induction Procedures: This procedure was used in study 1 and study 2. VAS-D, VAS-E, POMS and SOWS scales were administered before and after each induction to evaluate the effectiveness of the induction procedures. Elation induction (MIPE), Neutral induction (MIPN) and Depression induction (MIPD) were administered in the order presented.

For MIPD, the set of depressive statements had a tone of tiredness, indecision, pessimism and unhappiness. Most of the statements in the depression set fall into one of two categories – statements concerned with self-devaluation or statements suggestive of the somatic aspects of depression. Prototypical depressive statements that fall into the first category include "I have too many bad things in my life" and "I'm discouraged and unhappy about myself". Examples of depressive statements that fall into the second category include "I feel worn out. My health may not be as good as it's supposed to be" and "I feel rather sluggish now". In contrast, elated statements for MIPE had a tone of cheerfulness, optimism and happiness. Example statements from this set are "This is great – I really do feel good – I am elated about things" and "I'm full of energy". Neutral statements in MIPN were not self-referent and were designed to induce no change in emotion. An example in this set was 'This book or any part thereof must not be reproduced in any form'.

There is also a noted difference between the methodology of this procedure and some previous work. Previous work (Scherrer and Dobson 2009; Natale and Bolan 1980) utilised mood induction to mimic depressive symptomology, from which they would then administer the procedures of interest. Any subject who failed to show an increase in depression of usually 50% after induction was ineligible to participate in their studies. In comparison, in this

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thesis the procedure of primary interest is the mood induction itself. Therefore for inclusion into the studies described in this thesis, there was no minimum cut off score for change in induction.

Velten's mood induction procedures have been shown to be effective in inducing depressive or elative states, measurable using visual analogue scales, and inducing an intensity of depressive emotion equivalent to an intermediate clinical level (for a review, see Martin 1990). The specificity of the depressive mood induction has been mixed, with some studies showing that only depressive state increases after MIPD (Brewer and Doughtie 1980; Frost, Graf, and Becker 1979; Polivy and Doyle 1980), whilst another study suggests that both depressive and anxious states increase (Strickland, Hale, and Anderson 1975).

In study 1 and 2, VAS-D, VAS-E, and POMS scales were administered just prior and just after MIPD and MIPE to evaluate the effectiveness of the induction (see Figure 7).

2.3.2.2 Cold Pressor Pain Procedure

The cold pressor pain test was the same procedure used in previous research from this group (Doverty et al. 2001). Subjects immersed their non-dominant arm in a bucket of warm water (35° Celsius) for approximately two minutes. Just prior to this time elapsing, a blood pressure cuff was inflated to 20 mm Hg below diastolic pressure to minimise the role of vascular flow. The arm was then transferred to a bucket of icy cold water (1° C) with the assistance of the researcher. A water pump ensured that laminar warming around the immersed limb did not occur. Subjects indicated when they first feel pain (cold pain threshold [in seconds]) and when they could no longer tolerate the pain (cold pain tolerance [in seconds]), at which point they removed their arm from the water. Subjects were instructed not to employ pain coping strategies such as meditation, imagery or diversion (Fernandez 1986). A cut-off time of 180 seconds in the cold water was enforced. In study 1, just prior and just after the cold pressor pain procedure, VAS-D, VAS-E, POMS and SOWS scales were administered (see Figure 8). The cold pressor pain procedure was not administered in study 2.

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Cold Pressor Pain procedure
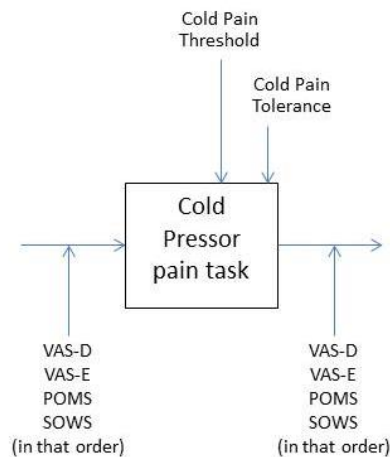
Figure 8: Cold Pressor Pain Procedure: The cold pressor pain task was administered in study 1. VAS-D, VAS-E, POMS and SOWS scales were administered before and after the cold pain task. Cold pain threshold and cold pain tolerance were measured during the task.

2.3.2.3 Plasma Opioid Concentrations

For methadone maintained subjects in study 1, blood samples (7 ml) were collected via venepuncture at 0 hour pre-dose to determine trough plasma methadone concentrations and at 3 hours post dose to determine peak plasma methadone concentrations. For methadone and buprenorphine maintained subjects in study 2, blood samples were only collected at peak plasma opioid concentrations (3 hours or 1.5 hours post dose respectively) to determine peak plasma methadone or buprenorphine concentrations. Plasma samples were frozen until assayed. R-(-) and S-(+) plasma methadone concentrations were quantified using high-performance liquid chromatography using established methods at the Discipline of Pharmacology, University of Adelaide (Mitchell et al. 2004). Similar techniques were used to quantify plasma buprenorphine and norbuprenorphine concentrations (Jensen et al. 2007).

CHAPTER 3 – STUDY 1 PROCEDURE AND RESULTS – METHADONE AND COLD PAIN SENSITIVITY

3.1   INTRODUCTION

Pain is frequently comorbid with psychiatric disorders. A large international population study showed that mental disorders were more common in people with chronic pain (Demyttenaere et al. 2007). Pooled odds ratios were 2.3 for a mood disorder and 2.2 for anxiety disorders in people with chronic pain versus those without pain. In particular, depression and pain seem strongly linked (Bair et al. 2003) though the exact nature of the relationship is still unclear. Directions of causality are equivocal with some researchers agreeing they are causative but disputing the direction of causation (Romano and Turner 1985; Fishbain et al. 1997). Though the relationship between pain and depression is often highlighted, anxiety disorders are also commonly comorbid with pain.

Treatments for depression may help determine the relationship between pain and depression. Pharmacological studies suggest that the use of anti-depressants to treat depression has only a small impact on chronic pain relief (Urquhart et al. 2008). As anti-depressants for example are more effective for rheumatologic conditions than lower back pain (Perrot et al. 2008), the type of pain may impact effectiveness. The role of reducing pain by treating depression is unclear, especially as one review reported that pain reduction did not correlate well with reduction in depression severity with antidepressant administration (O'Malley et al. 1999).

There has been considerable speculation concerning the mechanisms that may link depression with pain. The foremost candidates are catastrophising and emotion regulation, as both play key roles in depression and pain (Linton and Bergbom 2011). Catastrophising is seen to lead to negative affect, 'ramping up' further catastrophising. It also leads to fear, worry and anxiety. Higher levels of depression are also associated with higher levels of catastrophising, and studies show that higher levels of one or the other are associated with higher dysfunction (Bergbom et al. 2011). Emotional regulation has also been linked as a common mechanism of depression and pain, as pain experience may be modified by anger, anxiety and mood (Linton

2005; Main, Sullivan, and Watson 2007). Anxiety and emotional distress have also been implicated in both depression and chronic pain problems (Nicholas et al. 2011).

Contrasting the deleterious associations of depression and mood, experimental studies suggest that depressed patients have decreased pain sensitivity compared with non-depressed controls. For example, cold pain thresholds were increased (lower pain sensitivities) in patients with major depressive disorder (Schwier et al. 2010; Otto, Dougher, and Yeo 1989; Lautenbacher et al. 1999). However this effect is not universal with some studies showing more pain sensitivity (Gormsen et al. 2004) or no difference (Spernal, Krieg, and Lautenbacher 2003). A meta-analysis of six studies comparing depression (not induced) and pain perception showed that pain threshold was higher in depressed versus non-depressed subjects (Dickens, McGowan, and Dale 2003). However, no conclusions could be drawn in regards to cold pain tolerance and depression. Correlation analysis has revealed no significant association between cold pain threshold and measures of depression using Beck's Depression Inventory (BDI) or Hamilton Depression Rating Scale (HAMD) (Schwier et al. 2010). However Lautenbacher et al. (1994) reported a correlation between pain perception and disease severity only in a subgroup of patients.

Prevailing thought is that the modality of pain is a key factor in how depression interacts with pain. Bar et al 2005 reported that pain threshold and pain tolerance in thermal heat and electrical pain increases (hypoalgesia) in depressed patients versus controls (Bär et al. 2005). However, ischemic pain thresholds and tolerance decrease (hyperalgesia) in patients with depression. It is possible that depressed patients process surface pain differently than 'deep somatic' pain. A caveat of that study is that depressed patients were currently prescribed antidepressants. Furthermore, the study could not find any correlation between depression scores (HAMD) and altered pain parameters in depressed patients.

Using mood induction procedures to induce a depressive state has also been utilised to determine the effect of depression on pain experience in pain-free controls. However, results have been mixed with some studies showing cold pressor pain tolerance decreasing after depressed mood induction (Willoughby et al. 2002; Zelman et al. 1991) while other studies showed only elative mood induction increasing cold pain tolerance (Hertel and Hekmat 1994; Weisenberg, Raz, and Hener 1998). Using music mood induction, chronic pain patients induced into a depression mood reported higher pain intensities and lower pain tolerances when challenged on a bag-holding pain task (where subjects are timed on the duration that a

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heavy bag can be held up unassisted). Elative mood induction reported lower pain intensities and higher pain tolerances using the bag-holding pain task (Tang et al. 2008). Note that the study only measured pain tolerance and not pain perception threshold. Anxiety induced procedures have also been shown to reduce pain tolerance in a mechanical task (Fisher and Johnston 1996) and research by Rhudy and Meagher (2000b) using induction techniques and radiant thermal pain suggests that anxiety leads to reduced pain thresholds (hyperalgesia) whilst fear leads to increased pain thresholds (analgesia). Other research has showed that highly anxious male drug abusers had decreased pain response and increased bias to report pain (Malow, West, and Sutker 1987), and Al Absi and Rokke (1991) reported that females highly anxious about a cold pressor test reported the most pain.

A component approach to a psychological construct such as depression may better elucidate any relationship between depression and pain sensitivity. A two-factor approach to depression (Steer et al. 1999b) has shown that depression can be compartmentalised into two components – an affective component (e.g. mood) and a somatic component (e.g. physical effects such as loss of appetite). The two subscales were moderately correlated, suggesting that the physical and psychological aspects of depression are related rather than totally distinct. However, the author is unaware of the application of this approach in drug treatment populations. A factor analysis approach has been used in drug treatment groups, with a three factor model of depression providing the best fit (Buckley, Parker, and Heggie 2001). The model separated BDI depression into cognitive, affective, and somatic components. Some of these items are often also associated with symptoms of drug abuse/dependence (especially alcohol abuse): sleep disturbance, fatigue/loss of energy, appetite disturbance, change in sexual functioning, and psychomotor agitation (O'Mahony and Doherty 1996; Lowinson et al. 2004). The author is unaware of research exploring the relationship between pain sensitivity and components of depression, particularly in opioid maintenance patients.

As previous research demonstrates that methadone maintained patients have heightened pain sensitivity to certain types of pain (despite the daily administration of an analgesic such as methadone) and as methadone patients typically are also reported with higher levels of psychopathology such as depression, this chapter aims to investigate the relationship between cold pain sensitivity and higher order psychological factors (such as depression or anxiety).

3.2   AIM & HYPOTHESIS

The aim of this chapter was to investigate the relationship between pain sensitivity in methadone patients and higher order psychological constructs such as depression, factor components of depression, or anxiety. Subjects not using methadone and naïve to opioids were used as a comparison cohort. This chapter also aimed to verify in study 1 that methadone maintenance patients were hyperalgesic to cold pain compared with controls, as shown in previous studies (Doverty et al. 2001).

The following hypothesis was tested in Chapter 3:

> (i) Methadone patients will show a differing relationship of pain sensitivity to psychological components of depression than controls..

3.3   METHOD

3.3.1   SUBJECTS

Two groups of subjects were recruited. The opioid dependent group comprised 21 adults (14 males, 7 females; aged 27-53 years) currently on methadone maintenance treatment. Controls comprised 21 adults (14 males, 7 females; aged 18-40 years) and were opioid naïve. Inclusion criteria for the methadone group were: aged between 18 and 65 and on a stable once-daily dose of methadone, having been on methadone maintenance treatment for a minimum of two weeks, with no current or previous history of psychiatric illness, not currently diagnosed with a depressive illness, no current or previous history of chronic pain, and not taking any medication for a psychiatric condition (such as anti-depressants and anti-psychotics) apart from benzodiazepines. Inclusion criteria for controls were: aged between 18 and 65, with no current or previous history of opioid dependency, no current or previous history of psychiatric illness or chronic pain, not currently diagnosed with a depressive illness, and not currently prescribed anti-depressant medication. Pregnancy was an exclusion criterion for both groups. Controls were recruited primarily from governmental welfare assistance centres and were similar to the methadone group on employment status, nicotine use and 30 day recreational drug history. Preference in enrolled was given to controls that were using non-opiate illicit

drugs (e.g. amphetamines, cannabis) on a regular basis. The study was approved by the Royal Adelaide Hospital, Research Ethics Committee (#060917).

3.3.2   SCREENING

Demographic and background information was collected at screening. A battery of tests was also administered at the clinic to gauge psychological function at screening, including the state-trait anxiety inventory (STAI-R), the Beck Depression Inventory (BDI) and the Hassles and Uplifts Scale (HSUPS). Components of depression (cognitive, affective and somatic scores) were derived from the BDI.

3.3.3   PROCEDURE

The procedure to investigate the pain sensitivity of methadone maintenance patients and controls was part of a larger study (study 1) examining the effect of methadone on emotional reactivity. Each subject attended two sessions (0 hour and 3 hours) at a drug treatment clinic (Drug and Alcohol Services South Australia [DASSA], Warinilla, South Australia). This timeframe was chosen as methadone reaches peak plasma concentrations approximately 3 hours post dose (Dyer et al. 1999). For the methadone group, 0 hour was just prior to their next daily dose and corresponded with a time when methadone was at trough plasma concentrations, while 3 hours post dose corresponded approximately with peak plasma methadone concentrations. Controls attended two sessions at similar times (at 0 hour and 3 hours). To counter order effects, subjects were randomised to attend either a same-day 0 hour then 3 hours session, or a 3 hours then next-morning 0 hour session.

At 0 hour, methadone subjects and controls were administered elative and depressive mood induction procedures (results presented in subsequent chapters). Subjects then underwent the cold pressor pain test. All tests were administered by the same researcher throughout the study and with no session containing more than one subject. For methadone maintained subjects, blood samples were also collected via venepuncture pre-dose to determine trough plasma methadone concentrations. Finally methadone subjects were dosed oral methadone as prescribed by maintenance treatment. This concluded the 0 hour induction session. Subjects then had a three hour break, with lunch provided. The 3 hours mood induction and cold

pressor test were then conducted after the break. The 3 hours session followed the same structure as 0 hour, except without methadone dosing. For methadone maintained subjects, blood samples were also collected at 3 hours post dose to determine peak plasma methadone concentrations. See Chapter 4, Figure 13 for a diagram of the order of the procedures used.

3.4   RESULTS

3.4.1   STATISTICAL ANALYSES

All analyses used an alpha level of 0.05. Data format is Mean ± Standard Error unless otherwise noted. Correlations shown were calculated using two-tailed significance levels. All data were analysed using SPSS for Windows (version 11), except outlier detection using Graphpad Quickcalcs ('GraphPad QuickCalcs: Outlier Calculator' 2012). Repeated measures two-way ANOVA was used to assess the effect of the cold pressor pain on both groups at both session time points.

3.4.2   SUBJECT CHARACTERISTICS

3.4.2.1 Demographics

Table 1 shows the demographic breakdown of the methadone group and controls. As indicated, the ethnic composition of each group was predominantly Caucasian. The methadone group was significantly older (independent samples, $p < 0.001$) and had a significantly higher BDI score than controls (independent samples, $p < 0.001$). Gender breakdown was identical for both groups (methadone: 14 male, 7 female; controls 14 male, 7 female). The methadone group was significantly older than controls (methadone 36.9 ± 1.5 years, controls 26.9 ± 1.3 years; independent samples, $p < 0.001$), with males mean age in the methadone group also higher than in the controls. Both groups were primarily comprised of unemployed participants (methadone: 15 persons; controls: 12 persons). In the methadone group, more participants identified as being without a partner (methadone: 13 single, 8 with partner). The reverse was true in controls (controls: 9 single, 12 with a partner).

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Table 1: Demographics and Clinical Data for the methadone group (MMT) and controls. Abbreviations: BDI, Beck Depression Inventory; Unemp, Unemployed; Emp, Employed (either unskilled, skilled or professional); Stud, Student. [a]Significant Difference p < 0.001; [b]Significant Difference p < 0.001; [c]Significant Difference t(40) = 4.36, p < 0.00; [d]Significant Difference, t(40) = 4.16, p < 0.001; [e]Significant Difference t(40) = 2.65, p < 0.05; [f]Significant Difference t(29.2) = 3.6, p = 0.01; [g]Significant Difference t(29.1) = 4.7, p < 0.001; mean ± standard error (SE)

	MMT (n=21)	Controls (n=21)
Gender (Male/Female)	14/7	14/7
Ethnicity (Caucasian/Other)	21/0	20/1
Total Mean Age ± SE (yrs)	36.9 ± 1.5 [a]	26.9 ± 1.3 [a]
Males only Mean Age ± SE (yrs)	35.9 ± 1.4 [b]	24.9 ± 1.4 [b]
Females only Mean Age ± SE (yrs)	38.7 ± 3.6	31.0 ± 2.0
Current Methadone Dose (mg/day)	68.8 ± 5.8	NA
Occupation (Unemp/Emp/Stud)	15/6/0	12/7/2
Relationship (Single/Partner)	13/8	9/12
Stimulant use in last 30 days (number of users)	10	6
Marijuana use in last 30 days (number of users)	14	8
Benzodiazepine use, last 30 days (number of users)	8	2
Alcohol use in last 30 days (number of users)	8	16
Nicotine in last 30 days (number of users)	19	17
Any illicit used in last 30 days (number of users)	16	9
Mean BDI score ±SE	17.6 ± 2.0 [c]	7.4 ± 1.2 [c]
Mean Derived BDI score ± SE	15.3 ± 1.8 [d]	6.9 ± 1.1 [d]
Cognitive component of BDI ± SE	6.6 ± 0.9 [e]	3.3 ± 0.8 [e]
Affective component of BDI ± SE	3.4 ± 0.6 [f]	1.1 ± 0.3 [f]
Somatic component of BDI ± SE	7.5 ± 0.9 [g]	3.1 ± 0.4 [g]
STAI-R – State Anxiety (t(32.3) = 1.066, p = 0.295)	37.2 ± 2.1	43.0 ± 2.0
STAI-R – Trait Anxiety (t(40) = 0.814, p = 0.421)	34.6 ± 1.2	40.8 ± 1.9
HSUPS – Hassle items only (t(33) = 1.754, p = 0.089)	51.0 ± 7.6	35.5 ± 4.6
HSUPS - Uplift items only (t(40) = -0.92, p = 0.363)	51.7 ± 8.4	65.0 ± 11.7

In the methadone group, 16 subjects reported illicit drug use within the last 30 days. Controls had 9 subjects reporting such use. A battery of tests was used to gauge psychological function including BDI, STAI-R, STAIX-R and HSUPS. The two groups could not be differentiated

on state and trait anxiety (STAI-R), or hassle and uplifts (HSUPS). The methadone group scored significantly higher on BDI than controls (methadone: 17.6 ± 2.0, controls 7.4 ± 1.2; independent samples, $p < 0.001$). Note that a BDI score of 0-10 is considered to be minimal mood disturbance and a score of 11-19 is considered mild mood disturbance (Beck and Steer 1996). By this criterion, in the methadone group 14 subjects had minimal to mild mood disturbance and 7 subjects had at least moderate depression. In controls 20 subjects had minimal to mild depression and 1 subject had at least moderate depression. A derived BDI score which excluded two questions related to typical opiate withdrawal symptoms did not significantly change the difference in scores between the two groups. Therefore scores using the full BDI instrument were used in all further analyses. It should be noted that though the two groups differed on BDI score, there was no significant difference between the groups on state or trait anxiety scores. Norms (Spielberger and Gorsuch 1983) for Trait Anxiety for working adults are 34.9 ± 9.2 (mean ± SD) for males, and 34.8 ± 9.2 for females. Norms for male neuropsychiatric patients are 46.6 ± 12.4, and for general medical and surgical male patients 41.0 ± 12.7.

3.4.2.2 Plasma Methadone Concentrations

The average daily dose of methadone in the methadone group was 68.8 ± 5.8 mg (range 30 - 110 mg). Plasma methadone concentrations of R-(-) and S-(+) methadone at 0 hour were 119 ± 14 ng / ml and 117 ± 12 ng / ml respectively. Plasma concentrations at 3 hours were 179 ± 17 ng / ml and 212 ± 17 ng / ml respectively. Due to poor venous access with a proportion of methadone subjects, sample size was n = 14. R-(-) and S-(+) plasma methadone concentrations were significantly higher at 3 hours post dose compared to 0 hour pre dose [R-(-) paired samples, $p < 0.001$; S-(+) paired samples, $p < 0.001$]. Table 2 shows the relationship between changing R- and S- plasma methadone concentrations and as expected, that the change in R-(-) methadone from 0 hour to 3 hours was strongly correlated with the change in S-(+) methadone (r = 0.96, $p < 0.001$).

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Table 2: Correlations: Methadone dose and changes in plasma methadone concentrations. The relationship between methadone dose and plasma methadone concentration in the methadone maintenance group. *p < 0.05, ** p < 0.01.

		ΔR-(-) methadone	ΔS-(+) methadone
methadone dose	r	0.70**	0.62*
	sig	0.006	0.017
	N	14	14
ΔR-(-) methadone	r		0.96**
	sig		0.000
	N		14

3.4.3 COLD PAIN SENSITIVITY

Cold pain thresholds and tolerances were analysed in the methadone group and controls to determine whether methadone patients showed greater cold pain sensitivity than controls. Figure 9 and Figure 10 shows the cold pain threshold and cold pain tolerance scores for the two groups at 0 hour and 3 hours. As an extreme outlier was detected in the methadone group, it was excluded during analysis (Grubb's Test: $z = 4.11$, $p < 0.01$).

3.4.3.1 Cold Pain Threshold

For cold pain threshold (Figure 9), repeated measures ANOVA revealed no within subject effects (time: $F[1] = 0.94$, $p = 0.337$), between subject effects (group: $F[1] = 2.37$, $p = 0.132$), or interaction effects (time*group: $F[1] = 0.04$, $p = 0.836$). Therefore controls were no different at 3 hours (10.3 ± 1.4 seconds) than 0 hour (9.8 ± 1.4 seconds), and the methadone group at 3 hours (8.0 ± 1.1 seconds) had similar threshold scores as at 0 hour (7.0 ± 0.8 seconds).Though the methadone group overall had a lower cold pain threshold (estimated mean: 7.6 ± 1.2 seconds) than controls (estimated mean: 10.1 ± 1.1 seconds), it was not significantly different ($p = 0.132$). Controlling for potential confounders such as total BDI (not shown) did not reveal significant findings.

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Cold Pain Threshold
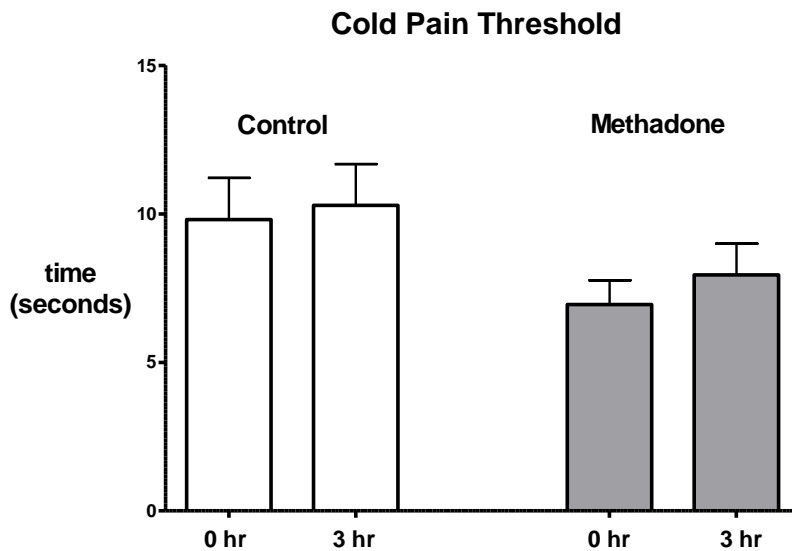
Figure 9: Cold Pain Threshold. The methadone group cold pain threshold scores were not significantly lower than controls (p = 0.132). Outlier deleted. Bars show mean ± standard error.

3.4.3.2 Cold Pain Tolerance

For cold pain tolerance (Figure 10), repeated measures ANOVA revealed no within subject effects (time: F[1] = 2.53, p = 0.12) or interaction effects (time*group: F[1] = 0.39, p = 0.535). Controls at 3 hours (33.9 ± 4.9 seconds) were not significantly different than at 0 hour (29.4 ± 2.6 seconds). The methadone group mean was also stable across time with a cold pain tolerance score at 3 hours (19.5 ± 2.2 seconds) similar to that at 0 hour (17.6 ± 1.7 seconds). However, there were significant between subject effects (group: F[1] = 10.59, p = 0.002) and estimated marginal means revealed that the methadone group (estimated mean: 18.5 ± 2.9 seconds) had a significantly lower cold pain tolerance than controls (estimated mean: 31.7 ± 2.8 seconds). Adding total BDI score as a covariate to the model did not change the pattern of findings.

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Cold Pain Tolerance
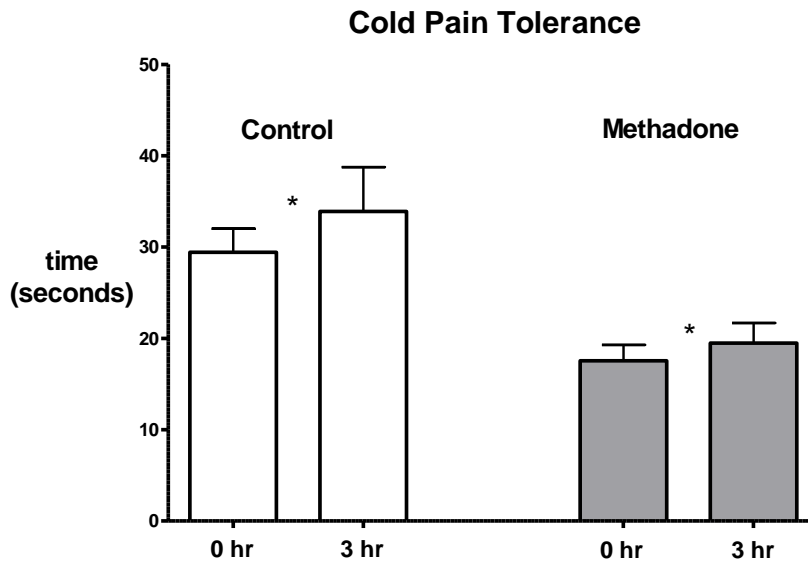
Figure 10: Cold Pain Tolerance. The methadone group had significantly (p = 0.002) lower cold pain tolerance than controls[*]. Outlier deleted. Bars show mean ± standard error.

3.4.3.3 Correlation between Cold Pain Sensitivity and Methadone Concentration

Table 3 shows there was no significant correlation between change in cold pain threshold and change in plasma R(-)-methadone concentration (r = 0.17, p > 0.05), or cold pain tolerance and change in plasma R-(-) methadone concentration (r = 0.230, p > 0.05). A lack of variability in one or both of the variables may have obfuscated any underlying relationship, as well as an insufficient sample size. See also the scatterplots for change in plasma R(-) methadone concentration versus change in cold pain threshold (Figure 11), and change in plasma R(-) methadone concentration versus change in cold pain tolerance (Figure 12).

Table 3: Correlations: Change in cold pain tolerance and changes in plasma methadone concentrations.

		ΔR-(-) methadone	ΔS-(+) methadone
Change in Cold Pain Threshold	r	0.17	0.17
	sig	0.585	0.572
	N	13	13
Change in Cold Pain Tolerance	r	0.23	0.15
	sig	0.449	0.636
	N	13	13
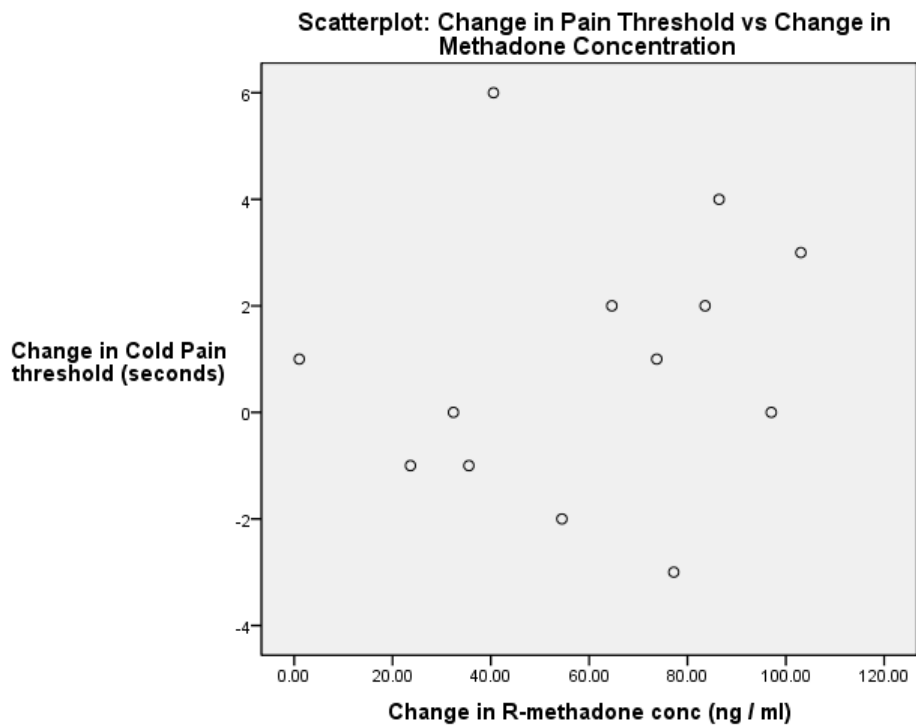
Figure 11: Scatterplot for change in plasma R(-) methadone concentration versus change in cold pain threshold. 'Change' is defined as the difference between 0 hour and 3 hour measures. Outlier deleted.
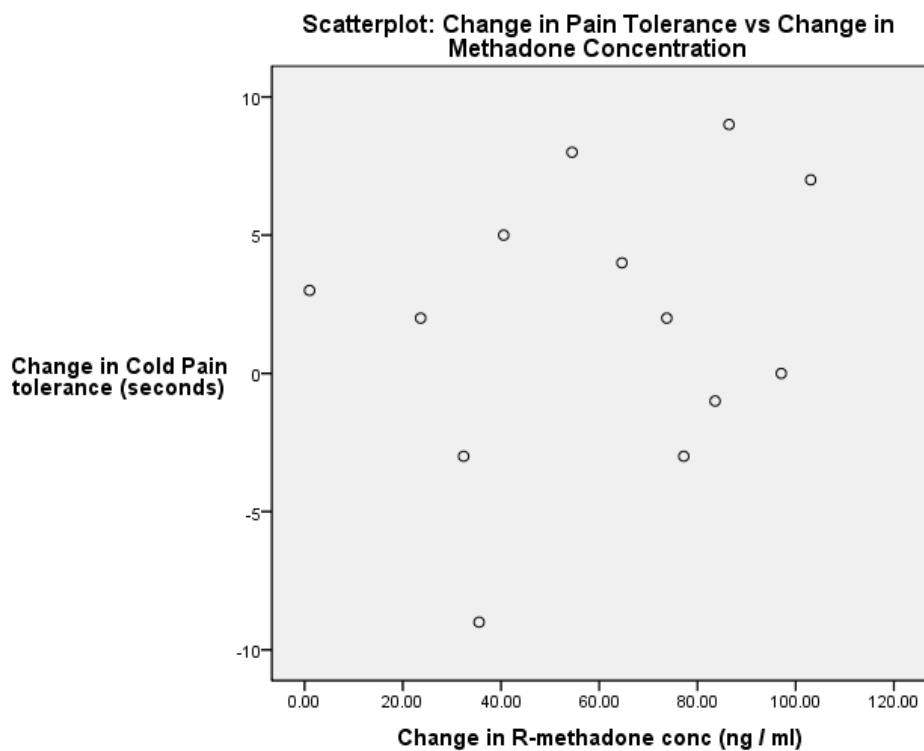
Figure 12: Scatterplot for change in plasma R(-) methadone concentration versus change in cold pain tolerance. 'Change' is defined as the difference between 0 hour and 3 hour measures. Outlier deleted.

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3.4.4 CORRELATIONS BETWEEN HIGHER ORDER PSYCHOLOGICAL FUNCTIONS AND PAIN SENSITIVITY

Higher order psychological measures such as depression, a three component approach to depression (cognitive, affective and somatic), and trait anxiety were tested for correlation with pain threshold and tolerance to determine their impact on cold pain sensitivity. First the higher order measures were correlated with each other to determine their inter-relationship. Table 4 shows the bivariate correlations between the psychological measures tested in the methadone group. Also shown are the partial correlations when age and methadone dose were accounted for. As expected, the factor components (cognitive, affective and somatic) were strongly correlated with total BDI. Trait anxiety was also strongly correlated with total BDI and components of BDI, whether accounting for age and dose or not. Table 5 shows the correlations amongst higher psychological measures for controls. Unlike the methadone group, the correlation of the factors of depression were lower in controls and the affective component of depression was not significantly correlated with cognitive or somatic components, or trait anxiety.

Table 4: Correlation Matrix: Psychological measures, Methadone Group (All). The correlations of the three components (cognitive, affective, somatic) of Beck Depression Inventory (BDI) with total Beck Depression Inventory Score (BDI) and State Anxiety (STAI), in the Methadone group. Uncorrected zero-order correlations and partial correlations corrected for age and dose. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Methadone Group	BDI, cog	BDI, affect	BDI, somatic	STAI, Trait
Total BDI	0.84^{***}	0.93^{***}	0.76^{***}	0.79^{***}
Partial - Age,dose	0.85^{***}	0.93^{***}	0.79^{***}	0.80^{***}
BDI factor, cognitive		0.79^{***}	0.32	0.70^{*}
Partial - Age,dose		0.80^{***}	0.37	0.73^{**}
BDI factor, affective			0.61^{**}	0.73^{***}
Partial - Age,dose			0.64^{**}	0.77^{***}
BDI factor, somatic				0.56^{*}
Partial - Age,dose				0.57^{*}

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Table 5: Correlation Matrix: Psychological measures, Controls (All). The correlations of the components of Beck Depression Inventory (BDI) with total BDI and State Anxiety (STAI), in Controls. Uncorrected zero-order correlations and partial correlations corrected for age. *p < 0.05; **p < 0.01; ***p < 0.001.

Controls	BDI, cognitive	BDI, affect	BDI, somatic	STAI, Trait
Total BDI	0.88***	0.65**	0.66**	0.79***
Partial - Age	0.88***	0.66**	0.67**	0.79***
BDI factor, cognitive		0.38	0.30	0.85***
Partial - Age		0.38	0.30	0.85***
BDI factor, affective			0.42	0.31
Partial - Age			0.43	0.29
BDI factor, somatic				0.36
Partial - Age				0.38

Table 6 shows that for the methadone group, psychological measures were not generally predictive of pain sensitivity. Only the somatic component of BDI showed a significant correlation with change in tolerance from peak to trough (r = -0.45, p < 0.05), and was robust to age and dose confounders (r = -0.53, p < 0.05).

Table 6: **Correlation Matrix: Cold Pain sensitivity and Psychological measures, Methadone Group (All).** The correlations of pain threshold (Thres) and tolerance (Tol) with total Beck Depression Inventory Score (BDI), the components of BDI and State Anxiety (STAI), in the Methadone group. Uncorrected zero-order correlations and partial correlations corrected for age and dose. Delta = Change from peak to trough. *p < 0.05; **p < 0.01; ***p < 0.001.

Methadone	Pain Thres 0hr	Pain Tol 0hr	Pain Thres 3hr	Pain Tol 3hr	Delta Thres	Delta Tol
Total BDI	-0.12	0.10	-0.31	-0.13	-0.13	-0.42
Partial - Age,dose	-0.16	0.08	-0.33	-0.15	-0.13	-0.42
BDI factor, cognitive	0.05	0.18	-0.10	0.04	-0.09	-0.22
Partial - Age,dose	-0.02	0.12	-0.14	0.01	-0.07	-0.19
BDI factor, affective	-0.18	0.03	-0.30	-0.15	-0.15	-0.32
Partial - Age,dose	-0.24	-0.01	-0.36	-0.16	-0.15	-0.30
BDI factor, somatic	-0.21	0.02	-0.36	-0.24	-0.09	-0.45[*]
Partial - Age,dose	-0.18	0.06	-0.36	-0.23	-0.11	-0.53[*]
STAI, Trait Anxiety	-0.11	0.29	-0.14	0.16	0.18	-0.21
Partial - Age,dose	-0.10	0.32	-0.11	0.17	0.20	-0.23

Table 7 shows the correlations between pain sensitivity and psychological measures for controls. The cognitive component of BDI was moderately correlated with pain tolerance at 3 hours (r = 0.44, p < 0.05), irrespective of the effect of age. Cognitive factors also were moderately correlated with pain threshold at 3 hours. The correlation between cognitive BDI component and cold pain threshold or tolerance at 0 hour was smaller and non-significant.

Table 7: Correlation Matrix: Cold Pain sensitivity and Psychological measures, Controls (All). The correlations of pain threshold and tolerance with total Beck Depression Inventory Score (BDI), the three components (cognitive, affective, somatic) BDI and State Anxiety (STAI), in Controls. Thres = Threshold. Tol = Tolerance. Delta = Change in Threshold or Change in Tolerance from peak to trough. Uncorrected zero-order correlations and partial correlations corrected for age. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

Controls	Pain Thres 0hr	Pain Tol 0hr	Pain Thres 3hr	Pain Tol 3hr	Delta Thres	Delta Tol
Total BDI	0.27	0.29	0.27	0.35	-0.00	0.26
Partial - Age	0.28	0.29	0.27	0.35	-0.02	0.26
BDI factor, cognitive	0.33	0.33	0.45[*]	0.44[*]	0.15	0.35
Partial - Age	0.33	0.33	0.45[*]	0.44[*]	0.15	0.35
BDI factor, affective	0.24	0.23	0.03	0.36	-0.26	0.30
Partial - Age	0.26	0.25	0.01	0.36	-0.35	0.30
BDI factor, somatic	-0.04	0.01	-0.13	-0.11	-0.12	-0.15
Partial - Age	-0.04	0.01	-0.13	-0.11	-0.11	-0.15
STAI, Trait Anxiety	-0.01	0.15	0.31	0.36	0.41	0.37
Partial - Age	0.01	0.16	0.30	0.37	0.38	0.37

The correlation matrices reveal a number of things. Trait anxiety correlated strongly with a number of the other higher psychological measures, showing anxiety and depression was related. This is not an unexpected result as it is widely reported that anxiety and depression are similar on a number of dimensions, and that the disorders are often co-morbid. The relationship between cognitive, affective and somatic components of depression was also dissimilar between the two groups. For controls there was no relationship between cognitive, affective and somatic factors of BDI. However, the inter-relationship in the methadone group was more complicated with the cognitive component correlated with the affective component, the affective component correlated with somatic component, but cognitive and somatic component were not associated.

The conclusions drawn from the correlation matrixes of the methadone group and controls were that somatic components were predictive of the change in pain tolerance in methadone maintained patients from trough to peak, with higher somatic scores associated with less improvement in cold pain tolerability. However this is not the case for controls, where

cognitive factors correlated positively with pain threshold and tolerance (at 3 hours). As the relationship between psychological factors and pain sensitivity was still unclear, a more sophisticated analysis was required.

3.4.4.1 Correlations between higher order functions and pain in low BDI group

The methadone group and controls were split into low and high BDI groups – the low group had a score consistent with minimal to mild depression (BDI = 0 to 19) and the high group had a score consistent with moderate to severe depression (BDI > 19). Using this coding, 20 of 21 controls and 14 of 20 methadone maintained patients were categorised into the low BDI group. As controls were predominantly composed of subjects with BDI score consistent with minimal to mild depression, correlations for both low BDI groups were investigated further using a similar methodology reported above in the entire sample.

Table 8 shows the correlation matrix of psychological measures in the low BDI methadone group. Total BDI correlated will all other higher order psychological measures. After accounting for age and dose, trait anxiety was not correlated with any psychological measures. Partial correlations revealed that total BDI was correlated with the affective and somatic components of depression after accounting for age and dose. Using partial correlations, the three factors of depression (cognitive, affective and somatic) were not correlated with each other. Compared with considering the full methadone sample, in methadone patients low on BDI the inter-relatedness of psychological measures was either not as strong, not significant, or both. This would suggest that evidence of a strong relationship between depression, components of depression, and trait anxiety was not as evident in a methadone patient group scoring low on depression (minimal to mild).

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Table 8: Correlation Matrix: Psychological measures, Methadone Group (Minimal to mild group only). The correlations of the three components (cognitive, affective, somatic) of Beck Depression Inventory (BDI) with total Beck Depression Inventory Score (BDI) and State Anxiety (STAI), in the Methadone group with minimal to mild depression scores. Uncorrected zero-order correlations and partial correlations corrected for age and dose. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

Methadone Group	BDI, cog	BDI, affect	BDI, somatic	STAI, Trait
Total BDI	0.70**	0.82**	0.62*	0.64*
Partial - Age,dose	0.57	0.80**	0.64*	0.38
BDI factor, cognitive		0.42	-0.12	0.52
Partial - Age,dose		0.27	-0.24	0.28
BDI factor, affective			0.56*	0.58
Partial - Age,dose			0.55	0.42
BDI factor, somatic				0.21
Partial - Age,dose				0.14

In comparison, Table 9 shows the correlation matrix of higher order psychological factors in minimal to mild BDI controls. Trait anxiety was highly correlated with all psychological measures except the affective and somatic factors of depression. The cognitive component of depression showed low and non-significant correlations with affective and somatic components, but the affective component was moderately correlated with somatic components. These correlations are comparable with the correlation matrix for the entire control group as only one subject had a score higher than the cut-off score for minimal to mild depression.

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Table 9: Correlation Matrix: Psychological measures, Controls. Minimal-mild Group only. The correlations of the three components (cognitive, affective, somatic) of Beck Depression Inventory (BDI) with total Beck Depression Inventory Score (BDI) and State Anxiety (STAI), in Controls with minimal to mild depression scores. Uncorrected zero-order correlations and partial correlations corrected for age. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Controls (Minimal-Mild)	BDI, cog	BDI, affect	BDI, somatic	STAI, Trait
Total BDI	0.85^{**}	0.48^{*}	0.71^{***}	0.77^{***}
Partial - Age	0.85^{***}	0.48^{**}	0.72^{**}	0.78^{***}
BDI factor, cognitive		0.10	0.28	0.84^{***}
Partial - Age		0.10	0.28	0.85^{***}
BDI factor, affective			0.46^{*}	0.15
Partial - Age			0.48^{*}	0.12
BDI factor, somatic				0.35
Partial - Age				0.36

Table 10 examines the correlation matrix between pain sensitivity and higher psychological measures, for the minimal to mild depression methadone group. Accounting for age and dose, pain tolerance at 0 hour and 3 hours was correlated moderately with total BDI. Investigating the three factors of depression revealed that it was the affective component of depression that was correlated strongly with cold pain tolerance at 0 hour ($r = 0.67$, $p < 0.05$) and 3 hours ($r = 0.73$, $p < 0.05$). Both cognitive and somatic components were not significantly correlated with cold pain tolerance at any time point. Trait anxiety was also strongly correlated with cold pain tolerance at 0 hour ($r = 0.85$, $p < 0.05$) and 3 hours ($r = 0.81$, $p < 0.05$).

Table 10: Correlation Matrix: Cold Pain sensitivity and Psychological measures, Methadone (Minimal-Mild only). The correlations of pain threshold and tolerance with total Beck Depression Inventory Score (BDI), the three components (cognitive, affective, somatic) BDI and State Anxiety (STAI), in the Methadone group with minimal to mild depression scores. Uncorrected zero-order correlations and partial correlations corrected for age and dose. Thres = Threshold. Tol = Tolerance. Delta = Change in Threshold or Change in Tolerance from peak to trough. *p < 0.05; **p < 0.01; ***p < 0.001.

Methadone (Minimal-Mild)	Pain Thres 0hr	Pain Tol 0hr	Pain Thres 3hr	Pain Tol 3hr	Delta Thres	Delta Tol
Total BDI	0.48	0.48	0.24	0.54	0.11	-0.12
Partial - Age,dose	0.55	0.64[*]	0.40	0.64[*]	-0.03	-0.43
BDI factor, cognitive	0.62[*]	0.48	0.43	0.49	0.07	0.05
Partial - Age,dose	0.63[*]	0.59	0.55	0.52	-0.14	-0.22
BDI factor, affective	0.37	0.58[*]	0.25	0.68[*]	0.20	0.24
Partial - Age,dose	0.36	0.67[*]	0.33	0.73[*]	0.11	0.11
BDI factor, somatic	-0.02	0.04	-0.30	-0.11	-0.01	-0.35
Partial - Age,dose	0.07	0.12	-0.21	-0.07	-0.00	-0.45
STAI, Trait Anxiety	0.26	0.64[*]	0.29	0.68[*]	0.48	0.07
Partial - Age,dose	0.18	0.85[*]	0.44	0.81[*]	0.43	-0.21

Table 11 shows the correlation matrix of higher psychological measures and pain sensitivity for controls with minimal to mild depression. Correlations were predominantly small and non-significant. Only after accounting for age was the affective component of depression negatively correlated with change in pain threshold from trough to peak (r = -0.49, p < 0.05). The association was moderate in strength.

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Table 11: Correlation Matrix: Cold Pain sensitivity and Psychological measures,Controls (Minimal-Mild only). The correlations of pain threshold and tolerance with total Beck Depression Inventory Score (BDI), the three components (cognitive, affective, somatic) BDI and State Anxiety (STAI), in Controls with minimal to mild depression scores. Uncorrected zero-order correlations and partial correlations corrected for age. Thres = Threshold. Tol = Tolerance. Delta = Change in Threshold or Change in Tolerance. *p < 0.05; **p < 0.01; ***p < 0.001.

Controls (Minimal-Mild)	Pain Thres 0hr	Pain Tol 0hr	Pain Thres 3hr	Pain Tol 3hr	Delta Thres	Delta Tol
Total BDI	0.21	0.12	0.19	0.14	-0.02	0.09
Partial - Age	0.21	0.13	0.19	0.14	-0.03	0.09
BDI factor, cognitive	0.28	0.19	0.41	0.28	0.16	0.22
Partial - Age	0.28	0.20	0.41	0.28	0.16	0.22
BDI factor, affective	0.15	-0.01	-0.14	0.07	-0.37	0.09
Partial - Age	0.18	0.01	-0.18	0.07	-0.49[*]	0.08
BDI factor, somatic	-0.06	-0.03	-0.16	-0.18	-0.13	-0.21
Partial - Age	-0.07	-0.04	-0.15	-0.18	-0.11	-0.20
STAI, Trait Anxiety	-0.07	0.05	0.27	0.26	0.42	0.30
Partial - Age	-0.05	0.06	0.25	0.27	0.40	0.30

3.4.4.2 Correlations between higher order functions and pain in high BDI group

The correlation between higher order psychological measures and pain sensitivity were also explored in subjects with a BDI depression score considered moderate to severe depression. Only seven methadone subjects met the criteria but the results are reported for completeness. No correlations were performed for moderate to severe depression controls as only one subject met the criteria. For the methadone group, Table 12shows the correlation matrix of psychological measures was analysed. After accounting for age and dose, only trait anxiety and total BDI score significantly correlated (r = 0.93, p < 0.05).

Table 12: Correlation Matrix: Psychological measures, Methadone Group (Moderate to Severe group only). The correlations of the three components (cognitive, affective, somatic) of Beck Depression Inventory (BDI) with total Beck Depression Inventory Score (BDI) and State Anxiety (STAI), in the Methadone group with moderate to severe depression scores. Uncorrected zero-order correlations and partial correlations corrected for age and dose. *p < 0.05; **p < 0.01; ***p < 0.001.

Methadone Group (Moderate to Severe)	BDI, cog	BDI, affect	BDI, somatic	STAI, Trait
Total BDI	0.86*	0. 86*	0.58	0.84*
Partial - Age,dose	0.41	0.08	0.68	0.93*
BDI factor, cognitive		0.95**	0.10	0.75*
Partial - Age,dose		0.64	0.84	0.56
BDI factor, affective			0.12	0.64
Partial - Age,dose			-0.64	0.25
BDI factor, somatic				0.52
Partial - Age,dose				0.49

Table 13 examined the pain sensitivity correlations with psychological measures for the methadone group with moderate to severe BDI depression. Trait anxiety correlated negatively with cold pain threshold at 0 hour and 3 hour. Trait anxiety was associated with hyperalgesia to cold pain threshold.

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Table 13: Correlation Matrix: Cold Pain sensitivity and Psychological measures, Methadone (Mod-Severe only). The correlations of pain threshold and tolerance with total Beck Depression Inventory Score (BDI), the three components (cognitive, affective, somatic) BDI and State Anxiety (STAI), in the Methadone group with moderate to severe depression scores. Uncorrected zero-order correlations and partial correlations corrected for age and dose. Thres = Threshold. Tol = Tolerance. Delta = Change in Threshold or Change in Tolerance. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

Methadone (Moderate to Severe)	Pain Thres 0hr	Pain Tol 0hr	Pain Thres 3hr	Pain Tol 3hr	Delta Thres	Delta Tol
Total BDI	-0.37	0.9	-0.50	-0.35	-0.41	-0.57
Partial - Age,dose	-0.79	0.38	-0.61	0.11	0.17	-0.16
BDI factor, cognitive	-0.43	-0.04	-0.51	-0.29	-0.33	-0.30
Partial - Age,dose	-0.74	-0.39	-0.50	0.18	0.35	0.53
BDI factor, affective	-0.26	-0.06	-0.46	-0.47	-0.51	-0.49
Partial - Age,dose	-0.64	-0.68	-0.56	-0.21	-0.00	0.27
BDI factor, somatic	-0.15	0.66	-0.20	-0.09	-0.17	-0.54
Partial - Age,dose	-0.16	0.74	-0.16	0.06	-0.04	-0.51
STAI, Trait Anxiety	-0.73	0.21	-0.78[*]	-0.32	-0.40	-0.49
Partial - Age,dose	-0.88[*]	0.06	-0.76	-0.07	0.00	-0.14

A summary of the results in this chapter:

- For cold pain threshold, repeated measures ANOVA revealed no within subject effects (time: $F[1] = 0.94$, $p = 0.337$), between subject effects (group: $F[1] = 2.37$, $p = 0.132$), or interaction effects (time*group: $F[1] = 0.04$, $p = 0.836$).

- For cold pain tolerance, repeated measures ANOVA revealed no within subject effects (time: $F[1] = 2.53$, $p = 0.12$) or interaction effects (time*group: $F[1] = 0.39$, $p = 0.535$). However, there were significant between subject effects (group: $F[1] = 10.59$, $p = 0.002$), showing that the methadone group had a significantly lower cold pain tolerance than controls.

- For the methadone group, psychological measures were not generally predictive of pain sensitivity. Only the somatic component of BDI showed a significant correlation with change in tolerance from peak to trough ($r = -0.45$, $p < 0.05$), and was robust to age and dose confounders. For controls, the cognitive component of BDI was moderately correlated with pain tolerance at 3 hours ($r = 0.44$, $p < 0.05$), irrespective

of the effect of age. Cognitive factors also were moderately correlated with pain threshold at 3 hours.

- For methadone subjects with BDI scores indicative of minimal to mild depression, pain tolerance at 0 hour and 3 hours was correlated moderately with total BDI (after accounting for age and dose). Investigating the three factors of depression revealed that it was the affective component of depression that was correlated strongly with cold pain tolerance at 0 hour ($r = 0.67$, $p < 0.05$) and 3 hours ($r = 0.73$, $p < 0.05$). Both cognitive and somatic components were not significantly correlated with cold pain tolerance at any time point. Trait anxiety was also strongly correlated with cold pain tolerance at 0 hour ($r = 0.85$, $p < 0.05$) and 3 hours ($r = 0.81$, $p < 0.05$). For controls with BDI scores indicating minimal to mild depression, only the affective component of depression negatively correlated with change in pain threshold from trough to peak ($r = -0.49$, $p < 0.05$), after accounting for age.

3.5   DISCUSSION

Controls and methadone maintained patients were tested in two sessions at 0 hour and 3 hours. For the methadone group, those times corresponded with trough and peak plasma methadone concentration respectively. Analysis of the plasma samples showed a good separation of concentrations of the active R enantiomer of methadone, indicating that the two different times of testing reflect substantial differences in opioid activity. The plasma R-(-) methadone concentrations reported here were also comparable with previous research by our group (Doverty et al. 2001). Furthermore, the average methadone dose administered was consistent with typical doses encountered in maintenance treatment practise in Australia (D'Aunno and Pollack 2002).

Subjects' pain sensitivity (cold pain threshold and tolerance) were measured using the cold pressor pain test. Using this method, the results showed that the methadone group were similar in cold pain threshold scores as controls. This is comparable with results from Hay et al. 2009. His research showed similar results at 0 hours, with no difference in cold pain threshold between controls and methadone patients (controls: 12.2 ± 1.7 seconds; methadone patients: 8.9 ± 1.0 seconds). Other research by Doverty et al. (2001) reported similar cold pain threshold levels.

The methadone group in this study also exhibited lower cold pain tolerance than controls at both 0 hour and 3 hours. These results are also remarkably similar to Hay's results, where a significance difference was reported between controls and methadone maintained patients in cold pain tolerance at 0 hour (controls: 30.7 ± 3.9 seconds; methadone: 18.9 ± 1.9 seconds). As Hay only tested cold pain prior to dosing, no 3 hour time point was available for comparison. Mitchell's study also reported a slightly lower but comparable cold pain tolerance for methadone patients identified as holders and non-holders, at 0 hour. Therefore the results of this study are consistent with the previous literature that show that methadone maintenance patients are hyperalgesic to cold pain (Hay et al. 2009). Subjects were also instructed not to adopt pain coping strategies whilst undergoing the cold pressor pain task. Coping strategies may have a significant impact on a persons' performance to pain tasks (Fernandez and Turk 1989), and Zelman et al. (1991) reported that on average 2.1 coping strategies were employed by subjects undergoing the cold pressor pain task, although they were not specifically instructed to do so. The strategies were sophisticated and included breathing techniques, relaxation, imagery and cognitive control and are consistent with coping strategies classified by Fernandez (1986). Though subjects in this study were not debriefed after the cold pain task as to whether they employed coping strategies, there was no evidence to suggest a bias for either group to employ coping strategies regardless of the instructions given. Previous research reporting hyperalgesia in methadone patients did not report about coping strategies, assumedly as coping strategies were not dis-encouraged (Doverty et al. 2001; Hay et al. 2009; Krishnan et al. 2012). To the authors knowledge, this is the first time that hyperalgesia in methadone patients has been reported where subjects were instructed not to employ pain coping strategies.

Methadone patients in this study did not show significant increases in cold pain tolerance at peak plasma methadone concentrations versus trough. These results conflict with Doverty et al. (2001) who reported that cold pain tolerance of methadone maintained patients increased at 3 hours compared to 0 hours, though the increase was relatively small in magnitude. The results in this study show that at trough plasma methadone concentrations, methadone patients were not more hypersensitive to cold pain than at peak plasma methadone concentrations. There is no theoretical explanation to account for why pain thresholds and tolerances at 3 hours were significant but at 0 hour was not, other than due to inherent variability in a small sample size. Due to poor venous access, the sample size was limited to a sub-set of the methadone group which may account for the non-significant findings.

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Correlational relationships in higher order psychological constructs also showed differences between the methadone group and controls, when using a three factor component approach to depression (Buckley, Parker, and Heggie 2001). Total BDI depression score was more strongly correlated with the affective component of BDI in the methadone group than in controls. Only in the methadone group was the affective component moderately to strongly correlated with the cognitive and somatic components. These results show that affective dysfunction was the strongest predictor of total depression score in the methadone group, despite somatic items sharing overlap with typical physical effects of methadone use/withdrawal. Cognitive and somatic components were also (less) predictive of total depression score, with similar predictive power between the methadone group and controls. Trait anxiety was correlated with total BDI depression score and all three components in the methadone group, whereas trait anxiety only correlated with the cognitive component in controls. As the cognitive component was also the most predictive component of total depression score, the results suggest that cognitive processes such as pessimism self-dislike, criticism of self, and worthlessness play a particularly important role in depression and anxiety in controls. In methadone patients, affective processes such as lack of pleasure and interest, and crying may be more important in psychopathology.

For the methadone group, higher order psychological constructs were not predictive of pain sensitivity. Only the somatic component of depression was moderately negatively correlated with change in pain tolerance from trough to peak, suggesting that increasing somatic disturbance is associated with smaller increases in cold pain tolerance at peak versus trough methadone concentrations. Correlations between psychological constructs and pain sensitivity were inconclusive for controls. Trait anxiety was correlated with change in pain tolerance from trough to peak, and pain tolerance at 3 hours. Cognitive factors of depression were correlated with pain threshold and tolerance at 3 hours. As pain threshold and tolerance at 0 hour was not significantly correlated with higher order psychological constructs, the effect of trait depression or anxiety on pain sensitivity in controls was equivocal.

As the methadone group was composed of patients with a wider spread of BDI depression score than that showed by controls, both groups were split into low and high depression groups. The low depression group was composed of subjects with total BDI scores approximating minimal to mild depression and the high depression group had subjects with scores equivalent to moderate to severe depression. For the low depression group, correlations between total depression and anxiety were not evident. Affective and somatic components

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were strongly predictive of total depression score. The three components of BDI depression did not correlate with each other in the methadone group. As only one subject in the controls had a score equivalent to moderate to severe depression, correlations changed little.

The correlations between higher order psychological constructs and pain sensitivity in the low depression methadone group revealed a number of associations that were absent in low depression controls. Accounting for age and methadone dose strength in the low depression methadone patients, pain tolerance at both trough and peak time points were correlated strongly with total depression score and trait anxiety. Furthermore, the affective component of depression was the only factor that correlated with pain tolerance. The results here suggest that higher psychological function may play some role in the pain sensitivity of methadone patients with negligible to mild depression symptomology. Comparable correlations in depression/anxiety and pain sensitivity in low depression controls were not significant. Though the depression scores for controls in this study were lower, this result mirrors a number of studies that found no correlation between depression and cold pain threshold in depressed subjects when using Beck's Depression Inventory (BDI) or Hamilton Depression Rating Scale (HAMD) (Schwier et al. 2010; Lautenbacher et al. 1994).

The strength of this study that differentiates it from previous work is that controls were similar to the methadone patients on a number of demographic indices. Both groups were predominantly Caucasian and in the majority unemployed. Both groups were largely composed of tobacco smokers. Though the methadone group reported higher numbers of stimulant, marijuana, and benzodiazepine use in the last 30 days, 43% of controls identified themselves as using an illicit drug in the last month. Both groups were also similar in state and trait anxiety, and hassles and uplifts experienced in the last month. The main differences between the two groups were that the methadone group were older in age, and reported higher BDI scores.

3.6   CONCLUSION

Study 1 aimed to verify that methadone maintained patients were hypersensitive to cold pain, consistent with the literature. The results here support this, showing that methadone patients had lower cold pain tolerances than controls. Furthermore, it is unlikely that this is due to pain coping strategies. In this study, cold pain tolerance was not significantly lower for methadone

patients at trough versus peak plasma methadone concentrations (i.e at 0 hour). This is inconsistent with the literature showing methadone patients with greater cold pain sensitivity at times corresponding with trough plasma methadone concentrations. However, poor venous access may have been a contributing factor. For methadone patients with no more than mild depression scores, higher order psychological functions such as trait anxiety, total depression score or the affective component of it, were predictive of cold pain tolerance. Opioid naïve controls showed no such association. In conclusion, this study did confirm that patients maintained on methadone were overall hyperalgesic to cold pressor pain tasks, as shown previously by our group (Hay et al. 2009) and that the hyperalgesia was associated with higher order psychological function.

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CHAPTER 4 – STUDY 1 RESULTS – METHADONE AND DEPRESSION REACTIVITY (PRIMARY MEASURES)

The results of Chapter 3 have so far confirmed that methadone maintenance patients were hyperalgesic to cold pain compared to controls. This chapter will now continue the analysis of the results of study 1, investigating the impact of methadone on depression reactivity using primary measures.

4.1   INTRODUCTION

A model to conceptualise the adaptations in the body that result from repeated administration of drugs are 'drug-opposite responses' (Solomon and Corbit 1974; White 2004). Drug-opposite responses develop with sustained drug use and can provide an explanation of concepts such as tolerance and withdrawal. Within this model, tolerance is a drug-opposite response that counteracts the typical effects of the drug on the body, and withdrawal is a drug-opposite response that is unopposed when drug administration has ceased. Both tolerance and withdrawal can therefore be visualised as arising from a common set of processes that underlies them (White 2004).

Opioids are powerful analgesic and euphoric drugs (Haertzen 1966) and have significant effects on the body. Opioid effects such as decreased respiration, pupil constriction, and analgesia to (some) types of pain all fit neatly within the conventional drug-opposite model. With repeated administration the body adapts to the effects of the drug (possibly a homeostatic response). This is evident as 'tolerance', is opposite in nature and reduces the magnitude of the opioid effects. Once drug administration is ceased, this 'opposite effect' is left unopposed and results in withdrawal (White 2004).

However, certain opioid effects may not act in a simple 'drug-opposite' manner with repeated opioid administration. Therefore they may form a subset that shows an atypical response within a drug-opposite model. For example opioid dependent populations have been shown to be hyperalgesic to certain types of pain, with methadone maintenance (Doverty et al. 2001),

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buprenorphine (Compton, Charuvastra, and Ling 2001), and morphine patients (Mitchell et al. 2006) all hyperalgesic to cold pressor pain tests. Using the drug-opposite model, users should be analgesic to pain with repeated opioid administration, with the magnitude of effect reduced due to tolerance. When the drug is ceased, opposing adaptions would then be evident as withdrawal. Instead with cold pain, opioid users are hyperalgesic during drug administration. ie the drug-opposite response has dominated any opioid effect. This atypical response is conceptualised using the hyperadaptation model by White, 2004 (White 2004).

A similar pattern seems evident with mood disturbance in opioid dependent users. Methadone maintenance patients have been shown to be more mood disturbed than controls (Dyer et al. 2001), rating higher on all negative POMS scales. Methadone administration alleviated mood disturbance but not to healthy control levels. Other research consistent with this finding has shown that heroin addicts showed elevated mood dysfunction four months after starting methadone maintenance treatment (Steer and Kotzker 1980). As opioids such as methadone are euphorigenic, a conventional drug-opposite response model would suggest that dependent users would show positive mood that is diminished in magnitude due to tolerance. However as mood is disturbed in methadone patients and remains disturbed at peak plasma methadone concentrations, hyperadaptation is observed. An important point is that these observations are not perfectly analogous as cold pain was induced using the cold pressor task whereas mood was not induced using any procedure. Nonetheless both cold pain and mood seem to share mechanism that sets them apart from typical drug-opposite responding.

There is considerable research that links pain experience and emotion (Price 2000). The Anterior cingulate cortex and other classical limbic regions have been implicated in modulating the unpleasantness of pain (Rainville 2002) and emotion induction using affective salient pictures modulated pain perception in the thalamus and amygdala (Roy et al. 2009). Furthermore, the modification of pain and mood by opioids has also implicated certain brain regions (Koepp et al. 2009a; Zubieta et al. 2003). A Positron Emission Tomography (PET) study directly comparing the effects of sustained pain and sustained sadness on the μ-opioid system concluded that pain and emotion share a common psychological and neurochemical pathway (Zubieta et al. 2003; Zubieta et al. 2002). Zubieta et al. (2003) showed a deactivation of the endogenous μ-opioid system (especially in the anterior cingulate cortex) after a subject is induced into a sustained sadness state (a depressive mood). It has also been inferred that the hippocampus has an increase in endogenous μ-opioid activity when inducing a positive mood state (Koepp et al. 2009a). This research also found a correlation between the degree of

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positive mood change and endogenous opioid binding in the amygdala. Finally, opioid receptors are found to populate areas of the brain linked to affect and emotion (such as the amygdala, anterior cingulate cortex, insular cortex, etc). Both the amygdala and the ventral basal ganglia (including the nucleus accumbens and the ventral pallidum) showed similar effects under both a sustained pain and a sustained sadness challenge. Some of these systems that are activated are more typically associated with the intensity and valence of emotions, and reward and reinforcement (Morris et al. 1996; Morris et al. 1998; Anderson, Bari, and Pierce 2003; Koob et al. 1989). This research may provide a possible mechanism explaining observed hyperalgesia to pain and seemingly hypersensitivity to mood.

As pain and emotion seem inextricably linked in opioid action, and opioid dependent users exhibit heightened pain sensitivity and mood changes, then there may also be a deleterious effect on emotion with long term opioid administration. That is, long term users showing hyperalgesia to pain tasks may also show hypersensitivity to mood tasks. However, little has been done on how reactive methadone patients are to mood stimuli whilst on methadone. The sensitivity of methadone patients to tasks designed to induce an emotionally positive or negative states (such as depression) has yet to be determined. An appropriate mood task to use are mood induction procedures [such as the Velten Mood Induction procedure (Velten 1968)] as they are effective in inducing a particular affective states such as depression, for a brief period.

4.2 AIM AND HYPOTHESES

Study 1 planned to demonstrate that methadone maintained patients were more reactive to emotional stimuli than controls, when using Velten's mood induction procedure to induce a depressive state. Furthermore greater depression emotional reactivity would be evident at times corresponding with trough plasma methadone concentrations. As methadone maintained patients have been shown to be hypersensitive to cold pain (in previous studies and as shown in Chapter 3), this study also aimed to show that methadone patients hyperalgesic to cold pain were also hypersensitive to depression mood tasks.

The following hypotheses will be tested in this Chapter (with the same numbering convention used previously):

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(ii) Methadone patients will show greater depression reactivity than controls, with greatest depression reactivity at times corresponding with trough plasma methadone concentrations

(iii) Therefore within subjects, increasing plasma methadone concentrations (trough-to-peak) will reduce cold pain sensitivity (Chapter 3) and depression reactivity in methadone maintained patients to a similar degree.

The effect of methadone on depression reactivity was measured by comparing changes in VAS-Depression (VAS-D) and POMS-Depression (POMS-D) after depression induction procedures (MIPD). POMS scales may be insufficiently sensitive to measure depression reactivity, so VAS-D was the primary measure. Changes on POMS scores were considered secondary measures and are presented in Chapter 5. To determine the effect of methadone on elation reactivity, changes in VAS-Elation (VAS-E) were also analysed. The effect of methadone on elation reactivity is presented in Chapter 6.

4.3   METHOD

4.3.1   SUBJECTS

Two groups of subjects were recruited – a methadone maintenance treatment group (14 males, 7 females; aged 27-53 years), and opioid naïve controls (14 males, 7 females; aged 18-40 years). Inclusion criteria for both groups were: aged between 18 and 65, no current or previous history of psychiatric illness, not currently diagnosed with a depressive illness, no current or previous history of chronic pain, not pregnant, and not taking any medication for a psychiatric condition (such as anti-depressants and anti-psychotics) apart from benzodiazepines. The methadone maintenance treatment group was on a stable once-daily dose of methadone, having been on methadone maintenance treatment for a minimum of two weeks. Controls were recruited to be similar to the methadone group on employment status, nicotine use and 30 day recreational drug history. Preference in enrolment was also given to controls that were using non-opiate drugs (e.g. amphetamines, cannabis) on a regular basis. Controls were primarily recruited from governmental welfare assistance centres. The study was approved by the Royal Adelaide Hospital, Research Ethics Committee (#060917).

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Demographic and background information was collected at screening. A battery of tests was also administered to gauge psychological function and included the state-trait anxiety inventory (STAI-R), the state-trait anger expression inventory (STAIX-R), the Beck Depression Inventory (BDI) and the Hassles and Uplifts Scale (HSUPS).

4.3.2   PROCEDURE

For both groups, each subject attended two sessions (0 hour and 3 hours) at a drug treatment clinic. For the methadone group, 0 hour was just prior to their next daily dose and corresponded with a time when methadone was at trough plasma concentrations, while 3 hours post dose corresponded approximately with peak plasma methadone concentrations. Controls attended two sessions at similar times (at 0 hour and 3 hours) to minimise any variability due to diurnal variation in mood (Hot, Leconte, and Sequeira 2005). To counter order effects, subjects were randomised to attend either a same-day 0 hour then 3 hours session, or a 3 hours then next-morning 0 hour session.

Figure 13 outlines the procedure for study 1. At 0 hour, methadone subjects and controls rated their current emotional state on two mood Visual Analogue Scales (VAS-D for depression and VAS-E for elation), Profile of Mood States (POMS) and Subjective Opiate Withdrawal Scale (SOWS). Subjects then underwent MIP-Elation before rating their current state again using VAS, POMS, and SOWS. Subjects were then administered the MIP-Neutral procedure and rated their emotional state and SOWS. Finally subjects were administered MIP-Depression and rated their emotional state and SOWS afterwards. Subjects then were administered the cold pain pressor procedure. To conclude the 0 hour testing session, methadone subjects were dosed oral methadone as prescribed by maintenance treatment. Subjects then had a three hour break. To minimise any external circumstance-inducing mood changes, subjects stayed onsite and were provided with wildlife documentaries for viewing (selected by the researcher to have low emotional valence and arousal). Lunch was also provided during this break. The 3 hours testing session was then conducted after the three hour break. The 3 hours session followed the same structure as 0 hour, except without methadone dosing. All tests were administered by the same researcher throughout the study and with no session containing more than one subject.

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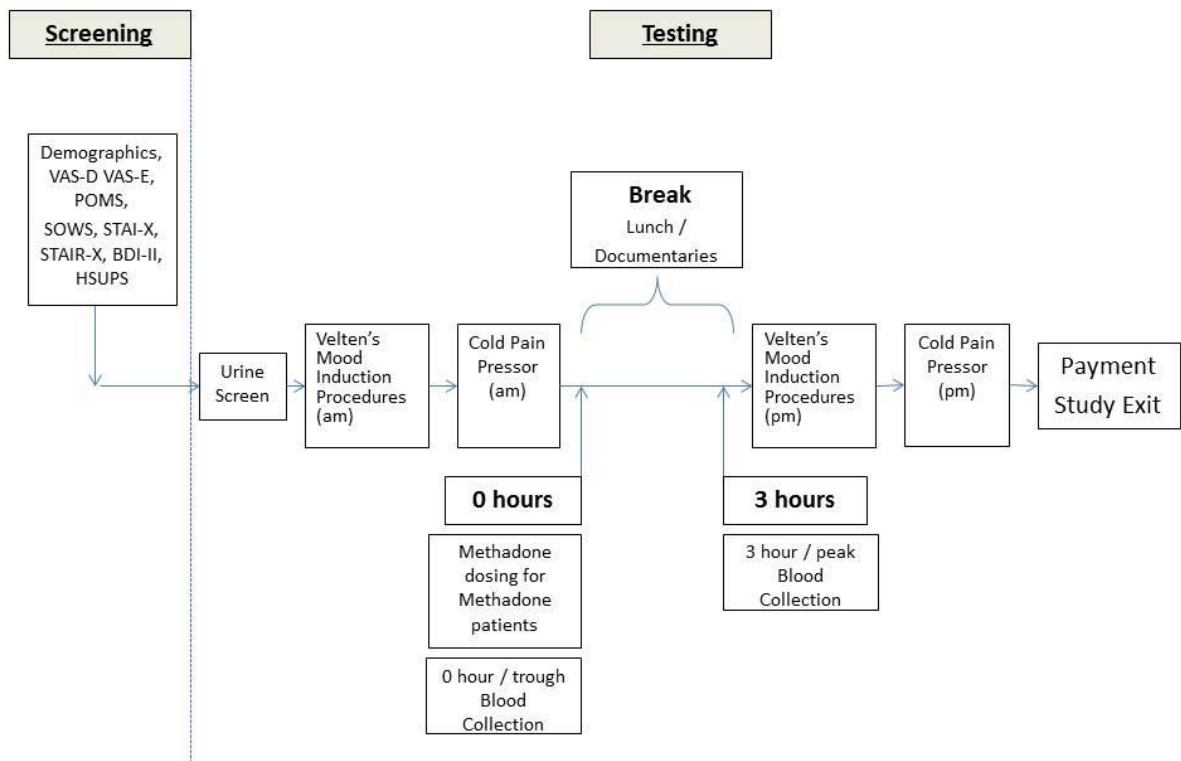
Figure 13: Study 1 procedure flow chart. The chart shows the procedure used in Study 1. At screening a battery of pen-and-paper tests were administered. The testing session was composed of 2 sessions (0 hours and 3 hours). Each session included Velten's Mood induction procedures (See Chapter 2, Figure 7), followed by Cold Pressor Pain procedures (See Chapter 2, Figure 8).

4.4   RESULTS

4.4.1   STATISTICAL ANALYSES

All analyses used an alpha level of 0.05. Data format is Mean ± Standard Error unless otherwise noted. Correlations shown were calculated using two-tailed significance levels. All data were analysed using SPSS for Windows (version 11). Repeated measures two-way ANOVA was used to assess the effect of the mood induction procedures on both groups at both session time points. The primary independent variable was depression reactivity as measured by VAS scales.

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4.4.2 DEPRESSION REACTIVITY MEASURED BY VAS-D (PRIMARY MEASURES)

There is no research known to the author that uses Velten's mood induction procedure in methadone maintained patients. As such, the effectiveness of the depression mood induction (MIP-Depression) in the methadone group and controls was first evaluated before investigating the effect of methadone on depression reactivity.

4.4.2.1 Evaluating MIPD measured by VAS-D

Spaghetti Plots

Figure 14 shows the depression (VAS-D) spaghetti plots before (pre MIPD) and after (post MIPD) depression mood induction at 0 hour and 3 hours, for each subject in the methadone group and controls. A visual inspection of the plots revealed no gross evidence that the methadone group was composed of two substantially contrasting sub-groups. A similar conclusion was drawn from the spaghetti plots for controls.
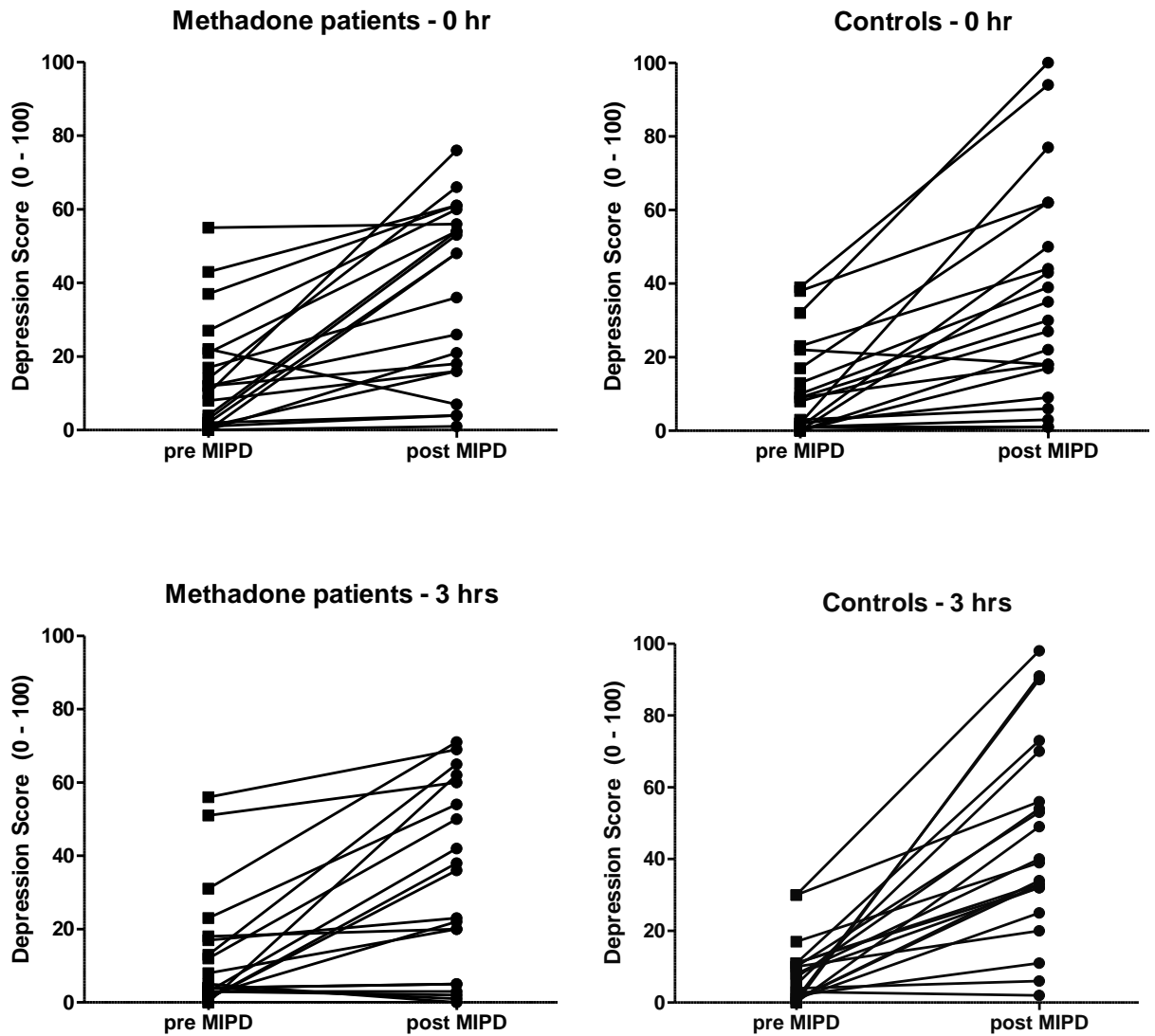
Figure 14: Spaghetti plots of depression score (VAS-D) pre- and post– depression induction. Spaghetti plots for the methadone group and controls shows the change in depression score before and after the depression mood induction task (MIPD), at 0 hour and 3 hours.

Mean Time Plots

A limitation of spaghetti plots is that subject trajectories may overlap so data features may be obscured. Therefore the effectiveness of the mood inductions was also assessed by comparing the mean VAS-D scores before and after each induction task. Figure 15 below shows the change in depression score for the methadone group and controls at 0 hour and 3 hours, before and after depression induction (MIPD). Time point 1 corresponds with pre MIPE, time point 2 with post MIPE, time point 3 with pre MIPD and time point 4 with post MIPD. The figure

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shows an increase in depression score post MIPD (as expected). Furthermore, there was a decrease in depression score post MIPE (not further analysed). As the procedure for testing was elation induction followed by depression induction, it would be expected that depression score would start at baseline (time 1), show a decrease in score due to the elation induction (time 2), increase in score as the effects of elation induction diminish (time 3), and then increase in score again due to the depression induction (time 4). This pattern would visually resemble a 'valley' in shape in a time series plot. Both groups at both time points showed this visual pattern with the most pronounced 'valley' shape for controls at 0 hour. Finally the mean scores fall comfortably within the lower (0) and upper bounds (100) of the scale, and together with the spaghetti plots suggest no indication of floor or ceiling effects.
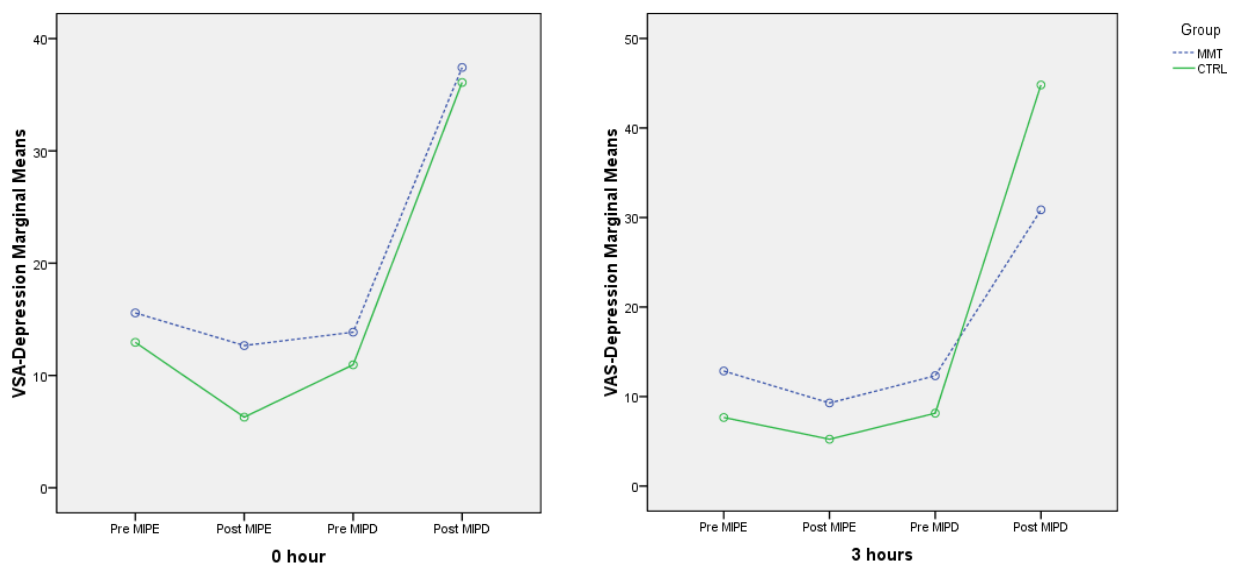
Figure 15: Mean time plots for Depression score (VAS-D). Plots show VAS-D at 0 hour and 3 hours at pre MIPE, post MIPE, pre MIPD and post MIPD. Plots show mean changes in depression score throughout the mood induction procedures, in the order that the measures were taken.

4.4.2.2 Effectiveness of MIPD measured by VAS-D

As Figure 15 shows that the depression task was effective in inducing depression in both groups at 0 hour and 3 hours, the figures were re-formatted to remove reference to the elation induction task on depression score as it is not of primary interest. Re-formatting the figure in this manner will aid the presentation of the effect of methadone on depression reactivity later in this chapter. Figure 16 shows the depression (VAS-D) scores for the methadone group and controls at 0 hour, before and after MIPD. This re-formatted figure shows the methadone

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group and controls showed higher depression scores after depression induction (methadone group depression before MIPD 13.9 ± 3.4, methadone group depression after MIPD 37.4 ± 5.2, paired samples p < 0.01; controls depression before MIPD 11.0 ± 2.8, control depression after MIPD 36.1 ± 6.4; paired samples p < 0.01).
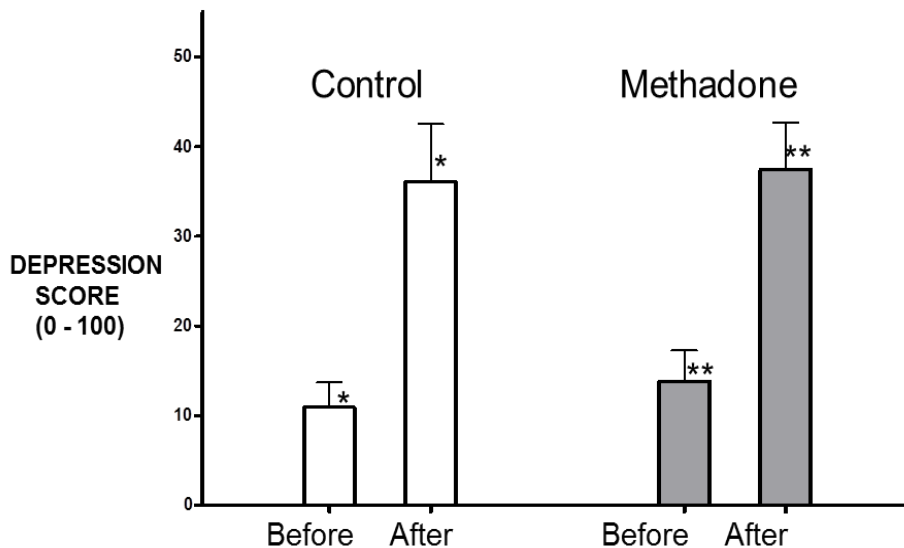
Figure 16: 0 hour emotional state (VAS-D) scores before and after MIP-Depression. Depression induction was successful for both groups at 0 hour (*controls, p < 0.01; **methadone group, p < 0.01). Methadone group, n = 21; controls, n = 21. Bars show mean ± se.

4.4.2.3 Depression Reactivity measured by Change in VAS-D

Depression reactivity was calculated as the difference between post-induction emotional state and pre-induction emotional state. Figure 17 shows depression reactivity (post-induction depression score – pre-induction depression score) of methadone and control groups at 0 hour and 3 hours. Repeated measures two-way ANOVA for change in depression score (depression reactivity) showed the methadone group had a significant decrease in change in depression reactivity 3 hours compared to controls, due to MIPD (methadone group depression reactivity 0 hour 23.6 ± 5.0, controls depression reactivity 0 hour 25.1 ± 5.0; methadone group depression reactivity 3 hours 18.5 ± 4.6, controls depression reactivity 3 hours 36.7 ± 5.7; p = 0.021). The decrease in depression reactivity was still significant when including BDI (p = 0.008) or age (p = 0.023) as covariates in the model. With both covariates in the one model, significant time*group interactions showed that depression reactivity was significant (repeated measures ANOVA, $F_{(1)}$ = 7.85, p = 0.008; with covariates in model BDI=12.5, age

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= 31.88: methadone group depression reactivity 0 hour 25.0 ± 6.2, controls depression reactivity 0 hour 23.7 ± 6.2; methadone group depression reactivity 3 hours 14.2 ± 6.3, controls depression reactivity 3 hours 41.0 ± 6.3).
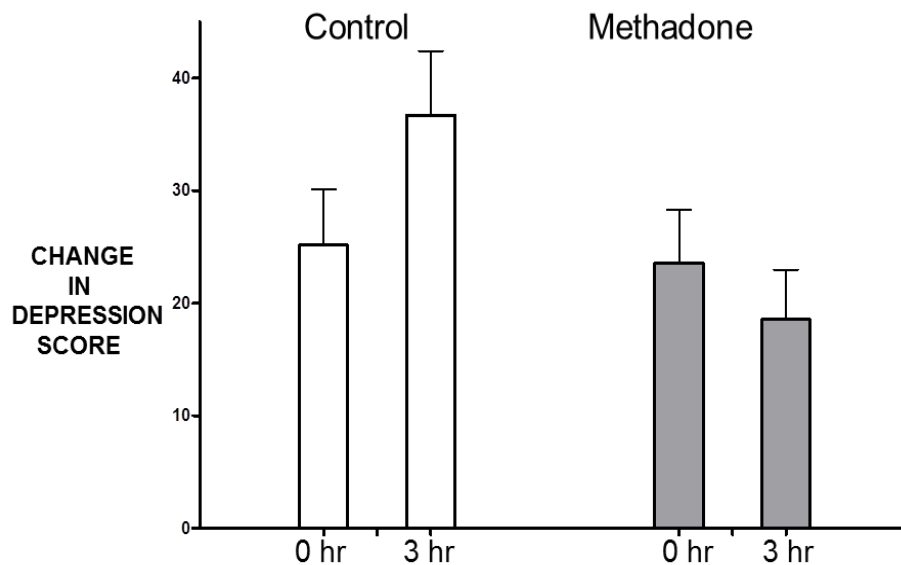
Figure 17: Change in depression scores (depression reactivity). Results show a significant decrease in change in depression scores (depression reactivity) in the methadone group at 3 hours compared to controls (p = 0.02). Bars show mean ± se.

The results showed that on primary measures, the methadone group showed a decrease in depression reactivity at 3 hours versus 0 hour, compared with controls. This effect was regardless of covariates such as age and BDI.

4.4.2.4 Correlations between Depression Reactivity and Methadone

Table 14 shows the correlations between change in depression reactivity (as measured by VAS) and methadone concentrations [as measured by change in R-(-), S-(+) plasma methadone concentrations, or methadone dosage]. Change in R-(-) plasma methadone concentration from 0 hour to 3 hours was not significantly correlated with a depression reactivity (r = -0.183, p = 0.53).

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Table 14: Correlations: Methadone vs depression reactivity.

		change in depression reactivity
ΔR-methadone	r	-0.183
	sig	0.530
	df	14
ΔS-methadone	r	-0.238
	sig	0.413
	df	14
Methadone Dose	r	-0.252
	sig	0.270
	df	21

Table 15 shows the correlations between depression reactivity and methadone concentrations or dose, controlling for BDI and Age. Changes in plasma R-(-) methadone concentrations from 0 hour to 3 hours was not significant, though the effect size was moderate ($r = -0.502$, $p = 0.096$). A significant correlation would suggest that increasing plasma methadone concentrations are associated with blunting of depression reactivity. i.e. larger changes in plasma concentrations would be associated with smaller (or negative) changes in depression reactivity. Methadone dose was moderately negatively correlated with change in depression reactivity, approaching significance ($r = -0.434$, $p = 0.063$). This suggests that higher methadone doses may be associated with a smaller change (blunting) in depression reactivity. Non-significant correlations may have been a function of an insufficient sample size.

Table 15: Partial correlations (controlling for BDI and Age) methadone vs depression reactivity.

Control Var			change in depression reactivity
Total BDI	ΔR-methadone	r	-0.502
& Age		sig	0.096
		df	10
Total BDI	ΔS-methadone	r	-0.524
& Age		sig	0.080
		df	10
Total BDI	Methadone Dose	r	-0.434
& Age		sig	0.063
		df	17

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4.5 DISCUSSION

In summary, methadone subjects and controls were induced into a depressive state, with both groups showing similar depression reactivity to induction at 0 hour (pre dose methadone). The aim was to demonstrate that methadone maintenance patients exhibit a larger increase in emotional disturbance than control, when challenged on the same mood inducing tasks. However 3 hours post dose, methadone subjects showed less emotional reactivity to depression induction on primary measures (VAS-D), contradicting hypothesis (ii).

After undergoing depression induction, methadone subjects at 0 hour (pre dose methadone administration, corresponding with trough methadone plasma concentrations) showed a similar increase in depressive state compared to controls. This illustrates two points - the induction techniques were effective for both groups, and that there was no evidence of a difference in magnitude of effect between the methadone group and controls at pre dose. In comparison with other research, the level of depression induction seen here is comparable (Zelman et al. 1991)(Bates, Thompson, and Flanagan 1999). Zelman et al. (1991) investigated the effect of Velten elation and depression induction on cold pain sensitivity, reporting a change of 6.4 ± 7.3 (mean ± SD) in Mood adjective Checklist (MACL) depression score after MIPD. As MACL is a 20-point scale, this equates approximately to a VAS score change of 32. Those results are comparable with the effect of depression induction in this study. Bates et al. (1999) used a reduced set of 30 Velten statements to induce depression and also reported a VAS score change of 32. Therefore, at the time of trough plasma methadone concentration, there was no difference in the depression reactivity of methadone maintained subjects compared to controls. The author is unaware of other research that shows the effectiveness of mood induction procedures in methadone maintained patients. Though the effectiveness of mood induction on control subjects has been well researched, the author is unaware of any research that investigates the effectiveness of these techniques on controls drawn from a sample that (apart from opioid use) was well-matched with methadone maintenance patients on a number of key demographics such as drug history and employment status.

The effect of the change in methadone concentration on the depression reactivity of methadone subjects was measured by comparing the relative effects of the induction procedures in both groups at pre dose (trough plasma methadone concentrations) and post

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dose (peak plasma methadone concentrations). Such a comparison revealed that the methadone group showed a decrease in depression reactivity at peak methadone concentrations compared with controls, as measured by primary measures (VAS). Furthermore, these results were robust to possible confounders such as BDI score or age. Moderate correlations suggest that larger changes in plasma methadone concentration or higher methadone doses may be associated with more severe blunting of depression reactivity, though the findings were not significant and under-powered. As a change in methadone concentration is the most straightforward explanation for why there was a change in depression reactivity at trough and peak methadone dose, further research may be fruitful in showing that larger changes in plasma concentrations are associated with smaller changes in depression reactivity. i.e. larger blunting in depression reactivity is evident. Ensuring subjects have good venous access before participating in research would be necessary. Typical of psychological measures, depression reactivity shows considerable variability between subjects. Future research should ensure a sufficient sample size to determine the exact relationship between emotional reactivity and changes in plasma methadone concentrations.

Previous research by Dyer et al. (2001) has showed pronounced disturbed mood state in methadone patients prior to methadone dose that was alleviated somewhat after methadone administration, as predicted by the hyperadaptation model (White 2004). The results of this study showed that depression reactivity does not fit within this framework and may better be placed within the conventional 'drug-opposite' response framework. A plausible explanation for the divergent results is that this study measured emotional reactivity whereas Dyer measured emotional appraisal (how you feel 'at the moment'), a related but distinct component involved in emotion/mood processing. Different brain regions are implicated with the amygdala identified as a particularly important region in emotional appraisal (LeDoux 1996; Adolphs and Tranel 2004) and the thalamus important for emotional reactivity processes (Orchinik et al. 1949). The results of this study also conflict with findings from related research showing a dysregulation of emotion processing when heroin users were shown pleasant and unpleasant stimuli (Aguilar de Arcos et al. 2008). These heroin polysubstance users showed more emotional responsiveness when shown negative stimuli (eg. mutilation imagery). The reason for the discrepancy between our results and that study is again likely to be procedural: this study tested emotional reactivity with subjects active in changing their mood with the help of appropriate emotional stimuli whereas the Aguilar de Arcos study measured emotional response with subjects staring at images passively. This is an

important distinction as it is more accurate to say that Aguilar tested emotional appraisal, which involves the processing of emotional stimuli.

This research suggests that methadone may blunt depression reactivity following an increase in plasma methadone concentration. As the methadone group showed similar depression reactivity to controls at trough methadone concentrations, it may be that regular opioid use has resulted in tolerance to any observable opioid effects on mood at trough methadone concentrations. Nonetheless, blunted depression reactivity at peak plasma methadone concentrations suggests that complete tolerance had not developed to this opioid effect. This is consistent with previous research demonstrating a range of physiological and psychological effects with increasing plasma methadone concentrations, including decreased pupil diameter and respiration rate, increased threshold/tolerance to specific types of pain (Dyer et al. 1999) and lesser mood disturbance (Dyer et al. 2001).

Generally, these results indicate that long-term substance abusers may use opioids in a manner analogous to antidepressants, and that it is the relief from emotionally painful experiences that may (along with opioid withdrawal relief) be a desired outcome of opioid abuse (as opposed to any pleasurable effects). This conclusion is supported by animal studies using learned helplessness/forced swim/social separation models that show that μ-opioid agonists increase antidepressant-like behaviour (Rojas-Corrales et al. 2002b; Fichna et al. 2007; Warnick, McCurdy, and Sufka 2005).

4.6 CONCLUSION

Study 1 aimed to demonstrate that methadone maintained patients are hyper-sensitive to depression inducing tasks and hyperalgesic to cold pressor pain. Though Chapter 3 showed that methadone patients were shown to be hyperalgesic to cold pain, they were not hypersensitive to emotion tasks as hypothesised. Instead methadone patients showed an opposite response, demonstrating blunted reactivity to mood induction tasks. The next chapter will further explore the effect of methadone on depression reactivity and global negative reactivity using secondary measures (POMS scales).

CHAPTER 5 – STUDY 1 RESULTS – METHADONE AND DEPRESSION EMOTIONAL REACTIVITY (SECONDARY MEASURES)

5.1 INTRODUCTION

There are a number of methods to measure emotion. For example, indirect instruments measure the expressive (eg smiling, frowning, facial action units) or physiological components of emotion (eg acoustic startle response, heart rate, skin conductance). The most widely used method though is verbal and non-verbal self-report. This is widely regarded as the preferred method by researchers as emotions are a subjective experience so some reflection from the participant is preferred. Non-verbal self-report instruments may use pictograms to represent emotional responses but may suffer from reduced specificity. Verbal self-report instruments are more naturalistic and can be used to measure mixed emotional states, however applicability across cultures may be problematic. Examples of verbal self-report instruments to measure emotion/mood are Visual Mood Analogue Scales (VAS) (Aitken 1969), Multiple Affect Adjective Check List (MAACL) (Zuckerman and Lubin 1965), Positive Affect-Negative Affect Scale (PANAS) (Watson, Clark, and Tellegen 1988), and Profile of Mood States (POMS) (McNair et al. 1971).

Visual Mood analogue scales have been shown to have moderate correlations with other scales that use verbal self-report (Stern et al. 1991), such as the Depression Adjective Checklist (r = 0.81) and the Profile of Mood States Depression-Dejection (r = 0.51). The VAS was administered to university students and was bipolar, with sad and happy as the anchors on the same scale. Unipolar VAS (similar to that used in study 1) showed correlation coefficients between VAS and POMS of between r = 0.33 to 0.66 (Stern et al. 1997).Subjects scoring significantly more sad on the VAS also scored significantly more depressed on the POMS in pain patients (House et al. 2012).

Profile of Mood States (POMS) is a 65-item scale that measures a subject's transient mood state along six dimensions (anger-hostility, depression-dejection, confusion-bewilderment, fatigue-inertia, vigour-activity, tension-anxiety). A composite score derived from the six

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dimensions also provides a global mood indicator. Devised to measure mood over a short period of time (default is 'the last week, including today'), the scale can also be used to self-report mood 'in the moment' (using the 'RIGHT NOW' setting). POMS is a 5 point scale with raters indicating the severity/frequency of their feelings from 'Not at all' (scored as 0) to 'Extremely' (scored as 4).

The six POMS dimensions are composed of between 7 and 15 items. Anger-Hostility is composed of 12 items that represent a mood of anger and antipathy towards others, including intense overt anger to milder feelings of hostility. Tension-anxiety is composed of nine items that describe heightened musculoskeletal tension. Including in this dimension are somatic tension that may not be observable, restlessness, and generalised states of discomfort or anxiety. Fatigue-Inertia is composed of seven items that represent feelings of low energy and weariness. Vigour-Activity is composed of eight items, representing high energy. It is the only factor negatively related to the other POMS dimensions and resembles a form of positive affect (though not necessarily happiness). Vigour-activity and Fatigue-Activity have been shown to be independent factors (McNair et al. 1971). Confusion-Bewilderment is composed of 8 items, defined by feelings of uncertainty and bafflement. Finally Depression-Dejection is the dimension with the largest number of items. The 15 items characterise feelings of inadequacy, depression, unworthiness, futility, emotional isolation, sadness and guilt. A Total Mood Disturbance (TMD) score can also be derived from the six dimensions measured by POMS. The summation of Anger-Hostility, Depression-Dejection, Confusion-Bewilderment, Fatigue-Inertia and Tension-Anxiety, with Vigour-Activity subtracted, provides an estimate of global affective state. Higher scores indicate a more dysphoric mood state.

The Profile of Mood States has been used extensively in research. A number of studies have shown its utility in measuring the effect of emotion-inducing conditions, for example anxiety inducing films (Pillard and Fisher 1967) and anxiety inducing situations (Pillard and Fisher 1970). and depression induction (Pomerleau et al. 2004). POMS have also been used in drug studies to determine the impact of drugs on affective state. Relevant studies have shown that opioid maintenance patients have POMS scores different to controls, and that opioid administration has an additional effect on those scores (Dyer et al. 2001; Mitchell et al. 2004; Mitchell et al. 2006).

Previous results from study 1 (Chapter 4) showed that methadone maintenance patients were less reactive than controls to depression induction measured by visual analogue scales at 3

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hours. This suggests that methadone blunts depression reactivity. This chapter will also test the original hypothesis that methadone patients will show greater depression reactivity compared with controls, measured with POMS. However it is expected that POMS scales will show a similar pattern of response as VAS scores in chapter 3.

5.2   AIM and HYPOTHESES

The aim of this chapter is to continue investigating the effect of methadone on negative state, using POMS scales (secondary measures). The following hypotheses will be tested (with the same numbering convention used previously):

> (ii) Using secondary measures, methadone patients will show greater depression reactivity than controls, with greatest depression reactivity at times corresponding with trough plasma methadone concentrations.

> (iii) Therefore within subjects, increasing plasma methadone concentrations (trough-to-peak) will reduce cold pain sensitivity (Chapter 3) and depression emotional reactivity in methadone maintained patients, as measured by secondary measures.

The effect of methadone on depression reactivity was measured by comparing changes in POMS-Depression (POMS-D) within subjects. Though changes in POMS-Total Mood Disturbance (POMS-TMD) did not specifically measure depression reactivity, it did indicate global negative emotional impact. Therefore it was also appropriate as a measure that indicated negative emotional reactivity.

5.3   RESULTS

5.3.1   STATISTICAL ANALYSES

All analyses used an alpha level of 0.05. Data format is Mean ± Standard Error unless otherwise noted. Correlations shown were calculated using two-tailed significance levels. All data were analysed using SPSS for Windows (version 11). Repeated measures two-way ANOVA was used to assess the effect of the mood induction procedures on both groups at

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both session time points. The independent variables were depression emotional reactivity as measured by POMS-D and total negative reactivity as measured by POMS-TMD.

5.3.2 DEPRESSION REACTIVITY MEASURED BY POMS (SECONDARY MEASURES)

As a secondary measure to assess the impact of methadone on depression reactivity, Profile of Mood States (POMS) were measured pre and post mood induction procedures at 0 hour and 3 hours for both the methadone group and controls. The subscales of POMS-Depression (POMS-D) and POMS-Total mood disturbance (POMS-TMD) were then used as secondary measures to measure the effect of methadone on depression and total negative disturbance respectively.

5.3.2.1 Evaluating MIPD measured by POMS-D

Spaghetti Plots

Figure 18 shows the depression (POMS-D) spaghetti plots before (pre MIPD) and after (post MIPD) depression induction at 0 hour and 3 hours, for each subject in the methadone group and controls. A visual inspection of the plots revealed that within the methadone group, there was no evidence there were two substantially different sub-groups. A similar conclusion was drawn from the spaghetti plots for controls. However as the plot of the methadone group appeared different to controls, it was analysed further.

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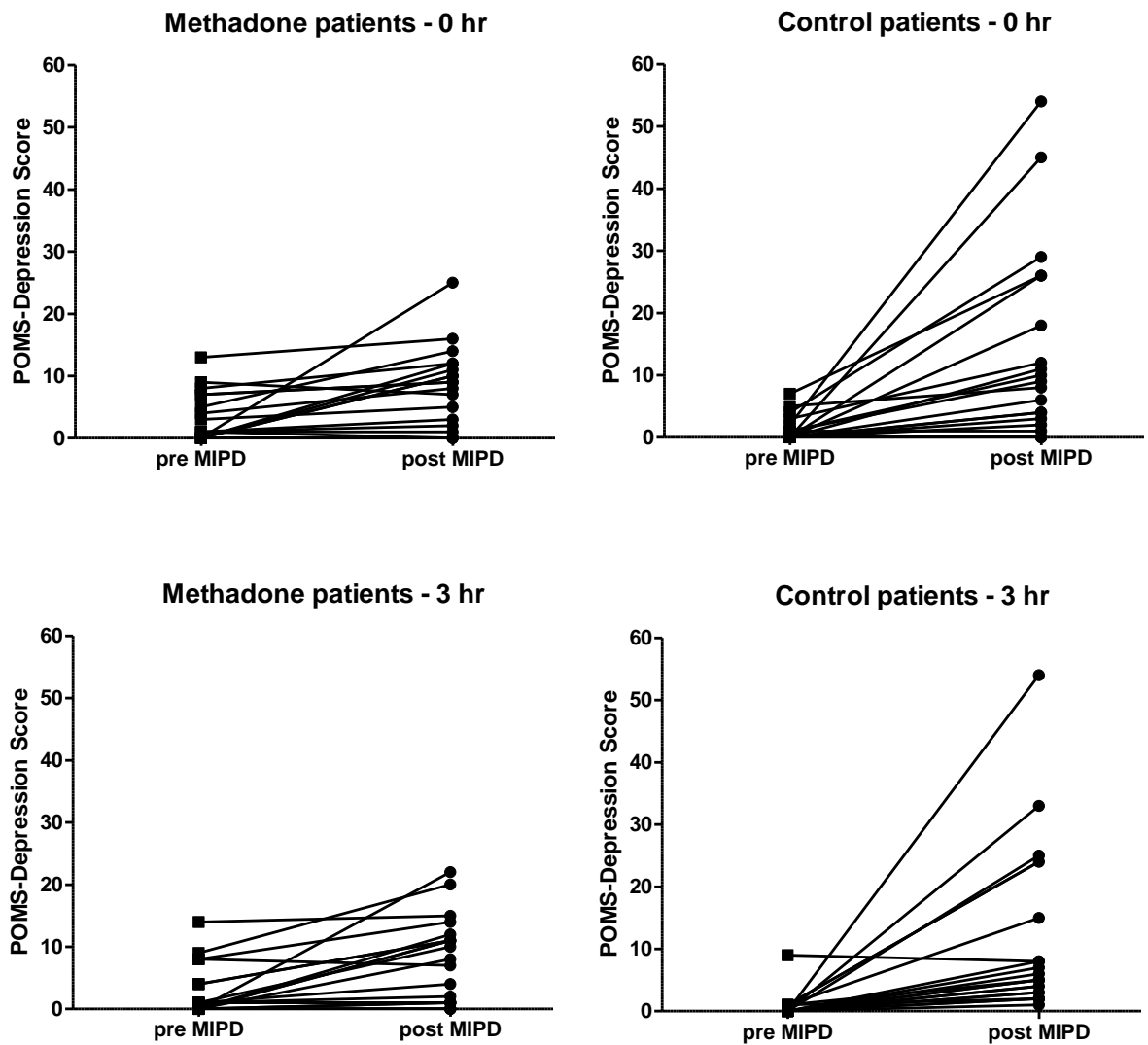
Figure 18: Spaghetti plots of depression score (POMS-D) pre and post depression induction. Spaghetti plots for the methadone group and controls at 0 hour and 3 hours.

Mean Time Plots

First the effectiveness of the mood induction procedure for depression as measured by POMS-D was evaluated for both groups. The following time plots (Figure 19) show the effect of elation and depression mood induction on POMS-D scores. Similar to VAS-D results, it was expected that the time plots would visually resemble valleys. The figures below show that elation induction had a minor impact on POMS-D, however POMS-D scores did increase after MIPD. To allow comparisons between the POM-D scores of the subjects in this study with previous studies in the literature, scores pre MIPE were used (i.e. prior to any mood induction tasks that session). Methadone POM-D scores at 0 hour were 4.1 ± 1.1 and at 3 hours were 3.1 ± 1.0. Controls POM-D scores at 0 hour were 2.5 ± 1.0 and at 3 hours were 1.2 ± 0.4. In comparison, Dyer et al. (2001) reported POMS-D for methadone patients at

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approximately threefold higher at 0 hour and about equivalent at 3 hours, than methadone subjects in this study. However, when differentiated by 'holders' versus 'non-holders', POMS-D for 'holders' at 0 hours were comparable with the results of this study. Normative POMS-D scores for adults have been reported as 8.0 (sd = 9.3) (Nyenhuis et al. 1999). As subjects were not asked whether they felt their dose 'held', holder status could not be ascertained in this study.
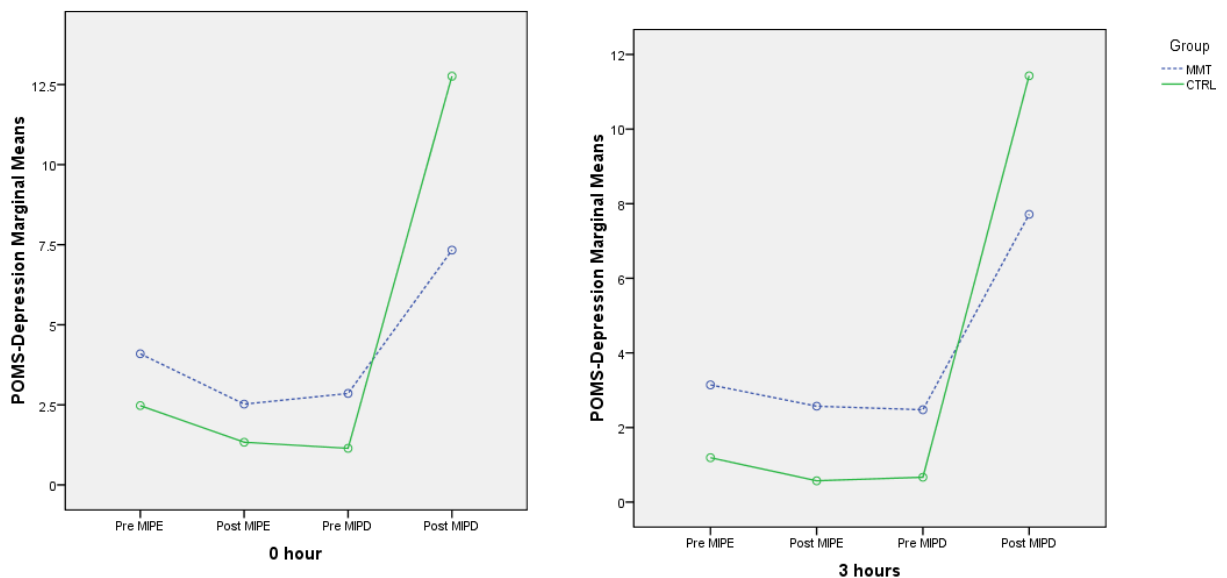
Figure 19: Mean time plots for Depression score (POMS-D). Plots show POMS-D at 0 hour and 3 hours at pre MIPE, post MIPE, pre MIPD and post MIPD. No outlier has been deleted.

5.3.2.2 Depression Reactivity measured by Change in POMS-D

Change in POMS-D (depression reactivity) after MIPD was measured by comparing the difference in POMS-D after depression induction compared to before induction. Repeated measures ANOVA showed no difference in within subject effects (time: $F[1] = 0.002$, $p = 0.976$) or interaction effects (time*group: $F[1] = 0.50$, $p = 0.484$). However, between subject effects approached significance (group: $F[1] = 3.98$, $p = 0.053$). Figure 20 illustrates that the methadone group showed a significantly smaller change in POMS-D (estimated group mean: 4.9 ± 2.8) compared with controls (11.2 ± 2.8).

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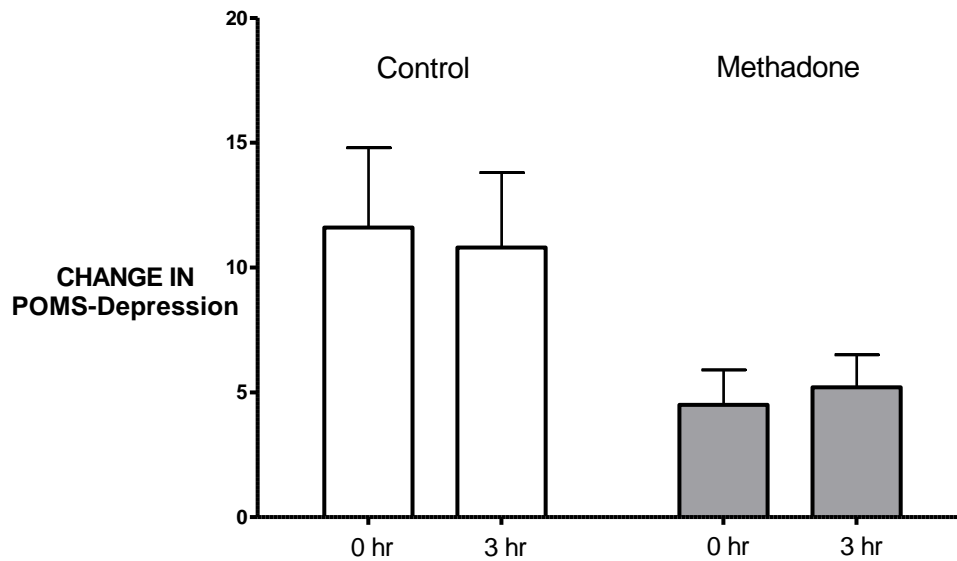
Figure 20: Change in POMS-Depression after MIP-Depression induction. After MIPD, change in POMS-Depression score for the methadone group approached significant difference (p = 0.053), compared with controls. Bars show mean ± standard error.

As the two groups differed in BDI and age, both variables were added as covariates into the model (Figure 21). There were no within subject effects (time: $F[1] = 1.96$, $p = 0.169$) or interaction effects (time*group: $F[1] = 0.61$, $p = 0.441$). However the between subject effects were significant (group: $F[1] = 6.58$, $p = 0.014$). Estimated group means showed that the methadone group had a significantly smaller increase in POMS-D (estimated group mean: 2.1 ± 2.8) than controls (estimated group mean: 14.0 ± 2.8). Estimated means at each time*group point with BDI and age as covariates were: change in POMS-D for controls at 0 hour, 13.3 ± 3.2; change in POMS-D for controls at 3 hours, 14.6 ± 2.8; change in POMS-D for methadone at 0 hour, 2.8 ± 3.2; change in POMS-D for methadone at 3 hours, 1.4 ± 2.8). The pattern of results using POMS-D was similar to the pattern for depression reactivity measured by VAS-D.

Figure 21: Estimated marginal means of POMS-Depression with age and BDI added as covariates. After MIPD, the methadone group showed a significantly smaller (p = 0.014) change in POMS-Depression score compared with controls*. Covariates appearing in the model are evaluated at the following values: age = 31.88, total BDI = 12.50. Bars show mean ± standard error.

5.3.2.3 Evaluating MIPD measured by POMS-TMD

Spaghetti Plots

Figure 22 shows the Total Mood Disturbance (POMS-TMD) spaghetti plots before (pre MIPD) and after (post MIPD) depression induction at 0 hour and 3 hours, for each subject in the methadone group and controls. A visual inspection of the plots revealed no gross evidence that the methadone group was composed of two substantially contrasting sub-groups. A similar conclusion was drawn from the spaghetti plots for controls.

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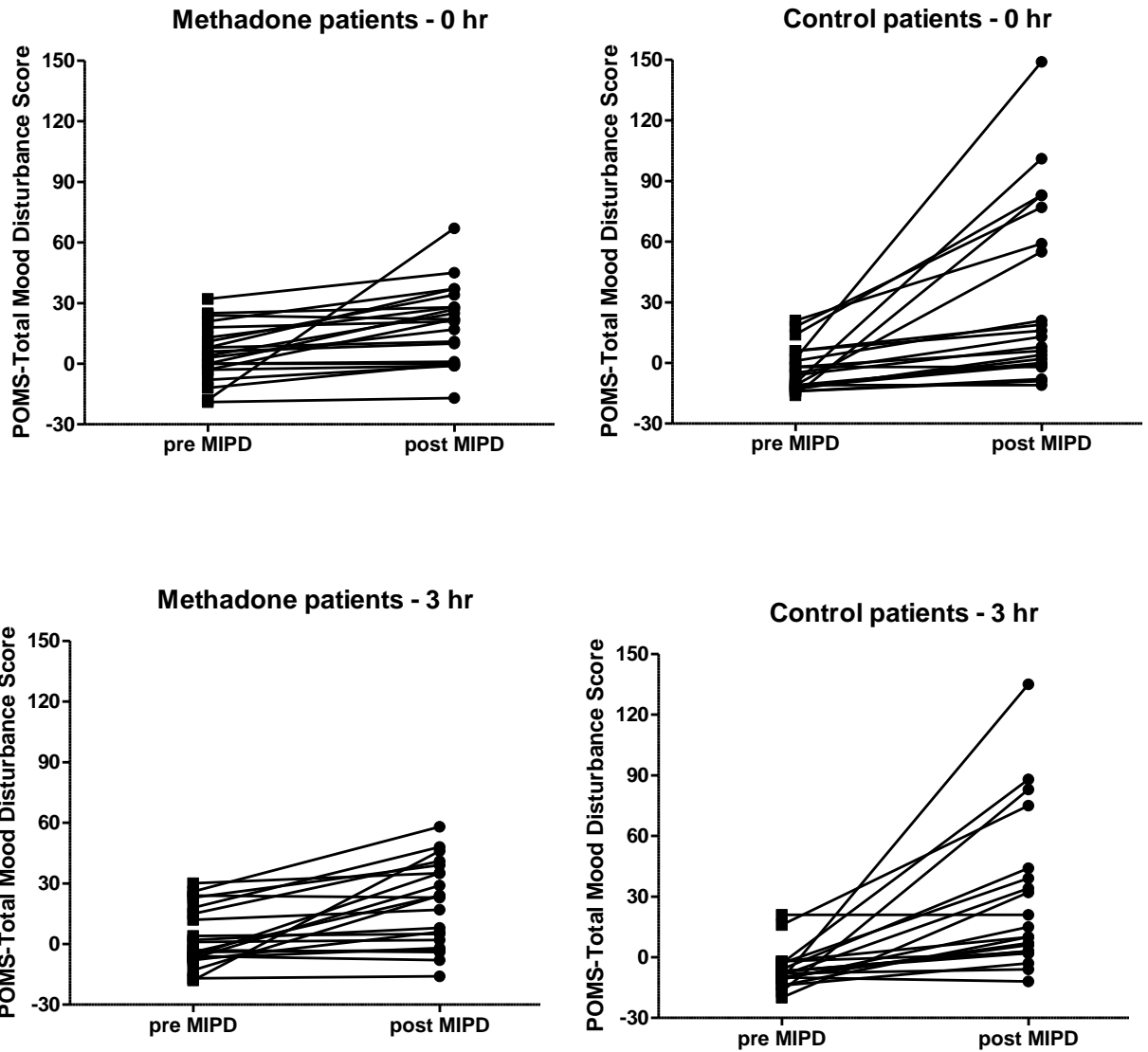
Figure 22: Spaghetti plots of Total Mood Disturbance score (POMS-TMD) pre and post depression induction. Spaghetti plots for the methadone group and controls at 0 hour and 3 hours.

Mean Time Plots

The following time plots show the effect of elation and depression mood induction on POMS-total mood disturbance (POMS-TMD) scores. The figures below (Figure 23) show that total mood disturbance scores decrease after elation induction, and then increased after depression induction. For comparison work with previous studies in the literature (Dyer et al. 2001; Mitchell et al. 2006; Nyenhuis et al. 1999), Pre MIPE POM-TMD scores for the methadone group and controls were determined: Methadone group POM-TMD scores at 0 hour were 10.1 ± 3.7 and at 3 hours were 7.8 ± 3.4. Controls POM-D scores at 0 hour were -0.1 ± 3.4 and at 3 hours were -1.7 ± 2.2. Dyer et al. (2001) reported POMS-TMD scores for methadone patients

as significantly higher (approximately 60 at 0 hours). However 'holders' scored POMS-TMD only slightly higher than this study. Controls scored a POMS-TMD lower than this study. Mitchell et al. (2006) reported lower POMS-TMD scores for methadone patients in a study comparing subjects on methadone and morphine. A methadone group composed of equal numbers of 'holders' and 'non-holders' reported a POMS-TMD score of about 28 at 0 hour. Normative POMS-TMD scores for adults have been reported as 17.7 (sd = 33) (Nyenhuis et al. 1999).
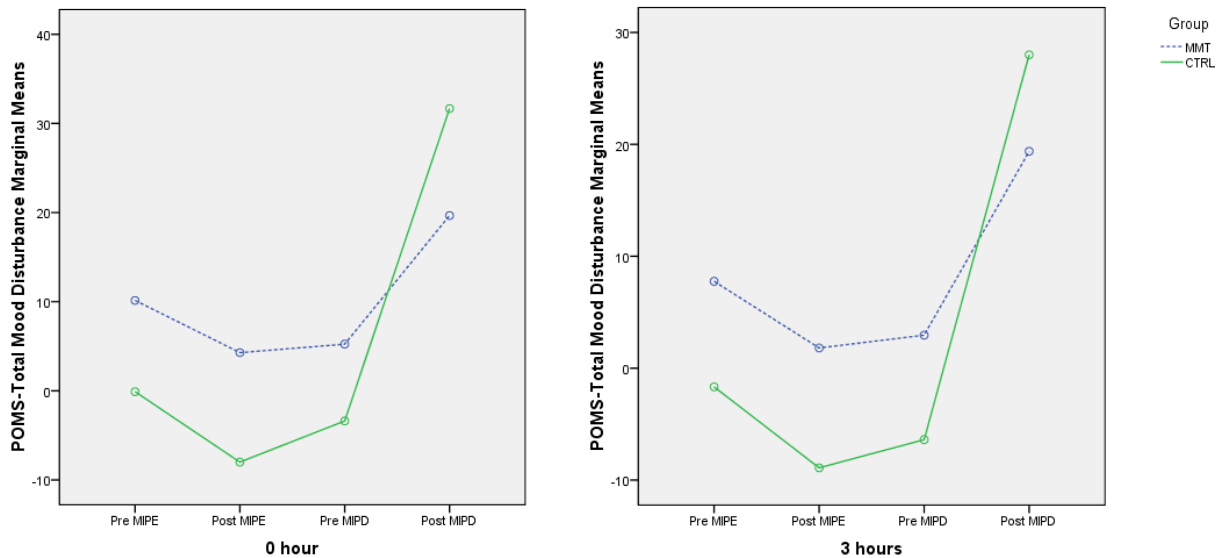
Figure 23: Mean time plots for Total Mood Disturbance score (POMS-TMD). Plots show POMS-TMD at 0 hour and 3 hours at pre MIPE, post MIPE, pre MIPD and post MIPD. No outlier has been deleted.

5.3.2.4 Depression Reactivity measured by Change in POMS-TMD

Change in POMS-TMD (total negative reactivity) after MIPD was measured by comparing the difference in POMS-TMD after depression induction compared to before induction. Repeated measures ANOVA showed that there were no within subject effects for time (time: $F[1] = 0.04$, $p = 0.84$) or any interaction effects (time*group: $F[1] = 0.17$, $p = 0.687$). However significant between subject effects ($F[1] = 4.58$, $p = 0.039$) show that the two groups on average were different (estimated means methadone POMS-TMD: 15.4 ± 6.4; estimated means controls POMS-TMD: 34.7 ± 6.4). See Figure 24.
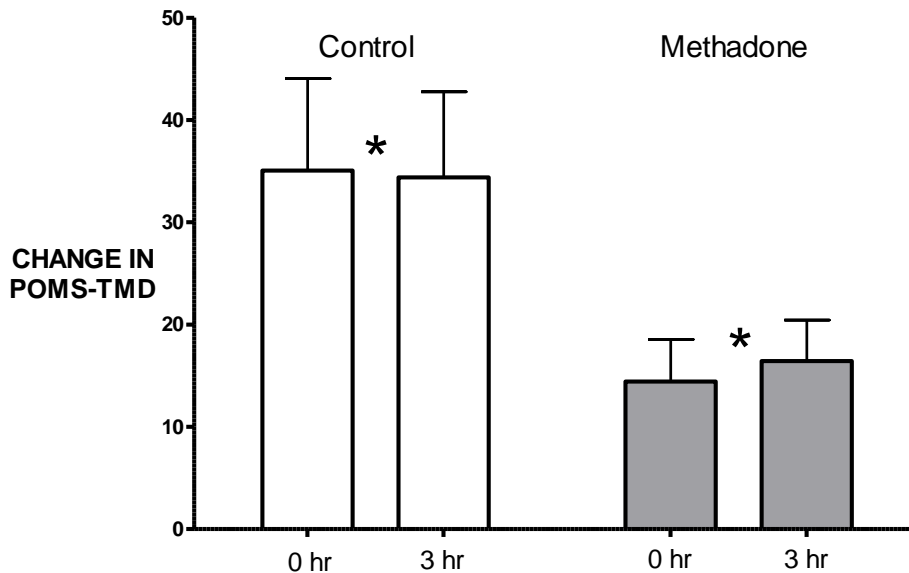
Figure 24: **Change in POMS-TMD after MIP-Depression induction.** After MIPD, the methadone group had a significantly smaller change in POMS-Total Mood Disturbance score than controls (p = 0.039)*. Bars show mean ± standard error.

Age and BDI were also added as covariates into the model. For within subject effects, there was an interaction effect between time*BDI (F[1] = 4.30, p = 0.045), but not for time*group (F[1] = 1.91, p = 0.175). More importantly and similar to the analysis without the covariates added, there were significant between subject effects (group: F[1] = 5.95, p = 0.019). Overall estimate group means showed that the methadone group had a smaller change in POMS-TMD (8.87 ± 8.03) than controls (41.3 ± 8.0). Figure 25 shows the estimated means at each time*group point (with BDI and age as covariates: change in POMS-TMD for controls at 0 hour, 37.8 ± 9.0; change in POMS-TMD for controls at 3 hours, 44.8 ± 8.0; change in POMS-TMD for methadone at 0 hour, 11.7 ± 9.0; change in POMS-TMD for methadone at 3 hours, 6.0 ± 8.0). Though the direction of change in POMS-TMD was similar to both the pattern measured using POMS-Depression or VAS depression scores, there was no significant interaction effect (p > 0.05).

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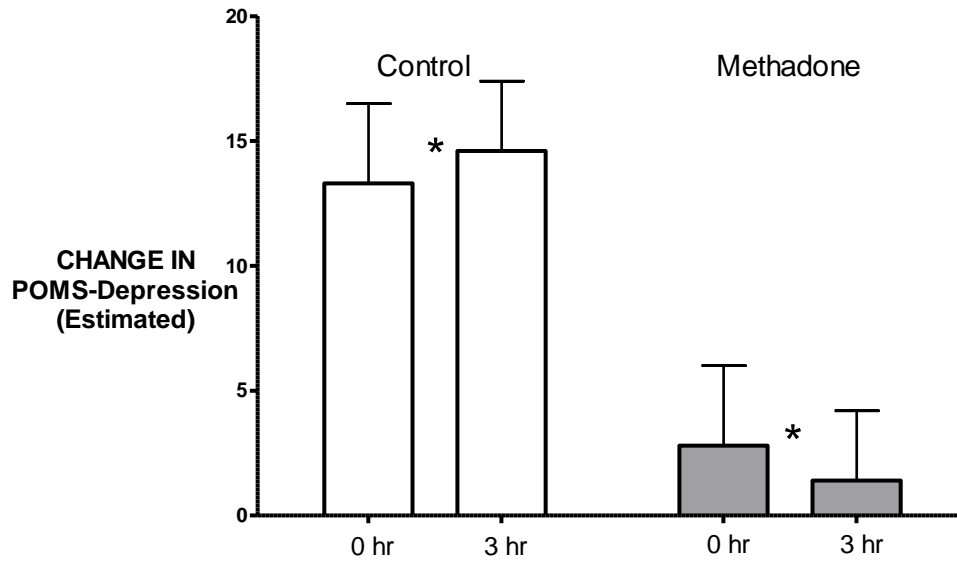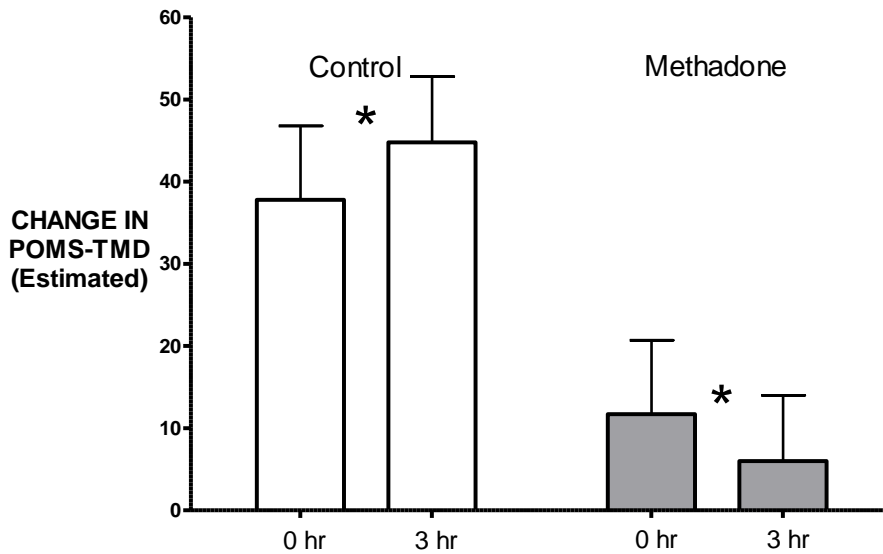**Figure 25: Estimated marginal means of POMS-TMD with Age and BDI as covariates.** After MIPD, the methadone group showed a significantly smaller (p = 0.019) change in POMS-Total Mood Depression score compared with controls*. Covariates appearing in the model are evaluated at the following values: age = 31.88, total BDI = 12.50. Bars show mean ± se.

In summary, this section has showed that the methadone group had significantly smaller change in POMS-Depression score compared with controls, when accounting for BDI and Age. Also the methadone group were significantly smaller in change in POMS-Total Mood Disturbance compared with controls, whether controlling for BDI and Age covariates or not.

5.4   DISCUSSION

In this chapter, methadone subjects and controls were induced into a depressive state. The aim was to demonstrate that methadone maintenance patients exhibited a larger increase in mood disturbance than control subjects, when challenged on the same mood inducing tasks. However when measured on secondary measures, methadone subjects showed less overall reactivity to depression induction (POMS-Depression) and less total negative reactivity (POMS-Total Mood Disturbance). At times corresponding with trough (0 hour) and peak (3 hours) plasma methadone concentrations, methadone patients showed blunted depression reactivity and blunted global emotional disturbance. This contradicts hypotheses outlined at the start of the chapter [hypotheses (ii) and (iii)]. These results contrast partially with Chapter

4 where methadone patients were similar in depression reactivity to controls only at trough plasma methadone concentrations as measured by VAS scales.

An explanation is not readily apparent to account for this partial discrepancy between POMS and VAS results. It may be that the two scales are measuring slightly different domains as POMS scales may be insufficiently sensitive to measure changes in emotional reactivity in short time spans. The induction procedures lasted only 12 minutes each, so the length of time between POMS administrations may have been too brief to reliable administer it. It may be possible that the short form of the POMS (POMS-Short) would be a more appropriate scale in the context of this study design. As such, a large item scale like the (full item) POMS may more accurately reflect the mood the subject has recently been in, rather than a 'snapshot' of the current emotional state. An instrument using a VAS score is brief and less demanding, and may therefore be more accurate in capturing the emotion 'at the time'. Therefore the two scales would be measuring slightly different domains. Another alternative explanation is that blunted depression reactivity may be an inherent characteristic of methadone maintenance patients and that POMS scales are more sensitive in capturing this salient point.

It should be noted that in a previous study by Dyer et al. (2001) the POMS-Depression and POMS-Total Mood Disturbance changed from trough to peak in methadone patients. However the magnitude of effect was amplified as patients whose methadone dose 'did not hold' were also included in the sample. These 'non-holders' were shown to have significantly large fluctuations in mood disturbance and contributed dis-proportionately. Methadone patients who reported that their dose 'held' had similar POMS-Depression and total mood disturbance scores as the patients in this study and showed little change in score from trough to peak. This study could not investigate this further as patients were not asked whether they felt their dose 'held'.

Though no strong conclusions could be made using secondary measures on the effect of changing methadone concentrations on depression reactivity, secondary measures clearly demonstrate that methadone maintained patients have blunted depression reactivity and blunted total negative reactivity compared with controls and this is possibly irrespective of plasma methadone concentration levels.

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5.5 CONCLUSION

Study 1 aimed to demonstrate that methadone maintained patients were hyper-sensitive to mood inducing tasks. Both primary and secondary measures have now shown that methadone patients were not hypersensitive to mood tasks as hypothesised. Instead methadone patients showed an opposite response, demonstrating blunted depression / negative reactivity to mood induction tasks. The results clearly show that methadone is a contributing factor in blunting depression reactivity when measured using visual analogue scales. The effect of methadone on elation reactivity is yet to be determined and will be explored in the next chapter.

CHAPTER 6 – STUDY 1 RESULTS – METHADONE AND ELATION REACTIVITY (PRIMARY MEASURES)

The results have so far shown that methadone maintained patients show blunted depression reactivity, as measured by primary measures in Chapter 4. This is despite methadone patients showing hyperalgesia to cold pain. Additionally secondary measures in Chapter 5 showed that methadone patients had blunted depression reactivity and blunted total negative reactivity, though POMS scales may be insufficiently sensitive to show relative different effects at trough and peak plasma methadone concentrations. This chapter will now continue the analysis of the results of study 1 by investigating the impact of methadone on elation reactivity.

6.1   INTRODUCTION

Opioids have been implicated in positive emotion generation and processing. Opioid administration can increase euphoria on MBG scales and Cole/ARCI stimulation-euphoria subscales (Webster et al. 2011). The fronto-limbic system (anterior cingulate cortex, orbito-frontal cortex and insular cortex) (Boecker et al. 2008) has been implicated in opioid modulation of euphoria. 'Pleasure' is a more broad term that describes a positive or enjoyable experience, and is related to euphoria. In animals, only a few subcortical brain regions have been implicated in modulating pleasure. These regions are highly localised and are termed 'hedonic hotspots' (Berridge and Kringelbach 2008) as they generate increases in 'liking' when stimulated. Hotspots are located in the nucleus accumbens, ventral pallidum, the brainstem, and possibly other forebrain and limbic cortical regions. Additionally, opioid administration in these very specific hotspots can amplify 'liking' reactions significantly (Smith and Berridge 2007). Activation of these areas does not seem to be related to non-specific arousal, as there is no amplification of negative 'disliking' when activating the hotspots (Smith et al. 2010). Research in affective neuroscience would therefore suggest that opioids enhance euphoria and pleasure.

However the precise effect of chronic opioid administration on positive emotion systems is still an unknown. A limited number of studies though would suggest that the emotional

regulation / processing of positive emotions are compromised in opioid dependent patients. A study by Aguilar de Arcos et al. (2008) showed that current heroin users had a significantly lower response to pleasantly arousing (erotic) images than healthy controls. Another study showed that methadone maintenance patients are impaired in decoding emotional facial expression compared with controls (Kornreich et al. 2003). Lubman et al. (2009) demonstrated that opioid dependent patients had reduced responsiveness to pictures of pleasant stimuli, including a lack of typical facial expression and inhibited reflex response. Recently abstinent heroin dependent men were also shown to have reduced brain activation to pleasant images (Zijlstra et al. 2009). Opioids have also been shown to modulate the palatability of sweet and salty foods (Kelley et al. 2002; Berridge and Kringelbach 2008). Overall these studies suggest an overall impairment in pleasure systems ie anhedonia.

Anhedonia is the inability to find pleasure in activities that previously were enjoyable. The prefrontal cortex, ventral striatum and the amygdala are systems particularly implicated as underlying anhedonia (Keedwell et al. 2005). Pleasure and elation are linked concepts with prevailing thought identifying pleasure as a core component of elation (Morten L Kringelbach and Berridge 2010). Though research in the literature has so far focussed on impaired pleasure processing in drug dependent populations, it may be indicative of a more general blunted response to positive stimuli.

Prolonged opioid drug use has been associated with anhedonia but it is still unclear to what degree the chronic administration of drugs themselves, pre-existing conditions that pre-date and predict drug dependence, and trait depression impact on diminished pleasure on opioid dependent populations. Adding to the difficulty is that the comorbidity of dependence and depression in opioid dependent populations is high, and that a central characteristic of depression is anhedonia. Nonetheless, a second line of indirect evidence also suggests compromised elative processing in opioid dependent groups with studies showing that depressive mood and total mood disturbance were higher in methadone maintenance patients. Dyer et al. (2001) showed that in a 24 hour cycle that included a time when plasma methadone concentrations were lowest (trough) and when highest (peak), methadone maintained patients showed higher depressive mood and more global mood disturbance than controls.

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These lines of indirect evidence would suggest that positive emotional systems are compromised in opioid dependent populations. Therefore, elative reactivity of methadone dependent patients may also be compromised.

6.2   AIM AND HYPOTHESIS

Study 1 aimed to investigate the effect of Velten's elation inducing tasks on the emotional state of methadone maintained patients. The following hypothesis will be tested (with the same numbering convention used previously):

(iv) Methadone patients will show reduced elation reactivity than controls.

To determine the effect of methadone on elation reactivity, changes in VAS-Elation (VAS-E) were analysed in a comparable approach used to analyse the impact of methadone on depression reactivity. POMS scales were not appropriate as secondary measures in this analysis as POMS do not directly measure elation (the only positive dimension measured by POMS is vigour-activity).

6.3   RESULTS

6.3.1   STATISTICAL ANALYSES

All analyses used an alpha level of 0.05. Data format is Mean ± Standard Error unless otherwise noted. Correlations shown were calculated using two-tailed significance levels. All data were analysed using SPSS for Windows (version 11), except outlier detection using Graphpad Quickcalcs ('GraphPad QuickCalcs: Outlier Calculator' 2012). Repeated measures two-way ANOVA was used to assess the effect of the mood induction procedures on both groups at both session time points. The primary independent variable was elation reactivity as measured by VAS scales.

6.3.2   ELATION REACTIVITY MEASURED BY VAS-E (PRIMARY MEASURE)

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A similar analysis as used in Chapter 4 (methadone and depression reactivity) was performed to determine the effect of methadone on elation reactivity. As the author is unaware of research using Velten's mood induction procedure in methadone maintained patients, the effectiveness of the elation mood induction (MIPE) in the methadone group and controls was evaluated before investigating the effect of methadone on elation reactivity.

6.3.2.1 Evaluating MIPE measured by VAS-E

Spaghetti Plots

The spaghetti plots (Figure 26) shows the VAS elation score before (pre MIPE) and after (post MIPE) elation mood induction, for each subject in the methadone group and controls at 0 hour and 3 hours. A visual inspection of the plots reveals no apparent evidence that either the methadone group or controls are composed of two quite different sub-groups.eg there is no visual evidence that the methadone group is composed of two distinct subgroups of mood induction responders and adverse mood induction responders. Note also that one methadone subject at 3 hours was identified as an outlier (Grubb's test: $z = 3.82$, $p < 0.01$), with a change in elation score of 70 VAS points (see Figure 26, identified by *).

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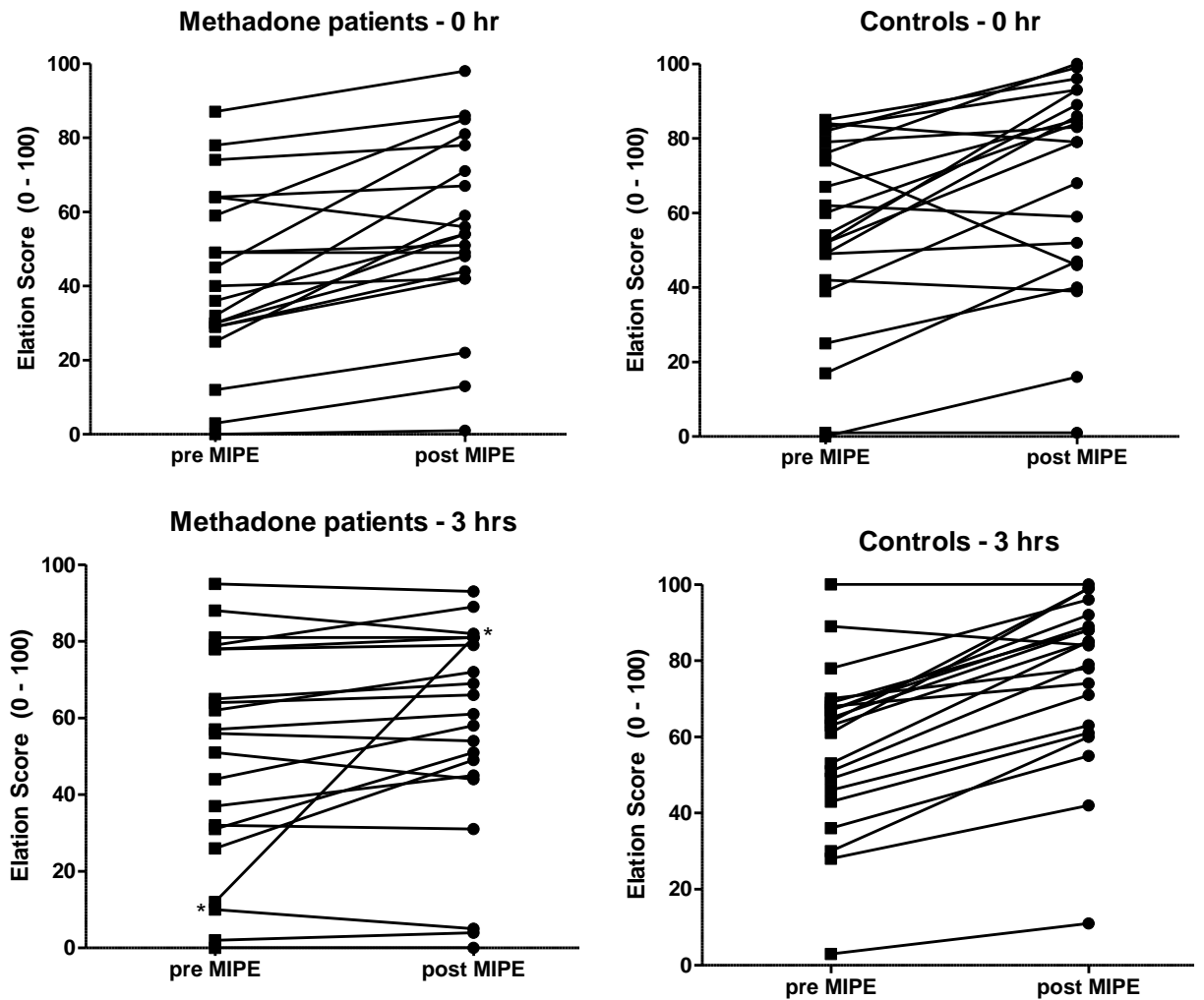
Figure 26: Spaghetti plots of elation score (VAS-D) pre and post elation induction. Spaghetti plots for the methadone group and controls at 0 hour and 3 hours. An extreme outlier was identified in the methadone group at 3 hours (*).

Mean Time Plots

Figure 27 shows the change in mean elation score for the methadone group and controls at 0 hour and 3 hours, before and after each mood induction. Time point 1 corresponds with pre MIPE, time point 2 with post MIPE, time point 3 with pre MIPD and time point 4 with post MIPD. The figure shows an increase in elation score post MIPE (as expected). Furthermore, there was a decrease in elation score post MIPD (not further analysed). The figures indicated the expected response to mood induction, that elation score increased after elation mood induction, and that elation score decreased after depression mood induction. As the mood induction sequence was elation induction followed by depression induction, it would be expected that elation score would start at a baseline (time 1), increase in score due to the

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elation induction (time 2), decrease in score as the effects of elation induction diminish (time 3), and then decrease in score due to the depression induction (time 4). This pattern would visually resemble a 'mountaintop' in a time series plot. As expected, both figures show this visual pattern. There was no indication of substantial floor or ceiling effects.
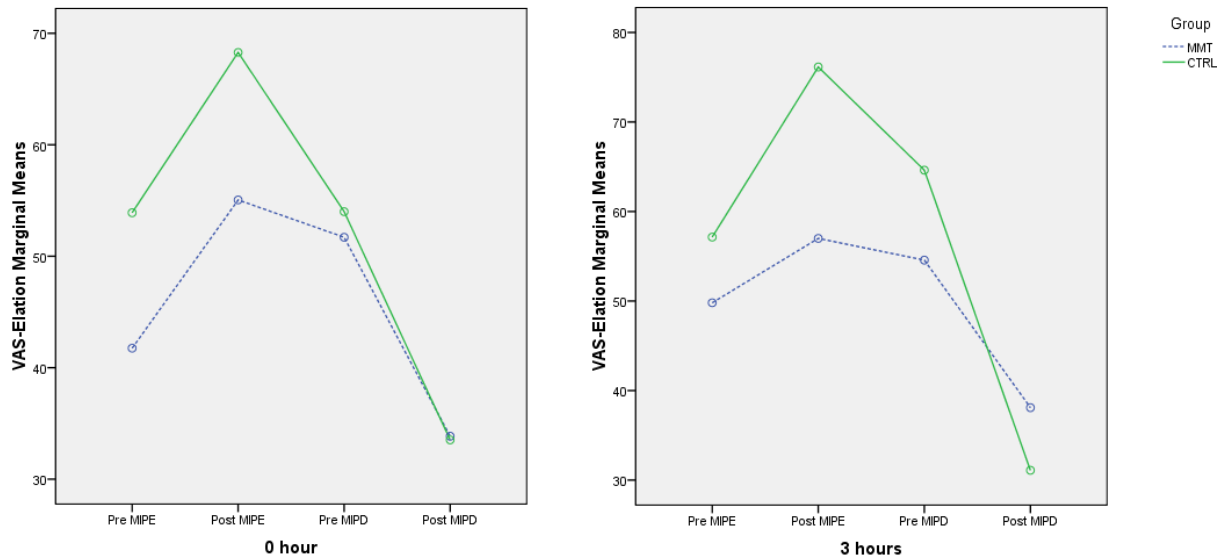
Figure 27: Mean time plots for Elation score (VAS-E). Plots show VAS-E at 0 hour and 3 hours at pre MIPE, post MIPE, pre MIPD and post MIPD.

6.3.2.2 Effectiveness of MIPE measured by VAS-E

As the effect of depression mood induction on elation scores was not central to the study, the following figures present the mean elation scores due to elation induction only, at 0 hour and 3 hours. The elation (MIP-Elation) induction was effective for both groups at 0 hour, as measured using VAS. Figure 28 shows the elation (VAS-E) scores for the methadone group and controls at 0 hour, before and after MIPE. Both methadone and controls showed higher elation scores after elation induction at 0 hour (methadone group elation before MIPE 41.8 ± 5.4, methadone group elation after MIPE 55.1 ± 5.5, paired samples p < 0.01; controls elation before MIPE 53.9 ± 5.7, controls elation after MIPE 68.3 ± 6.2, paired samples p < 0.01). Zelman et al. (1991) investigated the effect of Velten elation induction on cold pain sensitivity, reporting a modest change of 1.9 ± 3.2 (mean ± SD) in Mood adjective Checklist (MACL) elation score after MIPE. As MACL is a 20-point scale, this equates approximately to a change in VAS score of 9.5. The elation induction in this study was more effective, though not substantially more.

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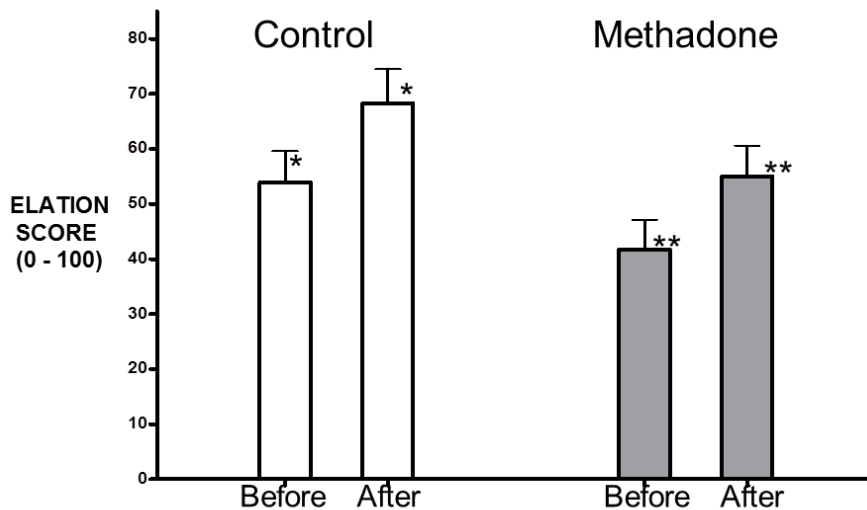
Figure 28: 0 hour emotional state (VAS-E) scores before and after MIP-Elation. Elation induction successful at 0 hour (controls, $p < 0.01$; methadone group, $p < 0.01$). Bars show mean ± standard error.

6.3.2.3 Elation Reactivity measured by Change in VAS-E

Elation reactivity was calculated as the difference between post-induction emotional state and pre-induction emotional state (i.e. elation reactivity = post-induction elation score − pre-induction elation score). Figure 29 shows the increase in elation due to MIPE at 0 hour and 3 hours for controls and the methadone group. Using repeated measures two-way ANOVA, the methadone group showed a decrease in change in elation score (elation reactivity) at 3 hours compared to controls that approached significance (methadone group elation reactivity 0 hour 13.3 ± 2.9, controls elation reactivity 0 hour 14.4 ± 3.7; methadone group elation reactivity 3 hours 7.7 ± 3.7, controls elation reactivity 19.0 ± 2.4; $p = 0.08$).

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Figure 29: Change in elation scores (emotional reactivity). Results show a partially significant decrease in change in elation score (elation reactivity) in methadone group 3 hours compared to controls (p = 0.08). Bars show mean ± standard error.

However, an extreme outlier was identified in the methadone group and with this outlier removed (z = 3.82, p < 0.01), the interaction effect was significant (methadone group elation reactivity 0 hour 13.2 ± 3.1, controls elation reactivity 0 hour 14.4 ± 3.7; methadone group elation reactivity 3 hours 4.4 ± 1.9, controls elation reactivity 3 hours 19.0 ± 2.4, p = 0.01). See Figure 30.

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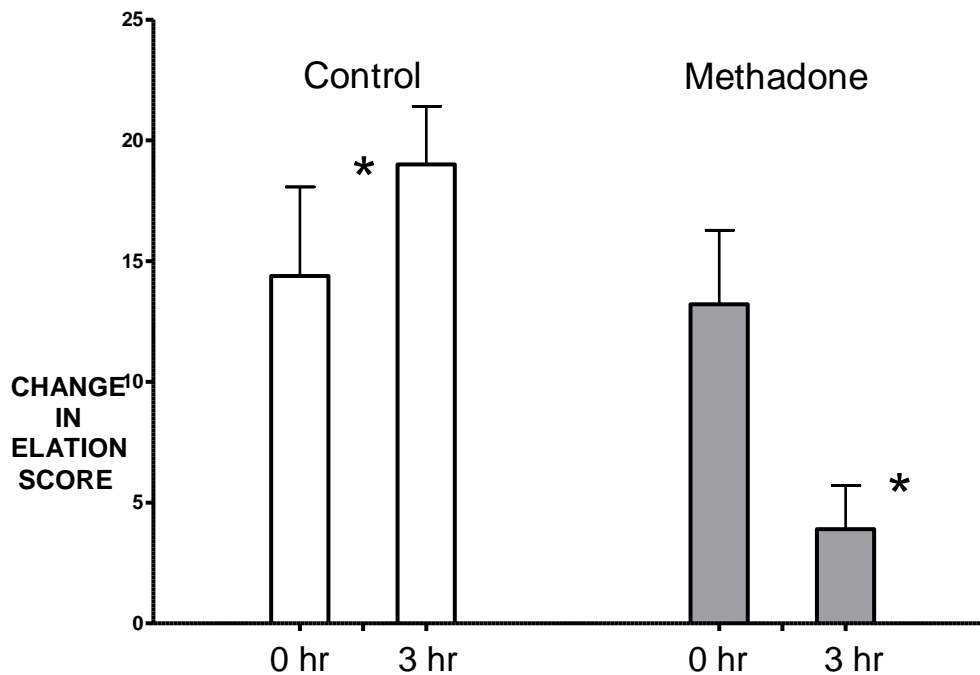
Figure 30: Change in elation scores (emotional reactivity). With the outlier removed, results show a significant decrease (p = 0.01) in change in elation score (elation reactivity) in methadone group 3 hours compared to controls. Bars show mean ± standard error.

As methadone and control groups differed on age and BDI, both dependent variables were added separately as covariates in a repeated measures two-way ANOVA. With BDI as a covariate, the methadone group showed no difference in elation reactivity 3 hours compared with controls (p = 0.167). With the extreme methadone subject outlier removed and BDI as a covariate, the methadone group showed a significant decrease in elation reactivity 3 hours compared to controls (p = 0.019). With age added separately to the model as a covariate, the methadone group showed no difference in elation 3 hours compared with controls (p = 0.167). When the extreme methadone subject outlier was deleted, the methadone group showed a decrease in elation reactivity at 3 hours compared to controls that approached significance (p = 0.076).

With both age and BDI as covariates in the one model, there was no time*group interaction (F[1] = 1.2, p = 0.273). When the outlier was deleted, the time*group interaction approached significance (Repeated measures ANOVA with BDI=12.55 and age = 31.65 as covariates, F[1] = 3.2, p = 0.082. methadone group elation reactivity 0 hour 15.6 ± 4.6, controls elation

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reactivity 0 hour 12.2 ± 4.3; methadone group elation reactivity 3 hours 6.7 ± 2.8, controls elation reactivity 3 hours 16.9 ± 2.6).

6.3.2.4 Correlations between Elation Reactivity and Methadone

Table 16 shows the correlations between change in emotional reactivity (as measured by VAS) and methadone concentrations [as measured by change in R-(-), S-(+) plasma methadone concentrations, or methadone dosage]. A change in R-(-) plasma methadone concentration from 0 hour to 3 hours was not correlated with change in elation reactivity from 0 hour to 3 hours (r = 0.06, p = 0.839). However it should be noted that with n = 14, this correlational analysis may lack power. Consistent with previous results reported here, the analysis was repeated with the extreme methadone outlier removed. Table 16 shows that increases in R-(-) methadone from 0 hour to 3 hours was not associated with elation reactivity (r = -0.12, p = 0.722).

Table 16: Correlations: Methadone vs elation reactivity

		change in elation reactivity	change in elation reactivity (outlier removed)
ΔR-methadone	r	0.06	-0.12
	sig	0.839	0.722
	df	13	12
ΔS-methadone	r	0.07	-0.06
	sig	0.827	0.853
	df	13	12
Methadone Dose	r	0.25	0.13
	sig	0.299	0.590
	df	20	19

Controlling for both BDI and age (with no outlier removed) showed no significant correlations between emotional reactivity and methadone concentrations or dose (table not shown). However, Table 17 shows the correlations with the outlier removed and controlling for BDI and Age. There was little effect on the change in elation reactivity due to change in

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R-(-) plasma methadone concentrations (r = -0.07, p = 0.848). Methadone dose showed no correlation in elation reactivity (r = 0.16, p = 0.551).

Table 17: Partial correlations (controlling for BDI and Age) methadone vs elation reactivity (outlier removed)

Control Variable			change in elation reactivity
Total BDI & Age	ΔR-methadone	r	-0.07
		sig	0.848
		df	8
Total BDI & Age	ΔS-methadone	r	-0.02
		sig	0.947
		df	8
Total BDI & Age	Methadone Dose	r	0.16
		sig	0.551
		df	15

6.4 DISCUSSION

Methadone maintained patients and controls were induced into an elative state, with both groups showing similar elation reactivity to induction at 0 hour (pre dose methadone). The aim was to demonstrate that methadone maintenance patients exhibit a smaller increase in elation emotional disturbance than control subjects, when challenged on the same elation inducing tasks. The results show that 3 hours post dose, methadone subjects did show less reactivity to elation (with the removal of an outlier) on primary measures (VAS scales).

After undergoing elative mood induction, methadone subjects at 0 hour (pre dose methadone administration, corresponding with trough methadone plasma concentrations) showed a similar increase in VAS measured elative state compared with controls. This result illustrates that the induction techniques were effective for both groups, and that there was no evidence of a difference in magnitude of effect between methadone and control groups at pre dose. Therefore, at the time of trough plasma methadone concentration, there was no difference in the elation reactivity of methadone maintained subjects compared to controls. Research that shows the effectiveness of mood induction procedures in methadone maintained patients is

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lacking. Though the effectiveness of mood induction on control subjects has been well researched, the author is unaware of any research that investigates the effectiveness of these mood techniques on control subjects drawn from a sample that (apart from opioid use) was well-matched with methadone maintenance patients on a number of key demographics such as drug history and employment status.

The effect of the change in methadone concentration on the elation reactivity of methadone subjects was measured by comparing the relative effects of the induction procedures in both groups at pre dose (trough plasma methadone concentrations) and post dose (peak plasma methadone concentrations). This study shows that such a comparison revealed that the methadone group showed a decrease in elative emotional reactivity at peak plasma methadone concentrations compared with controls (after an outlier has been deleted), as measured by VAS. Furthermore, these results were robust to BDI score as a confounder. These results support findings from related research showing a dysregulation of emotion processing when heroin users were shown pleasant and unpleasant stimuli (Aguilar de Arcos et al. 2008). These heroin polysubstance users were less emotionally responsive when shown positive stimuli (eg erotic imagery).

This research suggests that methadone blunts elation reactivity following an increase in plasma methadone concentration. As the methadone group showed similar elation reactivity to controls at trough methadone concentrations, it may be that regular opioid use has resulted in tolerance to any observable opioid effects on mood at trough methadone concentrations. Nonetheless, blunted elation reactivity at peak plasma methadone concentrations indicates that complete tolerance had not developed to this opioid effect. This is consistent with previous research demonstrating a range of physiological and psychological effects with increasing plasma methadone concentrations, including decreased pupil diameter and respiration rate, increased threshold/tolerance to specific types of pain (Dyer et al. 1999) and lesser mood disturbance (Dyer et al. 2001).

It cannot be stated with certainty that the present results can be translated to other opioids. While it seems likely on the basis of the comparable evidence from animal models, it would be of great interest to test whether other full agonists such as morphine produced similar effects and whether the partial agonist buprenorphine also elicits similar emotional blunting.

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6.5 CONCLUSION

The results from this chapter showed that methadone patients demonstrated a blunted elation response to mood induction tasks. Combined with the results from chapter 4 showing that methadone patients demonstrated blunted depression reactivity, methadone patients showed blunted reactivity to both elation and depression induction.

6.6 GENERAL LIMITATIONS OF STUDY 1

It is important to consider that there are a number of limitations to study 1. Subjects were not randomly assigned to groups. Instead group membership was pre-determined by whether the subject was enrolled in a methadone maintenance treatment program. Therefore any differences in emotional reactivity between the groups may be due to selection bias. However, the study was designed to minimise differences between groups by recruiting controls that were similar to the methadone group on a number of key demographics such as 30 day drug use, smoking status, and employment status. The groups were not different on anxiety scores or reported hassles and uplifts in the last 30 days. Though the groups were different in age and depression score (BDI), these were added to the statistical models are confounders. The two groups may also differ on other underlying conditions. Alexithymia is a deficiency in understanding, processing, or describing emotions (Krystal 1979). Alexithymics show a limited ability to experience positive emotions (Sifneos 1973) and some authors argue that alexithymia is a condition that may be prevalent in substance abuse populations (Hamidi et al. 2010). Whether opioid dependent populations specifically show prevalence for alexithymia has not yet been investigated, but it is possible that the methadone group was prone to alexithymia and as such was impaired in either processing elation or accurately describing it. Comparing the methadone group to other (non-opioid) drug dependent groups may be fruitful. Further studies are needed.

A number of mood induction procedures have been developed, including Velten Self-statement mood induction (Velten 1968), autobiographic recall of sad events, passive display of emotionally salient stimuli (such as the presentation of strongly emotive music and images), and situational mood induction (such as informing subjects that they will shortly present a public speech). Velten's mood induction has been shown as amongst the most effective (Gerrards-Hesse et al. 1994), but has been criticised as an artificial test with no

strong naturalistic grounding, and for its apparent 'demand' characteristics. Research has shown that 'demand' characteristics cannot adequately explain its mood inducing nature (Finegan and Seligman 1995). However, a greater limitation with this procedure is that it is not a 'naturalistic test'. Future investigations using a procedure that more closely mimics naturally occurring stressful events in 'normal life' may be of value. For example, mood induction techniques incorporating public speech preparation could be used to induce anxiety. The authors are unaware of other existing depression induction techniques that would be suitable.

It is uncertain whether the present results can be translated to other opioids, though it seems likely based on animal model evidence. It would be of interest to test whether other full agonists such as morphine or the partial agonist buprenorphine also elicits similar emotional blunting. This approach also has merit as any criticism that alexithymia may be an underlying cause of difference between two drug dependent groups is doubtful.

6.7   GENERAL CONCLUSION OF STUDY 1

The results of study 1 suggest that methadone may blunt emotional reactivity (elation and depression) following an increase in plasma methadone concentration, when measured using primary measures. As the methadone group showed similar emotional reactivity to controls at trough methadone concentrations, it may be that regular opioid use has resulted in tolerance to any observable opioid effects on mood at trough methadone concentrations. Nonetheless, a blunted emotional reactivity at peak plasma methadone concentrations indicates that complete tolerance had not developed to this opioid effect. This is consistent with previous research demonstrating a range of physiological and psychological effects with increasing plasma methadone concentrations, including decreased pupil diameter and respiration rate, increased threshold/tolerance to specific types of pain (Dyer et al. 1999) and lesser mood disturbance (Dyer et al. 2001). Secondary measures were less conclusive but did nonetheless indicate impairment as methadone patients had blunted depression reactivity at both trough and peak plasma methadone concentrations, even though methadone had a minimal effect in further blunting depression reactivity after administration.

The dominant view on the role of emotions is that they serve an important purpose in helping individuals respond to environmental demands (Nesse 1990; Levenson 1994). Emotion plays

a vital role in learning and memory (Bradley et al. 1992), motivation, and adaptive behaviour. They also help to alert individuals to any mismatch between formulated goals and the environment (Schwarz and Clore 1983). Baumeister et al. (2007) suggests that emotions play an adaptive function in behaviour, with individuals unable to experience appropriate negative emotions (such as guilt or anxiety) hindered in adjusting their behaviour to future threats that stimulate such emotions. Furthermore, there is growing consensus that emotion suppression is associated with worsened psychopathology (Gross and John 2003; Eftekhari, Zoellner, and Vigil 2009). This suggests that the findings here have important implications for the psychological and social functioning of people exposed to opioids.

Blunted emotional reactivity (sometimes called 'emotion context insensitivity') has been shown to be a deficit common to mental illnesses such as major depressive disorder, anxiety disorder, and personality disorder. Considerable research has investigated the role of emotional reactivity in depressive disorder and though the findings are equivocal, a meta-analysis by Bylsma et al. (2008) concluded that patients with major depressive disorder were unresponsive to emotional stimuli. Other research has investigated the effective treatment of emotional dysfunction evident in Post-Traumatic Stress Disorder (PTSD). Researchers hypothesise that emotional numbing in PTSD is due to overwhelming stress resulting in hyper-stimulation of the endogenous opioid system (Glover 1992). Nalmefene (an opioid antagonist) was shown to reverse or reduce emotional numbness in PTSD patients (Glover 1993). More research is needed to determine the exact role that blunted emotional reactivity has as a cause or consequence of psychopathology.

These results showing blunted emotional reactivity are consistent with anecdotal experiences reported by methadone maintenance patients. For example, Rosenbaum and Murphy (1987) interviewed 100 women in a two-year ethnographic study of the health and wellbeing of women on methadone. The researchers reported that many women on methadone maintenance regarded methadone as providing an emotional buffer against stressful situations. As stated by one woman interviewed, 'It's not euphoric. It's just that things don't bother you. Like bad things can happen and it just doesn't get to you like it would somebody else'. The results from this paper support these experiences, suggesting that any self-medication use of methadone may be due to a desire to blunt negative emotional responses to depressing situations, rather than or in addition to any potential euphoric effects. These results also are comparable with methadone and heroin maintained patients shown to have a reduced response to the startle reflex task (Walter et al. 2011), suggesting an impaired reaction to stress events.

Generally, these results indicate that long-term substance abusers may use opioids in a manner analogous to antidepressants, and that it is the relief from emotionally painful experiences that may (along with opioid withdrawal relief) be a desired outcome of opioid abuse (as opposed to any pleasurable effects). This conclusion is supported by animal studies using learned helplessness/forced swim/social separation models that show that μ-opioid agonists increase antidepressant-like behaviour (Rojas-Corrales et al. 2002b; Fichna et al. 2007; Warnick, McCurdy, and Sufka 2005).

The results of the present study show that methadone blunts both elative and depressive emotional reactivity and can be added to the range of effects that are observable at the time of peak plasma methadone concentrations. The decrease in depressive emotional reactivity is consistent with reports of users regarding the effects of methadone. Such a decrease in negative emotional response may also be a part of the motivation for using opioids. The decrease in each type of response is important in understanding the effects of opioids on social and psychological functioning. As it is unknown whether other opioids will also elicit similar emotional blunting, the next chapter will investigate the effect of buprenorphine on emotional reactivity.

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CHAPTER 7 – STUDY 2– OPIOIDS AND EMOTIONAL REACTIVITY (PRIMARY AND SECONDARY MEASURES)

This chapter outlines the second of two studies that examines the impact of opioids on emotion. Study 1 reported that methadone blunted emotional reactivity (both elation and depression) in methadone maintenance treatment patients . Study 2 expands on this finding by testing the effect of opioid maintenance drugs on emotional reactivity in a cohort of buprenorphine maintained patients compared with methadone maintenance patients and controls. In this Chapter, the effects of opioids on emotional reactivity are measured using Visual Analogue Scales (VAS) as primary measures and Profile of Mood States (POMS) as secondary measures.

7.1 INTRODUCTION

Opioid users frequently report that opioids have a significant impact on their emotional reactivity, particularly negative emotions (Rosenbaum and Murphy 1987; De Maeyer et al. 2011). Qualitative studies support these experiences. For example, De Maeyer et al. (2011) conducted in-depth interviews of methadone maintained patients and reported that "a large number of participants cited the paralysing impact of methadone on their emotions." A limited number reported that methadone had a stabilising effect on their psychological wellbeing, reducing the 'intensity' of negative feelings. A study on the health and wellbeing of women on methadone showed that many subjects reported methadone as providing an emotional buffer against stressful situations (Rosenbaum and Murphy 1987). As stated by one woman interviewed, "It's not euphoric. It's just that things don't bother you." These studies suggest that methadone may have a self-medicative role as a means to blunt negative emotional responses to depressing situations which overall may be detrimental to the person's psychological state.

These effects are likely to be general to all μ-opioid receptor agonists. Animal models and human experimental studies show that full opioid agonists modulate emotional reactivity in animals and modify emotional states in humans (Rojas-Corrales et al. 2002b; Fichna et al.

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2007; Torregrossa et al. 2006; Mague et al. 2003; Ribeiro et al. 2005; Dyer et al. 2001; Warnick, McCurdy, and Sufka 2005). In animals, μ-opioid agonists reduce the distress produced by social isolation. For example, the μ-opioid agonist peptide DAMGO reduced the number of vocalisations (a measure of distress) in rooster chicks when socially isolated (Warnick, McCurdy, and Sufka 2005). Furthermore, the rate of vocalisations in the high stress environment following administration of a μ-opioid agonist was comparable to the rate in a low stress environment with no opioid effect.

Changes in emotional reactivity (the change in emotional intensity upon presentation of an emotionally salient stimulus) could have a pronounced effect on general psychological functioning. Learning and memory (Bradley et al. 1992), motivation, and adaptive behaviour are all influenced by emotional systems. Baumeister et al. (2007) suggests that emotions play an adaptive function in behaviour, with individuals unable to experience appropriate negative emotions hindered in adjusting their behaviour to future threats that stimulate such emotions. Furthermore, consensus is growing that emotion suppression is associated with worsened psychopathology (Gross and John 2003; Eftekhari, Zoellner, and Vigil 2009). Therefore research in this area has important implications for the psychological and social functioning of people exposed to opioids.

As shown in study 1, opioids have been implicated in emotion regulation with methadone users reporting blunted emotional reactivity (Savvas, Somogyi, and White 2012). Methadone maintained subjects and controls (opioid naïve) were induced into elative and depressive moods at time-points corresponding with trough and peak plasma methadone concentrations. The results showed that the methadone group was less reactive than controls to both elative and depression mood induction at times of peak methadone concentration, as measured by VAS. Furthermore POMS Depression scales also suggested that methadone patients had impaired depression reactivity.

Buprenorphine is an alternative maintenance agent for the treatment of opioid dependence (Gowing, Ali, and White 2009). Both buprenorphine and methadone are recommended as equally appropriate for maintenance treatment as they are both equivalent in reducing illicit heroin use, though retention in treatment with methadone may be slightly more likely (Mattick et al. 2008). While methadone is a full μ-opioid agonist (Brown et al. 2004), buprenorphine is considered a partial μ-opioid agonist (Huang et al. 2001) and hence has a less pronounced effect on a number of opioid effect measures [particularly respiratory

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depression but not analgesia (Dahan et al. 2006)]. However buprenorphine is also a κ-opioid antagonist (Cowan, Lewis, and Macfarlane 1977). κ-opioid agonists are known to produce dysphoria (Land et al. 2008), so buprenorphine may reduce negative emotional states via this receptor. Whether this is true for the blunting of emotional response is not known, though a study comparing the difference in views of buprenorphine and methadone showed that opioid dependent patients believed that 'emotional numbing' was significantly more associated with methadone compared with buprenorphine (Pinto et al. 2010). In that study, methadone was rated as 2.8 (with a score of 5 as most emotionally numbing) whilst buprenorphine was rated as 1.9.

7.2   AIM AND HYPOTHESES

Study 2 tested whether buprenorphine maintenance patients react differently to emotional stimuli compared with methadone maintained patients or healthy controls, when using Velten's mood induction procedures. As buprenorphine is a partial μ-opioid agonist, this study aims to determine whether buprenorphine has a less pronounced effect than methadone, at times corresponding with peak plasma opioid concentrations. The aim of this study was to compare the effects of buprenorphine and methadone on emotional reactivity using elation and depression mood induction procedures. Subjects maintained on each of the drugs were tested at time points corresponding with peak plasma opioid concentrations as any opioid effect on emotional reactivity would be expected to be maximal at time of peak plasma concentration. Velten's mood induction procedures were used to induce elation and depression emotional reactions at either 1.5 hour or 3 hours postdose (corresponding with peak opioid plasma concentrations). Subjects naïve to opioid abuse were used as controls. As depression psychopathology may have a significant influence on emotional reactivity (Sloan and Sandt 2010) this was measured and statistically controlled in this study.

The following hypotheses will be tested in this Chapter:

> (v) Methadone patients will show greater blunting of emotional reactivity (elation and depression) compared with buprenorphine patients and controls, as measured by VAS (primary measures). Buprenorphine patients will show limited blunting of emotional reactivity compared with controls.

(vi) Methadone patients will show greater blunting of depression reactivity and total negative reactivity compared with buprenorphine patients and controls, as measured by POMS (secondary measures). Buprenorphine patients will show limited blunting of emotional reactivity compared with controls.

7.3 METHOD

7.3.1 SUBJECTS

Three groups of subjects were recruited: two opioid dependent groups (buprenorphine, methadone) and controls. The buprenorphine maintenance treatment group comprised 26 adults (16 males, 10 females; aged 26-60 yrs). The methadone maintenance treatment group comprised of 27 adults (19 males, 8 females; aged 27-58 yrs). Controls comprised 27 adults (16 males, 11 females; aged 19-50 yrs) and were opioid naïve. Inclusion criteria for the opioid groups were: aged between 18 and 65 and on a stable once-daily dose of methadone or buprenorphine, having been on opioid maintenance treatment for a minimum of two weeks and on a stable dose, and not currently prescribed Selective Serotonin Reuptake Inhibitor (SSRI) medication. Inclusion criteria for control subjects were: aged between 18 and 65, with no current or previous history of opioid dependency, and not currently prescribed SSRI antidepressant medication. Pregnancy was an exclusion criterion for all groups. Control subjects were primarily recruited from a list of current or prior University students who registered interest in participating in research. Unlike study 1, chronic pain patients and psychiatric illness patients were not an exclusion criteria. The Royal Adelaide Hospital, Research Ethics Committee approved the study (#091214).

7.3.2 EXCLUSIONS AND NON-COMPLETIONS

Potential subjects were identified and screened for inclusion and exclusion criteria. All subjects provided informed consent before commencement of the trial. Four subjects were excluded from analysis - two methadone subjects were on ultra-low doses on methadone (15 mg and 20 mg methadone daily respectively) and two other subjects either did not follow instructions or did not complete the session.

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Demographic and background information was collected at screening by the researcher. A battery of tests was also used to gauge psychological function at screening. These were administered at the government drug clinic (Drug and Alcohol Services South Australia [DASSA], Warinilla, South Australia) and included the state-trait anxiety inventory (STAI-R, form Y [Spielberger 1983]), the state-trait anger expression inventory (STAIX-R, form Y [Spielberger 1983]), and the Beck Depression Inventory (BDI-II [Beck et al 1996]). The Visual Analogue Scales–Depression (VAS-D) and Visual Analogue Scales-Elation (VAS-E) were also administered at screening as practice tests for subjects.

7.3.3   MATERIALS

To test the emotional reactivity of subjects, Velten's Mood Induction Procedure (MIP) was administered (see Chapter 2 for details). Elation (MIPE) and depression (MIPD) induction procedures were the same as used in study 1.

Blood samples were collected (where possible) from opioid subjects via venepuncture at approximately 3 hours post dose for methadone maintained patients and 1.5 hours post dose for buprenorphine maintained patients to determine peak plasma opioid concentrations (see chapter 4).

A number of scales and questionnaires were used at screening or during testing. All the scales employed are pen-and-paper tests completed by the subject and were unchanged from those used in study 1 (see Chapter 2). Scales used at screening were demographic and background information, Visual Analogue Scales (VAS-E and VAS-D). Profile of Mood States (POMS), Subjective Opiate Withdrawal Scale (SOWS), Beck's Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI-R), and the State-Trait Anger Inventory (STAIX-R). Visual Analogue Scales (VAS-E and VAS-D). Profile of Mood States (POMS), and Subjective Opiate Withdrawal Scale (SOWS) were used throughout testing.

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7.3.4 PROCEDURE

Each subject attended a single session at a drug treatment clinic. For the opioid groups, session times corresponded with the time when opioid concentrations were at peak plasma levels [3 hours post dose for methadone subjects (Dyer et al. 1999) and 1.5 hours post dose for buprenorphine subjects (Lopatko et al. 2003)]. Controls attended a session at a similar time to the methadone group.

Opioid groups were dosed in accordance with normal maintenance dosing regimens. For the testing session, all subjects rated their current emotional state on two mood Visual Analogue Scales (VAS-D for depression and VAS-E for elation). Subjects then underwent MIP-Elation (MIPE) before rating their current emotional state again using VAS. Subjects were then administered the MIP-Neutral procedure and rated their mood state. Finally, subjects were administered MIP-Depression (MIPD) and rated their emotional state. See Figure Figure 31.

Figure 31: Study 2 procedure flow chart. The chart shows the procedure used in Study 2. At screening a battery of pen-and-paper tests were administered. The testing session was composed of only 1 session (at 1.5 hours for buprenorphine patients, and 3 hours for methadone patients or controls). The session included Velten's Mood induction procedures (See Chapter 2, Figure 7).

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7.4 RESULTS

7.4.1.1 Statistical Analysis

Paired samples were used to assess the effect of the induction procedures for each group. GLM univariate one-way ANOVA was used to test for differences in emotional reactivity between groups. The primary independent variables were elation and depression emotional reactivity as measured by change in VAS. All analyses used $\alpha = 0.05$. Post hoc tests used Tukey HSD corrections. Pairwise comparisons used Least Significant Difference (LSD). Data format is Mean ± SEM unless otherwise noted. All data were analysed using SPSS for Windows (version 11).

7.4.1.2 Subject Characteristics / Demographics

Table 18 shows the demographic breakdown of all groups. The composition of each group was predominantly Caucasian and male. Gender breakdown for the three groups was predominantly male (controls: 16 male, 11 female; buprenorphine: 16 male, 10 female; methadone: 19 male, 8 female). The opioid maintenance groups were primarily unemployed (buprenorphine: 77% unemployed; methadone: 74% unemployed) whilst controls were primarily students (controls: 74% students). One way ANOVA revealed that the mean age for the opioid maintenance groups were significantly higher than controls (control: 24.2 ± 1.2; buprenorphine: 41.9 ± 1.7; methadone: 40.2 ± 1.9; $F[2] = 38.4$, $p < 0.001$; methadone vs controls < 0.001; buprenorphine vs controls < 0.001; methadone vs buprenorphine $p > 0.05$). The methadone and buprenorphine groups also had significantly higher BDI scores than controls ($F[2] = 12.25$, $p < 0.001$; Post-hoc tests: methadone vs controls, $p < 0.001$; buprenorphine vs controls, $p = 0.004$; methadone vs buprenorphine, $p > 0.05$). All three groups had similar single : relationship ratios. Compared with controls, the opioid dependent groups were also composed of higher numbers of patients with chronic pain, diagnosed depression or other mental illnesses. Average daily methadone dose was 81 ± 6 mg (range 39 - 150 mg). The buprenorphine group was composed of 6 subjects on buprenorphine maintenance treatment and 20 subjects on buprenorphine-naloxone maintenance treatment. Average daily buprenorphine dose was 16 ± 2 mg (range 3 - 32 mg). All groups tested negative for opioids in drug urine screens on the day of testing.

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Table 18: Demographics and clinical data for controls, buprenorphine (BMT), and methadone (MMT) groups. Abbreviations: BDI, Beck Depression Inventory; Unemp, Unemployed; Emp, Employed (either unskilled, skilled or professional); Stud, Student.

[a]F [2]=38.4, p < 0.001; mmt vs ctrl, p < 0.001; bmt vs ctrl, p < 0.001; mmt vs bmt p > 0.05

[b]F[2] = 32.0, p<0.001; mmt vs ctrl <0.001; bmt vs ctrl < 0.001; mmt vs bmt p > 0.05

[c]F[2] = 15.6, p<0.00; mmt vs ctrl, p= 0.041; bmt vs ctrl, p < 0.001; mmt vs bmt, p = 0.037

[d]F [2]=12.2, p<0.001; mmt vs ctrl, p <0.001; bmt vs ctrl, p = 0.001; mmt vs bmt, p > 0.05

[e]F [2]=11.7, p<0.001; mmt vs ctrl, p <0.001; bmt vs ctrl, p = 0.003; mmt vs bmt, p > 0.05

	Controls (n=27)	BMT (n=26)	MMT (n=27)
Gender (Male/Female)	16/11	16/10	19/8
Ethnicity (Caucasian/Other)	19/8	24/2	27/0
Total Mean Age ± SE (yrs)	24.2 ± 1.2^a	41.9 ± 1.7^a	40.2 ± 1.9^a
Males only Mean Age ± SE (yrs)	23.6 ± 1.2^b	39.1 ± 2.2^b	43.0 ± 1.9^b
Females only Mean Age ± SE (yrs)	25.1 ± 2.5^c	46.3 ± 2.3^c	35.5 ± 3.7^c
Current Maintenance Dose (mg/day)	NA	16 ± 2	81 ± 6
Occupation (Unemp/Emp/Stud)	2/5/20	20/6/0	20/5/2
Relationship (Single/Partner/missing)	13/14/0	14/12/0	12/13/2
Current diagnosis of: Chronic pain / Depression Disorder / Other mental illness	0/0/0	3/2/3	2/3/3
Stimulant last 30 days (no. of users)	2	4	6
Marijuana last 30 days (no. of users)	5	13	18
Benzo. last 30 days (no. of users)	0	14	8
Alcohol last 30 days (no. of users)	22	14	9
Nicotine last 30 days (no. of users)	4	20	17
Mean BDI score ±SE	9.9 ± 2.1^d	19.6 ± 2.1^d	24.0 ± 2.1^d
Mean Derived BDI score ± SE	8.6 ± 1.9^e	17.0 ± 1.9^e	21.4 ± 1.9^e
STAI-R – State Anxiety (F[2] = 2.2, p = 0.121)	36.9 ± 2.3	43.4 ± 2.4	39.1 ± 2.3
STAI-R – Trait Anxiety (F[2] = 2.5, p = 0.09)	41.2 ± 2.6	48.2 ± 2.9	47.7 ± 2.6

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Drug use differed for controls compared with the opioid maintenance groups. Controls were more likely to report alcohol use compared with buprenorphine and methadone groups. However nicotine and marijuana use in the last 30 days was lower for controls. This was expected for a university student and ex-student recruitment database. Unlike study 1, no attempt was made to preferentially recruit controls that smoked cigarettes or self-reported illicit drug usage. A battery of tests also gauged psychological function prior to inducing mood, including BDI-II and STAI. The three groups did not differ on state or trait anxiety (STAI-R). The buprenorphine and methadone group had similar BDI scores (buprenorphine: 19.6 ± 2.3; methadone 24.0 ± 2.5, $p > 0.05$). However, controls were significantly lower in BDI score (controls: 9.9 ± 1.2) than both opioid maintenance groups (F [2] = 12.2, $p < 0.001$; methadone vs controls < 0.001; buprenorphine vs controls $= 0.001$). A derived BDI score which excluded 2 questions from the BDI due to their relatedness to typical opioid withdrawal symptoms did not significantly change the difference in scores between the two groups. Therefore the score using the full BDI instrument was used in all further analyses. Note that a BDI score of 11-19 is considered mild mood disturbance (Beck and Steer 1996). The number of subjects with trait depression scores greater than 19 were: 13 Buprenorphine subjects, 17 Methadone subjects, 0 Controls.

7.4.1.3 Plasma methadone concentrations in the Opioid Maintenance Treatment Groups

The average daily dose of methadone in the methadone group was 81 mg $\pm$ 6 (39 − 150 mg). The average buprenorphine dose was 16 mg $\pm$ 2 (3 − 32 mg). Plasma opioid concentrations were also collected but due to poor venous access with a majority of the opioid maintained subjects, sample size was n =7 for the methadone group and n = 7 for the buprenorphine group. Plasma methadone concentrations of R-(-) and S-(+) methadone at times corresponding with the expected peak were 179 ± 28 ng / ml and 202 ± 33 ng / ml respectively. Plasma buprenorphine concentrations at times corresponding with the expected peak were 6.9 ± 3.4 ng / ml. Plasma norbuprenorphine concentrations were 12.0 ± 6.0 ng / ml. The norbuprenorphine : buprenorphine ratio was $1.8 \pm 0.31 : 1$.

Relationship between dose, R- methadone and S-methadone and buprenorphine.

Table 19 shows the relationship between R- and S- plasma methadone concentrations and as expected, that R-(-) methadone strongly correlated with S-(+) methadone (r = 0.96, p =

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0.001). Surprisingly methadone dose was not correlated with R-(-) or S-(+) methadone plasma concentrations. As the sample size is small, only a few divergent values would be sufficient to significantly impact the correlations. Table 20 shows that buprenorphine and norbuprenorphine were strongly correlated (r = 0.967, p = 0.003), and that dose was strongly correlated with buprenorphine plasma concentrations (r = 0.871, p = 0.011).

Table 19: Correlations: Methadone dose and changes in plasma methadone concentrations. *p < 0.05, ** p < 0.01.

		R-(-) methadone	S-(+) methadone
methadone dose	r	0.262	0.184
	sig	0.571	0.693
	N	7	7
R-(-) methadone	r		0.960
	sig		0.001**
	N		7

Table 20: Correlations: Buprenorphine dose and changes in plasma buprenorphine concentrations. *p < 0.05, ** p < 0.01.

		Buprenorphine	Norbuprenorphine
Buprenorphine dose	r	0.871	0.924
	sig	0.011*	0.003
	N	7	7
Buprenorphine	r		0.967
	sig		< 0.001**
	N		7

7.4.1.4 Emotional Reactivity – Primary Measures (VAS)

Spaghetti Plots for Depression Reactivity

The spaghetti plots (Figure 32) showed individual VAS-depression scores before and after depression induction. No outliers were identified and a visual inspection of the data did not reveal any apparent sub-groups within the data.

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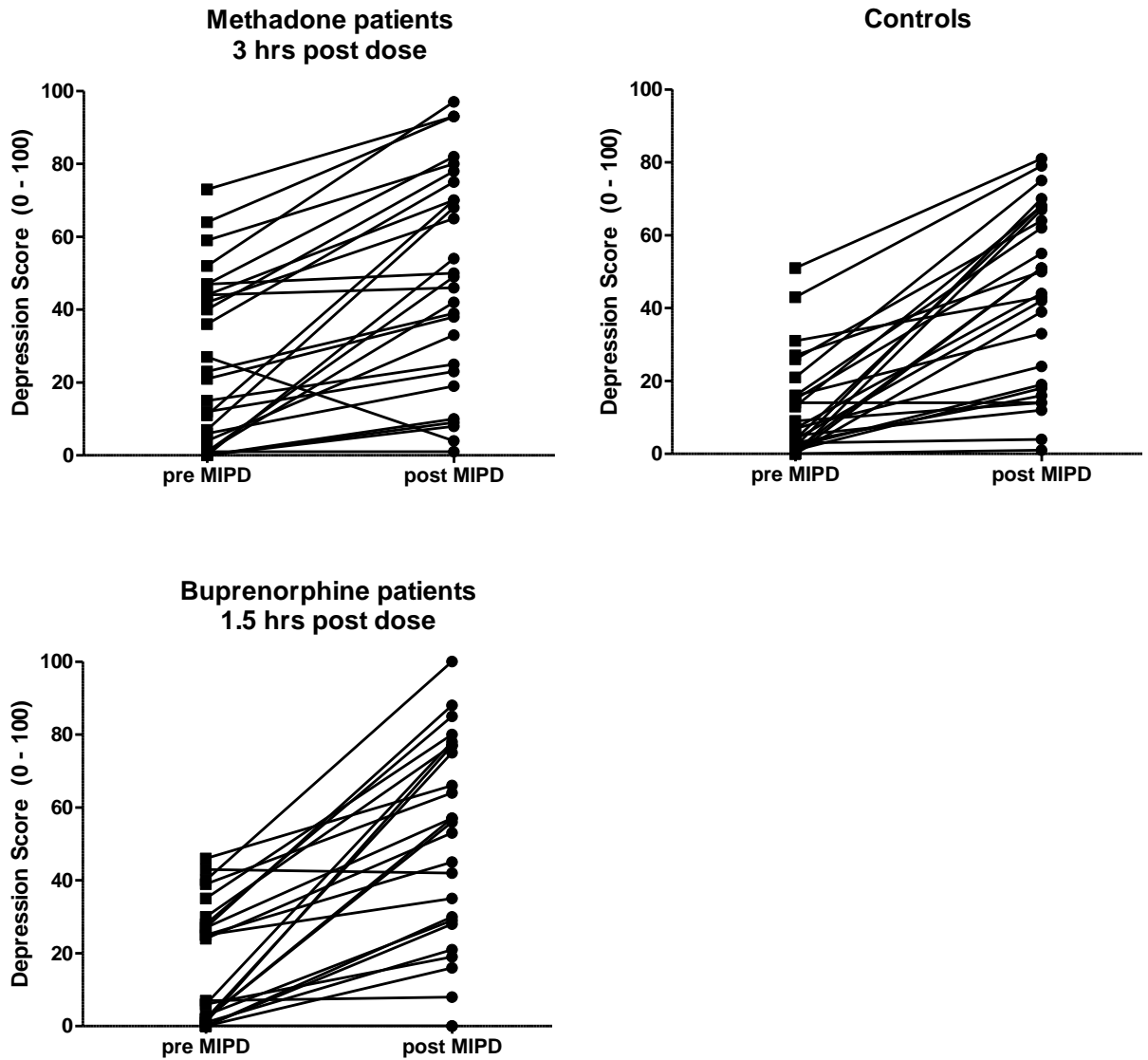
Figure 32: Spaghetti Plots of depression score (VAS-D) pre and post depression induction. Spaghetti plots for the methadone group, buprenorphine group, and controls at times corresponding with peak opioid plasma concentrations.

Spaghetti Plots for Elation Reactivity

The spaghetti plots in Figure 33 showed the VAS-elation scores pre and post elation induction of controls and opioid dependent groups. Though the plots revealed that the elation induction was detrimental to increasing elation in a few methadone patients, there is little evidence this was systemic in the group.
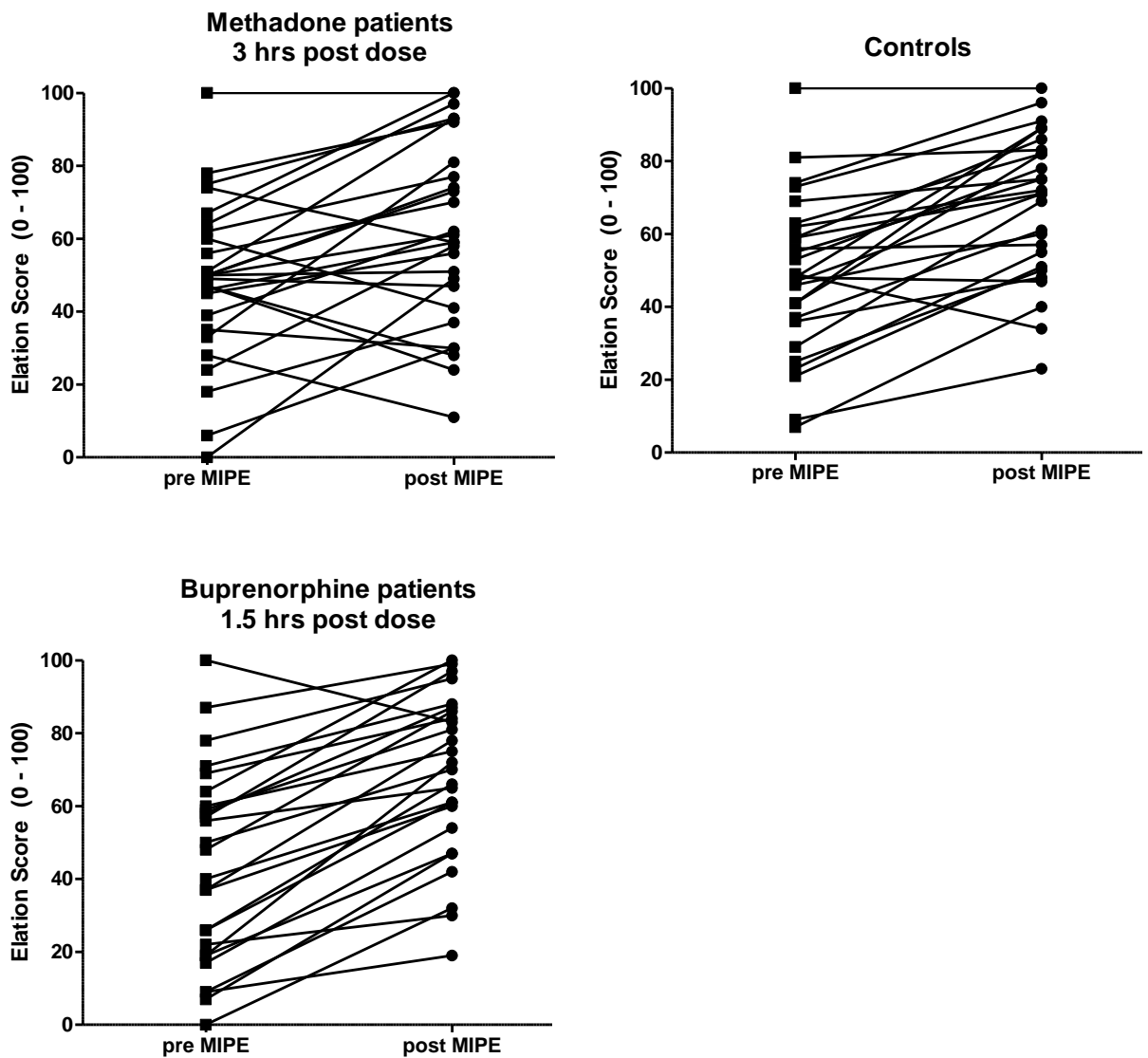
Figure 33: Spaghetti Plots of elation score (VAS-E) pre and post elation induction. Spaghetti plots for the methadone group, buprenorphine group, and controls at times corresponding with peak opioid plasma concentrations.

7.4.1.5 Mean Time Plots for Depression and Elation Reactivity

Mean time plots (Figure 34 and Figure 35) show the overall effect of the induction procedures on emotion. Comparing pre and post depression induction means (pre MIPD and Post MIPD), Figure 34 showed that all three groups responded to the depression induction procedure. Figure 35 likewise showed that the elation induction procedure was successful for all three groups (comparing pre MIPE and post MIPE). Comparing the two figures showed that depression induction was approximately twice as effective in inducing emotion than elation induction. This result is consistent with study 1 (Chapter 4) and the research literature in

general, where negative emotional induction is considered a more powerful inducer than positive induction.
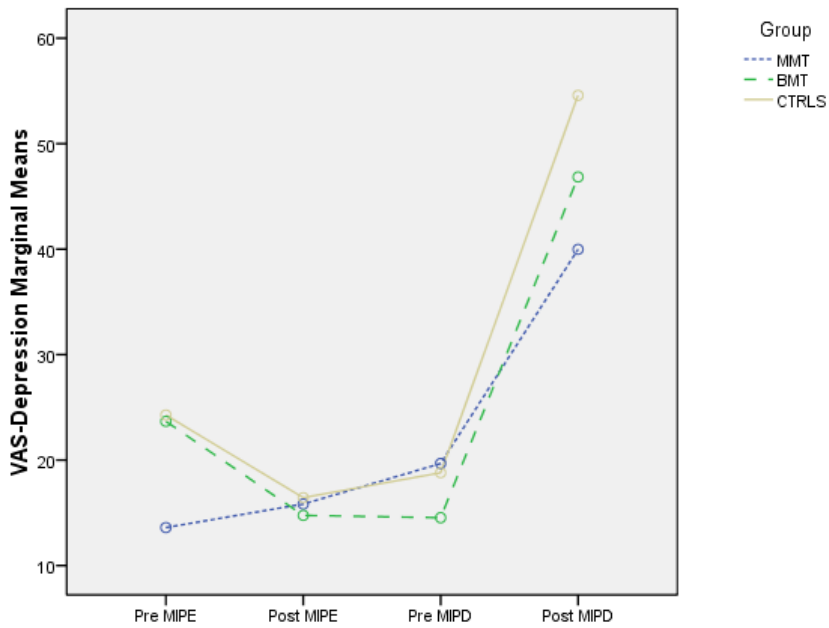
Covariates appearing in the model are evaluated at the following values: total BDI = 17.80

Figure 34: Mean time plots for Depression score (VAS-D). Plots show VAS-D scores pre and post mood inductions at time corresponding with peak opioid concentration times.
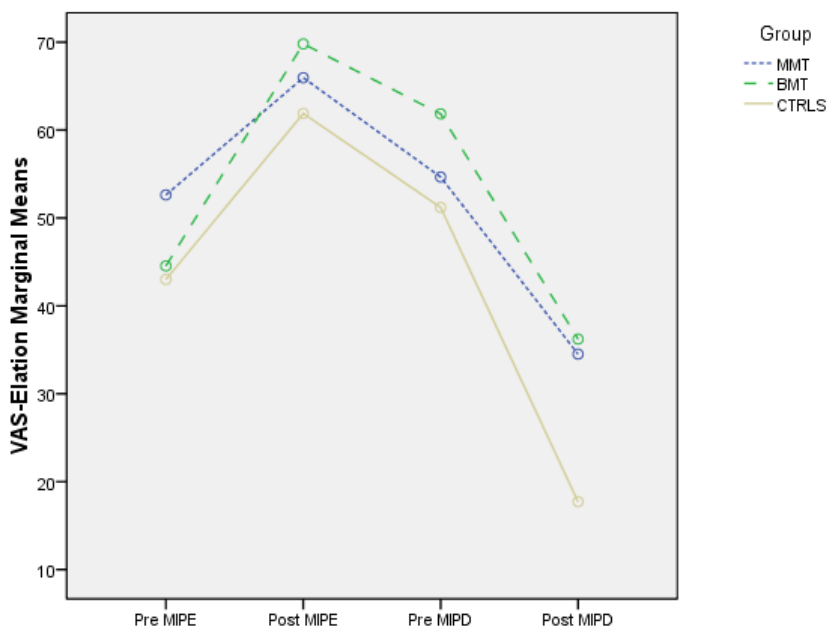
Covariates appearing in the model are evaluated at the following values: total BDI = 17.80

Figure 35: Mean time plots for Elation score (VAS-E). Plots show VAS-E scores pre and post mood inductions at time corresponding with peak opioid concentration times.

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7.4.1.6 Effectiveness of mood induction procedure measured by VAS

Similar to the analysis in study 1, the graphs were re-formatted to focus solely on the effect of elation induction on elation score (change in VAS-E after MIPE), and depression induction on depression score (change in VAS-D after MIPD). The effect of MIPE on VAS-D or MIPD on VAS-E was not of primary interest and therefore removed from further analysis. Figure 36 and Figure 37 shows elation (VAS-E) and depression (VAS-D) emotional state scores for controls, buprenorphine and methadone groups, pre- and post- induction. Figure 36 shows that controls ($p < 0.001$), buprenorphine ($p < 0.001$) and methadone ($p = 0.003$) groups showed higher elation scores after elation induction (means: controls pre-elation 48.6 ± 4.2, controls post-elation 68.0 ± 3.8; buprenorphine pre-elation 43.3 ± 5.3, buprenorphine post-elation 68.4 ± 4.4; methadone pre-elation 48.3 ± 4.2, methadone post-elation 61.2 ± 4.9). Figure 37 similarly shows that controls ($p < 0.001$), buprenorphine ($p < 0.001$) and methadone ($p < 0.001$) groups showed higher depression scores after depression induction (means: controls pre-depression 11.9 ± 2.6, controls post-depression 43.1 ± 4.7; buprenorphine pre-depression 16.1 ± 3.2, buprenorphine post-depression 49.5 ± 5.7; methadone pre-depression 25.1 ± 4.5, methadone post-depression 48.9 ± 5.7). Therefore the elation and depression inductions were effective for all groups.
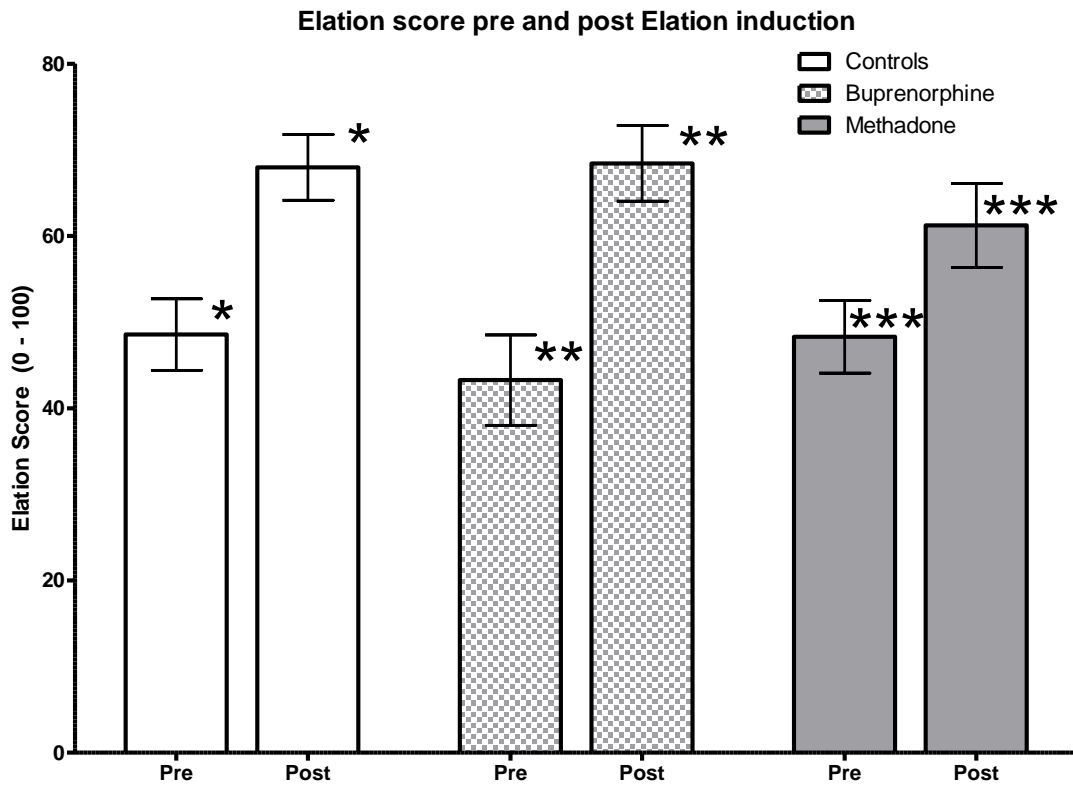
Figure 36: Emotional State scores for Elation. Elation induction successful for all groups (* controls p < 0.001; ** buprenorphine p < 0.001; *** methadone p = 0.003). Controls n = 27; buprenorphine n = 26; methadone n = 27. Bars show mean ± standard error.
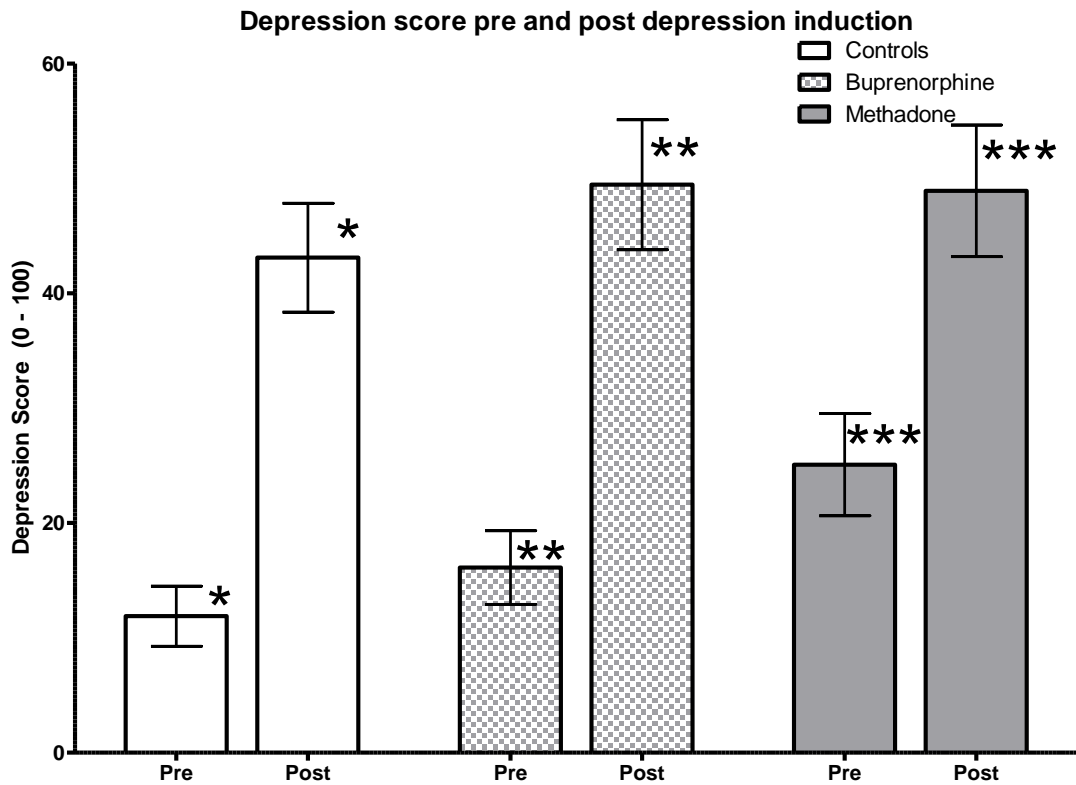
Figure 37: Emotional State scores for Depression. Depression induction successful for all groups (* controls p < 0.001; ** buprenorphine p < 0.001, *** methadone p < 0.001). Controls n = 27; buprenorphine n = 26; methadone n = 27. Bars show mean ± standard error.

7.4.1.7 Effects of methadone and buprenorphine on Emotional Reactivity – Primary Measures (VAS)

Emotional reactivity was calculated as the difference between post-induction emotional state and pre-induction emotional state. As there was significant difference in BDI scores between groups and trait depression may affect emotional reactivity, BDI was included as a covariate in the analysis. Figure 38 and Figure 39 shows elation and depression emotional reactivity of controls, buprenorphine and methadone groups corrected for BDI score, at a time corresponding with peak plasma opioid concentrations. Figure 38 shows the change in elation score after elation induction for controls, buprenorphine and methadone groups. Between group effects were significant for elation reactivity (F[2] = 3.16, p = 0.048. Estimated means: controls elation reactivity 18.9 ± 3.6; buprenorphine elation reactivity 25.3 ± 3.4; methadone elation reactivity 13.3 ± 3.5). Pairwise comparisons revealed that the buprenorphine (p > 0.05) and methadone (p > 0.05) groups were not significantly different to controls in elation

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reactivity, but were significantly different from each other (p = 0.015). No other comparisons were significantly different.

Figure 39 shows depression reactivity (post-induction depression score – pre-induction depression score) of controls, buprenorphine and methadone groups, corrected for BDI score, at a time corresponding with peak opioid plasma concentrations. There was a significant difference between the groups (F[2] = 3.27, p = 0.043. Estimated means: controls depression reactivity 35.8 ± 4.4; buprenorphine depression reactivity 32.3 ± 4.2; methadone depression reactivity 20.3 ± 4.3). Pairwise comparisons revealed that the methadone group showed lower depression reactivity than the buprenorphine group (p = 0.044). The methadone group was also less reactive than the control group (p = 0.021). The buprenorphine group was not different to controls (p > 0.05) on depression reactivity.
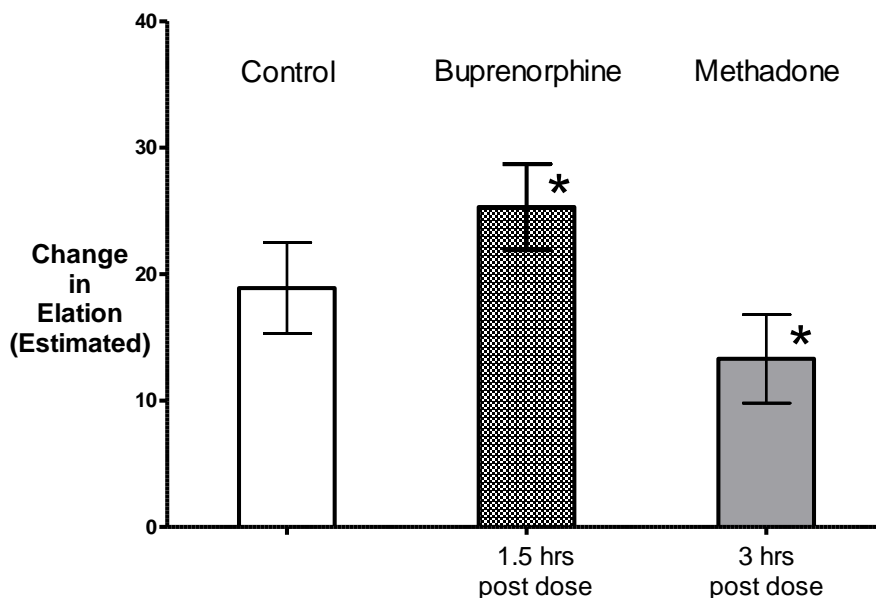
Figure 38: Change in Elation Scores (Elation Reactivity). Results show a difference in change in elation score (elation reactivity) between controls, buprenorphine and methadone groups. Pairwise comparisons showed the methadone group were lower in emotional reactivity compared with the buprenorphine group (* p = 0.011). Bars show mean ± standard error. Figure shown is corrected for BDI.

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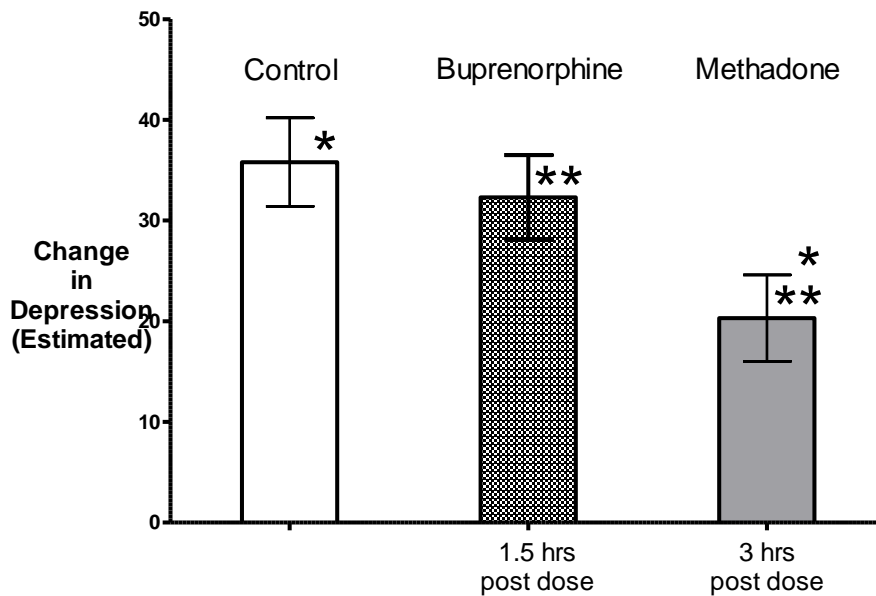
Figure 39: Change in Depression Scores (Depression Reactivity). Results showed no significant difference in depression reactivity between the three groups ($p > 0.05$). With BDI as a covariate, depression reactivity between groups was significantly different ($p = 0.043$). Pairwise comparisons showed that the methadone group were lower in depression reactivity compared to the buprenorphine (** $p = 0.044$) and controls (* $p = 0.021$). Bars show mean ± standard error. Figure shown is corrected for BDI.

7.4.1.8 Correlations between Elation and Depression Reactivity and Opioid Dose

Table 21 shows the correlations (zero-order correlations, and partial correlations with BDI as a covariate) between methadone or buprenorphine dose and emotional reactivity (as measured by VAS). After controlling for BDI, methadone dose negatively correlated weakly with elation reactivity ($r = -0.40$, $p < 0.05$). Methadone dose did not correlate with depression reactivity. Therefore in methadone patients, higher methadone doses were predictive of greater blunting in elation reactivity. In buprenorphine patients, dose correlated with depression reactivity ($r = 0.41$, $p < 0.05$). The correlation was non-significant after controlling for BDI. Opioid concentration [R-(-), S-(+) plasma methadone concentrations; buprenorphine, norbuprenorphine plasma concentrations] were also reported but sample size was insufficient to draw any conclusions.

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Table 21: Correlations: Opioid dose vs emotional reactivity. Zero-order correlations and partial correlations corrected for BDI. *p < 0.05; **p < 0.01, ***p < 0.001

	Elation Reactivity	Depression Reactivity
Methadone dose (n = 25)	-.36	-.09
Partial covariate BDI (n = 24)	-.40*	-.08
ΔR-methadone (n = 5)	-.95**	.35
Partial covariate BDI (n = 4)	-.95**	.30
ΔS-methadone (n = 5)	-.93**	.22
Partial covariate BDI (n = 4)	-.94**	.18
Buprenorphine dose (n = 24)	.36	.41*
Partial covariate BDI (n = 23)	.20	.25
Buprenorphine conc (n = 5)	.82*	.85*
Partial covariate BDI (n = 4)	1.0***	1.0***
Norbuprenorphine conc (n = 5)	.76*	.83*
Partial covariate BDI (n = 4)	.75	.85*

7.4.1.9 Emotional reactivity – Secondary Measures (POMS)

The Profile of Mood States (POMS) was also used as a secondary measure to quantify the effect of opioids on emotional reactivity. The effectiveness of the depression induction was determined by comparing the effect of the induction on the depression subscale (POMS-D) and on the total mood disturbance subscale (POMS-TMD).

7.4.1.10   Evaluating MIPD measured by POMS-D

Spaghetti Plots

The spaghetti plots (Figure 40) show the POMS-Depression scores before and after the depression induction procedure, for controls and the opioid dependent groups. There was no evidence of distinct subsets within each group that may bias findings. No outliers were identified.

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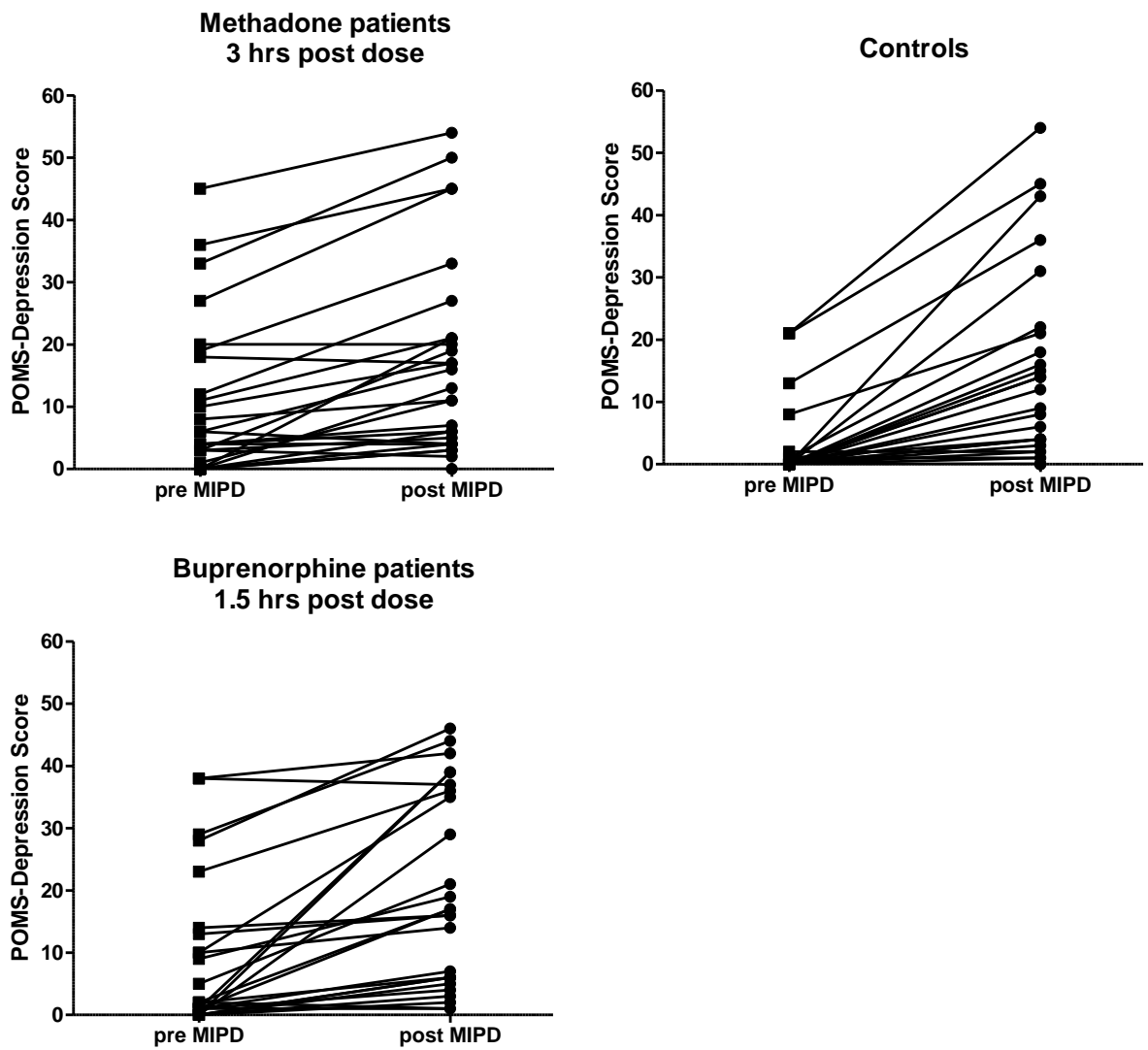
Figure 40: Spaghetti Plots of depression score (POMS-D) pre and post depression induction. Spaghetti plots for the methadone group, buprenorphine group, and controls at times corresponding with peak opioid plasma concentrations.

Mean Time Plots

Figure 41 shows the mean time plots before and after elation and depression induction procedures. The figure shows that in each group (controls, methadone and buprenorphine groups), the elation induction reduced POMS-D and that the depression induction increased POMS-D. As the effect of the elation induction on POMS-D was not of primary interest, it was not analysed further.
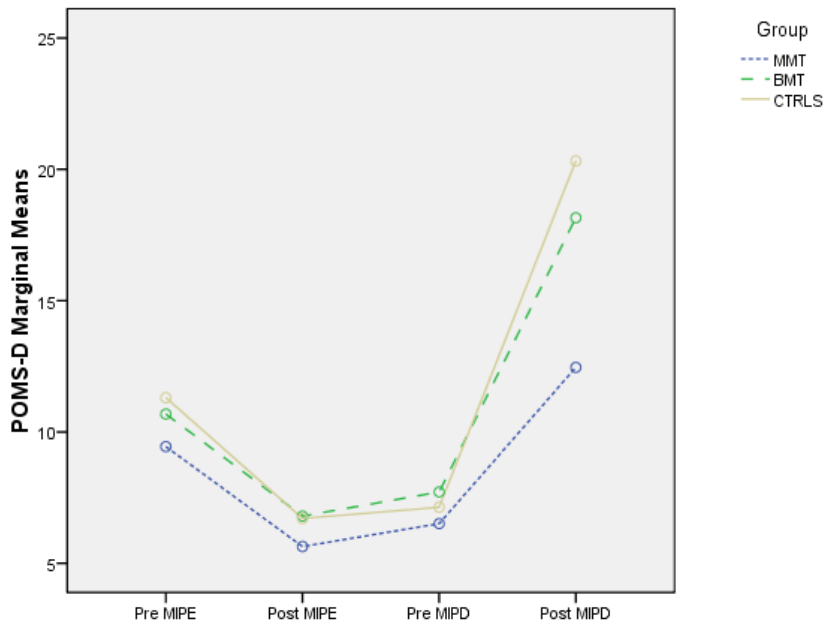
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Covariates appearing in the model are evaluated at the following values: total BDI = 17.80

Figure 41: Mean time plots for Depression score (POMS-D). Plots show POMS-D scores pre and post mood inductions at time corresponding with peak opioid concentration times. Graph corrected for BDI score.

7.4.1.11   Effects of methadone and buprenorphine on Emotional Reactivity – Secondary Measures (POM-Depression)

For change in POMS-D before and after depression induction (depression reactivity), one way ANOVA revealed that there was no significant differences between the three groups ($F[2]$ = 1.37, p = 0.260) and no pairwise comparisons were significant. As BDI was added as a covariate in the primary measure analysis, it was also added to the model here. With BDI as a covariate, there was no overall significant difference between the groups ($F[2]$ = 2.57, p = 0.083. Estimated means: methadone 6.2 ± 2.1; buprenorphine 10.4 ± 2.0; controls 13.2 ± 2.1), see Figure 42. However, pairwise comparisons revealed a significant difference between the methadone group and controls (methadone vs controls, p = 0.029; all other comparisons p > 0.05).

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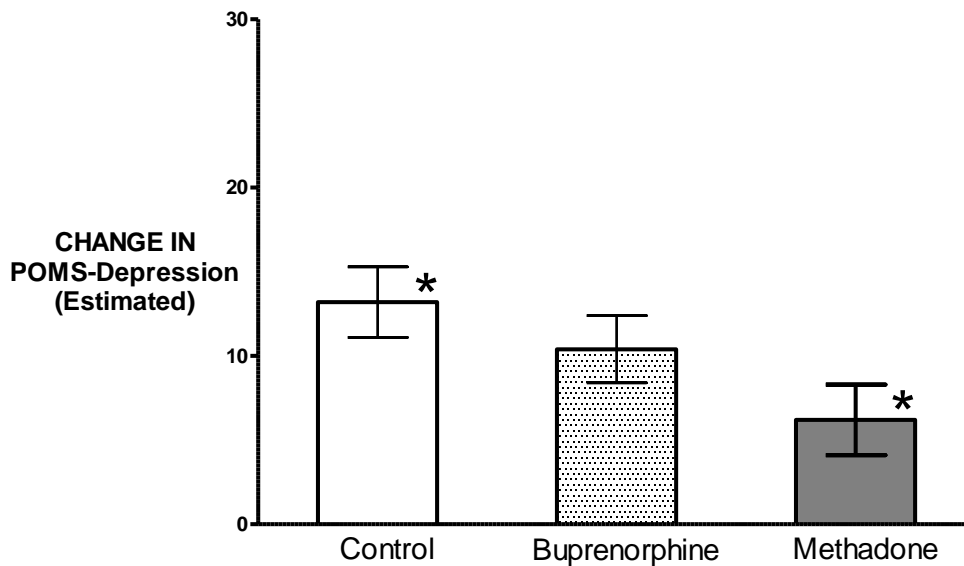
Figure 42: Change in Depression Scores (Emotional Reactivity) as measured by POMS-D. The methadone group was lower in depression reactivity compared with controls (* p = 0.029). Bars show mean ± standard error. Figure shown is corrected for BDI.

7.4.1.12   Evaluating MIPD measured by POMS-TMD

Spaghetti Plots

The pre and post depression induction spaghetti plots for POMS-Total Mood disturbance (Figure 43) showed a similar pattern evident with the spaghetti plots for POMS-Depression shown earlier. That is, the depressive induction procedure was effective in increasing global negative emotional disturbance.
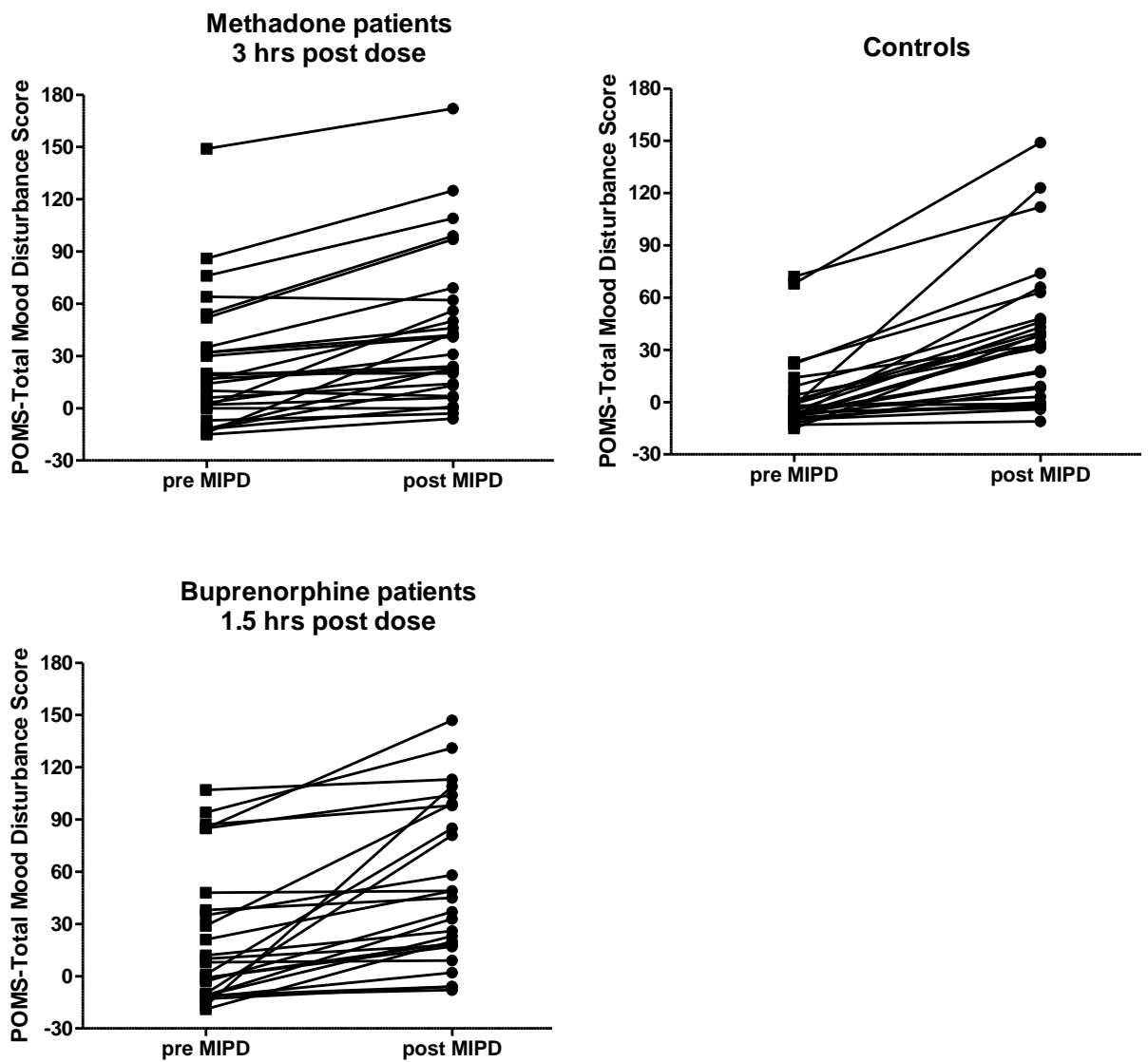
Figure 43: Spaghetti Plots of total mood disturbance score (POMS-TMD) pre and post depression induction. Spaghetti plots for the methadone group, buprenorphine group, and controls at times corresponding with peak opioid plasma concentrations.

Mean Time Plots

Figure 44 shows the mean total mood disturbance pre and post depression induction scores. The graph has also been corrected for the covariate BDI score (see next section). As the effect of elation induction on POMS-TMD was not of primary interest, it was not further analysed.
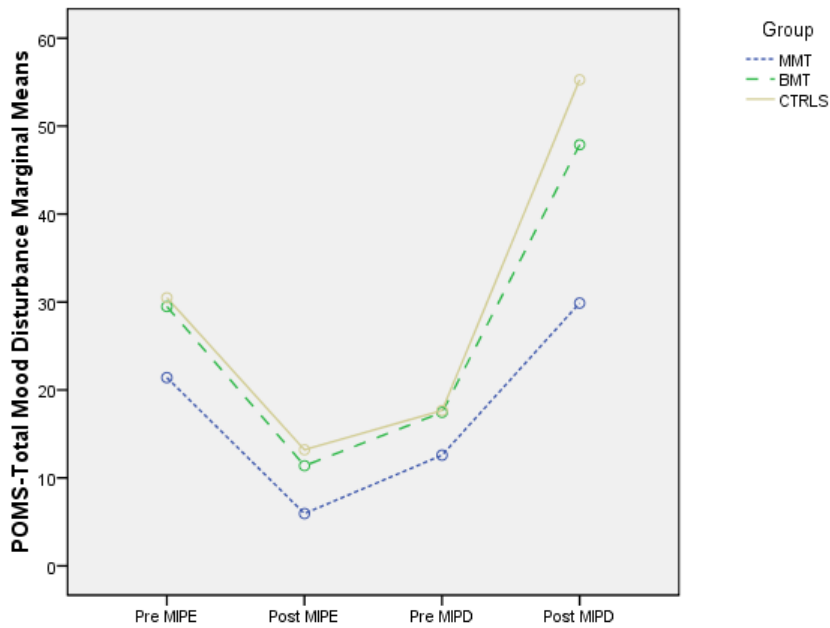
Covariates appearing in the model are evaluated at the following values: total BDI = 17.80

Figure 44: Mean time plots for Total Mood Disturbance score (POMS-TMD). Plots show POMS-TMD scores pre and post mood inductions at time corresponding with peak opioid concentration times. Graph corrected for BDI score.

7.4.1.13   Effects of methadone and buprenorphine on Emotional Reactivity – Secondary Measures (POM-Total Mood Disturbance)

Comparing the change in total mood disturbance (POMS-TMD) due to depression induction across the three groups revealed no significant difference amongst the three groups ($F[2] = 1.83$, $p = 0.167$) and no significantly different pairwise comparisons. With BDI added as a covariate (see Figure 45), there was no significant difference amongst the three groups ($F[2] = 2.95$, $p = 0.058$. Estimated marginal means: methadone 18.0 ± 5.5; buprenorphine 30.4 ± 5.2; controls 37.6 ± 5.5). Pairwise comparisons show that the methadone group and controls were significantly different ($p = 0.020$; all other comparisons $p > 0.05$).

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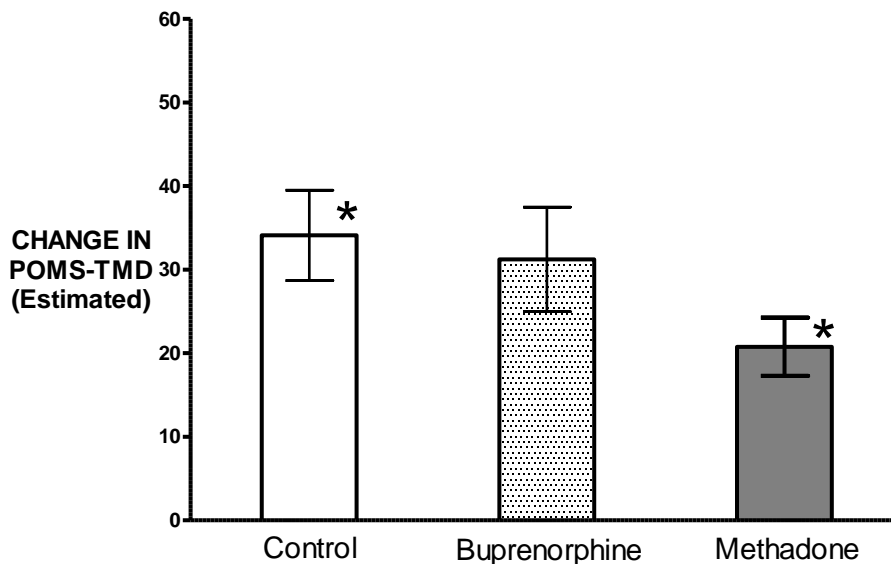
Figure 45: Change in Mood disturbance (Emotional Reactivity) as measured by POMS-TMD. The methadone group was lower in total mood disturbance reactivity compared to controls (* p = 0.020). Bars show mean ± standard error. Figure shown is corrected for BDI.

7.5   DISCUSSION

In this study, methadone, buprenorphine and control subjects were induced into elation and depression mood states. Results showed that both induction techniques were effective in inducing mood in all three groups at a time corresponding with peak plasma opioid concentrations. This supports previous research by our group showing that Velten's induction procedures are effective in inducing mood in control subjects and methadone maintained patients. The results also show that subjects reacted more strongly to depression mood induction than elation induction, consistent with research showing that depression induction techniques are more effective (Martin 1990). Also, depression scores prior to depression induction showed that the methadone group were higher in depression score than controls. After controlling for BDI, the methadone group and controls had similarly pre-induction depression scores. However, the buprenorphine group had lower depression scores than either the methadone group or controls, suggesting that buprenorphine may have a protective effect in depression state, and supporting the notion that buprenorphine has anti-dysphoric effects due to κ-opioid antagonism. It should be acknowledged that as subjects were not randomised into the groups, these results may be explained if there were pre-existing differences between the groups.

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Furthermore, emotional reactivity differed amongst the three groups. At a time corresponding with peak plasma opioid concentrations, methadone maintained subjects showed less elation reactivity compared with buprenorphine subjects after controlling for BDI. Likewise, primary VAS measures showed depression reactivity of the methadone group was significantly lower than controls and the buprenorphine group, at times corresponding with peak plasma opioid concentrations. The methadone group also showed smaller depression reactivity compared with controls when measured using secondary POMS measures. Unlike study 1 which added both age and BDI as covariates, this study only added BDI as a covariate. However there is some research showing that sadness reactivity increases in later life (Seider et al. 2011). As the opioid dependent groups were significantly older than controls, this may have attenuated the differences between the groups and that emotional blunting may be more pronounced in a younger opioid dependent cohort.

Overall these results suggest that at peak plasma opioid concentrations, buprenorphine has little impact on emotional reactivity whilst methadone reduces reactivity to mood induction (after controlling for BDI). This indicates that of the two opioids, only methadone blunts elation and depression reactivity. Our previous research has shown that methadone blunts emotional reactivity at peak versus trough methadone plasma concentrations. These results suggest that the differing pharmacological profiles of these two opioids differentially impact on emotional pathways. As methadone is a full μ-opioid agonist, activity at this receptor site may inhibit susceptibility to emotionally salient stimuli.

As decreased emotional reactivity may be associated with impairment in general psychological functioning, buprenorphine may be a more suitable maintenance treatment option under certain circumstance as it is a partial agonist, having a ceiling effect when bound to the μ-opioid receptor. There is increasing evidence of diminished adverse effects associated with use of buprenorphine, including lower risk of overdose (Auriacombe et al. 2004), fewer problems of erectile dysfunction (Hallinan et al. 2008) and reduced impairment of cognitive functioning (Pirastu et al. 2006; Rapeli et al. 2007). The present study suggests that reduced blunting of emotional response should be included as a potential advantage for buprenorphine administration as an opioid maintenance drug.

Further research is needed to determine the translatability of these results to other opioids. While it seems likely on the basis of the comparable evidence from animal models, it would

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be of great interest to test whether other full agonists such as morphine produce similar results as evident with the methadone group.

7.5.1   LIMITATIONS

Study 1 showed that methadone patients and controls showed similar emotional reactivity scores at trough plasma methadone concentrations. It was only at a time corresponding with peak plasma methadone concentrations that methadone patients showed blunted emotional reactivity. As only reactivity at peak plasma opioid concentrations was tested in study 2, comparisons of emotional reactivity at trough and peak plasma buprenorphine concentrations cannot be made. There is no evidence to suggest that emotional reactivity at trough plasma buprenorphine concentrations would be different than at peak times. However further research that tests buprenorphine patients at both time points would clarify this.

As study 1 and study 2 share a common methodology, the limitations considered in study 1 are also appropriate to consider in this study. Group membership in this study was not randomised, rather pre-determined by the maintenance treatment program each subject was enrolled in at time of participation. However, demographic data showed only a few differences between the opioid groups who were similar on: psychopathology (trait anxiety and trait depression), frequency of chronic pain, depressive illness or other mental illness, employment status, and age. However there were a number of differences between controls and the opioid group, with a major limitation being that the controls were university students. A better matched control group (similar to that used in study 1) would strengthen the findings. Though there is limited evidence (Hamidi et al. 2010) to suggest that alexithymia is prevalent in substance abuse patients (particularly with stimulant abuse), it is also an unlikely explanation for the findings in this study. This is because buprenorphine patients did not show impaired emotional reactivity in this study. However, replicating the findings of this study using a non-opioid substance dependent group as controls would have merit.

7.6   CONCLUSION

The results of the present study show that methadone blunts both elation and depression emotional reactivity and can be added to the range of effects that are observable at the time of peak plasma methadone concentrations. However, buprenorphine exhibits no blunting effect

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on emotional reactivity at peak buprenorphine plasma concentrations. The differences in effect on emotional pathways shown here are important in understanding the effects of opioid maintenance treatment on social and psychological functioning and on the pharmacology of these two opioids.

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CHAPTER 8 - OVERALL DISCUSSION OF BOTH STUDIES AND OVERVIEW

8.1 REVISITING BRIEFLY THE RATIONALE FOR THE THESIS

Opioids have been extensively researched, though the effect of this class of drugs on emotional systems is arguably lacking. As the psychopharmacological profile of a drug is important scientifically and clinically, this thesis determined the impact of two common therapeutic opioids on emotional reactivity. This question was first raised from the observation that individuals exposed to chronic opioid administration demonstrated hyperalgesia to certain types of pain. As opioids are implicated in both pain and emotion processes, this prompted whether opioid maintenance treatment patients were hyper-reactive to emotional stimuli in a similar manner to their evident hyperalgesia.

Opioids such as methadone and buprenorphine see widespread use as maintenance drugs in the treatment of opioid dependence. As mood and emotion have an important effect on daily living and mental health, it is important to look at the effect of opioids on emotional systems. This is especially important for opioid maintenance drugs as they are administered daily for considerable lengths of time during treatment. Methadone as a full μ-opioid agonist generates positive emotion and feelings such as elation and euphoria (Haertzen 1966). In the opioid dependent user these effects are often reported as milder or even absent. However little is known on the effect of methadone on emotional processing systems in opioid dependent users.

With repeated opioid administration, tolerance to opioid effects such as analgesia and euphoria develop. Using a 'drug-opposite' model (RL Solomon and Corbit 1974), tolerance is conceptualised as typical opioid effects of the drug on the body being counteracted by body responses that oppose and therefore attenuate those effects (though not sufficiently to completely nullify those effects). Many opioid effects fit this model. However some effects do not. For example, opioid dependent users experience profound hyperalgesia to cold pain and report negative mood states, despite opioid administration. Here the 'drug-opposite' response has dominated any opioid effect, resulting in an opioid effect opposite to that predicted.

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There are a few lines of evidence that establish a profile of the effect of opioids on emotions generally. The first is animal research that investigated the impact that opioids have on affective behaviours such as social attachment. Here μ-opioid agonists have been shown to have a significant impact on animals in distress. For example, morphine has been found to reduce the number of distress vocalisations in young animals induced by social separation (Warnick, McCurdy, and Sufka 2005). The forced swim test is another animal model and has shown that μ-opioids have an anti-depressant/anti-anxiety effect on rats (Fichna et al. 2007; Mague et al. 2003). The body of work on animal research therefore suggests that opioids reduce negative emotional reactivity. The second line of research comes from human studies, showing that opioids impact on emotional state. Opioids induce feelings of euphoria and elation with the reported strength of euphoria dependent on dosage (Webster et al. 2011). Opioids have also been shown to diminish mood disturbance (Dyer et al. 2001).

As opioids play a role in emotion and opioid dependent users show heightened pain sensitivity and report negative mood state, there may also be deleterious effects on emotional regulatory systems. Emotional reactivity was investigated in this thesis to determine whether patients in methadone maintenance treatment were hypersensitive to an emotional task in a manner analogous to their demonstrated hyperalgesia in cold pain tasks. The findings were then expanded to include patients in buprenorphine maintenance treatment to determine the effect of a partial μ-opioid agonist on emotion processing systems.

8.2   SUMMARY OF MAJOR FINDINGS

The primary aim of this thesis was to determine the effect of opioids on emotional reactivity in opioid dependent populations. A number of studies were devised and implemented that incrementally achieved this overall aim.

Study 1 verified that methadone maintenance patients were hyperalgesic to cold pain and that it was unlikely due to differences in pain coping strategies. Compared with trough plasma methadone concentrations, cold pain tolerance did not significantly increase at peak plasma methadone concentrations. For methadone treatment patients with no more than mild depression symptomatology, trait anxiety and total depression score or its affective

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component were predictive of pain tolerance. These higher order psychological measures were not predictive of pain tolerance in those with no previous history of opioid abuse.

Study 1 also demonstrated that methadone patients demonstrated blunted reactivity to elation and depression mood induction as assessed by Visual Analogue Scales, at times corresponding with peak plasma methadone concentrations. This was despite those patients showing hyperalgesia to cold pain. Though pain and emotion have a common neurobiological basis (Zubieta et al. 2001; Zubieta et al. 2003; Zubieta et al. 2002), deficits in brain systems affecting cold pain experience seem not to affect emotional reactivity processing in a similar manner. Measuring emotional reactivity using POMS scales showed that methadone patients demonstrated blunted depression reactivity compared with controls. POMS scales did not show a difference in magnitude with increased plasma methadone concentrations, though POMS may have been insufficiently sensitive to measure emotional reactivity.

Study 2 expanded the findings by determining the effect of buprenorphine on emotional reactivity in opioid dependent users. Buprenorphine and methadone maintenance treatment patients were induced into elative and depressive emotional states, and compared with opioid naïve controls. The eligibility criterion was relaxed so that the results were generalizable to typical opioid dependent users. The results showed that at the time of likely peak plasma opioid concentrations, methadone blunted elation and depression reactivity (replicating the findings of study 1). Buprenorphine maintenance treatment patients showed no evidence of impaired emotional reactivity, suggesting that partial µ-opioid agonists do not blunt emotional reactivity like the full µ-opioid agonist methadone. POMS scales also showed that depression reactivity was blunted in methadone patients, while buprenorphine patients were similar to controls.

The findings from this thesis have added to the pharmacodynamic prolife of opioids. This thesis has provided the first empirical evidence that µ-opioid agonists impact emotional reactivity.

8.3 IMPLICATIONS OF THE FINDINGS

This thesis demonstrates that opioids may have a more complex interaction with emotion than previously reported in the literature. Though research has so far been primarily interested in

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the effects of opioids in changing emotional state [either acutely (Haertzen 1966) or after repeated opioid administration (Dyer et al. 2001)], the effect of opioids on emotional processing systems has received less attention. So far researchers have investigated the effect of opioids on emotional appraisal (Kornreich et al. 2003; Aguilar de Arcos et al. 2008), primarily in the context of how dysfunctional appraisal may ultimately promote relapse to opioid abuse. Research have also focused considerably on the anti-depressant or anxiolytic properties of opioids (Berrocoso et al. 2009), generally using a methodology that evaluates the extent that opioids improve psychopathology. However, these studies do not address to what degree opioids impact emotional processing systems that may underlie such a change in psychopathology. The findings from this thesis adds to the knowledge base of how opioids affect emotional processing, and furthermore that the effect is moderated depending on pharmacokinetics.

There are a number of implications that should now be considered when choosing an opioid maintenance drug or whilst managing an opioid maintenance treatment patient, including the potential impact of a compromised emotional reactivity system on psychopathology and its treatment, potential long term effects of an impaired emotional response system, and other related implications in opioid maintenance treatment.

8.3.1   EMOTIONAL REACTIVITY AND PSYCHOPATHOLOGY

Emotional dysregulation is considered a key component of psychopathology (Berenbaum et al. 2003; Cicchetti, Ackerman, and Izard 1995; Gross et al. 1995; Kring and Werner 2004), with emotional disturbance being a symptom for most disorders (Kring and Moran 2008) in the DSM-IV-TR (American Psychiatric Association 2000). Changes in emotional reactivity could therefore have a pronounced effect on general psychological functioning. The findings of this thesis may explain why Maremmani et al. (1999) reported that methadone patients with psychiatric comorbidity needed 1.5 times the stabilisation dose of methadone patients diagnosed only with opioid dependence. The symptoms reported included anxiety, mood swings, and impulse dis-control. Stabilisation may have partly arisen from suppressing emotional reactivity driving or resulting from some of these symptoms. However Maremmani et al. (2006) also reported that both buprenorphine and methadone treatment improved psychopathology in patients still retained in treatment after three months. As baseline psychopathology was more severe in the methadone patients, methadone may be optimal for

drastic improvement while buprenorphine may be more appropriate for milder psychopathology. Though buprenorphine also improved psychopathology, there is some evidence that the mechanism for this may at least partly be through κ-opioid antagonism. For example, a case study of buprenorphine treatment patients administered buprenorphine (4mg / day) and naltrexone (50mg / day) reported better psychopathology including reduced dysphoria, depression, irritability, depression and anxiety (Lucchini 2003).

The effect of methadone on emotional systems may be particularly compounded in maintenance patients exhibiting depression symptomology. Though clinical report and practice suggests that individuals with major depressive disorder have heightened propensity for negative emotions (especially sadness), the research shows the opposite is true. Compared to the non-depressed, individuals with major depressive disorder have similar (Rottenberg et al. 2002) or blunted reactivity to negative emotional stimuli (J. Gehricke and Shapiro 2000; Renneberg et al. 2005). Likewise depressed subjects have a diminished reactivity to positive emotional stimuli such as imagery (J.-G. Gehricke and Fridlund 2002) and emotional films (Renneberg et al. 2005). It is possible that depressed patients on methadone maintenance may experience an additional effect on emotional blunting, though it is unclear to what extent. Methadone may thus impede recovery by maintaining a compromised emotional response system in patients with depression disorders. Alternatively, blunting emotional reactivity with repeated opioid use may contribute or drive depression symptomatology in susceptible individuals.

Conversely, lessoned emotional response may improve psychopathology in overly emotionally active individuals. According to the DSM-IV-TR (American Psychiatric Association 2000), hyper-reactivity to environmental stimuli is a feature in a number of disorders, particularly Borderline Personality Disorder (Johnson et al. 2003). The hyper-emotion theory by Johnson-Laird, Mancini, and Gangemi 2006 supports this notion, proposing that some psychological illnesses are bolstered by situation appropriate emotions but at inappropriate intensities. Anxiety disorders may also be another class of disorders where a heightened anxious emotional response extends beyond what is appropriate for the situation, with this dysfunctional response closely involved in the development or maintenance of the psychopathology of the disorder (Cole, Michel, and Teti 1994). Repeated opioid exposure that blunts emotional reactivity in these individuals may be beneficial under these circumstances, returning hyper-reactive emotional response systems towards healthier norms.

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In conclusion, the administration of opioids in maintenance treatment programs has an impact on the psychopathology of patients beyond that related to opioid abuse and addiction. Compromised emotional reactivity associated with co-morbid disorders is a factor that should be considered when implementing an opioid maintenance treatment plan. However a considered approach is needed as the relationship of psychological illness and the impact of suppressing emotion response systems for protracted periods using opioids has not been directly investigated. The importance of emotion response systems in general may provide further insight.

8.3.2   LONG TERM EFFECTS OF IMPAIRING EMOTION RESPONSE SYSTEMS

Emotion plays a vital role in learning and memory (Bradley et al. 1992), motivation, and adaptive behaviour. Baumeister et al. (2007) suggests that emotions play an adaptive function in behaviour, with an inability to experience appropriate emotions hindering future learning. Emotion suppression is also associated with worsened psychopathology (Gross and John 2003; Eftekhari, Zoellner, and Vigil 2009). This suggests that the findings here have important implications for the psychological and social functioning of people exposed to opioids.

Appropriate emotional reactions are vital in social behaviour and for the attainment of goals. For example, expressing too much anger when indignant may create hostility whilst too little anger may fail to express the significance the event has on oneself. As another example, an inability to express sadness may not convey to others the importance of an emotional event. Therefore emotional reactivity plays a critical role in healthy and adaptive responses. A study by Coifman and Bonanno (2009) investigated the effect of emotional context sensitivity in recovery from sudden unexpected bereavement. In individuals showing significant distress and depressive symptoms after bereavement, those that recovered after 18 months were differentiable from those that did not recover, by having context sensitive emotional responses. This suggests that appropriate and context sensitive emotions are required for normal functioning and recovery from significant traumatic events.

The findings of this work therefore suggest that long-term methadone maintenance may be detrimental in patients where, after considering the effects of other co-morbid disorder on emotionality, the overall emotional reactivity of the individual is blunted.

8.3.3   OTHER IMPLICATIONS IN OPIOID MAINTENANCE TREATMENT

The findings of this thesis may also explain why some individuals on methadone find it difficult to adhere to buprenorphine maintenance treatment after switching from methadone. Methadone's effect of blunting emotional reactivity may be an added incentive for patients 'self-medicating' with methadone as a way of coping with any heightened negative affect they would otherwise experience (Trull et al. 2000). Khantzian's 'self-medication' theory (Khantzian 1997) is consistent with this line of thought.

On a related point, emotional reactivity / lability has been found to be a predictor of opioid abuse. Emotional lability was predictive of higher scores on the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), with higher scores indicative of greater opioid abuse potential (Datz et al. 2011). Therefore, showing that emotional reactivity is blunted in methadone but not buprenorphine maintained patients suggests that the opioids used in treatment may play an additional role in opioid misuse. As emotional lability predicts opioid abuse, methadone's effect of blunting emotion may be a protective factor, a notion supported by evidence that suggests that when comparing treatment outcomes, methadone is slightly superior to buprenorphine treatment in reducing illicit opioid use (Barnett, Rodgers, and Bloch 2001; Schottenfeld et al. 1997; Strain et al. 1994).

8.3.4   IMPLICATIONS FROM OTHER FINDINGS IN THIS THESIS

Of more minor points, this thesis is the first to show that controlling for pain coping strategies in opioid dependent users is of merit. When controlling for coping strategies, methadone maintained patients still showed hyperalgesia to cold pressor pain. However the effect of methadone administration on cold pain tolerance may not be as marked as previously reported (Doverty et al. 2001). Further research is needed to better understand the role that methadone (or other opioids) have on pain sensitivity and pain coping strategies. A final minor point is that a three factor approach to assessing depression using the BDI scale may show differences

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between opioid maintenance patients and the opioid naïve. These may include differences in affective, cognitive and somatic components of depression that may aid interpretation in research work.

8.4   LIMITATIONS

A number of limitations of the thesis have already been addressed in previous chapters. Limitations include the lack of a randomisation between groups, use of convenience sampling, lack of matched controls, and the use of only one mood induction procedure.

As discussed previously, subjects were not randomised between groups. Instead opioid maintenance treatment currently undertaken by the patient defined group membership. Controls were not given opioids. Though randomisation minimises between group variability, it is impractical to have randomised subjects. For study 1, controls were recruited from sources that would increase the likelihood of decreasing between subject differences on a number of key indicators such as smoking and recreational drug use, and unemployment status. Study 2 used controls that were primarily university students or had previously attended university. A subsequent study comparing buprenorphine treatment patients with matched controls would be of interest. Furthermore, convenience sampling was used in both studies. Subjects were recruited only from South Australia and limited to metropolitan Adelaide. Subjects on opioid maintenance treatment were recruited either due to their contact with the drug clinic where the research was based, or were patients of the two pharmacies that participated in recruitment. Though these limitations do put restraints on the generalisabilty of the findings in this thesis, sampling subjects from both a public source (the drug clinic) and private sources (two community pharmacies) has improved the study's ability to speculate that these findings may be more widely generalised. Though controls from study 2 were not as closely matched as anticipated, the inclusion of two different control groups across both studies does increase generalisability.

Another limitation is the use of only Velten's mood induction procedure to induce emotion. Velten's induction procedure was chosen due to its simplicity and directness of technique. However there are a wide range of induction procedures that include autobiographic recollection, audio or visual manipulation, suggestion techniques, manipulation inductions, or methods that combine a number of these procedures (Martin 1990). Further research that

investigates the effect of other emotional induction techniques would be of value to confirm the findings of this thesis. The inclusion of a physiological measure of emotion such as the startle reflex would be of particular value as it may be easier to adapt into a clinician tool.

Arguably the largest limitation of this body of work is the difficulties that arise in measuring and manipulating emotion. Physiological measures are typically afforded small variability, but a construct such as emotion often exhibits large inter-rater variability in research. As such, larger sample sizes are needed for psychopharmacological research. Measuring emotion requires a level of self-awareness that may vary between subjects (and even within subjects from one time point to the next). Furthermore, it is an added challenge to control external variables that may influence emotion such as unexpected daily or life events. Though subjects in this thesis weren't tested if they confirmed a major negative life event had just occurred, a further study with the same design but also incorporating re-test sessions may be prudent.

8.5   FUTURE RESEARCH

The methodology of the studies in this thesis has demonstrated the utility of mood induction procedures in opioid dependent users. Velten's mood induction procedures were shown to be effective in inducing elation and depression induction in both methadone and buprenorphine groups. Though the only full μ-opioid agonist evaluated here was methadone, there is no evidence to suggest that other full opioid agonists such as oxycodone or fentanyl would not likewise show similar results. It is probably of little interest whether other partial opioid agonists respond similar to buprenorphine as few are used therapeutically. However tramadol is used frequently and as a weak μ-opioid agonist, its effect on emotional reactivity may be of interest.

There are four major aspects of emotional processing – emotional appraisal, emotional understanding, emotional regulation, and emotional reactivity. The effect of opioids on emotional appraisal has been investigated previously, while this thesis addresses the effect of opioids on emotional reactivity. Further research of opioid effects on emotional understanding and emotional regulation will provide a fuller understanding on opioids and psychopathology.

Finally the effect of opioids on other emotions also remains unknown. Adopting a similar methodology used in this thesis, research could investigate the effect of methadone on anger

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as an anger mood induction using a variation of Velten's procedure (Engebretson et al. 1999) has been developed and shows promise. Furthermore animal research shows that opioid administration is effective in reducing aggression levels (Haney and Miczek 1989; Shaikh, Dalsass, and Siegel 1990), suggesting that human research in this area may be illuminating.

8.6   CONCLUSION

This thesis details a body of work using mood induction procedures to measure emotional reactivity in opioid maintenance treatment patients. In the first study, methadone maintenance patients were induced into elated and depressed emotional states at times corresponding with peak and trough methadone plasma concentrations, and measured on emotional reactivity. In the second study, buprenorphine and methadone maintained patients were induced into elated and depressed emotional states at a time corresponding only with peak opioid plasma concentrations, and measured on emotional reactivity. With both studies, opioid naïve subjects were used as a control group.

These results have improved our understanding of the psychotropic effects of opioid maintenance drugs. The results show that methadone blunts both elation and depression emotional reactivity in opioid dependent users and can be added to the range of effects that are observable at the time of peak plasma methadone concentrations. Buprenorphine, a partial μ-opioid agonist, does not blunt emotional reactivity in buprenorphine maintained treatment patients. As emotional reactivity has consequences in social and psychological functioning, consideration of the effect of opioids on emotional processing systems may improve treatment outcome.

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APPENDIX A

<u>INSTRUCTIONS FOR VELTEN'S MOOD INDUCTION PROCEDURES</u>

NOTE:
This appendix is included on pages 193 - 194 of the print copy
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APPENDIX B

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APPENDIX C

VELTEN'S MOOD INDUCTION PROCEDURE – NEUTRAL CARD SET

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NOTE:

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APPENDIX D

VELTEN'S MOOD INDUCTION PROCEDURE – DEPRESSION CARD SET

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