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Targeting Opioid-Related Deaths: Prevalence, Perspectives and The Potential Role of Oxytocin in Opioid Use Disorder

by

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BSc (Hons), MSc



A thesis submitted in accordance with the requirements of St
Georges University for the degree of Doctor of Philosophy

Institute of Medical and Biomedical Education

St Georges University

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STATEMENT OF ORIGINALITY

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Ben Houghton

ABSTRACT

Opioid-related deaths are at record levels in the UK and contribute to over half of all drug-related deaths. Opioid use is complex and involves biological, psychological and socioeconomic influences which can trigger craving for opioids. Without craving management tools accidental overdose can occur from reduced tolerance and adulterants in supply. Solutions are urgently needed. The oxytocin system regulates dopamine, stress and reward systems but can become dysregulated through biological (e.g. chronic opioid use), psychological (e.g. psychiatric disorders, trauma) and socioeconomic (e.g. social exclusion, disparities) interactions. Emerging evidence suggests oxytocin could reduce craving.

This thesis considered the role of oxytocin in opioid use disorder and asked can a nasal spray of oxytocin reduce cue-induced craving at 7, 15 and 30 minutes post cue exposure?

The prevalence of psychiatric disorders in opioid-related deaths during 2006-2015 was analysed finding under diagnosis of psychiatric disorders in comparison to the general population when people were known to use illicit drugs. A systematic review of nasal oxytocin to reduce drug craving studies ($n=17$) then found heterogeneity and inconsistent methodological reporting. A randomized, double-blind crossover study ($n=24$) for nasal oxytocin (single dose, 40IU) to reduce cue-induced craving in males currently using heroin in addition to prescribed substitute opiates found no significant effect for oxytocin to reduce subjective craving ($F = 0.73$, $df=1$, $p=0.79$, $\eta^2=0.04$) but did find a moderate effect size for oxytocin to reduce likelihood of using heroin following cue assessment ($F = 2.83$, $df=1$, $p=0.10$, $\eta^2=0.11$). Finally the experience of participants ($n=14$) was explored supporting evidence of Alexithymia in self-identification of craving.

The findings were unable to reject the null hypothesis for nasal oxytocin to reduce cue-induced opioid craving. Theoretical arguments, quantitative and qualitative data supporting nasal oxytocin as being beneficial to reducing cue-induced opioid craving were put forward suggesting the need for further research.

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LIST OF ABBREVIATIONS

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BOLD	Blood Oxygen Level Dependent
CI	Confidence Interval
CMHT	Community Mental Health Team
COREQ	Consolidated Criteria For Reporting Qualitative Research
CONSORT	Consolidated Standards of Reporting Trials
DOR	Delta Opiate Receptor
DSM5	Diagnostic and Statistical Manual version 5
DTP	Drug Treatment Professional
fMRI	Functional Magnetic Resonance Imaging
GP	General Practitioner
HPA	Hypothalamic-Pituitary-Adrenal
ICD11	International Classification of Diseases version 11
KOR	Kappa Opiate Receptor
IU	International Units
MHP	Mental Health Professional
MOR	μ Opiate Receptor
NOR	Nociception Opiate Receptor
NPSAD	National Programme on Substance Abuse Deaths
OCS	Opioid Craving Scale
PHQ9	Patient Health Questionnaire-9

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	Post-Traumatic Stress Disorder
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SUD	Substance Use Disorder
VAS	Visual Analog Scale

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DISSEMINATION

Publications Incorporated In This Thesis

Houghton, B. (2022). Automated responses to opioid-related cues as a dysregulated allostatic oxytocin response: a short review. *Heroin Addiction and Related Clinical Problems*, 24(5) 27-35 (Chapters 1, 3 and 7)

Houghton B., Bailey A., Kouimtsidis C., Duka T., Notley C. (2021). Perspectives of Drug Treatment and Mental Health Professionals Towards Treatment Provision for Substance Use Disorders with Co-Existing Mental Health Problems in England *Drug Science, Policy and Law* 7 (Chapter 2)

Houghton B., Kouimtsidis C., Duka T., Paloyelis Y., Bailey A. (2021). Can Intranasal Oxytocin Reduce Craving In Automated Addictive Behaviours? A systematic review *British Journal of Pharmacology* 178(21) 4316-4334 (Chapter 3)

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Notley C., **Houghton B.**, Maskrey V., Holland R., Lingford-Hughes A., Punukollu B., Duka T. Kouimtsidis, C. (2022). An exploration of Identity Change in Post-Detoxification Alcohol Dependent Individuals *Drugs and Alcohol Today* 23(1) 48-61

Kouimtsidis, C., **Houghton B.**, Gage H., Notley C., Maskrey V., Clark A., Holland R., Lingford-Hughes A., Punukollu B., Touray M., Duka T., (2021). A Feasibility Study of an Intervention for Structured Preparation Before Detoxification in Alcohol Dependence: the SPADe Trial Results *Pilot and Feasibility Studies* 7:148

Kouimtsidis C., Salazar C., **Houghton B.** (2020). Motivational Interviewing, Behaviour Change in Addiction Treatment in B.A, (Ed.) G.M. (Ed.), C.G. (Ed.), G.N. (Ed.). *Textbook of Addiction Treatment International Perspectives* (2nd Edition, pp. 349-365). New York City: Springer Publishing

Kouimtsidis C., **Houghton B.**, Gage H., Notley C., Maskrey V., Clark A., Holland R., Lingford-Hughes A., Punukollu B., Duka T. (2019). A Feasibility Study Of An Intervention For Structured Preparation Before Detoxification In Alcohol Dependence: The Spade Trial Protocol *Pilot and Feasibility Studies* volume 5, Article number: 59

Conference Presentations

- National/International Conferences

Substance Use and Associated Behaviours Research Group PhD Symposium, Manchester, UK 2021 ‘Investigating The Mechanism Mediating The Effects Of Oxytocin On Opioid Craving: The Road To Ethical Approval And Data Collection’ (**virtual oral presentation**)

Society for the Study of Addiction National Conference, Newcastle, UK, 2020 ‘Can Intranasal Oxytocin Reduce Craving In Automated Addictive Behaviours? A Systematic Review’ (**e-poster presentation**)

Improving Outcomes in the Treatment of Opioid Dependence, Amsterdam, 2020 ‘Opioid Analgesic Medications Found at Post-Mortem in Opioid-Related Deaths in England Increased by 230% from 2006-2015’ (**e-poster presentation**)

Public Health England National Conference 2019, Warwick UK, 2019 ‘The Prevalence of Co-Existing Mental Health Problems in Opioid-related Deaths: 2006-2015’ (**e-poster presentation**)

Society for the Study of Addiction PhD Symposium, Newcastle, UK, 2018 ‘The Feasibility for Ad-Hoc Intranasal Oxytocin to Reduce Craving in Opioid Dependent Individuals’ (**oral presentation**)

- University Presentations

Addiction and Mental Health Group, University of Bath, 2022 ‘Methods For Successfully Recruiting People Actively Using Heroin To A Pharmacotherapy Proof Of Concept Trial’ (**virtual oral presentation**)

Addiction Research Group, University of East Anglia, Norwich, 2021 ‘An Allostatic Theory for The Role of Oxytocin in Opioid Use Disorder’ (**virtual oral presentation**)

Population Health Summer Seminar, St Georges University, London, 2019 ‘The Prevalence of Co-Existing Mental Health Problems in Opioid-related Deaths: 2006-2015’ (**oral presentation**)

Blogs and Podcasts

Society for the Study of Addiction, Northampton, UK, 2021 '5 Things nobody told me about running a double-blind human study' *Retrieved from* <https://www.addiction-ssa.org/5-things-nobody-told-me-about-running-a-double-blind-human-study/> **(website)**

Society for the Study of Addiction, Northampton, UK, 2020 'PhD Blog: Oxytocin and Navigating COVID-19 in New Research' *Retrieved from* <https://www.addiction-ssa.org/phd-blog-oxytocin-and-navigating-covid-19-in-new-research/> **(website)**

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'Education: the path from cocky ignorance to miserable uncertainty'
– Mark Twain,

Chapter One

Introduction: Understanding Opioid Use Disorder and Why Oxytocin

*‘Heroin - A drug that helps you to escape reality,
while making it much harder to cope when you are recaptured’*
– Nikki Sixx, The Heroin Diaries: A Year in the Life of a Shattered Rock Star

1. Introduction

This chapter sets out the foundation of evidence underpinning this thesis. Beginning with a description of the opioid crisis, the introduction continues with an overview of substance use disorders (SUD) drawing on risk factors, neurobiology, treatments and the challenges faced by people who use substances. Finally this chapter presents oxytocin and provides an overview of relevant evidence suggesting a role for oxytocin within opioid use disorder. Further detail of the key concepts introduced here are discussed in the relevant chapters. The chapter closes with a clear description of the aims and hypotheses of the thesis.

Opioids is a broad term that includes opiates given to a range of psychoactive substances i.e. any legal or illegal substance which changes mood, thoughts, awareness or behaviour which interact with opioid receptors. Whereas ‘opiates’ are compounds derived from the opium poppy such as heroin, morphine and codeine, ‘opioids’ includes opiates alongside man made synthetic and semi-synthetic compounds with morphine-like effects such as buprenorphine and fentanyl. Opioids are an extremely effective painkiller however people can become physically dependent on them and the main risk associated is overdose as a result of respiratory depression. In 2017 the number of people who used opioids worldwide was estimated to be 53 million people (range 47-60 million), increasing 56% on the previous year and opioids were responsible for two thirds of 585,000 global drug-related deaths (World Drug Report, 2019). The synthetic opioid fentanyl remains a key problem in North America but West, Central and North Africa are experiencing a crisis involving a different synthetic opioid, tramadol (World Drug Report, 2019). In the United States 400,000 people died between 1993 and 2017 of an opioid overdose and 68% of all drug-related United States deaths in 2017 involved opioids (Scholl et al., 2019) , triggering the United States government to declare a national emergency due to escalating opioid-related deaths (Health and Human Sciences, 2017). Safe opioid use is a global health problem.

In the United Kingdom there are an estimated 337,574 (95% confidence interval (CI), 331,688 – 352, 763) high risk opioid users (European Monitoring Centre for Drugs and Drug Addiction, 2019). United Kingdom drug-related deaths continue to be considerably higher than the rest of Europe; of 4,859 registered drug-related deaths in 2021, 45.7% involved opioids (Figure 1.1; Office for National Statistics, 2022). The scope of the

escalating opioid problem is not limited to illicit opioids such as heroin. Thirteen percent (n=5.6 million) of the English population received one or more legal opioid analgesic prescriptions in the period 2017 to 2018 and the number of people receiving a continuous opioid analgesic prescription between 2015 and 2018 was 540,000. As opioid analgesic prescriptions lasting 90 days or longer is associated with dependence and overdose (Taylor et al., 2019) it is estimated that there are approximately half a million people living in England at risk of dependence and overdose from legal opioid prescriptions. The leading cause of opioid-related deaths in the United Kingdom is accidental overdose (Office for National Statistics, 2019) and as such understanding psychological, social and neurobiological drivers of opioid use is key to tackle escalating opioid-related deaths. The thesis will address key potential factors contributing to opioid related death such as craving, comorbidities with mental health disorders, associated pharmacotherapy and finally will seek to understand the experience of people who use opioids when they are craving. Section 1.1 provides an overarching explanation of SUD before opioid use disorder is further discussed in isolation.

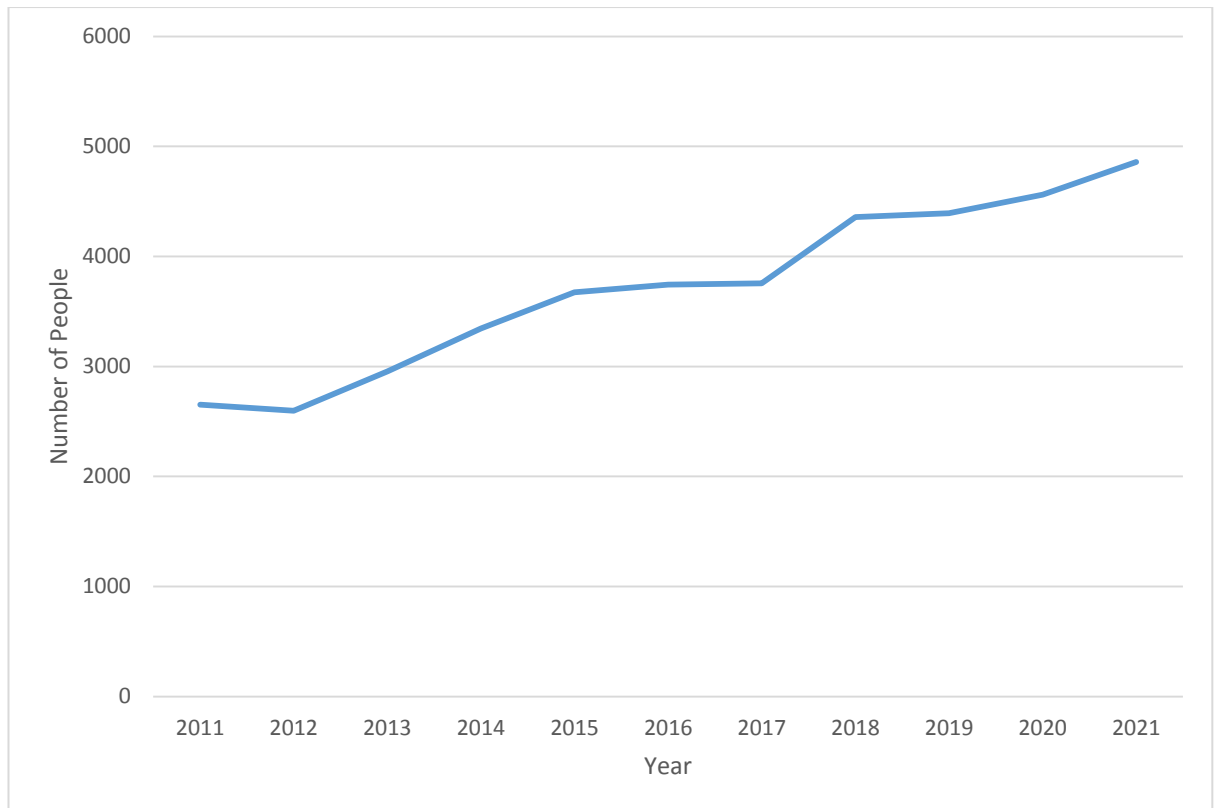


Figure 1.1: Number of drug-related deaths (all causes) in England and Wales 2011-2021

Notes: Cause of death was defined using the International Classification of Diseases, Tenth Revision (ICD-10). In January 2011 and January 2014 the Office For National Statistics introduced new versions of ICD-10. The change in January 2011 affected the assignment of underlying cause of death for drug-related deaths, so figures for 2011 onwards are not directly comparable with earlier years. Figures are for deaths registered, rather than deaths occurring in each calendar year. The median time to complete a coroner's inquest in to a drug-related death, and register the death, is six months. Source: Office for National Statistics

1.1 Understanding Substance Use Disorders

There is no medical diagnosis of substance *misuse* or substance *abuse*. The Diagnostic and Statistical Manual version 5 (DSM5) uses the term 'substance use disorder' (American Psychiatric Association, 2013) as does the International Classification of Diseases version 11 (ICD11) (World Health Organisation, 2018). To continue referring to these disorders as misuse or abuse perpetuates judgemental and stigmatising perspectives (Ashford et al., 2018). For this reason, terms 'substance abuse' and 'substance misuse' will not be used throughout this thesis and instead the term substance use disorder will be used.

To be diagnosed with SUD in DSM5 (American Psychiatric Association, 2013) an individual needs to exhibit any two of the following within the last year; Hazardous use; social/interpersonal problems related to use; neglected major life roles to use; legal problems; withdrawal; tolerance; used larger amounts or used for longer than usual; have repeated attempts to quit/control their substance use; much time spent using; exhibit physical or psychological problems related to use; has given up activities to use substances and/or exhibit craving. To be diagnosed with an SUD in ICD11 (World Health Organisation, 2018) an individual needs to exhibit at least two of the following within one year; Physical Dependence (Tolerance or Withdrawal), Priority of Use (Much Time or Reduce Activities, or Psychological/Physical harm), and Impaired Control (Quit/Cut or Larger/Longer, or Craving).

Substance use disorders occur on a continuum, often referred to as recreational use, dependence and addiction. Recreational use refers to the vast majority of people who use substances (alcohol and cannabis for example) without ever experiencing the problems which precede the transition to dependency (Schlag, 2020). Dependency is typically understood to mean reliance on a substance to function daily without necessarily suffering physical withdrawal symptoms upon abrupt cessation although in the case of opioids, dependency is typically characterised by tolerance and physical withdrawal symptoms in the absence of opioids (World Drug Perception problem, 2017). Of those people who become dependent on substances, not all will develop an addiction (Schlag 2020; Szalavitz et al., 2021). Dependence on a substance and addiction to a substance is not the same and the terms dependence/addiction are not used interchangeably throughout this thesis. Definitions of addiction are highly contested within the field but for the purpose of this thesis, addiction is defined as ‘compulsive drug seeking and use, despite harmful consequences’ (American Psychiatric Association, 2013) and is characterised by (1) compulsion to seek and take the drug (2) Loss of control in limiting intake (3) emergence of a negative emotional state when access to the drug is prevented (Koob and Volkow, 2010). Although onset is heavily influenced by both genetics and environment, addiction is fundamentally a disease of neuroplasticity (the ability of the brain to change in response to experience or injury) manifested by reflexive activation of the reward system (O’Brien, 2009) resulting in repeated drug seeking behaviours. The above definition introduces a new term to explain which is not present in dependence, compulsion. The following section will discuss cycles of impulse control and compulsion within addiction.

1.1.1 Impulse control and compulsive disorder cycles

Substance use disorders can be characterised as either impulse control disorders or compulsive control disorders (Figure 1.2).

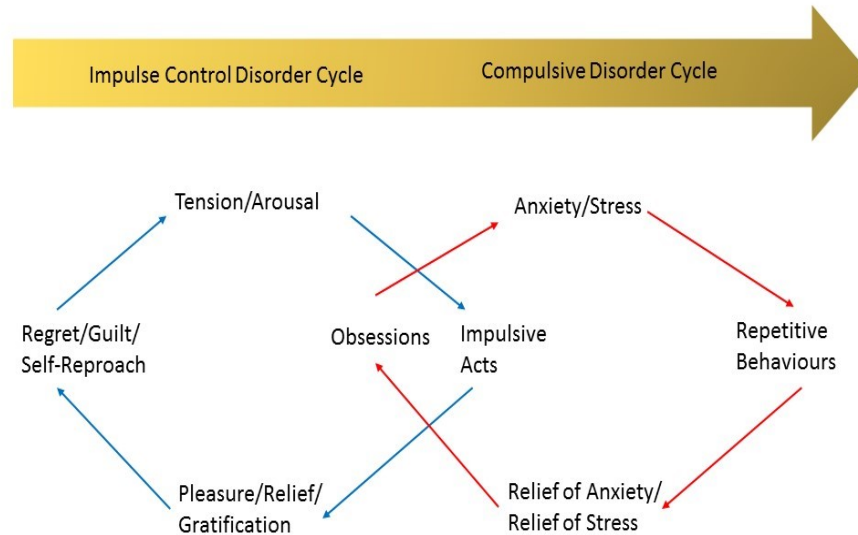


Figure 1.2: The Impulse control disorder cycle and compulsive disorder cycle of addiction

Notes: Impulse control disorders follow a cycle of tension/arousal leading to impulsive acts with the aim of pleasure/relief/gratification culminating on regret/guilt/self-reproach before tension/arousal continues in the cycle. Compulsive disorders follow a cycle of anxiety/stress leading to repetitive behaviours, relief of anxiety/stress, obsessions and then reverting back to a state of anxiety/stress. Overlaps with impulse control disorders and compulsive disorders exist in the stages of impulsive acts and obsessions. Source: Adapted and updated from Koob G: "Neurobiology of Addiction," in Textbook of Substance Abuse Treatment. Galanter M, Kleber HD (eds). Washington, DC, American Psychiatric Publishing, 2008, pp 3–16.

Impulsivity is defined as 'a predisposition towards rapid, unplanned reactions to internal and external stimuli without regard for negative consequences of these reactions to themselves or others' (Moeller et al., 2001). Compulsivity is defined as perseveration of behaviour despite adverse responses or persistent reinitiating of habitual acts (Everitt and Robins, 2005). Whilst the two definitions seem very similar, the difference depends on:

- 1) Whether goal focus is pursuit of reward (impulse control disorders) or relief (compulsive disorders) (Koob and Volkow, 2010) and
- 2) The lower level of self-control for impulse control disorders versus consciously choosing to experience negative consequences which are valued less than provision of immediate relief from continuing behaviours in compulsive disorders

People who use substances recreationally are less susceptible to ‘automatic’ reactions to emotional or environmental triggers and able to control drug use. Impulsive use of substances may lead to greater remorse/guilt/self-reproach afterwards in comparison to compulsive use of substances where relief of negative feelings irrespective of foreseeing detrimental consequences is the main driver (Figure 1.2). Section 1.2 begins to hone the focus from general substance use disorders to opioid use disorder.

1.2 Opioid Use Disorder

Opioid use disorders in DSM5 are rated as mild, moderate or severe (American Psychiatric Association, 2013). If any 2-3 of the following criteria are present in the last year then the opioid use disorder is mild, 4-5 criteria is moderate and 6 or more is severe. In DSM5 the criteria for opioid use disorder is; opioids are often taken in larger amounts or over a longer period of time than intended; there is a persistent desire or unsuccessful efforts to cut down or control opioid use; a great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects; craving, or a strong desire to use opioids; recurrent opioid use resulting in failure to fulfil major role obligations at work, school or home; continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids; important social, occupational or recreational activities are given up or reduced because of opioid use; recurrent opioid use in situations in which it is physically hazardous; continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids; tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of an opioid; withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms.

Craving was reintroduced to DSM5 following absence in earlier versions indicating the growing importance, understanding and recognition for the role of craving within SUD. The following section explores craving in more detail.

1.2.1 Craving

Craving is defined by DSM5 as a “strong desire or urge to use” (American Psychiatric Association, 2013) and ICD11 as “...a subjective sensation of urge or craving to use the substance” (World Health Organisation, 2018). The concept of craving has historically been a controversial area in addiction with many models and prospective studies postulating that craving is neither necessary for relapse nor predictive of relapse (Drummond et al., 2000). Instead relapse into drug seeking is shown to be dependent on one’s self-efficacy in applying coping behaviours to craving-related events (Hendershot et al., 2011).

One theory frames craving as a motivational construct, the process of which is dissociated from conscious awareness (Berridge and Robinson, 1995). However if no urge, desire or conscious will is present then human beings would be reduced to no more than automated learned behaviours in response to environmental stimuli. This is illogical as human beings are capable of free will, the majority of drug use is not problematic and people choose to stop taking drugs as they get older. As research has advanced current clinical perspectives argue craving is a multifaceted but established antecedent to drug seeking behaviour and is a predictor of relapse for both legal and illicit substances (Tiffany and Wray, 2012). The relationship between onset of craving and intensity of the craving experience is crucial. A systematic review of 91 studies observing participant behaviours in real-time prior to relapse found higher craving scores closest to time of substance use in 92% of studies (Serre et al., 2015). This highlights the important role of craving in self-management of drug use and for avoiding relapse.

Though many different theoretical cognitive and phenomenological models of craving exist (Drummond, 2001), drug craving can be broadly categorised into two types – withdrawal-related and cue-induced. Withdrawal-related craving refers to the continuous underlying stress that is induced by withdrawal from substances like nicotine, alcohol or opioids (Shalev et al., 2002). Under these withdrawal states craving and subsequent reinstatement of substance use is an attempt to relieve stress (Mantsch et al., 2016). Withdrawal-related craving in opioid use disorder can be managed through substitute

medications and are discussed later in section 1.5.3. Cue-induced craving is induced by cues associated with substance use (e.g. people, places, things, emotions). These cues are central to the loop of continued drug use, and can be conscious or subliminal and may involve any of the sensory modalities (Jasinka et al., 2014). Recent meta-analyses of 237 studies including 51,788 human participants (21,216 with confirmed substance use disorders) found that a single point increase in cue and craving indicators more than doubled the risk of relapse (Vafaie and Kober, 2022). This important review highlighted the need for interventions that can reduce cue-induced craving and prevent accidental overdose. The neurobiology underpinning withdrawal-related and cue-induced craving is discussed in chapter three whilst a novel cue-induced opioid craving mechanism which integrates social, psychological and biological influences is the focus of a proof of concept study conducted as part of this thesis. The methods for this study are explained in chapter four and quantitative results are presented and discussed in chapter five.

Many people who use substances report not experiencing cravings (Drummond, 2001). However just as people can experience dangerously high blood pressure but be unaware until an objective blood pressure measurement is taken, people may experience craving without being aware. Classical conditioning suggests that following exposure to a cue the conditioned behaviour becomes automated. The first identifiable ‘symptom’ of this would traditionally be a feeling of craving. But if craving was seen as an entire neurobiological mechanism which followed exposure to a cue (and not limited to a subjective feeling that is either felt by people or not felt by people), then the feeling of craving may only be one of a range of possible symptoms. For example just as people may carry a virus and be asymptomatic, the mechanism of craving may be triggered without any feeling of craving. It would then be useful if there was an objective measurement of craving which could tell people that they were at higher risk of relapse because of exposure to a drug-related cue. One possible measurement could be attentional bias (people being drawn towards opioid-related environmental cues) and is discussed next.

1.2.2 Attentional bias

If an individual was on a diet and missing sugar, then opened the fridge and saw a chocolate bar then that chocolate bar would likely grab their attention; or if they had just watched a horror film at the cinema, got home and the lights did not turn on, maybe that person would focus on the shadows until they realised that the shadows were just

shadows. This attention focus happens because emotions underpin behaviour, affect decision making and memory and signal the presence of environmental stimuli (Pool et al., 2016). When stimuli are detected there is competition for limited attentional resources and an attentional bias is created. Attentional bias towards emotional stimuli ensures rapid detection, preparation of behavioural response (Pool et al., 2016) and is traditionally explained as Pavlovian Conditioning (where presence of a stimuli associated with an outcome produces the behavioural and physiological response). Attentional bias in the context of opioid use disorders is the tendency for opioid-related cues to capture attention in the lived environment and is well documented in opioid dependent individuals (Franken et al., 2000; Waters et al., 2012; Zamani et al., 2014; Zhang et al., 2018; Maclean et al., 2018). Though results are mixed, possibly because of individual differences in participants, attentional bias can predict future opioid use (Garland et al., 2014; Maclean et al., 2018). Meta-analyses of attentional bias in healthy populations (n= 9,120) has shown a significant bias for positive as opposed to neutral stimuli i.e. stimuli which trigger arousal rather than stimuli which only focus attention. (Pool et al., 2016). This meta-analyses also demonstrated the following which are central to this thesis;

- 1) The magnitude of attentional bias varies as a function of arousal and the bias is significantly larger when the emotional stimulus is relevant to a person's current state e.g. attentional bias towards food would be expected to be larger for a hungry person compared to a non-hungry person because hunger increases the value of the outcome, food
- 2) Moderator analyses has demonstrated attentional bias was greater during early attentional processing (when stimuli are not fully processed for meaning i.e. when stimuli first capture attention) rather than late attentional processing (after stimuli have been fully processed for what they mean) and suggests early attentional bias for positive stimuli occurs rapidly and involuntarily

In relation to opioid use, the findings of this meta-analyses suggest that if the reason for using opioids was the reward or relief associated with their use which they had not recently received, then the attentional bias would be larger, be experienced rapidly and involuntarily (Pool et al., 2016). Decreased control of attentional bias towards opioids in the early stage of processing would make it harder to resist using opioids because the consequence of using opioids has not yet been fully processed. This interpretation has

been supported by an earlier meta-analysis of 68 independent data sets which aimed to identify correlation coefficients between subjective craving and attentional bias. The pooled analysis demonstrated an association between higher attentional bias and higher self-reported craving scoring suggesting that attentional bias might be an indicator of craving. Indeed the same study found the presence of attentional bias towards drug-related cues in abstinent people was able to predict relapse (Field et al., 2009). This thesis proposes that attentional bias operates as one component of the larger craving mechanism which explains why research suggests some people report not to feel craving but continue to consume opioids. Under this conceptual model if craving can be stopped quickly, less opioids will be used and accidental overdose can be dramatically reduced. This has the possibility to effectively reduce the public health burden of opioid use and the associated human and economic costs. The conceptual model is outlined further in chapter three and cue-induced attentional bias towards opioid-related words forms part of the proof-of-concept study presented in chapters four (methods), five (quantitative results and discussion) and six (qualitative results and discussion). It is important to recognise that opioid use, as with other SUDs, cannot be reduced to a single biological response. Further genetic, social and economic risk factors for initiation and continuation of opioid use disorders are introduced in section 1.3.

1.3 Genetic and Socioeconomic Risk Factors For Opioid Use Disorder

Substance use disorders do not occur in isolation from other health, social and environmental factors. Despite 271 million people using any kind of illicit drug in the past year and 53 million opioid users, only 35 million people have a SUD of any kind (World Drug Report, 2019). Research has established there is a strong genetic risk associated with susceptibility to develop SUD (Jensen, 2016). Genetic risk is tied to epigenetic changes. Broadly speaking ‘epigenetic change’ refers to changes in a living thing caused by modification of how the gene works rather than by changes to the gene itself (Walker and Nestler, 2018). These can be likened to changes in how an employer can make small amendments to existing job descriptions rather than creating entirely new jobs. The existing job adapts to the change in the new working environment. The implications of epigenetic changes are that these modifications can alter the development and health of people and their children (Rothstein et al., 2009). However up to 90% of all substance use is non-problematic and only 20-30% of heroin use is problematic for the person who uses heroin (World Drug Perception problem, 2017; Schlag, 2020). This

suggests there must be other determinants which contribute to development of SUDs. Although epigenetic change can be caused by the known psychological or social risk factors for SUD (Cunliffe, 2016), as well as by substance use itself (Browne et al., 2020), the over-medicalising of substance use is a matter of contentious debate within the field. For more information the reader is referred to Heilig et al. (2021) and Hart (2017). Nevertheless taken together genetic risk factors for SUD and external influences on substance use highlight's the complex interplay between people and their environments. Psychological and socioeconomic risk factors for SUD are introduced next.

In England and Wales the mean age of all opioid-related deaths is 44 and people with co-existing psychiatric comorbidities are at the highest risk of death (European Monitoring Centre for Drugs and Drug Addiction, 2019a). Other risk factors preceding mortality include family and social environmental influences, unemployment, sleep apnoea, co-prescribing of antidepressants or benzodiazepines, prescribed or non-prescribed use of gabapentinoids (reclassified in 2019 due to their increasing presence in drug-related deaths) alongside opioids, childhood trauma, younger age, untreated psychiatric disorders, past or current SUD and poor academic performance (Webster, 2017). Socioeconomic risk factors for SUD are shown in Figure 1.3.

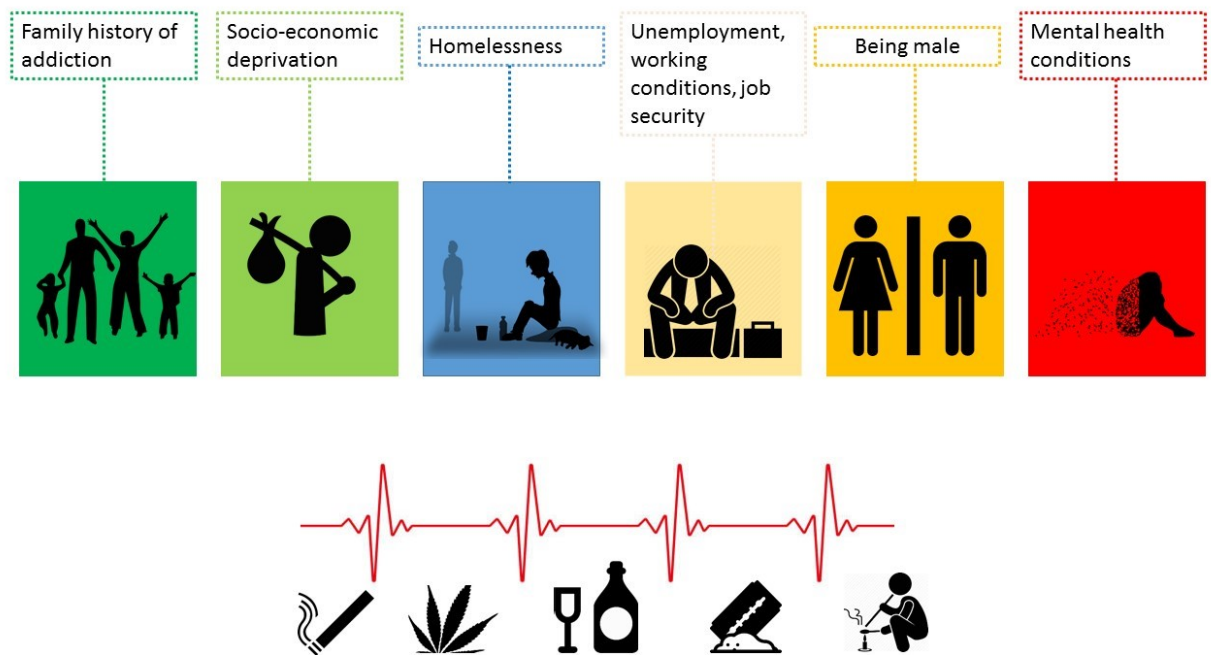


Figure 1.3: Risk factors for substance use (Public Health England, 2017a)

Notes: Family history of substance use, socioeconomic deprivation, homelessness, unemployment and working conditions, being male and the presence of mental health conditions are risk factors for substance use. The relationship is bidirectional meaning that substance use is a risk factor for initiation of these factors also.

Risk factors for substance use disorders (Figure 1.3) are bidirectional and include poor physical and mental health, offending or risky sexual behaviour (Public Health England, 2017a) and the socioeconomic risk factors are closely intertwined with determinants of poor mental health. Whilst there is no biological substrate yet identified to differentiate non-addicted people from addicted people, the possibility of epigenetic changes further compounding these risk factors cannot be eliminated. As prevalence of mental health disorders in deaths where opioids were found at post-mortem is the main focus of chapter two, the next section will focus on mental health as a specific risk factor for opioid use disorders.

1.3.1 Mental health as a risk factor

Mental health problems can be influenced by and linked to an array of diverse and dynamic socioeconomic factors. These factors are set out in Figure 1.4.

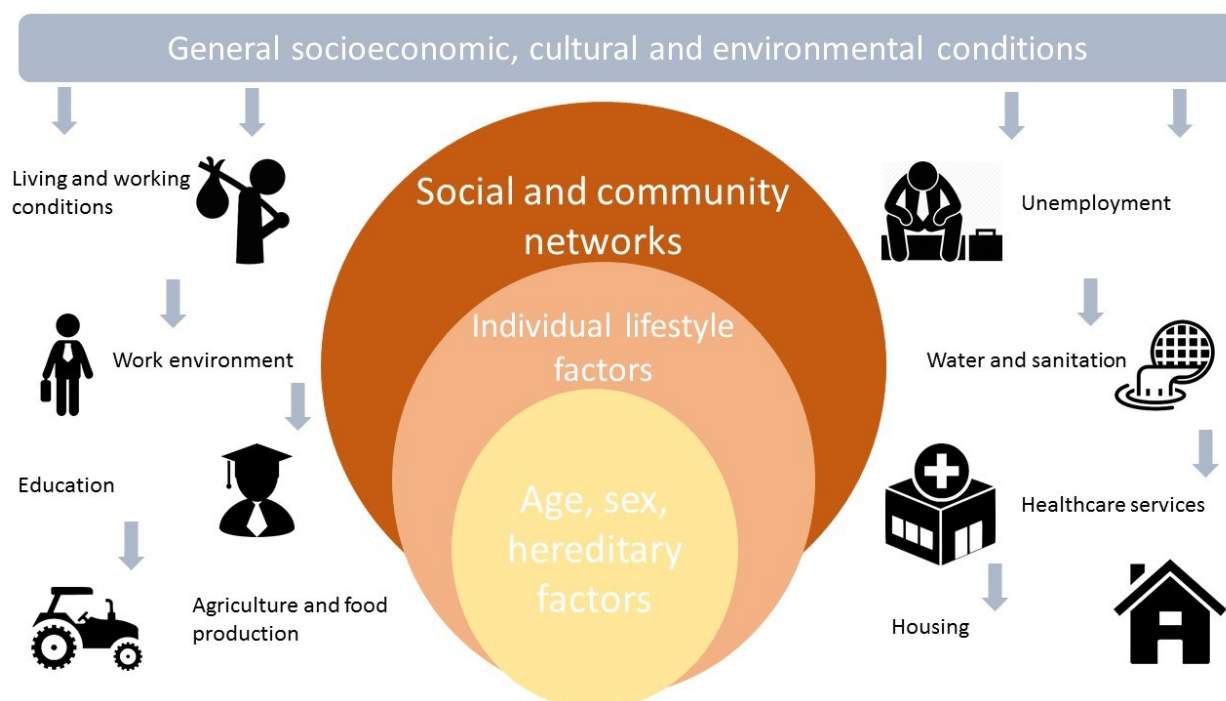


Figure 1.4: Diagram of the social determinants of mental health adapted from The Determinants of Health (Dahlgren and Whitehead, 1993)

Notes: At the core of determinants of mental health are age, sex and hereditary factors which are influenced by individual lifestyle choices including social and community networks. General contributors to the individual include living and working conditions including the work environment and unemployment itself. Levels of education, access to healthcare services, water and sanitation as well as availability of nutrition all intertwine with individual factors to impact mental health.

The co-existence of mental health problems with opioid use is well documented. Exposure to traumatic events has been found in up to 88% of heroin users with childhood sexual abuse, emotional abuse, physical neglect and violent trauma most prevalent (Lawson et al., 2013). As a result Post Traumatic Stress Disorder (PTSD) can develop and is associated with poorer physical and mental health, suicide attempts, major depressive disorder and borderline personality disorder (Mills et al., 2006). Links to early trauma are not limited to heroin use and one study comparing the trauma histories (general, sexual, physical and emotional) of non-treatment seeking individuals dependent on opioids (n=41), nicotine (n=87) or cocaine (n=73) found the prescription opiate group

experienced a higher number of general traumatic events than the nicotine group, reported a younger first age of traumatic event than the cocaine group and were significantly more likely to report childhood traumatic events than both the nicotine and cocaine groups (Lawson et al., 2013). PTSD is often diagnosed alongside schizophrenia and psychosis (NICE, 2014), however PTSD symptoms can be missed at assessment when symptoms of opioid withdrawal such as hypervigilance are present (Patel et al., 2017). Similar confounding effects can be seen in depression and anxiety where symptoms of opiate withdrawal overlap, impeding psychiatric diagnosis (Clinical Guidelines on Drug Misuse and Dependence Update, 2017).

Trauma responses are not the only psychiatric experience associated with or highly prevalent among people with co-occurring opioid use disorders. In particular axis II personality disorders are thought to have prevalence in up to 61% of heroin users with borderline personality disorder and antisocial personality disorder most common (Casadio et al., 2014). Patients with borderline personality disorder are also twice as likely to be prescribed opioid medications in comparison to patients with other axis II disorders with likelihood increasing from 10% to 26% over a ten year period (Frankenburg et al., 2014). Borderline patients struggle greatly with self-control over intense emotional responses and opioid use may be linked to efforts to manage these emotions as found in one systematic review of 17 qualitative studies exploring the progression of prescription opiate use from initiation to abuse (Cicero and Ellis, 2017). Psychological therapy without consideration for pharmacotherapies is recommended in community patients with borderline personality disorder to aid this (NICE, 2009). Psychological therapies are recommended treatment alongside pharmacotherapy by National Institute for Health and Care Excellence for psychosis and schizophrenia (NICE, 2014) and bi-polar (NICE, 2014b) whilst psychological therapies are recommended with consideration for pharmacotherapy for people with PTSD (NICE, 2018). Without formal diagnosis support becomes limited to reliance on pharmacotherapies for symptomatic relief without psychological treatments which aid the person to consciously adjust behaviours associated with each disorder. With so many factors which overlap opioid withdrawal and identification of psychiatric disorder at assessment, the opportunity to provide evidence based psychological therapies may be missed. If evidence based treatments are not provided then health outcomes are likely to suffer. To date there is no retrospective analysis of psychiatric disorders in opioid-related deaths during periods of socioeconomic

change. Chapter two explores the prevalence of co-existing psychiatric disorders with all opioid-related deaths that occurred between 2006-2015 in England during changes to the UK drug treatment strategy and welfare system reform.

Just as environmental influences are intertwined with how good or bad a person's mental health can be there are also neurobiological influences to psychiatric disorders which are beyond the remit of this thesis to discuss in depth (Etkin et al., 2013). And as with psychiatric disorders, neurobiological influences and genetic susceptibility for increased likelihood of developing SUDs are also widely accepted (Prom-Wormley et al., 2017; Racz, 2014). Section 1.4 provides an overview of addiction neurobiology.

1.4 The Neurobiology of Addiction

The brain develops from the back to front beginning two weeks after conception with creation of basic structures (Tierney and Nelson, 2009). In early childhood and adolescence neural networks are refined beginning with sensation and perception systems by age 5. Continuing with memory and emotion throughout childhood then in adolescence (ages 10-24) where decision making, risk taking and emotional responses of events are strongly formed until maturity around 25 years old (Arain et al., 2013).

During adolescence is when most substance use is initiated (Nock et al., 2017) and so drug-induced neuroplastic alterations begin. What these alterations are, how they affect behaviour and how difficult they are to overcome are discussed in 1.4.1.

1.4.1 The three stages of the addiction cycle

The addiction cycle moves through three different stages (Figure 1.5), each involving different brain regions (Koob and Volkow, 2010). This section will explain these stages further.

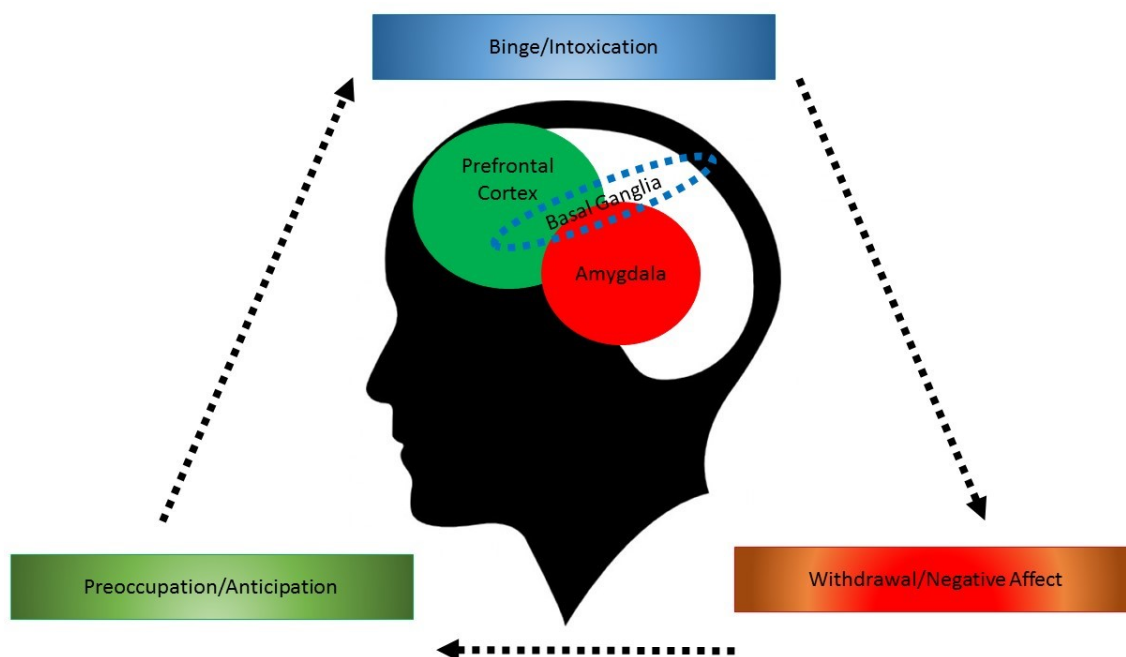


Figure 1.5: The three stages of the addiction cycle and associated areas of the brain. Amended from source: Substance Abuse and Mental Health Services Administration (US) (2016)

Notes: Neural circuitry associated with the three stages of the addiction cycle (a) Binge/intoxication stage; Reinforcing effects of drugs may engage reward neurotransmitters and associative mechanisms in the nucleus accumbens shell and core and then engage stimulus–response habits that depend on the dorsal striatum. (b) Withdrawal/negative affect stage; the negative emotional state of withdrawal may engage the activation of the extended amygdala. The extended amygdala is composed of several basal forebrain structures, including the bed nucleus of the stria terminalis, central nucleus of the amygdala, and possibly a transition zone in the nucleus accumbens. Major neurotransmitters in the extended amygdala hypothesized to have a function in negative reinforcement are corticotropin-releasing factor and dynorphin (c) Preoccupation/anticipation stage; this stage involves the processing of conditioned reinforcement in amygdala and the processing of contextual information by the hippocampus. Executive control depends on the prefrontal cortex and includes representation of contingencies, representation of outcomes, and their value and subjective states (ie, craving and, presumably, feelings) associated with drugs (Koob and Volkow, 2010).

Binge/Intoxication

There are many different neurobiological substrates involved in the reinforcing effects of differing substances and it is beyond the scope of this thesis to discuss them all in detail however the reward centre is key to all SUDs.

A person who uses drugs without any dependence, perhaps for the first few times of using the drug for example, at binge/intoxication stage, is teaching their brain through activation primarily of nucleus accumbens that taking a substance has a rapid, positive effect of dopamine release which strengthens reward/gives relief and feels good. An environmental or internal, emotional cue becomes associated with relief/reward following drug use and the early stage of drug use may be when attentional bias towards this cue is initially formed. The binge/intoxication stage is not limited to first time use of drugs and the neurobiological mechanisms are activated continuously following exposure. An overview of these mechanisms is given next.

Central to the binge/intoxication stage are basal ganglia, a group of neurons responsible primarily for motor control, motor learning, behaviours and emotions (Lanciego et al., 2012). Part of the limbic system are a group of dopaminergic neurons that project from the ventral tegmental area to the nucleus accumbens that are activated in drug use;

- Cocaine, amphetamine and nicotine act directly on their respective molecular target on the mesolimbic dopaminergic neurons to release dopamine in nucleus accumbens
- Alcohol induced dopamine release in the nucleus accumbens enhances GABA_A receptor activity, blocking NMDA receptors and enhancing the release of endogenous opioids
- Heroin is rapidly deacetylated to 6-monoacetylmorphine which is then deacetylated to morphine (Milella et al., 2023)

The nucleus accumbens are placed strategically to receive information involving learning, motivation and memory from amygdala, hippocampus and frontal cortex which is converted to behaviour (Koob and Volkow, 2010) and plays a critical role in the reinforcing effects of drugs.

It is of note that whilst the dopamine theory of addiction (i.e. that dopamine release mediates reward and leads to addiction in all substances) has dominated contemporary

discussion, it over simplifies the complexity of SUDs by assuming all substances act the same. Whilst strong evidence shows that stimulants increase striatal dopamine levels, and there is some albeit weaker evidence for alcohol, there are very few studies showing that cannabis and opiates do the same. In addition not only has it been shown there is decreased striatal dopamine release in people dependent on opiates but studies have shown lower striatal dopamine receptor availability. If dopamine release was responsible for the euphoric effects of opiates then lower dopamine receptor availability would result in less-rewarding effects (Nutt et al., 2015).

The next stage following drug use is withdrawal/negative affect.

Withdrawal/Negative Affect

In this stage, withdrawal-related craving is likely to be present. For basal ganglia and limbic system to function appropriately, they require dopamine release from nucleus accumbens (Lanciego et al., 2012). One component of the withdrawal/negative affect stage includes within-system neuroadaptations in response to chronic drug exposure. Within-system adaptations reduce functioning of neurotransmitters involved in the binge/intoxication stage such as dopamine and serotonin production (Koob and Volkow, 2010). This leads to lower motivation for non-drug-related stimuli and increased sensitivity to the drug although in the case of opioid use disorders this is speculative given the paucity of human evidence for the involvement of dopamine (Nutt et al., 2015).

A second component is between-system adaptations. This occurs when different neurochemical systems involved in stress modulation attempt to compensate for over-stimulated normal functioning due to chronic presence of a drug (Koob and Volkow, 2010). Drug withdrawal induces the recruitment of stress pathways; this includes a hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis and elevation of corticotropin-releasing-factor in amygdala. This produces a negative anxiety-like state where systems involved in stress management, i.e. noradrenergic systems, play a key role (Koob and Volkow, 2010).

Protracted withdrawal reduces reactivity of dopamine to drug-related stimuli, whereas during detoxification sensitivity to drug-related cues increases (Koob and Volkow, 2010). For people who use stimulants this means people receive less reward for using drugs when withdrawing but experience heightened sensitivity to drug-related cues during withdrawal. For people who use opiates, the stress hormone cortisol is suppressed during

active use and elevated during withdrawal (Kakko et al., 2019) alongside excess noradrenaline which creates unpleasant though not fatal physical symptoms, and is discussed further in section 1.5.2 (Kosten and George, 2002). As the person who uses substances is aware that the unpleasant feelings of withdrawal can be removed by using the substances whose cues they are now unconsciously more sensitive to reacting to, it is easy to see how the cycle of relapse is perpetuated.

It is not clear whether there is an accumulative effect from within-system and between-system adaptations however there is clear disruption in the brains ability to maintain normal functioning when withdrawing from chronic drug use. The third stage is preoccupation/anticipation.

Preoccupation/Anticipation

This stage is whereby people who use drugs are susceptible to cue-induced craving exhibiting heightened awareness and reactivity to drug-related cues overlapping with the withdrawal/negative affect stage and can lead to relapse. Volkow et al. (2011) has found that striatal dopamine release occurs in anticipation of receiving stimulants and have previously suggested when people are addicted whilst the dopamine release is reduced, the effects of the drug have become conditioned responses themselves (Volkow et al., 2010). These conditioned responses were thought to drive the positive-association between cue and drug, heightening the desire to take the drug thus perpetuating the loop of automatic behaviour leading to relapse.

This may not be the case in people who use opiates. It could be that much of the enthusiasm for dopamines role within opioid use disorders stems from rodent models where resting dopamine levels in response to intravenous heroin administration have tripled and lever pressing for more heroin increased 20-fold as dopamine levels depleted (Wise et al., 1995; Wise and Jordan, 2021). However there are far more rodent models demonstrating only modest or negligible increases in dopamine following lever pressing, inhibition of dopaminergic neurons in association with heroin self-administration and disruption or blockade of dopaminergic transmission having little effect on heroin self-administration (Milella et al., 2023). Recent reviews suggest while there is hardly any change in dopamine concentration in the striatum of rats following intravenous morphine administration, dopamine concentration in the striatum following intravenous 6-

monoacetylmorphine acutely increases between 4 and 8 minutes before rapidly decreasing between 8 and 14 minutes (Milella et al., 2023).

Limited human studies do not support a role for dopamine in perpetuating opioid use disorder. One human study of ten opioid dependent people receiving methadone or buprenorphine underwent positron emission tomography whilst being scanned three times receiving reward from 50mg intravenous diamorphine. The first scan was to generate expectation of reward at the second scan where participants received only 0.1mg intravenous diamorphine and no injection was received on the third scan. Results found no striatal dopamine increase to either reward or expectation of the reward (Watson et al., 2014). Findings replicated earlier research by Daglish et al. (2008) although human studies have been largely limited by recruiting participants dependent on opiates. One small positron emission tomography study of non-opioid-dependent males (n=10) found 10mg intravenous morphine administration only increased dopamine receptor occupancy by 8% and had an inverse relationship with 'highs' and other measures of reward (Milella et al., 2023). It may be that in the study by Daglish et al. (2008) 6-monoacetylmorphine had already converted to morphine by the time the tracer was injected as diamorphine was injected 5 minutes prior to the tracer. This limitation was later addressed by Watson et al. (2014) but results also found no striatal dopamine response pre or post diamorphine injection. As participants were opioid dependent it is difficult to differentiate whether this is a pharmacological response or an adaptation from cue conditioning. Further imaging studies of healthy people versus opioid dependent people receiving intravenous morphine and 6-monoacetylmorphine are needed to explore differences including a possible within-system neuroadaptation of dopamine receptor downregulation in people who are dependent on heroin rather than people who use other opioids which do not metabolize to 6-monoacetylmorphine. For more information on dopamine and opioid use disorder the reader is directed to Nutt et al. (2015), Wise and Jordan (2021) and Milella et al. (2023).

Whilst the role of dopamine is not central to this thesis the contrasting evidence for the role of dopamine between stimulant and opioid use poses an interesting question regarding the neurological drivers for continued opioid use. The neurocircuitry is further expanded upon in Chapter three (Figure 3.1) explaining how the hippocampus (involved in learning and memory), the orbitofrontal cortex (involved in reward and punishment

related behaviours) and the anterior cingulate (involved in impulse control and decision making) are key components in any mechanism of cue-induced opioid use.

Chronic, repeated relapse is one of the most challenging yet misunderstood problems to people who use drugs and are exhibiting compulsive behaviours. The general public and healthcare professionals have been found to have a negative and stigmatizing perception of SUDs (Ashford et al., 2018) regarding relapse to drug use. Relapse can be seen by laypeople as a failing or weakness in the person trying not to use drugs. Aside from the moral judgements attached to stigmatizing views, the evidence demonstrates such beliefs are misplaced. Substance use disorders have comparable, if not favourable, relapse rates with other chronic illnesses (National Institute on Drug Abuse, 2018) which require lifestyle change alongside medical management (Figure 1.6). Relapse is not preordained, is preventable (Heyman, 2013) and relapse prevention is a key component of SUD treatment.

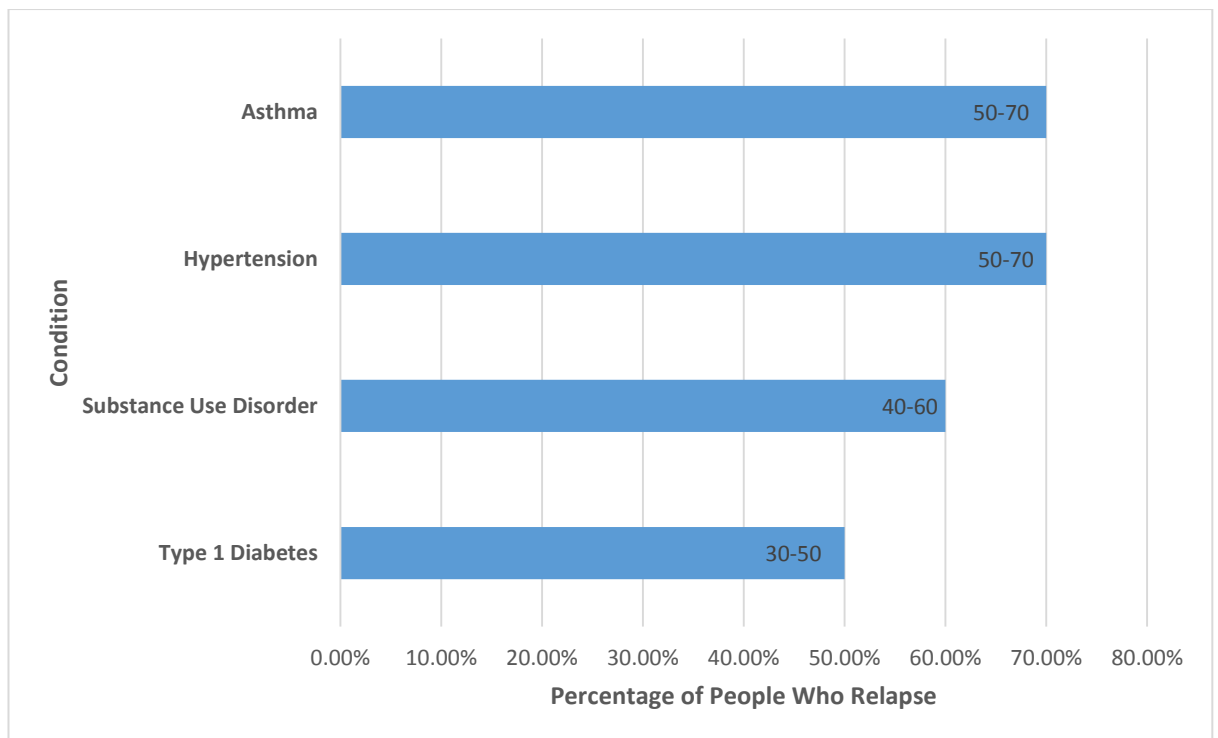


Figure 1.6: Comparison of relapse rates between substance use disorders and other chronic illnesses

Notes: Relapse rates for people treated for substance use disorders are compared with those for people treated for high blood pressure and asthma. Relapse is common and similar across these illnesses. Therefore, substance use disorders should be treated like any other chronic illness. Relapse serves as a sign for resumed, modified, or new treatment. Amended from source: Source: National Institute on Drug Abuse, 2018.

In order to understand how the three stages of the addiction cycle affect the brain, section 1.5 applies the generalised neurobiology discussed here to the neuropharmacology behind opioid use disorders in the binge/intoxication and withdrawal/negative effect stages. Understanding the challenges of relapse and the brain mechanism driving the preoccupation/anticipation stage is central to chapters three, four and five whilst the experiences of people who use opioids in the preoccupation/anticipation stage are the focus of chapter six.

1.5 The Neuropharmacology of Opioid Addiction

Neuropharmacology is a complex subject which relates to how drugs affect the brain and central nervous system. Changes to the brain are widely accepted as part of the cycle of drug use but changes can differ depending on which substances are taken. As this thesis focuses specifically on opioid dependence, only neurobiological changes in response to repeated opioid use/withdrawal will be discussed here.

Opioids induce their effects by interacting with the natural (endogenous) opioid system. The opioid system regulates pain, pleasure and reward among other physiological functions. Acute administration of opioids will induce reward by disinhibiting the mesolimbic dopaminergic neurons as discussed above but repeated opioid exposure can lead to tolerance, dependence and addiction which are all manifestations of brain neuroadaptations in brain chemistry resulting from chronic opioid use (Kosten and George, 2002). Repeated exposure to opioids induces short and long term compensatory homeostatic changes leading to physical dependence where the brain functions normally when opioids are present and abnormally when opioids are not present (Kosten and George, 2002). Following physical detoxification, adaptations revert to normality relatively quickly in *dependent* opioid users but adaptations formed as a result of *addiction* take significantly longer which may at least partially explain the persistence of emotional withdrawal symptoms, cravings and relapse vulnerability even after a long time following abstinence (Kosten and George, 2002). The following section will focus on the endogenous opioid system which is the target of opioids and the neuroadaptations which take place following prolonged and persistent opioid use.

1.5.1 The endogenous opioid system: peptides, their receptors and their functions

When opioids are consumed they are first converted to morphine and bind on opioid receptors located throughout the central nervous system which then trigger the pharmacological effects. Nonetheless the body also naturally produces opioid peptides (endorphins, enkephalins and dynorphins) which bind to the same receptors. Opioid receptors are widespread throughout the central nervous system as well as in the knee joint, gastrointestinal tract, heart and immune system and more (Pathan and Williams, 2012). These receptors are known as μ (MOR), delta (DOR), kappa (KOR) and nociception (NOR). Table 1.1 shows the receptor types, which of our endogenously

created opioids bind to them and the anticipated physical responses when these receptors are occupied.

<i>Receptor Type</i>	<i>Endogenous Opioid</i>	<i>Physical Response</i>
μ, or MOR	endorphins enkephalins endomorphin-1 endomorphin-2	analgesia sedation respiratory depression hypothermia reinforcing effects euphoria pupil constriction decreased gastrointestinal mobility nausea and vomiting urinary retention
delta, or DOR	enkephalins endorphins	analgesia respiratory depression reinforcing effects nausea and vomiting
kappa or KOR	dynorphin A dynorphin B neoendorphin	analgesia sedation dysphoria diuresis
NOR	nociceptin/orphanin FQ	analgesia reinforcing effects decreased gastrointestinal mobility

Table 1.1: Opioid receptor type classification and action

Notes: The endogenous opioids, the typical receptors they bind to and the anticipated response. Analgesia is the anticipated response to all endogenous opioids however reinforcing effects are present in all but activation of KOR receptors.

Once binding to receptors, opioids produce different effects. Opioid drugs are classified in to agonists, partial-agonists and antagonists depending on the different effects. The most clinically useful opioids bind to MOR receptors as agonists meaning they generate a full response from receptors. Examples of MOR agonists include morphine, fentanyl, methadone, codeine and heroin. Partial agonists such as the substitute opiate buprenorphine bind to MOR also but do not generate a full response and have a ceiling

effect thereby reducing risk of overdose. Antagonists such as naloxone or naltrexone produce no functional response whilst simultaneously blocking agonists from displacing them (Pathan and Williams, 2012).

MOR receptor

The pharmacological effects which MOR mediates can be seen in Table 1.1. The primary mechanism for the clinically relevant actions of opioids like pain relief is through MOR and as such must form the foundation for this introduction to opioid receptors (Williams et al., 2013). MOR is also primarily responsible for a range of adverse of opioid including constipation, emesis, respiratory depression, sedation, euphoria as well as tolerance, dependence and withdrawal. The latter three are discussed in section 1.3.2.

As well as these, MOR is involved in drug and social reward processes (Lutz and Kieffer, 2013). In individuals who progress through substance use to dependence and eventually addiction, social isolation increases ‘social pain’ which is thought to share connection with physical pain (Lutz and Kieffer, 2013). Relief from social pain is a driver of substance use and social isolation is a constant theme within addiction lifestyles. As such, dysregulation of the MOR system has been thought to contribute to this “social pain” which is relieved by use of opioids and is highlighted in chapter six.

Kappa receptor

Although there is significant cross-talk between receptors, the majority of opioid effects are a result of MOR activation whilst the KOR receptor is associated with opposite effects of MOR activation such as inhibiting the reinforcement properties of drugs and reinstatement of drug seeking in animal models and humans (Lalanne et al., 2014). The endogenous peptide dynorphin acts on KOR and counteracts MOR activation. Dynorphins are implicated in stress, anxiety, depression, anhedonia and dysphoria (Knoll and Carlezon, 2010). Whilst their role in mood is largely unknown, they are implicated in negative emotional states and noradrenergic systems (Knoll and Carlezon, 2010). Dynorphin release in the striatum has been widely associated with the stimulation of the anti-reward system. Opioid use stimulates the release of dopamine in the nucleus accumbens to induce reward but repeated opioid use and/or withdrawal can induce dynorphins in the striatum in response to increased dopamine thus stimulating dysphoria, negative emotional states and anti-rewarding effects (Lutz and Kieffer, 2013).

Dopamine signalling is not the only neurotransmitter which affects KOR. Serotonin transmission may be modulated by KOR in stress and social-defeat based models of depression (Lalanne et al., 2014). Social-defeat models suggest adverse social experiences such as trauma histories induce depressive behaviours which may further interlink the role of KOR in SUDs. KOR signalling is also central to opioid withdrawal processes, discussed in 1.5.2.

Delta receptor

Reducing anxiety and improving mood are widely accepted functions of DOR activity but implications within reward and addictive behaviours remain contentious. Figure 1.7 provides a visual representation of the interplay of the three opioid receptors throughout the addiction cycle however there is also one further adopted orphan receptor to the opioid family, the Nociception receptor.

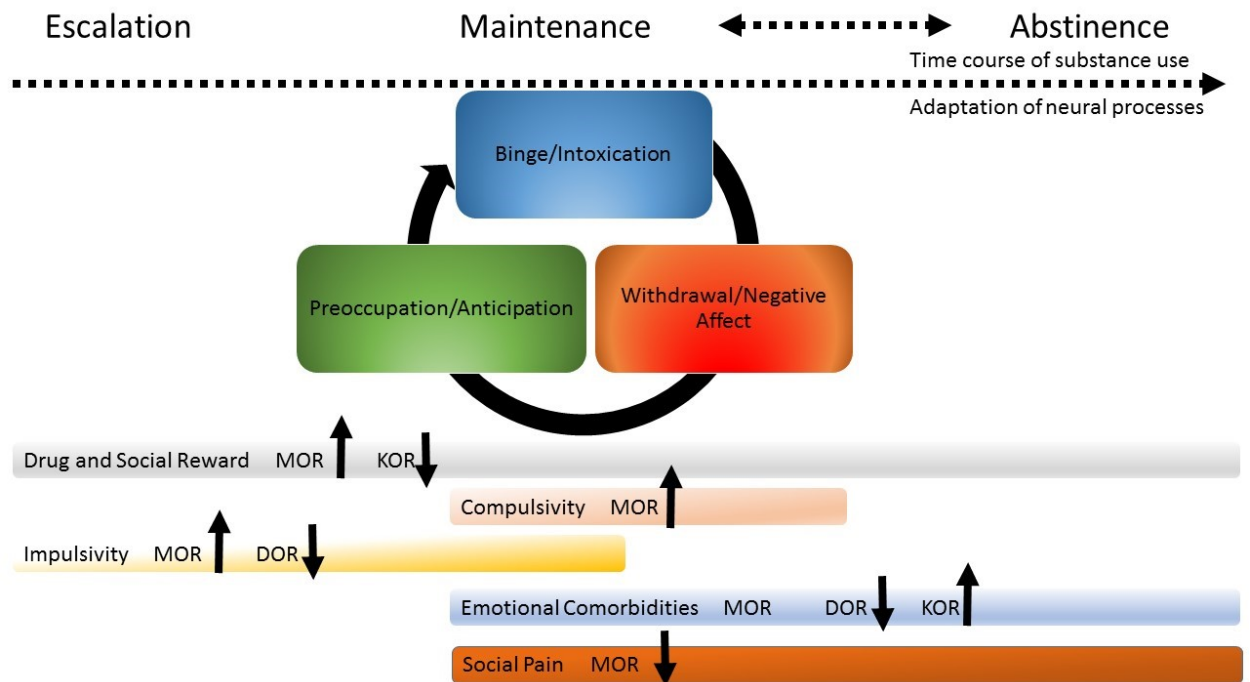


Figure 1.7: The Interplay of opioid receptors in the cycle of addiction

Notes: The MOR and KOR apply opposite influence over drug and social reward, with MOR enhancing and KOR reducing reward processing. MOR and DOR opioid receptors regulate inhibitory controls, with MOR and DOR activities increasing and decreasing motor impulsivity, respectively. These three opioid receptors fulfil distinct roles in addiction-related emotional disorders, with pro- and antidepressant-like activity for KOR and DOR and a complex role for MOR. The MOR may also be a key player in brain pathways encoding social pain. Arrows indicate the effects of opioid receptors activities. Amended from Source: Lutz, P. E., & Kieffer, B. L. (2013). The multiple facets of opioid receptor function: implications for addiction. *Current opinion in neurobiology*, 23(4), 473–479.

Nociception receptor

Discovered in 1994 NOR is not strictly an opioid receptor as natural opioids do not bind with it and natural NOR release does not bind with other opioid receptors (Zaveri, 2016). The NOR system differs to other opioid receptors. An increase in NOR receptors is associated with Parkinson's disease, depression and chronic pain. Pharmaceutical interest has been significantly larger in these areas than for the treatment of SUDs (Zaveri, 2016). Data for NOR agonists in the use of alcohol dependence is most promising and for opioid use limited mice studies demonstrate efficacy for NOR to reduce the rewarding effects of opioids (Zaveri, 2016). The most promising use for NOR agonists may lay with chronic pain where NOR-MOR agonist medication in nonhuman primates has been able to

provide pain relief without inducing respiratory depression, opioid-induced hyperalgesia or physical dependence (Ding et al., 2018). Progressing any medication to human trials would take significant time and therefore not suited to targeting the immediate crisis of opioid-related deaths.

Complete discussion of the pharmacokinetics and pharmacodynamics of opioids are beyond the scope of this thesis but brain changes involving opioid receptors are observed within behaviours of all three stages of opioid addiction. Section 1.5.2 introduces a further three components central to general SUD but approached specifically regarding opioid use disorders: tolerance, dependence and withdrawal.

1.5.2 Opioid tolerance and withdrawal

Tolerance is defined as ‘a decrease in pharmacologic response following repeated or prolonged drug administration’ (Dumas and Pollack, 2008) and is classified as either innate or acquired. Innate tolerance is due to genetic predisposition whereas acquired tolerance comes as a result of repeated exposure to a drug (Dumas and Pollack, 2008).

Tolerance to opioids is a molecular change process far more complex than simply requiring more drugs to produce the desired effect. The long held belief argues tolerance to opioids is induced with downregulation of opioid receptors following chronic agonist exposure however studies demonstrate this is not the case with all agonists. This downregulation may actually be desensitization, decoupling from signalling pathways or a combination of both mechanisms (Al-Hasani and Bruchas, 2013). The opposite to desensitization is incentive-sensitization theory (Berridge and Robinson, 2016). Incentive-sensitization theory interlinks social behaviour to genetic changes suggesting that drug-related cues reduce effects of drugs but removal of these cues, such as when using drugs in new environments, enhances the effects of the same dose (Berridge and Robinson, 2016). The effect presents an alternative suggestion on how drug-related environments could prolong drug using by reducing effects of drugs thereby making drug users continue to chase the high by using more of the same drug. Whereas using drugs in new environments and forming new drug-related stimuli could increase risk of overdose because reinforcement of the same drug is no longer reduced by drug-related environments.

Following the binge/intoxication stage, tolerance is established as a self-regulating process with the aim of ensuring optimal body functioning for stability (Ghezzi and

Atkinson, 2011) but these adaptive changes bring dependence to opioids and the emergence of opioid withdrawal symptoms when opioids are not bound to receptors. Physical opioid dependence forms partly due to changes in the Locus Coeruleus, the center of the brain where noradrenergic neurons project from to release noradrenaline in different brain regions. Here a chemical called noradrenaline which promotes wakefulness, breathing, alertness and other functions is produced. Acute opioid administration causes suppression of noradrenaline release resulting in drowsiness, respiratory depression and lowered blood pressure. With repeated exposure to opioids, the Locus Coeruleus adjusts and increases productivity of noradrenaline to compensate so that when opioids are present the brain is able to function normally. When opioids are removed, then too much noradrenaline is present resulting in jitters, anxiety, cramps and diarrhoea which will last days or weeks (Kosten and George, 2002). Elevated noradrenaline can also be a rebound effect following cessation of alcohol, cocaine and opioid use but studies are mixed in relation to nicotine and cannabis withdrawal. Noradrenaline changes in users of these substances may be more likely initiated by other psychological stress (Fitzgerald, 2013). The result of elevated noradrenaline levels following cessation of opioid use is an extremely unpleasant but not fatal experience is otherwise known as opioid withdrawal (Table 1.2).

<i>Direct Effects</i>	<i>Withdrawal Signs</i>
<i>Euphoria</i>	<i>Dysphoria</i>
<i>Carefree</i>	<i>Irritability</i>
<i>Sedation</i>	<i>Restlessness</i>
<i>Analgesia</i>	<i>Insomnia</i>
<i>Respiratory Depression</i>	<i>Respiratory Stimulation, Yawning</i>
<i>Constipation</i>	<i>Diarrhoea</i>
<i>Pupil Constriction</i>	<i>Pupil Dilation</i>
<i>Decreased Body Temperature</i>	<i>Fever, Chills</i>
<i>Dry Mouth</i>	<i>Salivation, Lacrimation, Rhinorrhea</i>
<i>Nausea</i>	<i>Nausea</i>
<i>Vomiting</i>	<i>Vomiting</i>

Table 1.2: Direct effects and withdrawal signs of opioids

Notes: Withdrawal signs of opioid withdrawal are the reverse of the direct effects of opioid administration. The exceptions are nausea and vomiting which can be signs of both opioid use and opioid withdrawal.

While physical withdrawal symptoms are relatively short lived and effectively managed by opioid substitution therapy, opioid dependent individuals often suffer from emotional withdrawal symptoms which unlike physical withdrawal symptoms may be long lived, even after several months following abstinence. Nonetheless, they are entirely clinically relevant as they constitute a motivational trigger to relapse. There are various pharmacological and non-pharmatherapeutic approaches to management of opioid use disorder which will be discussed in the next section.

1.5.3 Treatment of opioid use disorder

Pharmacological interventions for opioid use disorder can be divided in to substitute medications, relapse prevention and withdrawal management. Substitute medications such as the μ -receptor agonist methadone and μ -receptor partial-agonist buprenorphine are the first line treatments for opioid use disorders (Clinical Guidelines on Drug Misuse and Dependence Update, 2017). The aim of these is to transfer dependence from illicit opioid use where there is greater uncertainty in purity of the illicit opioid due to adulterants (pesticides, brick dust, caffeine, benzodiazepines and higher strength opioids such as fentanyl) that are mixed with the illicit opioid to a safer, controlled alternative. Substitute medications are shown to have anticraving efficacy when prescribed for daily consumption within optimal dosing range (Clinical Guidelines on Drug Misuse and Dependence Update, 2017). Optimal dosing for methadone is 60mg-120mg per day and for buprenorphine based medications, above 12mg daily (Clinical Guidelines on Drug Misuse and Dependence Update, 2017). Within opioid-use disorders, withdrawal-related craving is relatively easy to manage by providing substitute opiate medications such as the μ -receptor agonist methadone and μ -receptor partial-agonist buprenorphine. However, these medications are unsuitable for cue-induced craving which requires rapid relief when craving is triggered. If taken ad-hoc as required by cue-induced craving, inconsistent dosing levels of substitute opiates heighten risk of accidental opioid overdose (Clinical Guidelines on Drug Misuse and Dependence Update, 2017). Withdrawal-related craving and cue-induced craving are further discussed in chapter three. Naltrexone, an opioid receptor antagonist, can be used as a relapse prevention medication by blocking the effects of any opioids and also holds anticraving properties but suffers from poor compliance rates and people must be abstinent from all opioid use prior to initiation making Naltrexone unsuitable for people who are dependent on opioids (Bart, 2012). To reduce the effects of opioid withdrawal Lofexidine Hydrochloride, an

adrenergic receptor agonist, can be prescribed. Lofexidine Hydrochloride works via noradrenaline α_2 receptors to decrease cyclic adenosine monophosphate. In turn this reduces the symptoms of opioid withdrawal and has comparable efficacy with methadone and buprenorphine for treating opioid withdrawal though is not associated with anticraving effects (Rehman et al., 2019; Pergolizzi Jr. et al., 2019). Other pharmacological interventions under investigation to aid opiate withdrawal include the use of anti-nausea neurokinin antagonist medications typically used in chemotherapy in brain imaging cognitive tasks whilst undergoing methadone detoxification (IRAS: 262604) and proof-of-concept Ibogaine investigating the maximum tolerated dose or treat-to-target dose in opiate withdrawal (Clinical Trials Number: NCT05029401).

Although substitute medications are the first line treatment for opioid use disorders, psychosocial interventions (e.g. motivational interviewing or cognitive behavioural therapy focused on improving psychological and social factors related to opioid use) are recommended alongside them (Clinical Guidelines on Drug Misuse and Dependence Update, 2017; Rice et al, 2020). The aim of these is to provide tools which support 'recovery'. The definition of recovery is contested within the field and ranges from 'total abstinence of all substances' to being entirely client defined but always includes aspects of 'recovery capital' (things which people have that protect them from relapse) such as housing, physical health, mental health, relationships and social engagement. Proponents often cite Robins (1993) study on Vietnam soldiers as seminal research underpinning recovery capital. This study argued only 1% of a previously 34% addicted soldier population became re-addicted in the first year following return from the Vietnam War and that the often communicated reason for this was the high levels of recovery capital that each soldier possessed (Robins, 1993). However these findings do not tell the full story. Soldiers were not allowed to return to the US until they had given clean urine drug screens, therefore were not physically dependent on their return; soldiers had continued to use barbiturates, cannabis and amphetamines throughout the war and after the war in the same frequency and amount; the majority of soldiers were not using enough heroin with enough frequency or quantity to be physically dependent and the microcosm environment of Vietnam cannot be considered ecologically valid for generalised drug treatment. Interviews with the soldiers upon their return to the US confirmed that their reasons for not continuing to use heroin were in line with existing evidence – the purity of heroin was far greater in Vietnam; the cost of heroin was far cheaper in Vietnam; heroin

was far more readily available in Vietnam and soldiers were not physically dependent on heroin in Vietnam (Hall and Weier, 2016). Robins study reaffirms the established and widely accepted known role of purity, cost and availability in initiation and ongoing substance use even within a microcosm environment such as the Vietnam War but the reduction in opioid use is only correlated with and not caused by the presence of recovery capital. The soldier self-reports (Hall and Weier, 2016) imply a level of cognitive control not seen in compulsive models of addiction or associated with longer lasting changes in the brain resulting from addiction rather than dependent substance use. For these reasons the role of recovery capital in overcoming SUD remains a focal yet contested subject which may be more relevant at this stage of research to relapse prevention interventions rather than interventions aimed at cessation or regaining control of substance use. For more information on the recovery capital the reader is directed to Best et al. (2020) and Collinson and Best (2019).

Another oft-cited study when discussing psychosocial treatments is Bruce Alexanders (1978) 'Rat Park' and the subsequent follow on experimental studies. These studies found that rats living in social housing were less likely to administer oral morphine than those living in isolation (Alexander et al., 1978) though this is often wrongly communicated that rats in social housing stopped taking morphine completely. The link was then extrapolated to human behaviour i.e. if people were occupied they would not use drugs or at least they would use less of them. Alexander et al attempted to replicate the studies however publication submissions to high impact factor journals including Nature were rejected due to problems with methodology. These problems included the small sample size of rats, differing methods of collecting data between socially housed and isolated rats and eight days of missing data in the original study when the machine measuring morphine consumption had broken. Similarly although subsequent experimental studies also found isolated rats preferred morphine solution this was only found in the solution highly sweetened with low levels of morphine (indicating the rats may simply have preferred the sweeter taste) or in rats already 'pre-addicted' to morphine (indicating relapse to a learned behaviour rather than novel initiation). There was also no indication of what happened to rat pups born in the social housing side which would have impacted behaviours of the rats (Gage and Sumnall, 2019). Third party attempts to replicate Alexanders (1978) series of studies have found mixed results highlighting that the original set of studies are far from the indisputable panacea of 'how to treat addiction' as they are

often portrayed. Nevertheless these important studies do support the importance of the environment on substance use even if the studies gloss over (or just ignore) the richness and complexity of human experience in comparison to a small number of rats. For this reason, psychosocial interventions focused on exploration of housing, how people spend their time and who people socialise with (Clinical Guidelines on Drug Misuse and Dependence Update, 2017) are recommended for everybody who enter structured drug and alcohol treatment in the UK.

Another recommended but rarely implemented treatment is Contingency Management. Contingency Management is a behavioural therapy whereby people are ‘reinforced’ or rewarded for positive behavioural change (Petry, 2011). Contingency Management is highly effective, notably in reducing opioid use by providing reinforcement for the morphine negative urine drug screens, but some of the barriers to implementation include ideological concerns from practitioners, poor training on how to implement it and the cost of implementation (Petry, 2011). Most recently in the UK researchers retrospectively analysed the use of the ‘Capital Card’ (Moss et al., 2020), a contingency management intervention given by the drug treatment provider to every person who entered treatment which worked like a retail loyalty card. People earned points for engagement in treatment (attending appointments, completing blood borne virus screening etc) which could be exchanged for community activities (cinema tickets, gym membership, discounted driving lessons etc). The results showed no difference in changes to quality of life or psychological wellbeing when people completed treatment directly opposing theory of recovery capital. Although reported treatment outcomes improved, the options for recording successful completions in the UK are wide ranging and should be interpreted with caution. For example, an alcohol user who reduces from drinking ten beers daily to nine beers daily could be recorded successful by the treatment provider due to the reduction in use if that was the goal of the person in treatment but an opioid user who reduces heroin use from daily administration to once a week could not be closed successful using the same rationale. This means other factors such as treatment providers meeting commissioned performance indicators may influence the length of a reported treatment journey. Analysis of these factors are beyond the scope of this thesis. Within the Capital Card scheme there were many limitations which could affect the data. Researchers were not aware of the socioeconomic status or the presence of any co-existing psychiatric disorders of each person in treatment and there were a high number

of points earned by people that were not spent (Moss et al., 2020) without any explanation given for this. If the Capital Card was given routinely to everybody in treatment it is difficult to see if the high number of points earned but not spent was evidence of engagement in the scheme or an inevitable by-product of it. As with recovery capital, contingency management interventions do not account for neurobiological changes as a result of addiction and rely on the individual efficacy of people to exercise cognitive control over automated, compulsive decision making processes in order to accrue rewards.

Available medication options for opioid use disorder are effective in stabilisation and prevention of physical withdrawal but are limited in their ability to reduce cue-induced compulsive behaviours associated with addiction. Psychosocial treatments are wide ranging, recommended and efficacious alongside substitute medications but are highly sensitive to individuality and do not demonstrate clear benefits of one treatment over another (Rice et al., 2020). It is clear that onset and continuation of opioid use can be influenced by both medical symptoms and lifestyle choices. The above evidence demonstrates that treatments should target both these domains. Indeed a recent government commissioned review of the UK drug and alcohol treatment system supported within the UK Drug Strategy 2021 recommended that more innovative research takes place, specifically in pharmacotherapies which have seen no recent advances other than long-acting buprenorphine depot injection and prior to that the introduction of Naltrexone in 1984 (Black, 2021; HM Government, 2021). Oxytocin is a strong candidate for this research. Oxytocin is a neurohormone which has drawn particular attention for its part in SUDs due to its unique properties on the neurobiology of SUD and role in social interactions. Oxytocin is discussed in the following section.

1.6 The Potential Role of Oxytocin

Commonly referred to as ‘the love hormone’ (Magon and Kalra, 2011) due to being released naturally when we hug others and experience sexual intimacy, understanding of the flexibility and complexity of oxytocin is increasing. Section 1.6 explains what the oxytocin system is, how early life environments with caregivers affect develop of the oxytocin system, how social interactions (a key role for oxytocin) affect opioid use and the implications for oxytocin dysregulation in psychiatric disorders where prevalence alongside opioid use disorder is high.

1.6.1 What is our oxytocin system?

Oxytocin is a hypothalamic neuropeptide involved in the regulation of physiological and behavioural responses including uterine contraction, pair bonding, prosocial behaviour, stress modulation, processing of social cues, social memory and interpersonal behaviours (Macdonald and Macdonald, 2010; Churchland and Winkielman, 2012; Johnson and Young, 2017). Interesting, recent opposing research by Berendzen et al. (2023) involving prairie voles without oxytocin receptors has demonstrated the presence of oxytocin receptors is not critical to all social behaviours. In the next section the pharmacology of oxytocin is given an overview.

1.6.2 The pharmacology of oxytocin

Oxytocin is a nine amino acid neurohormone which has a role as both a neurotransmitter (chemicals which transmit messages across neurons or cells) and a neuromodulator (the physiological process of regulating other neurons) (Zanos et al., 2018). Oxytocin is synthesised by paraventricular, supraoptic and accessory nuclei of the hypothalamus (Althammer and Grinevich, 2017). Once released oxytocin has high affinity to bind to oxytocin receptors widely distributed in olfactory processing regions (regions implicated in sense of smell), limbic brain structures, hippocampus (learning and memory), hypothalamus (maintenance of homeostasis), brainstem (regulation of eating, breathing, heartbeat) (Russell and Brunton, 2017) and also binds to vasopressin receptors. Vasopressin is also a nonapeptide synthesized by the hypothalamus and plays a role in osmotic balance (regulation of salt and water balance in the body), blood pressure regulation, sodium homeostasis and kidney functioning (Cuzzo et al, 2020).

To date there is no positron emission tomography radioligand available for use in humans though some animal studies are underway (Lee et al., 2016). Extrapolating from primate data and human studies which used autoradiography in post-mortem human brains it can be concluded that; oxytocin and vasopressin receptors are found in the hypothalamus, vasopressin receptor expression occurs throughout the central nervous system though oxytocin receptor expression is localised, oxytocin receptors are consistently seen in the limbic system with inconsistent evidence for the amygdala and oxytocin receptor staining is most prominent in the basal forebrain which plays an important role in visual attention, memory and learning (Baribeau & Anagnostnou, 2015). Single-photon emission computed tomography, a cheaper option to positron emission tomography but producing

poorer contrast and spatial resolution in comparison, has shown the oxytocin and dopamine systems work together in healthy human participants to regulate corticostriatal circuitry which are essential components of motivated behaviour (Wei et al., 2020). It is unclear how, if at all, a dysregulated oxytocin could impact motivation for opioid use when no striatal dopamine release following opioid use in humans has been identified (Nutt et al., 2015). However if a healthy oxytocin system in part helps to regulate motivated behaviours then perhaps a dysregulated oxytocin system is unable to regulate the motivational circuitry irrespective of any increase in dopamine release. Further imaging research is needed to explore this idea.

Although it was originally thought there just two types of oxytocin neurons, magnocellular and parvocellular, current research has found at least four different types of oxytocin neurons (Althammer and Grinevich, 2017). Magnocellular oxytocin neurons project to over fifty forebrain regions at cortical and subcortical levels and are involved in fear response, maternal aggression, social fear and male dominance behaviour. Parvocellular oxytocin neurons are predominantly involved in cardiovascular functioning, hunger/feeding, sexual behaviour and pain modulation but current research shows parvocellular oxytocin forebrain projections which may modulate complex autonomic homeostatic behaviours (Althammer and Grinevich, 2017). For example it has been shown that pain-related cues stimulate parvocellular neurons to trigger oxytocin release (Althammer and Grinevich, 2017) and it is thought the same mechanism may occur during fear responses and other situations where environmental cues trigger a rapid behavioural response such as drug use.

When given as a medication different methods of administration act differently in the body. Administered intravenously or intramuscularly uterine contractions' begin within 3-5 minutes with a half-life (the time it takes for half the drug to leave the system) of 2-3 minutes. Nasal administration takes approximately 15 minutes (Kabilan, 2014) to see motor and perceptual responses with a half-life of approximately twenty minutes. In humans, almost all studies target the central oxytocin system by administering oxytocin nasally. Oxytocin is unable to cross the blood-brain barrier and is degraded in the gut but human studies use nasal oxytocin under the assumption the nasal cavity provides a direct route to the brain, circumventing the blood-brain barrier. The exact mechanism remains unknown but recent evidence has shown an increase in regional cerebral blood flow following nasal oxytocin administration not seen when oxytocin was administered

intravenously which can only be explained by a direct nose-to-brain pathway (Martins et al., 2020). Recent functional magnetic resonance imaging (fMRI) brain imaging studies have shown that 40 International Units (IU) nasally administered oxytocin can decrease resting blood flow in the amygdala starting as early as 15 minutes post-dosing (Martins et al., 2020). Oxytocin kinetics and small dose dependency studies have demonstrated through fMRI a blood oxygenation level response in amygdala extending up to 70 minutes post-dosing (24IU; Spengler et al., 2017) providing initial evidence for nasal oxytocin capability to target amygdala functionality. It may be that oxytocin enters the blood stream through nasal capillaries and is transported directly to the brain by receptor for advanced glycation end-products on capillary endothelial cells (Yamamoto et al., 2019) but this mechanism is far from proven.

Chapters four and five of this PhD provides novel understanding of the neurobiological mechanism of craving which suggests that environmental cues involve amygdala hyperactivity, increased craving and decreased control of attentional bias culminating in relapse. It is proposed that nasal oxytocin, if used when environmental cues trigger this mechanism, can reduce craving.

1.6.3 Early life, socialisation, psychiatric disorders and substance use disorders

People continually interact with their environment throughout their lifetime. These interactions shape the development of the oxytocin system and the implications are wide ranging and long lasting. The following section discusses how three inter-related themes (early life, socialisation and psychiatric disorders) can impact the onset and continuation of opioid use disorder through dysregulation of the oxytocin system. These themes are then further explored as pre-identified themes in the qualitative interviews found in chapter six to provide a link between the experience of people who use opioids with the oxytocin dysregulation evidence and theory outlined below.

Early life

Social, psychological and economic drivers as well as neurobiological mechanisms drive continued drug use (Roddy et al., 2011). Oxytocin is interlinked with influencing social development and the large individual differences in basal oxytocin levels and the reactivity of people's oxytocin systems which exist are thought to be the result of environmental and early experiences (Bales and Perkeybile, 2012). High levels of affectionate contact between human mothers and infants show oxytocin increase

following interaction, likewise in father-infant interaction with stimulatory contact (Feldman et al., 2010) whereas early adverse life experience however has been shown to lead to lower levels of oxytocin, higher depressive symptoms and higher state-trait anxiety in males (Opacka-Juffry and Mohiyeddini, 2012). For a full review on early-life stress and the impact on the oxytocin system, the reader is directed to Baracz et al. (2020).

As discussed previously the majority of people who use opioids have experienced a traumatic childhood. Substance use by self and others is a common theme throughout the literature regarding adverse childhood experiences. Adverse childhood experiences are associated with use of psychological services later in life, internalising emotional distress when emotional neglect has been experienced and externalising behaviours where emotional and physical abuse of family members has been present (Van Duin et al., 2019). Chapter six explores the experience of people who currently use opioids in relation to craving and part of the interview is to understand the progression from childhood to initial use of opioids. The following section will provide background relating to the impact of childhood trauma and adolescent socialisation on dysregulation of the oxytocin system which is likely to play a role for each person interviewed (Figure 1.8).

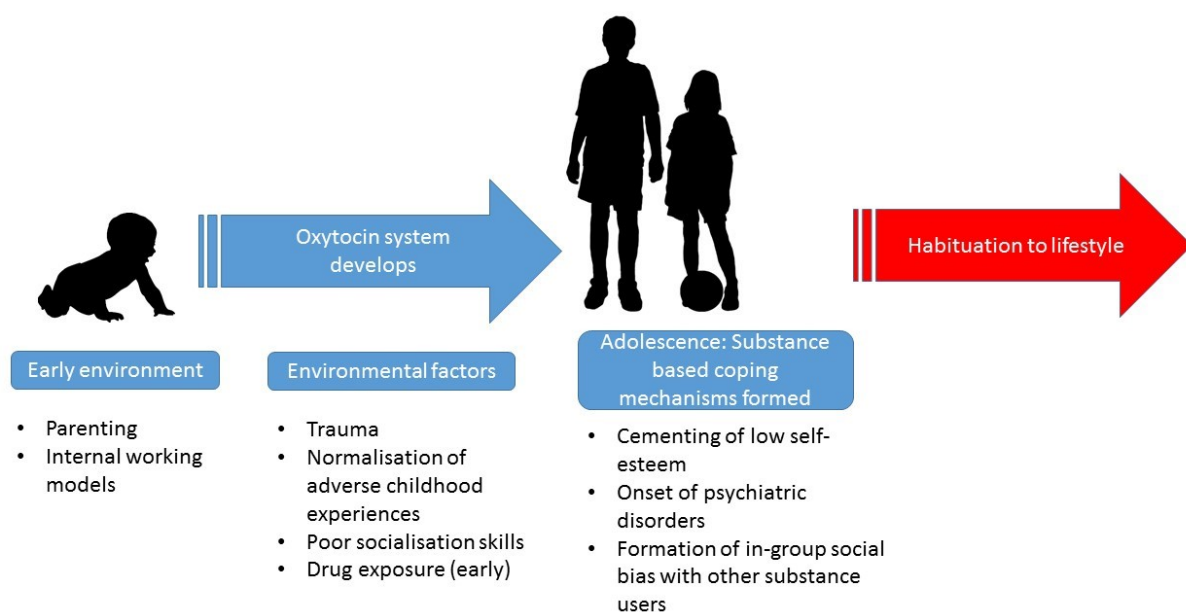


Figure 1.8: Suggested model of oxytocin system dysregulation from birth to adolescence affecting susceptibility to addiction

Notes: The early environment shapes internal working models for negotiating interactions with other humans. Parenting styles and exposure to trauma can dysregulate the oxytocin system leading to normalisation of these experiences and the coping mechanisms they create. These mechanisms can then impact socialisation with other children because behaviours of children unaffected by trauma are unexpected and inconsistent with the experienced norms. Children exposed to trauma have not developed socially normative internal rule sets for managing these interactions and so by adolescence these children seek acceptance within peer groups with similar experiences whose behaviours are more consistent with their own. Peer group experience then leads to risky behaviours such as drug taking which can also dysregulate oxytocin systems. It is during adolescence where the onset of psychiatric disorders is most common and oxytocin dysregulation is also observed. Amended from source: Buisman-Pijlman FT., Sumracki NM., Gordon JJ., Hull PR., Carter CS., Tops M (2014) Individual differences underlying susceptibility to addiction: role for the endogenous oxytocin system *Pharmacology, Biochemistry, Behaviour* Apr;119:22-38.

The prenatal developmental effects of oxytocin on the brain remain largely unknown although postnatal and peripubertal emerging evidence suggests a complex role in the organisation, structure and functioning of neurons in particular with relation to the HPA axis (Miller and Caldwell, 2015). Oxytocin release during traumatic experiences has been thought to interfere with the consolidation of memories making memories weaker and

more susceptible to extinction (Singewald et al., 2015) but high rates of enduring PTSD stemming from childhood trauma (Lawson et al., 2013) within people who use opioids challenges this and may suggest a role for oxytocin in consolidating the learned behaviour arising from these experiences.

Learned behaviour can manifest psychologically within an ‘internal working model’ - mental representations of expectancies for how to control, predict and manipulate an environment (Bowlby, 1980). It is known that oxytocin can strengthen familiarity from novel cues in order for positive and negative socially contextual information to be constructed within internal working models (Tops et al., 2014). As well as social context, an individual’s attachment type (Wagner and Echterhoff, 2018) influenced by childhood experiences (Fletcher and Schurer, 2017) also helps to shape the internal working model. Taken together this may mean that adverse childhood experiences become normalised internally, are consolidated with the help of oxytocin (Tops et al., 2014; Wagner and Echterhoff, 2018) and lead to maladaptive behavioural responses. In this example the purpose of oxytocin could be to consolidate behavioural responses to inconsistent or aggressive primary caregivers in order to facilitate future rapid avoidance of negative experiences like abuse. So the oxytocin system may not be *compromised* through adverse environmental experiences but is simply performing a core evolutionary function – survival. Although beneficial short-term, maladaptive internal working models could lead to poor socialisation starting in childhood and continuing in to adolescence when persuasive peer groups are typically formed (Nock et al., 2017). Socialisation is discussed next.

Socialisation

The groups which humans bond with are highly influential with in-group bias a dominant factor (Tajfel and Turner, 1986). People within our in-group, the people we align ourselves with, tend to justify and enable our behaviours based on discriminatory perceptions of people outside of our in-groups who are assumed not to share our beliefs and ideals. The influence of social groups on drug use is well documented and will not be covered in depth by this thesis however readers are directed to Bohnert et al. (2009) and Bardo et al. (2013) for specific information regarding social influences on heroin use and the neuropharmacology of drugs. Instead chapter five will explore the novel area of the individual experience of obtaining illicit drugs when craving. People do not ‘just use’

drugs, there is always a thought and behaviour process involved of getting money, contacting dealers, buying, preparing the drugs and finally using. These stages may or may not involve other people in group contexts. People who use opioids are known to have low personal self-esteem (Hendy et al., 2018) and individuals with low personal self-esteem but high self-esteem when contributing to a social group express greater levels of in-group bias to compensate for lack of self-worth (Jelic, 2009). This may suggest presence of a bias towards drug-seeking when encouraged by others within opioid using social networks and dysregulated oxytocin systems could impair the ability to reevaluate the pros and cons of using drugs, in part through fear of being shunned by the group. One double-blind, placebo controlled study showed that members of a three person group who received 24IU nasal oxytocin versus members of a three person group who received placebo were more likely to exchange new information whereas the placebo group remained biased towards the existing information in decision making processes (De Wilde et al., 2017). This interesting finding may be of relevance to people who use opioids who are likely have a dysregulated oxytocin system. Part of that dysregulation may involve decision making in response to environmental cues, the neurobiological mechanism of which is hypothesised further in chapters three and five and the decision making experience of people when they are craving opioids is explored in chapter six.

How socioeconomic factors dysregulate the oxytocin system is largely unknown. Animal models have shown increased oxytocin receptor expression in the bed nucleus of the stria terminalis (important for stress response, extended fear states and social behaviours) irrespective of sex in socially isolated rats (Perkins et al., 2019) and decreased plasma levels of oxytocin in socially isolated rats, also irrespective of sex (Harvey et al., 2019). Dysregulation may involve chronic stress induced prolonged activation of the HPA axis leading to hyper secretion of oxytocin to regulate this activation (Vargas et al., 2020). Oxytocin's proposed allostatic role in learned cue-response behaviour combined with oxytocin blunting social vigilance behaviour in rhesus monkeys (Ebitz et al., 2013) could suggest manifestations of learned behaviours necessary for survival in deprived communities. Indeed, mice with higher levels of oxytocin receptors displayed enhanced fear, anxiety and aggression after a single negative social experience (Guzmán et al., 2013). Alternatively, it may be that during prolonged exposure to chronic stress when allostatic overload occurs (Guidi et al., 2021), the brain is unable to synthesize adequate

volume of oxytocin required to continually regulate HPA axis activation leading to lower levels of oxytocin and unoccupied oxytocin receptors.

Research in humans has shown the effects of nasal oxytocin can be mediated by socioeconomic status. Nasal oxytocin administration versus placebo increased emotional theory of mind (the ability to recognise and understand others' emotions) in people with low socioeconomic status but not those with high socioeconomic status. This may support the idea of lower natural levels of oxytocin in socially deprived communities, indicate general difficulty interacting with others and perhaps leading to social isolation (Sun et al., 2020) – all of which are associated with people who use opioids. Opioid-related mortality is highest in deprived communities in the UK and there are also significant associations between socioeconomic deprivation and psychiatric disorders such as major depressive disorder, bi-polar disorder, self-harm and anxiety (Remes et al., 2019; Ye et al., 2021), again all associated with people who use opioids. Exposure to socioeconomic disparities alongside access to opioids could lead to a conditioned relief based response of opioid use. This thesis proposes that as a means to reduce craving triggered by one or more of the aforementioned risk factors, nasal oxytocin could reduce opioid use by modulating dysregulated oxytocinergic processes.

Psychiatric disorders

Just as most substance use disorders begin in adolescence (Nock et al., 2017), the same can be said for the onset of psychiatric disorders (Jones, 2013). But outlining a theoretical role for oxytocin from early trauma and attachment to social, group-led components of substance use is clearer than understanding a role of oxytocin within the onset of psychiatric disorders. Oxytocin dysfunction is associated with psychiatric disorders such as panic disorder, obsessive compulsive disorder, depression, PTSD, schizophrenia and autism spectrum disorder (Misrani et al., 2017). Specifically variation in the oxytocin receptor gene, also known as genetic polymorphism, has been shown in people with schizophrenia (Haram et al., 2016; Misrani et al., 2017), bipolar disorder (Winterton et al., 2021), autism spectrum disorders (Misrani et al., 2017; Ocakoğlu et al., 2018) and is associated with increased risk for anxiety, stress and depression in individuals who experienced early life trauma (Myers et al., 2014). Genetic polymorphisms in people with schizophrenia and autism spectrum disorders have been shown to be associated with impairments in social cognition, repetitive behaviours, communication and attention

(Misrani et al., 2017). These influences and symptoms share substantial commonality with opioid use disorders adding further justification for this thesis to explore the role of oxytocin.

Oxytocin is not only released in the brain, it is also released in the blood circulation in the posterior pituitary. The relationship between oxytocin levels in the brain and oxytocin levels in blood is not fully understood and it cannot be assumed that quantity of oxytocin necessarily relates to function of oxytocin. Oxytocin is a key regulator of anxiety due to its role in suppressing HPA axis activity (Misrani et al., 2017) however levels of oxytocin in blood found in people with anxiety disorders versus healthy people have not been found to be significantly different though time and task dependent fluctuations were seen (Cochran et al., 2013). Similar findings are found in people with schizophrenia and people with major depressive disorder (Cochran et al., 2013). That being said, small studies of people found that healthy people (n=60) with higher levels of plasma oxytocin were more likely to seek support from informal sources such as family and friends than people with major depressive disorder (n=63) who had lower levels of plasma oxytocin (Thomas and Larkin, 2018). Although no effect on formal help-seeking was found these findings support prosocial theories of oxytocin but also limits individuals to their established social groups and, speculatively, this may mean support of behaviours such as opioid use. A systematic review of 35 qualitative studies looking at oxytocin levels and trauma in humans found significant associations between people who had experienced emotional trauma and their oxytocin levels (Donadon et al., 2018) specifically finding reductions of oxytocin in people who experienced early trauma and people who have PTSD. Levels of oxytocin in blood may be associated with psychiatric disorders but what these levels mean behaviourally, if anything at all, is unclear.

Nasal spray oxytocin studies in people with psychiatric disorders show inconsistent results. Promise is shown in suppressing negative symptoms of schizophrenia with nasal oxytocin and although there are no randomized, placebo-controlled studies measuring the long term effects of nasal oxytocin on major depressive disorder, smaller studies have found no improvement in general mood state or depressive scoring versus placebo (Cochran et al., 2013). Acute anti-anxiety effects of nasal oxytocin are generally accepted to be the result of reduction in the increased amygdala activation as seen in human fMRI studies (Misrani et al., 2017). The potential for nasal oxytocin to modulate behavioural deficits in autism spectrum disorders is one of the most researched effects though results

have been inconsistent, inconclusive and suffer from heterogeneity. The largest trial to date for nasal oxytocin to reduce aberrant behaviour in 290 children and adolescents (aged 3 to 17) found no significant differences versus placebo (Sikich et al., 2021). For a full review the reader is directed to Okamoto et al (2016). Similar inconsistency can be found within investigation for the utility for nasal oxytocin in the treatment of borderline (Bertsch and Herpertz, 2018) and antisocial personality disorders (Gedeon et al., 2019), which are both highly prevalent in people who have a co-existing opioid use disorder (Casadio et al., 2014). One finding of interest from 35 studies systematically reviewed for the role of oxytocin in trauma, due to the high prevalence of trauma events experienced by people who use opioids, is that oxytocin has been able to re-establish functioning of brain networks associated with emotional control and cognitive performance in people with PTSD (Donadon et al., 2018). The mechanism for this is through oxytocin's ability to reduce hypervigilance and increase the person's ability to feel pleasure from normal activities (Donadon et al., 2018). This indication may be especially relevant to the focus of chapters four and five which assess the role of oxytocin in the modulation of opioid craving. The effects of nasal oxytocin administration could help people who use opioids feel greater social inclusion and gain pleasure from daily life instead of seeking escape through opioid use.

1.6.4 Allostatic theory of oxytocin

Oxytocin is not just involved in prosocial behaviours and one current theory suggests that it may have evolved to serve an allostatic function (Quintana and Guastella, 2020). Allostasis is when the body *predicts changes* in external environments and adjusts accordingly in order to 'maintain stability through change' (McEwen, 1998). Homeostasis is the body making adjustments *in response* to changes in external environments. The purpose of both types of changes is for the body to continue functioning as best it can. For example, increased heart rate and pulse is an allostatic change when people start to run that enables people to jog whereas sweating is a homeostatic response to jogging itself which keeps people cool.

Allostasis hypotheses for addiction are not new. Previous hypotheses suggest that the normal homeostatic limitation of reward functions fail to return within the homeostatic range following opioid use. Chronic opioid use then causes a dysregulation which produces an allostatic state that drives further opioid use expanding the parameters of

reward limitations, and ultimately leads to compulsive opioid use (Koob and Le Moal, 2001). This thesis suggests that cue-induced opioid use has always been an allostatic response and is not produced by chronic opioid use, rather that the allostatic response to cues is amplified by chronic opioid use.

Oxytocin dysregulation may be a symptom of allostatic overload. Allostatic overload occurs when environmental challenges exceed the individual's ability to cope leading to continually activated stress response systems without adequate buffering factors. There are ten known biological parameters of allostatic overload; cortisol, dehydroepiandrosterone, epinephrine, norepinephrine, cholesterol, glycosylated hemoglobin, resting systolic and diastolic blood pressure, body mass index and waist-hip ratio. The HPA axis (regulated by oxytocin) plays a key role in managing allostatic load suggesting that oxytocin could be an eleventh parameter for allostatic overload if oxytocin becomes dysregulated during allostatic overload rendering itself unable to regulate the HPA axis (Koob and Le Moal, 2001; Guidi et al., 2021).

Allostatic overload is defined by two criterion. Firstly by 'the presence of a current identifiable source of distress in the form of recent life events and/or chronic stress; the stressor is judged to tax or exceed the individual coping skills when its full nature and full circumstances are evaluated'. Secondly when 'the stressor is associated with one or more of the following features which have occurred within six months after the onset of the stressor: 1) at least two of the following symptoms; difficulty falling sleep, restless sleep, early morning awakening, lack of energy, dizziness, generalised anxiety, irritability, sadness, demoralisation 2) significant impairment in social or occupational functioning 3) significant impairment in environmental mastery (feeling overwhelmed by the demands of everyday life)' (Guidi et al., 2021). These criterion, specifically significant social and environmental impairment, share commonality with the DSM5 criteria for opioid use disorder (American Psychiatric Association, 2013).

Situations which can lead to allostatic overload are (a) exposure to frequent stressors that may determine a status of chronic stress and repeated physiological arousal (i.e. chronic opioid use); (b) lack of adaptation to repeated stressors (i.e. lack of coping mechanisms for opioid-related triggers); (c) inability to shut off the stress response after a stressor is terminated (i.e. compulsive opioid use); (d) allostatic response not sufficient to deal with the stressor (i.e. oxytocin unable to regulate the HPA axis). Further parallels with opioid

use disorder risk factors and heightened allostatic load are low socioeconomic status, lower income levels, impoverished or segregated neighbourhoods, a decline in cognitive and physical functioning among older people, adverse childhood events including abuse and maltreatment which can predict avoidant and anxious attachment styles, poor diet whilst higher allostatic load shows a significant association with mood disorders such as anxiety and depression and a range of physical comorbidities (Gaudi et al., 2021). The environmental influences on allostatic overload are strikingly similar to environmental risk factors for opioid use disorder and although the perspective of allostatic load within addiction has been explored previously (Koob and Le Moal, 2001), the influence of oxytocin on regulation of the reward circuitry during allostatic overload has not yet been investigated. Dysregulation of the regulatory hormone oxytocin may lead to substance use as a learned behavioural response to allostatic overload from environmental stressors rather substance use disorder being a disease.

1.6.5 The proposed role of oxytocin in opioid use disorder

Preclinical studies have identified several mechanisms of action of oxytocin agonists that could explain its effect on drug seeking behaviour. These include the modulation monoamine and glutamatergic systems, and the suppression of the HPA axis and amygdala hyperactivity. Following oxytocin administration animal models have demonstrated a 50% reduction in cocaine self-administration (Sarnyai and Kovacs, 2014; Morales-Rivera et al., 2014), the elimination of amphetamine self-administration in voles (Young et al., 2014), decreased intravenous heroin self-administration in rats (Sarnyai et al., 1998) and oxytocin analogues are capable of preventing reinstatement of opioid seeking behaviour in mice (Zanos et al., 2014).

Oxytocin antagonists seem to negatively impact regulatory processes. While agonists have shown that dose dependent oxytocin in rodents can reduce acute and chronic tolerance to morphine, antagonists were able to reverse the effect (Lee et al., 2016). If antagonists were to increase tolerance to opioids in human it may lead to higher doses of opioids being used with limited effect of opioids on reducing pain. This would likely also cause an increase in noradrenaline raising blood pressure, causing headaches, increased sweating and anxiety as well as generate possible physical dependence. It is not advantageous for humans to become physically dependent on any exogenous substance hence a possible role for endogenous oxytocin to moderate tolerance formation. Similarly

where agonists reduced glutamate levels following stress-primed reinstatement of methamphetamine, antagonists reversed the effect (Lee et al., 2016). If glutamate is not reduced this could result in increased stress-related relapse or seizures should there be an imbalance with GABA. Again it would not be advantageous for humans to have no regulation of glutamate hence endogenous oxytocin's involvement in regulatory processes. Indeed the opioid antagonist Naloxone induces a flood of endogenous oxytocin release post administration (Russell and Bicknell, 1995), perhaps to assist restoration of normal functioning. Therefore as oxytocin is a regulatory hormone it makes sense that antagonists would block some regulatory processes. There are no known studies of oxytocin antagonists used in human substance use studies and readers are directed to Lee et al. (2016), Bowen and Neumann (2017), Zanos et al. (2018) and Leong et al. (2018) for extensive reviews.

Evidence for the mechanism of agonists consistently show two components for how nasal oxytocin exerts its effects;

- 1) by reducing activation of amygdala
- 2) through perceptual selectivity of cues

It is likely both components overlap and are heavily influenced by different cues uniquely important to individuals (Bethlehem et al., 2013). The reduction of amygdala activity and perceptual selectivity (features of a stimulus in a particular setting used to make judgements about that stimulus) of cues holds particular interest for the use of oxytocin as a medication because not every opioid user has craving triggered by the same cues. Craving and the specific role of the amygdala is deliberated further in chapter three. Chapter four outlines the methods used to investigate the proposed mechanism further.

One of the many functions of the central oxytocin system is the regulation of the opioid, reward and stress systems (Buisman-Pijlman et al., 2014) but chronic drug use has been shown to be detrimental to the balance between these systems and increase the chance of continued drug use (Zanos et al., 2018). How and to what extent chronic drug use reduces oxytocin synthesis in stress and reward systems is largely unknown in humans (Lee and Weerts, 2016). The balance is further hindered by heroin use inhibiting oxytocin release stimulated by the endogenous opioid system (Vuong et al., 2010). Quintana and Guastella (2020) have proposed a theory for the oxytocin system to be allostatic, introduced earlier

in 1.6.1. If endogenous oxytocin release is allostatic in nature then the oxytocin system must react to cues in environments. Evidence has shown oxytocin concentrations fluctuate in the presence of social stimuli (Vrachnis et al., 2011; Churchland and Winkielman, 2012) and that oxytocin is not only influential in attributing motivational importance to cues (Love, 2014) but crucially also in Pavlovian cue acquisition and extinction (Acheson et al., 2013; Cavalli et al., 2017). The evolutionary function for an allostatic oxytocin system could be to maximise survival i.e. when primitive man saw the paw print of a predator (a visual cue) they knew to stay away because of danger (the conditioned response) or when primitive man heard running water (an audible cue) they knew to go towards the sound if they were thirsty (the conditioned response). This is important for opioid use disorders where oxytocin has already likely played a role in the conditioning of opioid-related cues as providing reward/relief which would then trigger the established physiological and mood response otherwise known as ‘craving’ (Preston et al., 2018). An impaired oxytocin system would be unable to reduce the amygdala hyperactivity which happens when people encounter opioid-related cues (Murphy et al., 2018) and the hyperactivity may contribute to the onset of craving, increased attentional bias and drive behaviour towards opioid-related cues where there is an inability to reassess and implement new behaviours (Zare-Sedeghi et al., 2019). The result is automated behaviour because endogenous oxytocin is unable to essentially ‘lubricate’ the mechanism for reassessment of opioid-related cues. Indeed research shows a negative association between plasma oxytocin levels and opioid craving in abstinent heroin users receiving methadone treatment (Lin et al., 2018). The involvement of craving and attentional bias within the mechanism are elucidated further in chapter three with the results of a novel proof-of-concept study conducted to explore the effect of nasal oxytocin on cue-induced craving and attentional bias in chapter five.

The overlaps from oxytocin dysregulation within people who use opioids are obvious (Figure 1.9). There is dysregulation in oxytocin systems seen in psychiatric disorders most prevalent alongside opioid use disorders, the extent of which are discussed in chapter two’s analysis of deaths where opioids were found at post-mortem. These psychiatric disorders may have been influenced by early life trauma, again highly prevalent in opioid use disorders, and lead to difficulties with socialisation in adolescence where opioid use is initiated. As opioid use is initiated, cue conditioning begins where the healthy oxytocin system is once more involved. Opioid use dysregulates the endogenous

oxytocin system and the craving mechanism triggered by opioid-related cues becomes hijacked and automated. Chapter three synthesises the evidence for nasal oxytocin to reduce craving and chapter four and five assesses the effect of nasal oxytocin on the craving mechanism following cue-inducement. However generating a data set from controlled experiments built on existing theory is not enough to progress treatment approaches without seeking to greater understand the experience of people who use opioids when they are actively seeking drugs. A large variety of confounding variables will be encountered in real world situations that have been intentionally removed from experimental designs. Chapter six interviews explore the life stories towards initial opioid use, individual experiences of opioid craving and the process of obtaining opioids to identify the themes discussed throughout section 1.6.3 of the thesis, adding contextual meaning. Chapter seven then closes with conclusions and directions for future work.

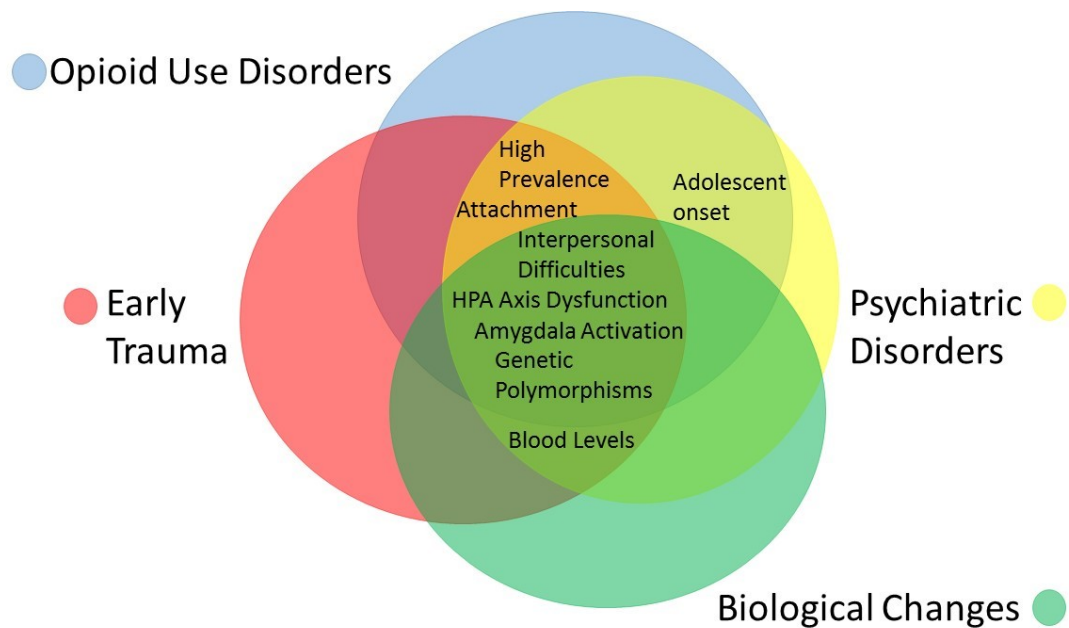


Figure 1.9: Early trauma, psychiatric disorder and biological change overlaps where oxytocin-related dysfunction is implicated within people with opioid use disorder

Notes: Venn diagram depicting the overlaps with oxytocin-related dysfunction implications and people with opioid use disorder. Both psychiatric disorders and opioid use disorders typically start in adolescence where high prevalence of early life trauma and interpersonal problems can affect socialisation. The interpersonal difficulties such as those found in people with schizophrenia and autism spectrum disorders and the implications of HPA axis dysfunction, heightened amygdala activation and oxytocin receptor genetic polymorphisms are all found in people with opioid use disorders, people with psychiatric disorders and people with a history of early life trauma. The relationship of blood levels of oxytocin is inconsistent between people who have experienced early trauma and people who have psychiatric disorders with behavioural implications unclear.

1.7 Aims

There is a worldwide opioid crisis with mortality at unprecedented levels while at the same time there is a reduction of people seeking treatment throughout Europe. Solutions are urgently needed. Opioid use disorder is complex where ‘opioid use’ does not mean ‘opioid dependence’ and only a minority of people develop ‘opioid addiction’. Nevertheless there are long lasting changes in the brain as a result of opioid use disorders. These changes take time to reset when people stop using opioids but this period is when the risk of relapse is increased. Along with risk of relapse comes risk of fatal overdose from reduced tolerance to opioids. It is vital to find ways to reduce relapse in order to

reduce opioid-related deaths. This thesis takes a biopsychosocial perspective of opioid use disorder to suggest that it may be possible to manipulate one of the body's regulatory systems that becomes dysregulated by chronic opioid use and is consistently involved throughout psychosocial environmental interactions – the oxytocin system.

The overall aim of this PhD is to provide insight to the role of oxytocin in to the burgeoning health crisis of opioid-related deaths (Figure 1.10) through four mixed methods studies.

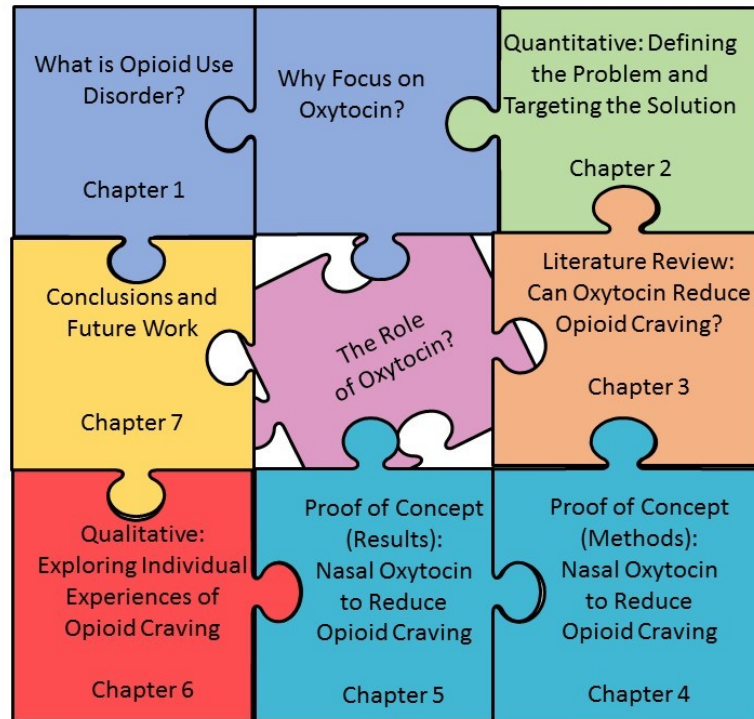


Figure 1.10: How each PhD chapter is linked

Chapter one introduces the disease burden of addiction and the rationale for studying oxytocin as chapter two analyses the extent of the opioid crisis in England with a focus on prevalence of psychiatric disorders within deaths where opioids were found at post-mortem. Chapter three synthesizes the existing evidence in to a systematic literature review underpinning the rationale for the methods outlined in chapter four for use in chapter five. Chapter fives proof of concept study is aimed at interrupting the proposed neurobiological mechanism of opioid craving by means of administering nasal oxytocin. Chapter six uses a qualitative approach to explore the experience of opioid craving in people who are dependent on opioids and chapter seven closes this thesis with conclusions and directions for future work.

This PhD has 7 key aims;

Because opioid-related deaths are at crisis point it is important to investigate them as the greatest harm caused by opioid use. Evidence suggests that the oxytocin system can be dysregulated in people with psychiatric disorders and that people are using opioids to self-medicate. The knowledge gap identified is that we do not know the prevalence of psychiatric disorders in opioid-related deaths. This is important as the opportunity to provide psychological treatments may have been missed leading to self-medication with opioids resulting in accidental overdose therefore the first aim of this thesis is:

- 1) To conduct a retrospective analysis of deaths in England between 2006 and 2015 where at least one opioid was found at post mortem as recorded in the National Program of Substance Abuse Deaths database to explore the prevalence of psychiatric disorder of each death where a medical history has been confirmed (Chapter two)
- 2) To conduct a retrospective analysis of deaths in England between 2006 and 2015 where at least one opioid was found at post mortem as recorded in the National Program of Substance Abuse Deaths database to explore rates of antidepressant, antipsychotic, antiepileptic, hypnotic/sedative and opioid analgesic medication medications found at post mortem (Chapter two)
- 3) To explore the experience and perspectives of community drug worker and mental healthcare professionals working within the field in relation to people who use substances with co-existing mental health problems (Chapter two)

Accidental overdose is the leading cause of opioid-related deaths in the UK. It is vital to improve self-control when people are triggered to crave opioids as it could lead to accidental overdose. One component of craving is heightened amygdala activity which would usually be managed by the natural oxytocin system. However the natural oxytocin system becomes dysregulated by chronic opioid use. Preclinical work has suggested that oxytocin may affect drug craving and small studies have suggested that a nasal spray of oxytocin may reduce craving but no systematic review of oxytocin for drug craving has been conducted to systematically synthesise the information. The second aim of this thesis is:

- 4) To conduct a systematic review of the existing literature for nasal oxytocin to reduce craving and/or consumption in human substance use disorders and behavioural addictions (Chapter three)

Craving is complex, some people report not to even feel craving yet the same people continue to use opioids. Attentional bias to opioid-related cues has been established in existing literature, is able to predict relapse and is one likely component in the multifaceted mechanism of craving. No study to date has examined the influence of oxytocin on cue induced craving in a population of opioid dependent individuals in receipt of opiate substitution therapy who are currently using heroin and no studies to date have

examined how attentional bias changes during cue-induced craving or how nasal oxytocin could affect attentional bias. Aims three and four of this thesis are:

- 5) To assess the effect of an acute dose of nasal oxytocin administered 7 minutes prior to cue-inducement on opioid craving in opioid dependent males (n=34) currently enrolled in a UK community drug service and receiving substitute opiate therapy (Chapter five)
- 6) To assess the effect of an acute dose of nasal oxytocin administered 7 minutes prior to cue-inducement on inhibition of attentional bias in opioid dependent males (n=34) currently enrolled in a UK community drug service and receiving substitute opiate therapy (Chapter five)

Oxytocin systems development is intertwined with how people experience their environments from birth but the impact of dysregulated oxytocin systems overlaps with many core features of opioid use disorders. Understanding how environments affect the behavioural using opioids is important but there is a lack of studies seeking to understand how external environments and social interactions influence the internal experience of craving. The final aim of this thesis is:

- 7) To explore the experiences and perspectives of opioid dependent males (n=34) currently enrolled in a UK community drug service and receiving substitute opiate therapy regarding craving and influences of drug seeking (Chapter six)

1.8 Hypotheses

The hypotheses are;

- 1) Psychiatric disorders were under diagnosed in opioid-related deaths in England 2006 – 2015 compared to evidence of prevalence of psychiatric disorders within people who use opioids (Chapter two)
- 2) Prescribed medications in opioid-related deaths in England 2006 – 2015 would be elevated in comparison to the prevalence of psychiatric disorders within the opioid-related mortality data gathered in hypothesis one (Chapter two)
- 3) Nasal oxytocin administration compared to placebo decreases opioid related cue-induced subjective feeling of craving (Chapter five)

- 4) Nasal oxytocin administration compared to placebo decreases opioid related cue-induced attentional bias (Chapter five)
- 5) In the placebo condition, opioid-cue-induced changes in attentional bias at min 7 is associated with changes in subjective feelings of opioid craving at 7, 15 and 30 minutes post-exposure, relative to baseline (Chapter five)
- 6) The effect of nasal oxytocin administration compared to placebo on cue induced subjective feeling of opioid craving at minutes 15 and 30 post exposure is predicted by its effect on attentional bias at minute 7 (Chapter five)
- 7) There are no hypotheses for the qualitative arms as qualitative research is hypothesis-generating (Chapters two and six; Sullivan et al., 2011)

Chapter Two

Mental Health Problems in Deaths Involving Opiates in England, 2006 – 2015: Prevalence and Perspectives

‘The question is not why the addiction, but why the pain’
– Gabor Maté, Hungarian-Canadian physician

Abstract

Psychiatric disorders are risk factor for opioid use disorder however only 4% of people accessing treatment receive integrated treatment for substance use and co-existing mental health problems. Socioeconomic changes are known to progress the onset of psychiatric problems. This chapter aimed to identify the prevalence of psychiatric disorders in deaths where opiates were found at post-mortem pre and post the change in the 2010 UK drug strategy during benefits reform, identify rates of psychiatric medication found at post-mortem and explore the perspectives of professionals towards the population. Chapter two presents a mixed methods study. Firstly, a retrospective analysis where opioids were found at post-mortem in deaths which occurred in the period 1st January 2006 and 31st December 2015. Only records where a medical history was provided by the coroner were included in the initial analysis of historic psychiatric disorder (n=2,150). Records were then further separated between people who were and were not known to use illicit drugs. All deaths were included when identifying the presence of antidepressant, antiepileptic, antipsychotic, opioid analgesic and hypnotic/sedative medications (n=10,460). Semi-structured interviews were undertaken with professionals to explore perspectives of people who use substances with co-existing mental health problems. Prevalence of historic psychiatric problems in people known to use illicit drugs was underreported. Excluding schizophrenia, depression and bi-polar, historic psychiatric problems were lower than expected in opioid-related deaths involving known illicit drug users. Historic psychiatric problems in people not known to use illicit drugs unexpectedly reflected prevalence rates in illicit opioid users and exceeded general population prevalence in all historic psychiatric problems except paranoia, PTSD and eating disorders. Detection of prescription medications and opioid analgesics exceeded NHS prescribing data suggesting increased recreational non-prescribed prescription use or self-medication where people are unable to access psychological treatment. Interviews found that organisational barriers were thought to block access to psychological treatments for people who use opioids. Findings suggested an urgent need to reduce non-prescribed prescription medication use, specifically opioids. Organisational barriers prohibited access to psychological therapies in people who are known to use illicit drugs.

2.0 Introduction

To fully understand opioid use disorders this thesis will work backwards, beginning in this chapter with the greatest harm that opioid use can result in – death. Death can tell us little about a person's quality of life, mortality can only make inferences on these, but it is possible to identify which aspects of life may influence decisions to use opioids (employment status, social isolation, presence of other drugs etc) from post-mortem results. Having introduced the presence of psychiatric disorders as a risk factor for opioid use in chapter one it is unsurprising that studies suggest the number of people with co-existing psychiatric disorders within drug and alcohol services is estimated to be between 60-93% yet only 4% of people accessing treatment receive integrated SUD and mental health treatment (Guest and Holland, 2011). This may, in part, be because just 1% of the global healthcare workforce are projected to provide mental health care (World Health Organization, 2016). Such high prevalence of co-existing psychiatric disorders in SUDs coupled with the lack of specialist mental health treatment provision suggests seeking symptomatic relief from psychiatric disorders may be a recurring theme in continued opioid use.

Understanding the multiple factors which affect progress of psychiatric disorders and the influence of societal structures is important for improving holistic treatment of SUDs. Social-ecological models of SUD identify complex interactions between the individual, social relationships, community engagements and societal structures which influence drug-seeking behaviours (Jalali et al., 2020). In 2010 UK government launched a new drug strategy (HM Government, 2010) focused on recovery from dependence of illicit substances and substitute opiate medications. This differed from previous policy where opioid dependent individuals could receive substitute opiates indefinitely without reducing off. Although the new UK strategy did not state that people could not be maintained indefinitely on substitute opiates, pressure on community treatment services increased as nationally reported monitoring began for number of successful completions. In the case of opioid users this meant exiting treatment free of all opioid use including substitute opioids for at least one month and not returning to structured treatment for at least six months. A payment-by-results model was trialled whereby treatment services received payments for each successful completion amongst other key performance indicators such as reduced injecting practice. Observational studies of 154,175 people accessing drug and alcohol treatment (10,716 in payment-by-results localities and

143,459 in treatment-as-usual localities) between 2010 and 2014 found that payment-by-results led to lower numbers of treatment initiation and lower numbers of completions but no significant changes in housing, criminal activity or mortality within services (Jones et al., 2018). Retention in treatment on substitute opiates is a protective factor in reducing opioid-related deaths with most opioid-related mortality found in people not accessing treatment (Clinical Guidelines on Drug Misuse and Dependence Update, 2017) and so if there are less people in treatment under a payment-by-results model but retention in treatment is a protective factor against mortality, it is unsurprising to see a payment-by-results model being ineffective where UK drug treatment services were not fully incentivised to provide evidence based treatment provision that reduces opioid-related deaths.

Immediately following 2010, major social and economic changes were announced creating a period of uncertainty, eventually leading to benefits changes in 2013. The welfare system amalgamated existing payments in to one which immediately created payment delays, increasing debt and a rise in the usage of food banks (Walker, 2019). Major economic and political changes such as drug policy and universal credit are shown to adversely affect anxiety, depression and stress levels leading to an increase in suicidal behaviours (Vandoros and Kavetsos, 2015), increasing risk of overdose for people who use substances. Indeed the Office for National Statistics has shown using the Index of Multiple Deprivation (a deprivation measure based on factors such as income, employment, health, education, crime, the living environment and access to housing) that drug-related deaths can be 5.5 times higher in the most deprived areas of England and Wales (Office for National Statistics, 2020).

Recent impact of social change on psychiatric disorders can be seen as a result of the coronavirus-19 pandemic where one study of 3097 UK adults found 64% of participants reported symptoms of depression and 54% reported symptoms of anxiety (Jia et al., 2020). Of these 31.6% met criteria for moderate to severe depression and 26% moderate to severe anxiety qualifying for high intensity NHS psychological treatments (Jia et al., 2020). In contrast 10% of the general English population are typically estimated to meet criteria for depression and 5% are expected to meet anxiety criteria (Stansfeld et al., 2016). It is obvious that changing social and economic environments affect mental health. Recent qualitative evidence from the UK in people who use drugs revealed the negative

impact on wellbeing during the pandemic as well as an increase in drug use such as Fentanyl and Pregabalin (May et al., 2022).

Social conflict theory, ecological view and social disorganisation theories of addiction suggest that opioid use is the result of inequalities in class, race, wealth, population density and social decay (Shafiee et al., 2019). Ethnic density (the proportion of our communities with similar ethnic background), income inequality, social fragmentation (rental housing, living arrangements, proportion of single/divorced people and neighbourhood disorder), lack of belonging and social exclusion are all suggested to alter the oxytocin system (Vargas et al., 2020) whilst systematic review has shown socioeconomic marginalization to be associated with opioid overdose (Van Draanen et al., 2020) hinting at a complex interplay between both.

This chapter presents the mixed methods study conducted to begin the PhD. To date there is no retrospective analysis of psychiatric disorders in opioid-related deaths during periods of socioeconomic change. By better understanding the prevalence of psychiatric disorders in opioid-related deaths across a period of time, it may be possible to increase understanding of missed opportunities for treatment intervention which will improve future treatment. This study aimed to address the gap in literature by (1) identifying the prevalence of reported history of psychiatric problems and analyse sociodemographics of the population in deaths where opiates were found at post-mortem which occurred between 2006-2015 in England during changes in drug treatment strategy and welfare system reform (2) identifying quantities of antidepressant, antiepileptic, antipsychotic, opioid analgesic and hypnotic/sedative medications found at post-mortem in all deaths where opiates were found at post-mortem within this period (3) interview drug treatment and mental health professionals to contextualise findings within real world perspectives on psychiatric diagnosis.

2.1 Methods

2.1.1 Definitions

“antidepressant” includes amitriptyline, citalopram, clomipramine, dothiepin, fluoxetine, imipramine, mirtazapine, nortriptyline, sertraline, trazodone, venlafaxine; *“antiepileptics”* include carbamazepine, gabapentin, lamotrigine, pregabalin, sodium valproate; *“antipsychotics”* include amisulpride, clozapine, flupenthixol, lithium,

olanzapine, quetiapine, risperidone; “*drug poisoning*” includes deaths where opiates were found at post-mortem but excluded suicide, natural causes and people killed unlawfully as these are reported separately in the database; “*hypnotics/sedatives*” include alprazolam, amylobarbitone, barbiturates other, benzodiazepines other, butobarbitone, chlordiazepoxide, diazepam, flubromazepam, lorazepam, nitrazepam, pentobarbitone, temazepam, trichloroethanol, zolpidem, zopiclone; “*opioid analgesics*” includes buprenorphine, codeine, dextropropoxyphene, fentanyl, hydrocodone, pethidine, tramadol; “*opioid*”, heroin, methadone and ‘opioid analgesics’; “*opioid-related*” refers to any death where any opioid was detected at post-mortem by toxicology; “*Suicide*” includes deaths where opioids were found at post-mortem but were not implicated in the cause of death i.e. hanging.

Medication definitions were taken from The National Programme on Substance Abuse Deaths (NPSAD) categories and cross-referenced with the British National Formulary (Joint Formulary Committee, 2019).

2.1.2 The national programme on substance abuse deaths

The National Programme on Substance Abuse Deaths was established in 1997. It receives voluntary information from Coroners regarding deaths involving drugs in England and Wales, Northern Ireland, Channel Islands and Isle of Man. Information available in coronial inquest files differs from case to case however Coroners have access to: statements from witnesses, family and friends; General Practitioner (GP) records; reports from first responders; hospital emergency departments and clinical ward reports; psychiatric and substance abuse team reports; post-mortem and toxicology reports.

Coroners in England have voluntarily submitted data to NPSAD in up to 75% of deaths which feature one or more of the following:

- (i) Presence of one or more psychoactive substances directly implicated in death.
- (ii) History of dependence or abuse of drugs.
- (iii) Presence of controlled drugs at post-mortem.

The Central Office for Research Ethics Committees, of the National Patient Safety Agency confirmed in writing (February 2006) the NPSAD Programme does not require NHS Research Ethics Committee review as the subjects of the research are deceased.

2.1.3 Case identification

A retrospective study design was employed to identify deaths between 1st January 2006 and 31st December 2015 (n=10,460) via an access request to NPSAD. This range was chosen to encompass five years pre and post 2010 UK drug strategy change. The data extraction defined opioid-related deaths as deaths where any opioid was detected at post-mortem. All cases reported here have confirmatory evidence that toxicology reports indicates presence of opioid(s) in the decedents' tissue(s).

2.1.4 Interviews on attitudes and care of opioid users

In order to contextualise the quantitative findings within real world experiences interviews were conducted with drug treatment and mental health professionals. Convenience sampling was used to recruit both drug treatment (n=6) and community mental health (n=2) professionals. Convenience sampling recruits participants based on accessibility and availability, is quick and inexpensive (Elfil and Negeda, 2017). Interviewees were comprised of community drug workers who provide psychosocial interventions (such as Motivational Interviewing and low level Cognitive Behavioural Therapy) to people who use substances (n=4), substance use disorder specialist nurse (n=1) prescribing administration worker who generates prescriptions within the drug service for people who use substances (n=1), mental health nurse (n=1) and clinical psychologist (n=1). Participants were recruited from two community drug treatment services operated by a single non-statutory treatment provider, Cranstoun, and one NHS organisation, Berkshire Healthcare Foundation Trust, who provide mental health services to the region where both drug treatment services operate were approached. Professionals working within the mental health treatment pathways only were included. The final sample comprised of 1 male and 5 females from two drug treatment services and 1 male, 1 female from the mental health services in one location. Participants were white British (n=5), Black African (n=2) and Asian (n=1).

Interviews were conducted with 8 professionals by one investigator (BH). The interview schedule was designed by BH and reviewed by CN prior to interview start. One drug treatment professional had been working in the field for less than two years with the remainder having at least 5 years experience of working with people who use substances. The drug treatment professionals had broad experience of working with people who use substances in multiple settings across differing geographical regions such as community

drug treatment services, the criminal justice system, homeless hostels and women's refuges. One substance misuse nurse had worked within statutory mental health services and one community drug worker was qualified in counselling. Mental health professionals had experience working with people who use substances in supported living, on acute wards in inpatient psychology units, leading psychology teams, within child and adolescent mental health services and with crisis teams. All drug treatment professionals and one clinical psychologist from the mental health professionals described a personal experience either through self or others with addiction.

Participants were interviewed once in June 2019, privately digitally recorded at each participant's place of work with nobody else present during interview. No participant had visibility of the interview schedule prior to interview. Emails to all staff were sent by their managers informing them of the non-mandatory and confidential opportunity to attend a research interview regarding substance use and mental health. Interviews with drug treatment professionals took place on two dates, one week apart. Three attempts across two months to interview mental health professionals were made however despite organisational willingness to participate, continued staffing shortages meant only 2 were interviewed. The nature of the interview was explained and participants were given the opportunity to wait 24 hours before deciding whether they wanted to take part prior to signing consent forms. No participant asked to consider their involvement or withdrew following consent. Interviews ranged between 15:06 and 39:19 minutes in length, no hand written notes were made during the interviews and no interviews were repeated. All participants were offered visibility of their final transcript, none requested them. No reimbursement was given. The interview schedule can be found in Appendix 1.

There was complete discussion with potential participants who gave written informed consent. NHS ethical approval is not required for professional interviews as this was deemed service evaluation.

2.1.5 Data analysis

Quantitative data entry and analysis were performed using IBM SPSS statistics version 25 and Microsoft Excel 2013.

Records where no previous medical history was provided by coroners were excluded (n=8310) to ensure accuracy of the final sample in identifying whether a historic psychiatric disorder was known. Previous medical history was assigned where the

NPSAD field ‘otherinfo’ stated GP/psychiatry contact, cites a medical or mental health diagnosis or previous medical history was explicitly referred to. Records where prescription medications were listed without reference to previous medical history were excluded as medications may be prescribed without diagnosis and so the analysis of historic psychiatric problems would be skewed if it was assumed that every person receiving a medication or had used prescription medications illicitly had also received psychological assessment and diagnosis. Prevalence of any historic psychiatric problem was calculated in people with previous medical history between known illicit drug users and people who were not known to use illicit drugs but who may have used opioids for other reasons e.g. pain relief in cancer patients. Known illicit drug users cases were assigned according to records identified by the Coroner as illicit drug users from information reported (information from the drug and alcohol service for example) at time of death. People not known to use illicit drugs were assigned to the remainder of records with previous medical history where toxicology detected opiates at post-mortem. Cases were separated in order to explore whether there was a difference between them in prevalence of historic psychiatric problems. Cases were assigned as having historic psychiatric problems where evidence within previous medical history of one or more following conditions were recorded by Coroners: anxiety, psychosis, paranoia, eating disorder, depression, bi-polar, PTSD, schizophrenia (but not necessarily have any medication detected at post-mortem) as per NPSAD categorization. The term ‘historic psychiatric problems’ was used where NPSAD database limitations prevented confirmation of whether psychiatric problems were current at time of death and included any reports of psychiatric diagnosis within that period.

General population prevalence statistics are cited from NHS Adult Psychiatric Morbidity Survey (Stansfeld et al., 2016). Illicit opioid prevalence statistics are cited from various sources; anxiety, depression, paranoia, and psychosis (Weaver et al., 2003), bipolar affective disorder (Cerullo and Strakowski, 2007), schizophrenia (Chiapelli et al., 2018), PTSD (Roberts et al., 2016) and eating disorders (Canan et al., 2017).

Descriptive statistics were obtained for “*opioid-related deaths by age range*” (percentage, means), “*deaths by drug poisoning*” (percentages within group), “*suicide only deaths*” (total number only), “*additional years of life*” (total difference, standard error), “*historic psychiatric problem by gender*” (percentages within group), “*prevalence of historic psychiatric problems*” (percentages, number), “*historic psychiatric problems*

per year” (total number), “*number of medications found at post mortem*” (total number, percentage difference across years). Descriptive statistics will be graphically presented.

Data to be tabulated included “*prevalence of historic psychiatric problems*”, “*historic psychiatric problems per year*” and “*common topics identified during interview*”.

Interview recordings were transcribed verbatim and anonymized. A deductive framework was devised and thematic framework analysis was conducted (Gale et al., 2013). Themes were preconceived by BH. Nvivo12 software was used to aid analysis. Digital recordings of interviews were deleted immediately following transcribing. Interviews were read with an open mind however BH had an established relationship with 3 of the drug treatment professionals and 0 of the mental health professionals. Due to convenience sampling interviews were susceptible to self-selection bias either from community drug workers desire to support an ex colleague or from a desire to express existing opinions on the interview topic. To minimise the influence of BH preconceptions and rationale for undertaking the research, coding was checked by one author with no relationship to the participants (CN) and discussed where disagreements in coding were found. As the senior academic, CN decision was final.

Although a number between 6-12 interviews may be enough to reach data saturation (the point at which no new information, codes or themes are found), the preconceived deductive approach of our analysis in a small sample size meant achieving data saturation was questionable and neither appropriate nor useful for our study design (Braun and Clarke, 2021).

The study was conducted in accordance with the Declaration of Helsinki. The qualitative reporting herein complies with the consolidated criteria for reporting qualitative research reporting standards (COREQ; Tong et al., 2007).

2.2 Results

In total 10,460 deaths involving opiates occurred in England between 2006-2015. The number of cases in which opioids were implicated in deaths peaked in 2009 (n=1255), declining until 2012 (n=865) rising thereafter until the end of analysis period in 2015 (n=1189). The total number of cases available with previous medical history for prevalence of historic psychiatric problem analysis was 2,150 (known illicit drug users

n=1400, people not known to use illicit drugs n=750). Of the people who were not known to use illicit drugs, heroin was detected in 47.50% (n=357) at post-mortem.

2.2.1 All-cause mortality, drug poisoning-related mortality, suicide-related mortality and life expectancy

This section presents key data relating to all-cause mortality, drug poisoning-related mortality, suicide-related mortality and how the presence of historic psychiatric problems affected life expectancy in opioid-related deaths. Figure 2.1 shows that people aged between 35 and 64 were at increased risk of opioid-related death. Opioid-related deaths involving people aged 15-24 have declined from 2006 (12.78% of all opioid-related deaths) to 2015 (4.54% of all opioid-related deaths). People aged 25-34 have also declined from 2006 (36.29%) to 2015 (19.93%). There is an increasing trend in 35-44 and 45-54 age ranges. Whilst people aged 55-64 increased up to 2012, this was followed by a two year dip before a 1% increase from 2014 to 2015. People aged 65 and over remained stable between 2006 (2.53% of all opioid-related deaths) and 2015 (3.11% of all opioid-related deaths).

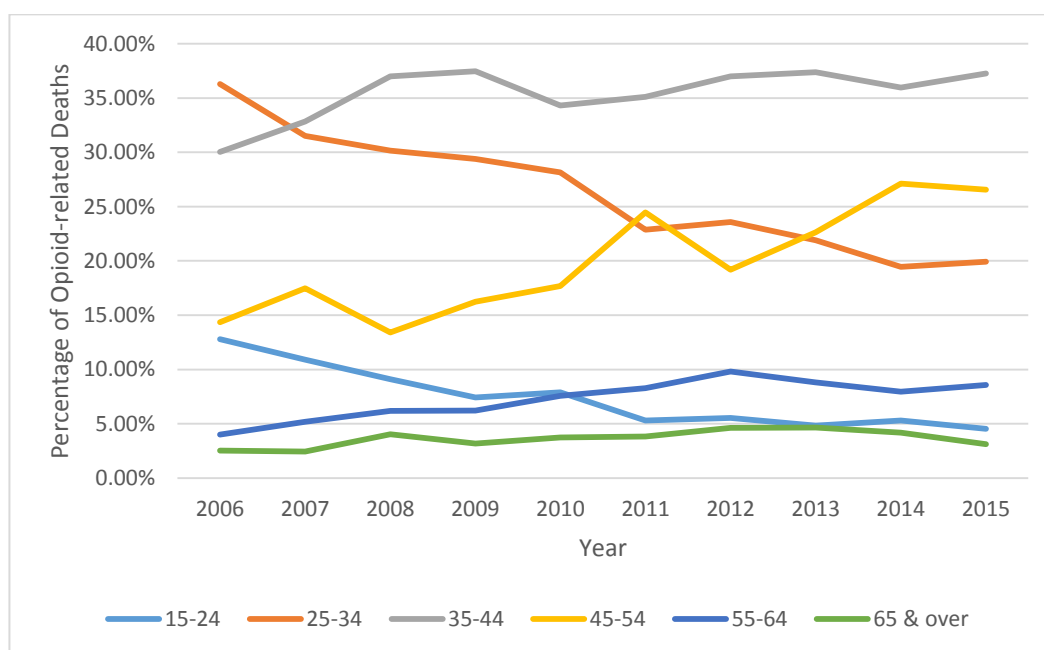


Figure 2.1: Proportion of opioid-related deaths (n=10,460) split by age range from 2006 – 2015

Notes: Data are for deaths which occurred in this period rather than deaths registered in this period. Figures are for England only. Data represent the percentage of opioid-related deaths by age range per year.

Figure 2.2 depicts drug-poisoning deaths (e.g. accidental overdose) reported by the coroner where opiates were found at post-mortem but excludes suicide (e.g. hanging), natural causes (e.g. underlying conditions) and people killed unlawfully (e.g. murder). The percentage of opioid-related deaths in people without at least one historic psychiatric problem whose cause of death was related to drug poisoning peaked at 94.81% (2015, n=128) with a low of 76.19% (2011, n=64) compared with a range of 90.37% (2015, n=216) and 71.59% (2010, n=63) in those with at least one historic psychiatric problem.

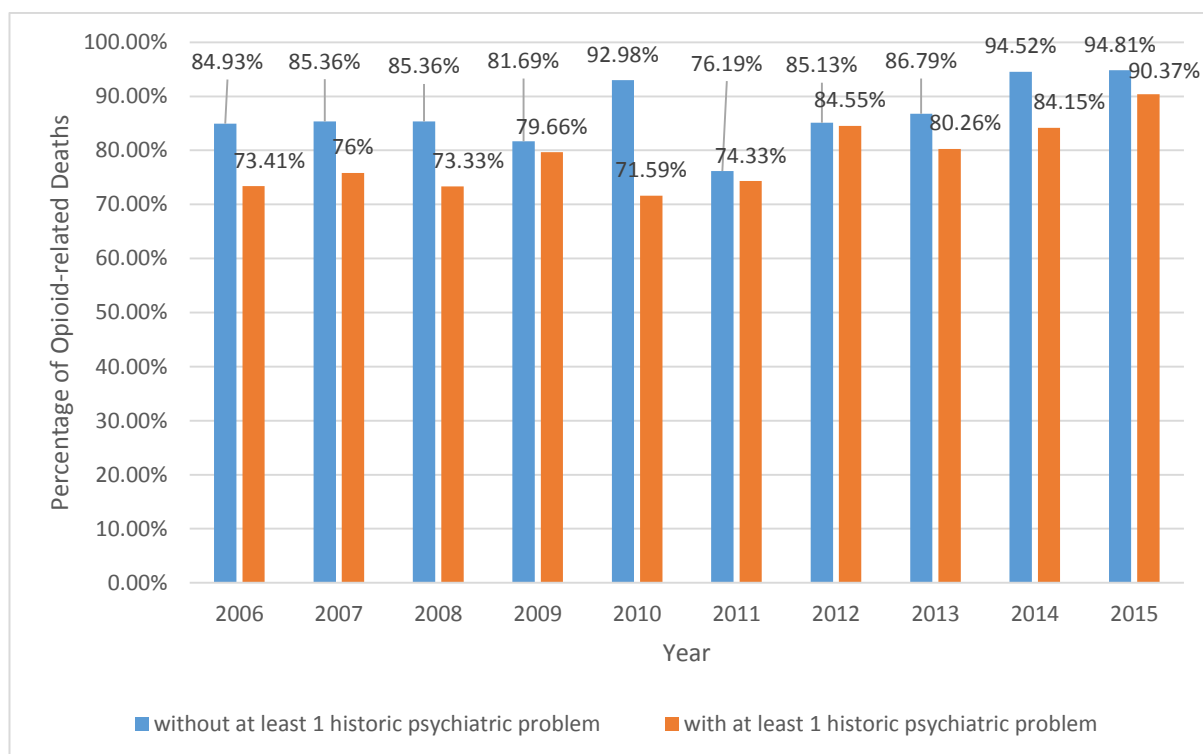


Figure 2.2: Drug-poisoning opioid-related deaths 2006 – 2015 with confirmed previous medical history (n=2150)

Notes: Data are for deaths which occurred in this period rather than deaths registered in this period. Figures are for England only. Only deaths where a medical history was confirmed by the coroner were included (total n=2150). Deaths were then divided by people without at least 1 historic psychiatric problem (n=784) and people with at least 1 historic psychiatric problem (n=1366). Percentages were calculated within each group and not from total deaths. Data show the percentage of drug poisoning deaths were consistently higher in people without at least 1 historic psychiatric problem. Drug poisoning deaths were defined by the coroners recorded verdict and excludes suicide (these would include hanging for example), natural causes (e.g. underlying conditions) and killed unlawfully (e.g. murder) which were recorded separately.

Opioid-related deaths where suicide was recorded as cause of death are shown in figure 2.3. The terms ‘drug-related death’ and ‘drug/alcohol related death’ were introduced in 2011 for coroners to use when reporting. Until 2011 there was a difference of 9 – 12% between the two cohorts (people with and without at least one historic psychiatric problem) regarding deaths recorded as drug-poisoning with exception of 2010 when the difference was 20.39%. Post 2011 when new recording terms were introduced the percentage of ‘Drug-related death’ and ‘drug/alcohol related death’ recorded as coroner verdict in the period 2011-2015 inclusive for people without a historic psychiatric problem was 40% (n=148) whereas for people with at least one historic psychiatric problem was 41.90% (n=316) across the same period. Notably following introduction of these new generic recording terms, the number of deaths where the coroner’s verdict was suicide fell post 2011 in those without a historic psychiatric problem but acutely elevated between 2012 and 2013 in those with at least one historic psychiatric problem.

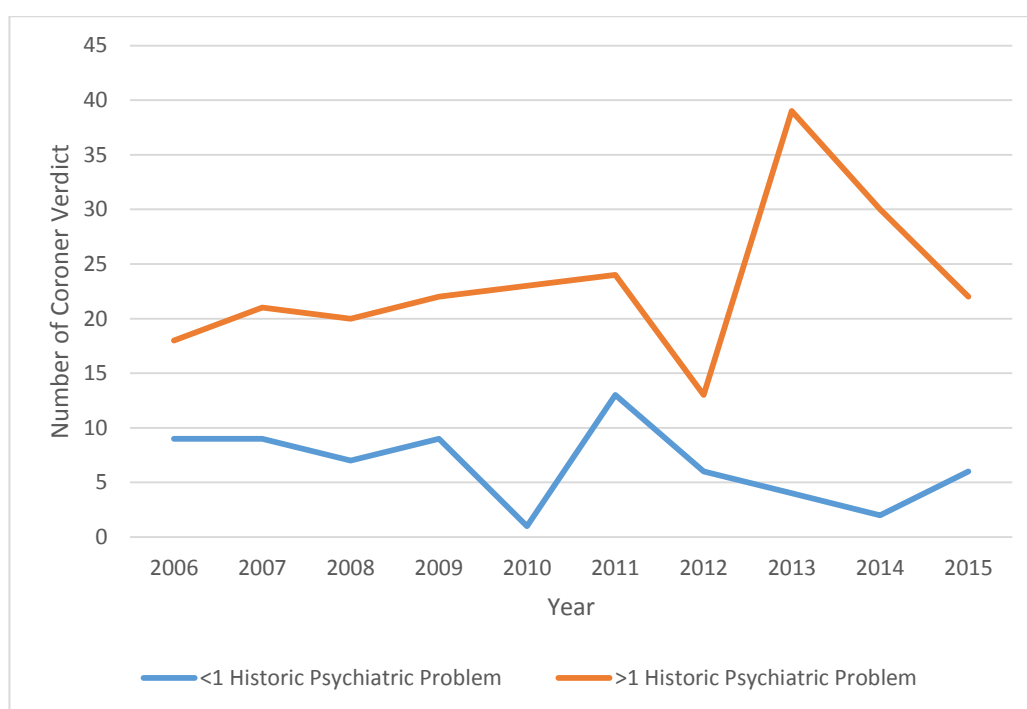


Figure 2.3: Opioid-related deaths with confirmed previous medical history where suicide was recorded as the cause by the coroner in 2006 – 2015 (n=2150)

Notes: Deaths are for deaths which occurred in this period rather than deaths registered. Figures are for England only. Suicide, a verdict as recorded by the coroner excluding drug poisoning. Total number of opioid-related deaths without historic psychiatric problem (n=784), with at least one psychiatric problem (n=1366).

Analysis of additional years of life in people with at least one historic psychiatric problem versus people with no historic psychiatric problem is shown in Figure 2.4. The average life expectancy in people with at least 1 historic psychiatric problem exceeded those without a recorded historic psychiatric problem by 6 years (15-24 group), 3 years (45-54, 55-64 group). In three cohorts the average life expectancy was shortened in people with at least one historic psychiatric problem by 6 years (25-34 group), 9 months (35-44 group) and 8 years (65 and over group).

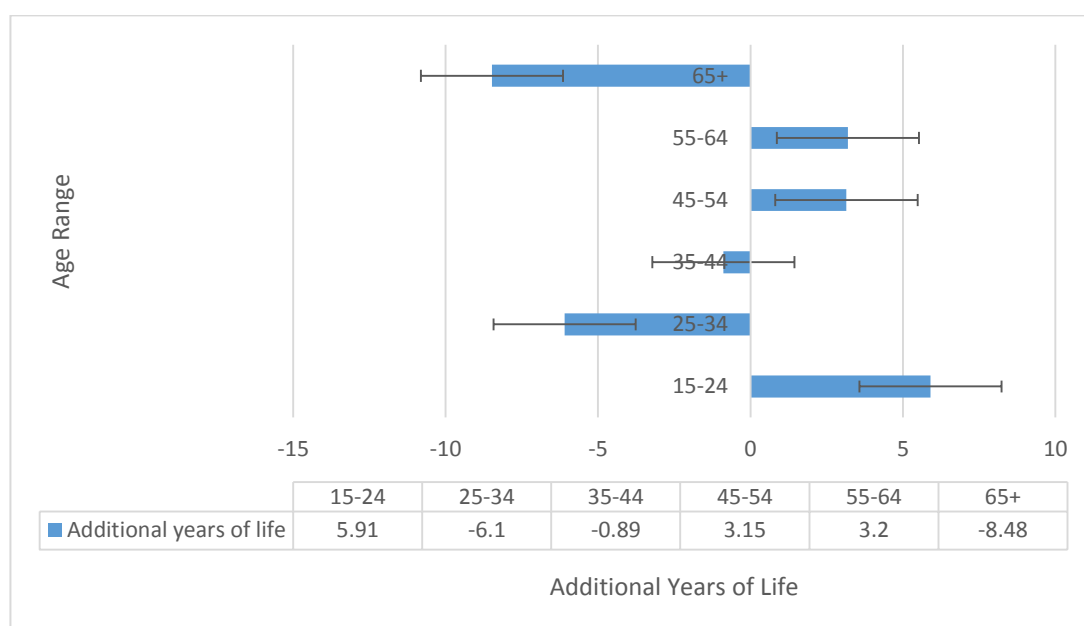


Figure 2.4: Additional years of life in people with at least 1 historic psychiatric problem (n=1366) versus people with no historic psychiatric problem (n=784)

Notes: Figures are for England only (n=2150). Calculated as the difference in age at death per age group between people with at least one historic psychiatric problem and those without any historic psychiatric problem. Standard error shown.

2.2.2 The Prevalence of historic psychiatric problems

This section will present the results of the analysis in relation to the presence of historic psychiatric problems. Anxiety, psychosis, paranoia, eating disorders and PTSD prevalence was reported to NPSAD below expectancy for illicit opioid users in known illicit drug users (Table 2.1). Opioid-related deaths of people not known to use illicit drugs had higher prevalence of anxiety, eating disorder, depression and bi-polar than known illicit drug users. Prevalence of anxiety, psychosis, depression, bi-polar and schizophrenia were higher in people not known to use drugs than was expected in the general population.

Schizophrenia prevalence in people not known to use illicit drugs was 2x greater than reported in known illicit drug users and 10x greater than the general population in known illicit drug users.

Table 2.1: The Prevalence of historic psychiatric problem diagnosis in deaths 2006-2015

Psychiatric Problem	Estimated Prevalence in England Total Population	Estimated Prevalence in Illicit Opioid Users	Reported Prevalence of Historic Psychiatric Problems in KDU (NPSAD 2006 – 2015) n=1400	Reported Prevalence of Historic Psychiatric Problems in NDU (NPSAD 2006 – 2015) n=750
<i>Anxiety</i>	4.4-5.9%	19%	10.84% (n=152)	13.46% (n=101)
<i>Psychosis</i>	0.40%	7.90%	5.06% (n=71)	4.13% (n=31)
<i>Paranoia</i>	2-30%	37% *	5.35% (n=75)	3.20% (n=24)
<i>Eating Disorder</i>	6.40%	21%	0.78% (n=11)	1.73% (n=13)
<i>Depression</i>	9.10%	21 - 47%	35.11% (n=492)	50.40% (n=378)
<i>Bi-Polar</i>	2%	0 - 8%	3.14% (n=44)	5.06% (n=38)
<i>PTSD</i>	4.40%	19-35%	0.71% (n=10)	0.40% (n=3)
<i>Schizophrenia</i>	1.10%	5-10%	9.42% (n=132)	4.80% (n=36)

Notes: Deaths are for deaths which occurred in this period rather than deaths registered. Figures are for England only. Estimated prevalence in England total population, taken from the NHS Adult Psychiatric Morbidity Survey (Stansfeld et al 2016). Estimated prevalence in illicit opioid users, taken from a range of studies; anxiety, depression, paranoia, and psychosis (Weaver et al 2003), bipolar affective disorder (Cerullo, Strakowski, 2007), schizophrenia (Chiapelli et al 2018), PTSD (Roberts et al 2016) and eating disorders (Canan, et al 2017)*Paranoia taken as symptom of axis 2 personality disorders known to have high prevalence in population but not specifically recorded on Coroner NPSAD reports. KDU, known drug user; NDU, person not known to use illicit drugs.

Figure 2.5 shows that reporting of previous medical history increased between 2006 (n=152, 14.82%) and 2015 (n=374, 31.45%) finding opioid-related deaths in people not known to use illicit drugs were more likely than opioid-related deaths in known illicit drug users to have historic psychiatric problems. From 2013 (n=276, 27.87%) to 2015 (n=374, 31.45%) as previous medical history increased, historic psychiatric problems in known illicit drug users (2013 n=130, 75.14% - 2015 n=175, 62.72%) and people not known to use illicit drugs (2013 n=93, 90.29% - 2015 n=64, 67.36%) decreased.

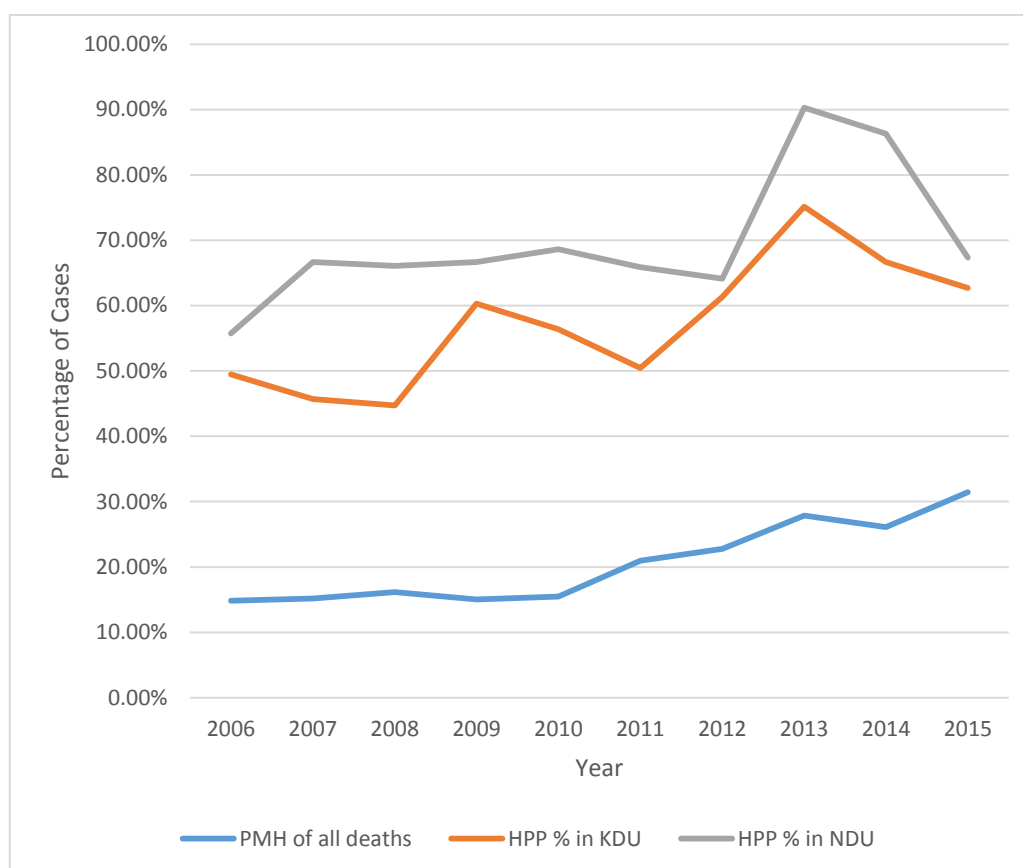


Figure 2.5: Prevalence in psychiatric diagnosis reporting versus recording of previous medical history in NPSAD

Notes: Previous medical history of all deaths is the percentage data are for all deaths which occurred in this period (n=10,460) rather than deaths registered in this period where a medical history was provided. Historic psychiatric problem percentage was calculated as percentage of deaths yearly with at least one historic psychiatric problem where previous medical history was provided (total n=2150). Known illicit drug user (total n=1400), people not known to use illicit drugs (total n=750). Figures are for England only. HPP, historic psychiatric problems; KDU, known illicit drug user; NDU, person not known to use illicit drugs; PMH, previous medical history.

Figure 2.6 shows prevalence of psychiatric problems were highest in women who were not known to use illicit drugs between 2006 and 2015. Following 2013 the prevalence of opioid-related deaths with historic psychiatric problems in all cohorts declined.

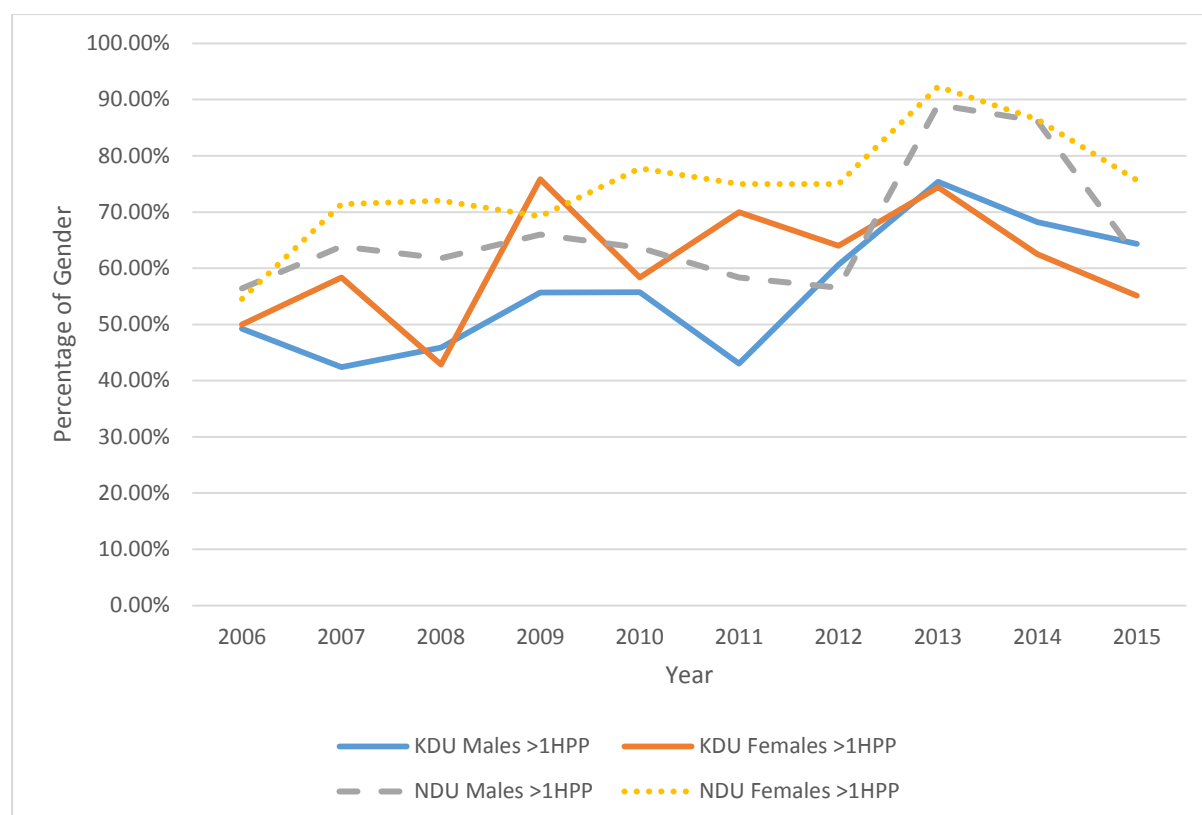


Figure 2.6: Comparison of prevalence of recorded historic psychiatric problem per year in known illicit drug users and people not known to use illicit drugs split by gender

Notes: Data are for deaths which occurred in this period rather than deaths registered in this period. Figures are for England only. Total known illicit drug using males (n=1078), total known illicit drug using females (n=322), total people not known to use illicit drugs males (n=466), total people not known to use illicit drugs females (n=284). KDU, known drug user; NDU, person not known to use illicit drugs. More details can be found in the discussion section.

Figure 2.7 shows the mortality percentage of each gender by cohort (known illicit drug user or person not known to use illicit drugs) who were unemployed. Unemployed male mortality increased between 2011 (known illicit drug users n=18, people not known to use illicit drugs n=10) and 2013 (known illicit drug users, n=47, people not known to use illicit drugs n=15) by 73.15% and 76.69% in known illicit drug users and people not known to use illicit drugs respectively, coinciding with the introduction of universal credit. Reporting of previous medical history increased by 33.03% within this period (2011 n=197, 2013 n=276) whilst mortality of unemployed females declined.

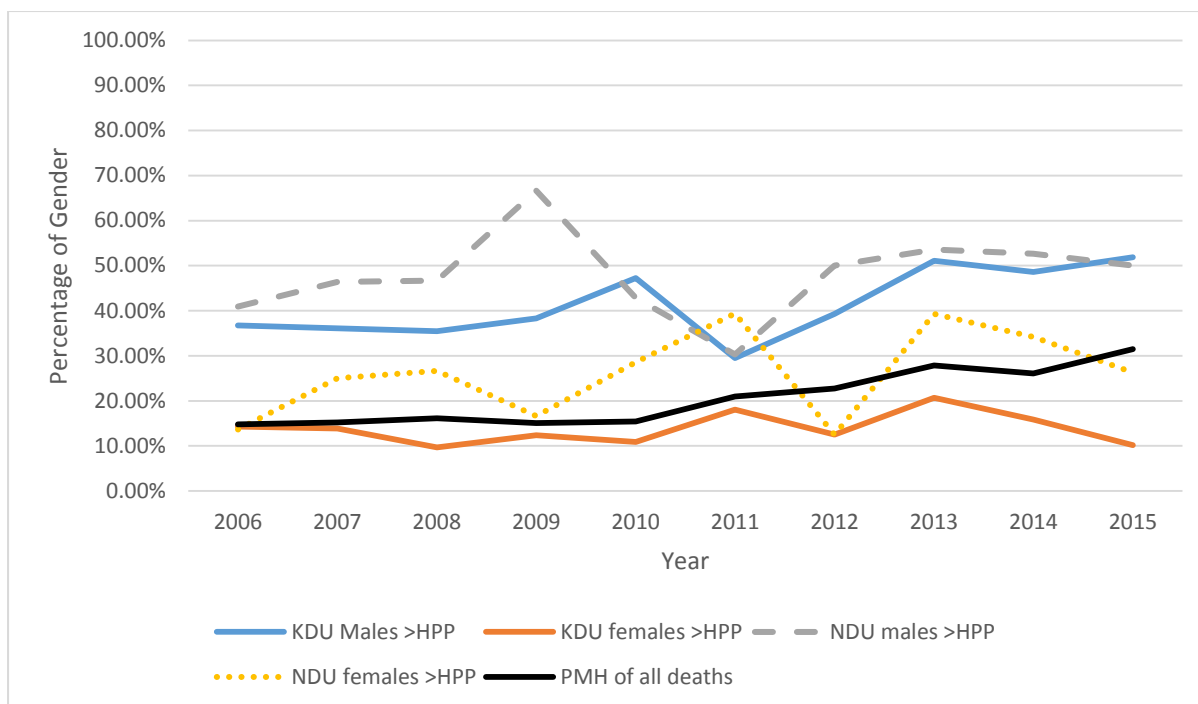


Figure 2.7: Mortality by gender, historic psychiatric problems in unemployed people per year

Notes: Previous medical history is the percentage data are for all deaths which occurred in this period (n=10,460) rather than deaths registered in this period where a medical history was provided in order to display reporting trend increase. Historic psychiatric problem percentage calculated as percentage of deaths per year with at least one historic psychiatric problem, where previous medical history was provided (total n=2150) and employment status was ‘unemployed’. Known illicit drug users (total n=471) or people not known to use illicit drugs (total n=194). Figures are for England only. Total known illicit drug using males (n=359), total known illicit drug using females (n=112), total people not known to use illicit drugs males (n=123), total people not known to use illicit drugs females (n=71). HPP, historic psychiatric problems; KDU, known drug user; NDU, person not known to use drugs; PMH, previous medical history.

Figure 2.8 shows Mortality in all opioid-related deaths by housing status and historic psychiatric problems where a previous medical history was confirmed (n=2150).

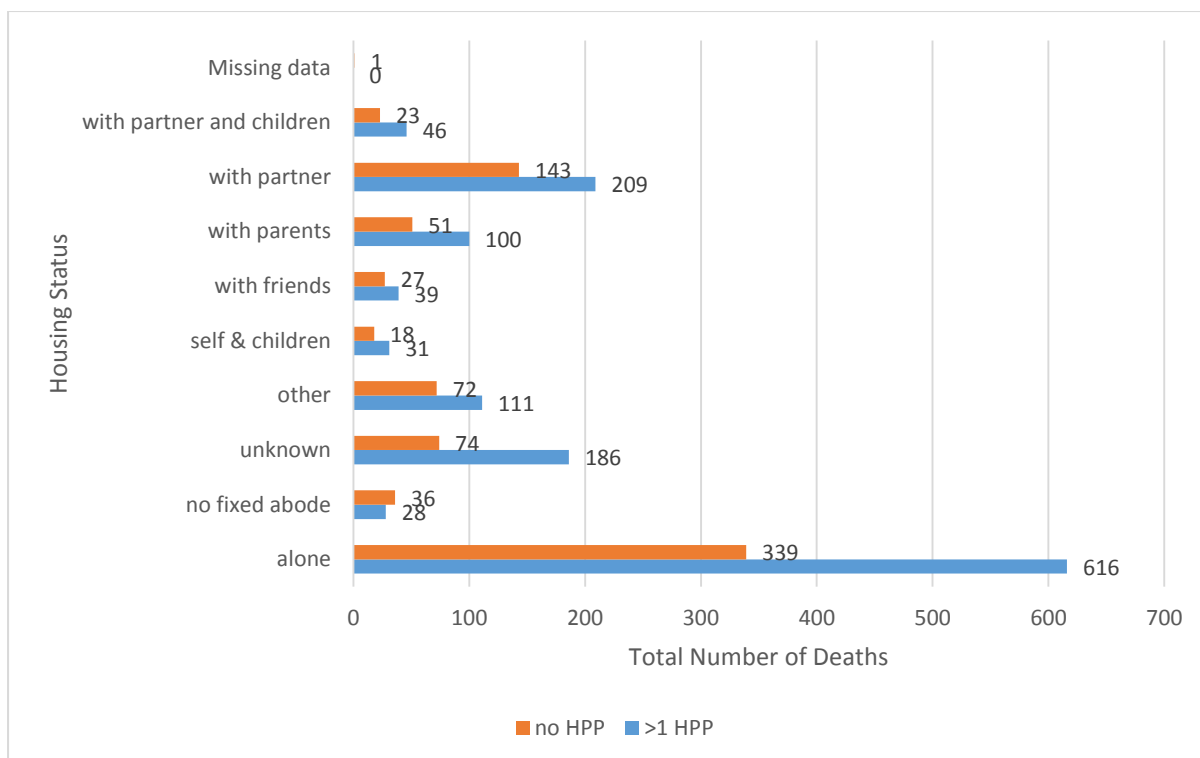


Figure 2.8: Mortality in all opioid-related deaths by housing status and historic psychiatric problems where a previous medical history was confirmed (n=2150)

Notes: Figures are for England only. Missing data, where the coroner has not reported any housing status; other, may have been used by coroners to refer to temporary hostel accommodation or homelessness; unknown may have been used by coroners to refer to temporary hostel accommodation or homelessness

The majority of opioid-related deaths where previous medical health was reported by coroners involved people both with and without historic psychiatric illness who lived alone followed by people who lived with their partner. There were more people with no historic psychiatric problem who died with no fixed abode (n=36) than people with at least one reported historic psychiatric problem who died with no fixed abode (n=28) though the categories ‘other’ and ‘unknown’ may have been used by coroners to refer to temporary hostel accommodation or homelessness. Opioid-related deaths in people with historic psychiatric problems were double than people without historic psychiatric problems.

2.2.3 Presence of prescription medications at post-mortem

This section presents the results of the analysis in relation to the presence of prescription medications at post-mortem irrespective of whether the medication was known to be prescribed or taken illicitly.

Figure 2.9 shows the number of times each medication was detected at post-mortem in all opioid-related deaths (n=10,460). Detection of medications in toxicology at post-mortem increased between 2006 and 2015; antidepressants 3.3x (2006 n=191, 2015 n=631), antiepileptics 8.9x (2006 n=27, 2015 n=242), antipsychotics 5.69x (2006 n=33, 2015 n=188), hypnotic/sedative 2.09x (2006 n=357, 2015 n=707) and opioid analgesic medications 2.3x (2006 n=378, 2015 n=884).

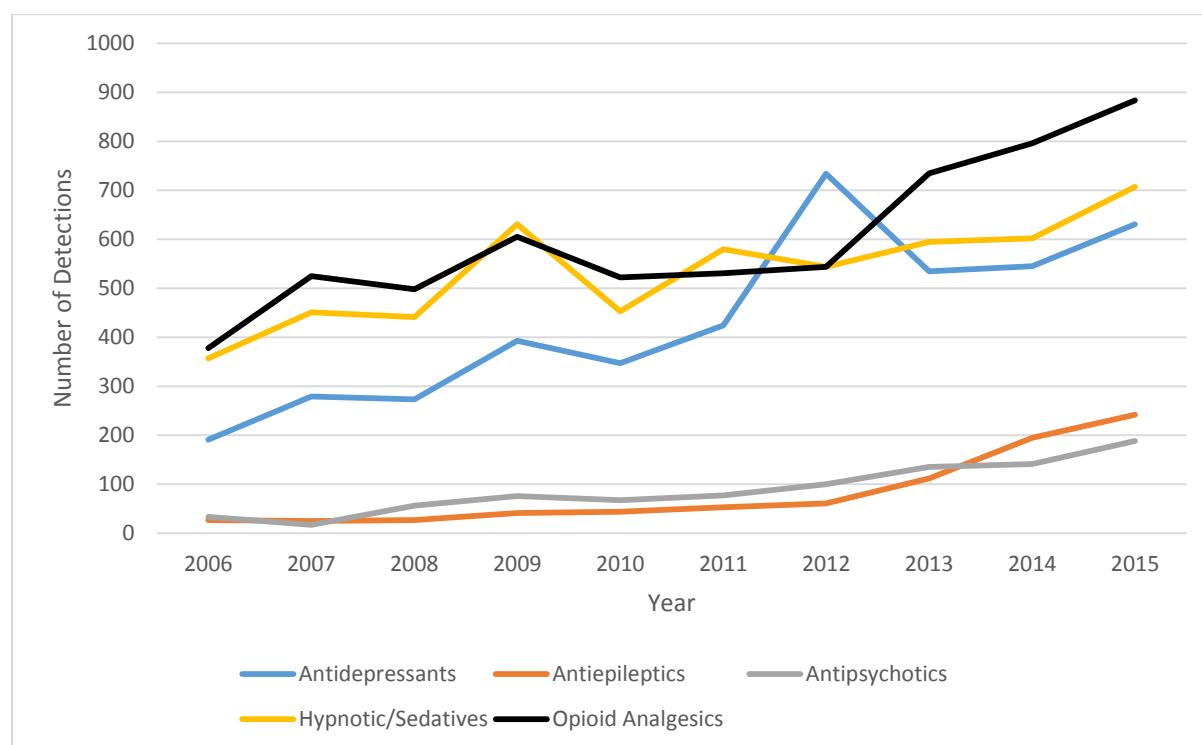


Figure 2.9: Number of medications detected at post mortem in opioid-related deaths (n=10,460) 2006 – 2015

Notes: Figures are for England only. Number of detections includes licit prescribed medications and illicit non-prescribed prescription medications found at post mortem. Antidepressant, includes amitriptyline, citalopram, clomipramine, dothiepin, fluoxetine, imipramine, mirtazapine, nortriptyline, sertraline, trazodone, venlafaxine; Antiepileptics, include carbamazepine, gabapentin, lamotrigine, pregabalin, sodium valproate; Antipsychotics, include amisulpride, clozapine, flupenthixol, lithium, olanzapine, quetiapine, risperidone; Hypnotics/sedatives, include alprazolam, amylobarbitone, barbiturates other, benzodiazepines other, butobarbitone, chlordiazepoxide, diazepam, flubromazepam, lorazepam, nitrazepam, pentobarbitone, temazepam, trichloroethanol, zolpidem, zopiclone; Opioid analgesics includes buprenorphine, codeine, dextropropoxyphene, fentanyl, hydrocodone, pethidine, tramadol.

Figure 2.10 shows that opioid analgesic detection acutely increased following 2012 in both known illicit drug users and people not known to use illicit drugs with at least one historic psychiatric problem coinciding with the peak and subsequent decline in antidepressant presence (n=734) and an increase in males and females who were not known to use illicit drugs with historic psychiatric problems (Figures 2.6). After 2013 this increase continued in people known to use illicit drugs without historic psychiatric problems and people not known to use illicit drugs without historic psychiatric problems. The only cohort where the presence of opioid analgesics found at post-mortem decreased after 2012 was in people not known to use illicit drugs with at least one historic psychiatric problem.

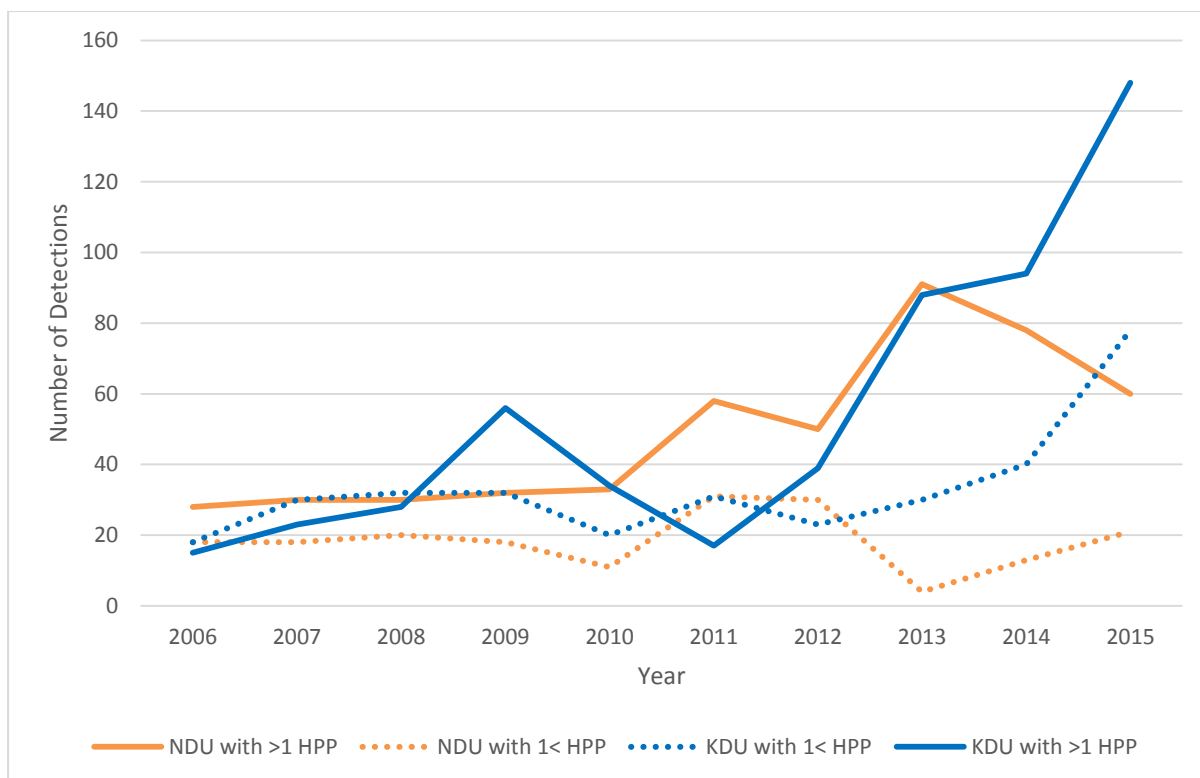


Figure 2.10: Year-on-year trend of opioid analgesic medication detections at post-mortem in people with a confirmed previous medical history by cohort (n=2150)

Notes: Figures are for England only. Opioid analgesics include buprenorphine, codeine, dextropropoxyphene, fentanyl, hydrocodone, pethidine, tramadol and excludes heroin and methadone. People not known to use illicit drugs with at least 1 historic psychiatric problem (total n=535), people not known to use illicit drugs deaths with no historic psychiatric problems (total n=215), known illicit drug users with at least 1 historic psychiatric problem (total n=831), known illicit drug user deaths with less than 1 historic psychiatric problem (total n=569), total known illicit drug users (total n=1400), total people not known to use illicit drugs (total n=750). HPP, historic psychiatric problems; KDU, known drug user; NDU, person not known to use illicit drugs.

The number of medication detections at post-mortem in opioid-related deaths between 2006-2015 where a previous medical history was confirmed (n=2150) are shown per cohort in figure 2.11. There were 490 detections of opioid analgesics in people not known to use illicit drugs (mortality n=535) with at least one historic psychiatric problem and 184 detections in people not known to use illicit drugs without historic psychiatric problems (mortality n=215). In known illicit drug users with at least one historic psychiatric problem there were 542 detections (mortality n=831) and 334 detections (mortality n=569) in known illicit drug users without.

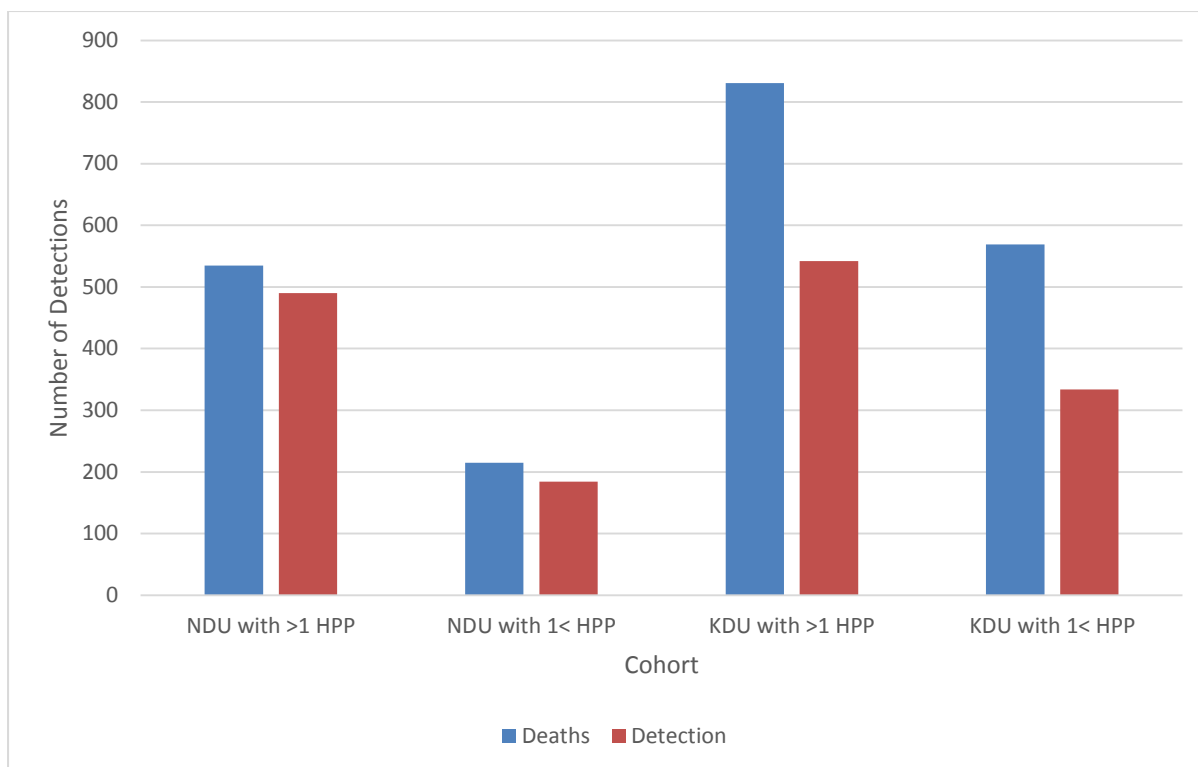


Figure 2.11: Number of opioid analgesic medication detections at post-mortem by cohort with confirmed previous medical history compared with number of deaths where opiates were found at post-mortem (n=2150)

Notes: Figures are for England only. Opioid analgesics include buprenorphine, codeine, dextropropoxyphene, fentanyl, hydrocodone, pethidine, tramadol and excludes heroin and methadone. People not known to use illicit drugs deaths with at least 1 historic psychiatric problem (total n=535), people not known to use illicit drugs opioid analgesic detections with at least 1 historic psychiatric problem (total n=490). People not known to use illicit drugs deaths with no historic psychiatric problems (total n=215), people not known to use illicit drugs opioid analgesic detections with no historic psychiatric problems (total n=184). Known illicit drug user deaths with at least 1 historic psychiatric problem (total n=831), known illicit drug user opioid analgesic detections with at least 1 historic psychiatric problem (total n=542). Known illicit drug user deaths with no historic psychiatric problems (total n=569), known illicit drug user opioid analgesic detections with no historic psychiatric problems (total n=334). Total known illicit drug users (total n=1400). Total people not known to use illicit drugs (total n=750). HPP, historic psychiatric problems; KDU, known drug user; NDU, person not known to use drugs.

Opioid analgesic detection in people not known to use illicit drugs with at least one historic psychiatric problem increased 20% between 2012 (n=50) and 2015 (n=60). Detection of opioid analgesics in people not known to use illicit drugs with no historic psychiatric problem decreased 30% between 2012 (n=30) and 2015 (n=21). These findings suggest that risk of

developing opioid use disorders may have been unnoticed in people not known to use illicit drugs.

2.2.4 Interviews with professionals

The interviews were conducted to contextualise quantitative findings. Table 2.2 demonstrates topics identified by all Drug Treatment Professionals (DTP) and Mental Health Professionals (MHP). Interviewees agreed that psychiatric disorders were highly prevalent in people who use substances. Interviewees agreed that funding cuts on treatment services had stretched services and that there was an over reliance on prescribed medication.

Table 2.2: Common topics identified during interview

Drug Treatment Professionals	Mental Health Professionals
Understanding of funding cuts and stretched services	Understanding of funding cuts and stretched services
High prevalence of CEMH in substance users	High prevalence of CEMH in substance users
Over reliance on mental health medication from prescribers	Over reliance on mental health medication from prescribers
Referrals to mental health teams declined due to current substance use	Referrals from drug services declined due to current substance use
Unrealistic expectations of drug/alcohol abstinence from mental health services prior to accessing psychological services	Lack of personal responsibility from substance users to manage lifestyle and reduce drug/alcohol use

Notes: Topics which were identified by all interviewees (n=8) during thematic framework analysis coding.

One psychotherapist at the mental health service declined to be interviewed stating:

“there is no secondary care pathway for substance misuse...if we see people it is only by accident” (reason for decline, psychotherapist, mental health professional)

Minor themes were not explored as the small sample size meant minor themes were assessed as being individual opinion but descriptions can be found within the coding tree (see Figure 2.12). To protect anonymity the three preconceived major themes are described through anonymous quotations labelled by cohort i.e. DTP or MHP.

Perspectives of Drug Treatment and Mental Health Professionals Towards Treatment Provision for Substance Use Disorders with Co-Existing Mental Health Problems in England

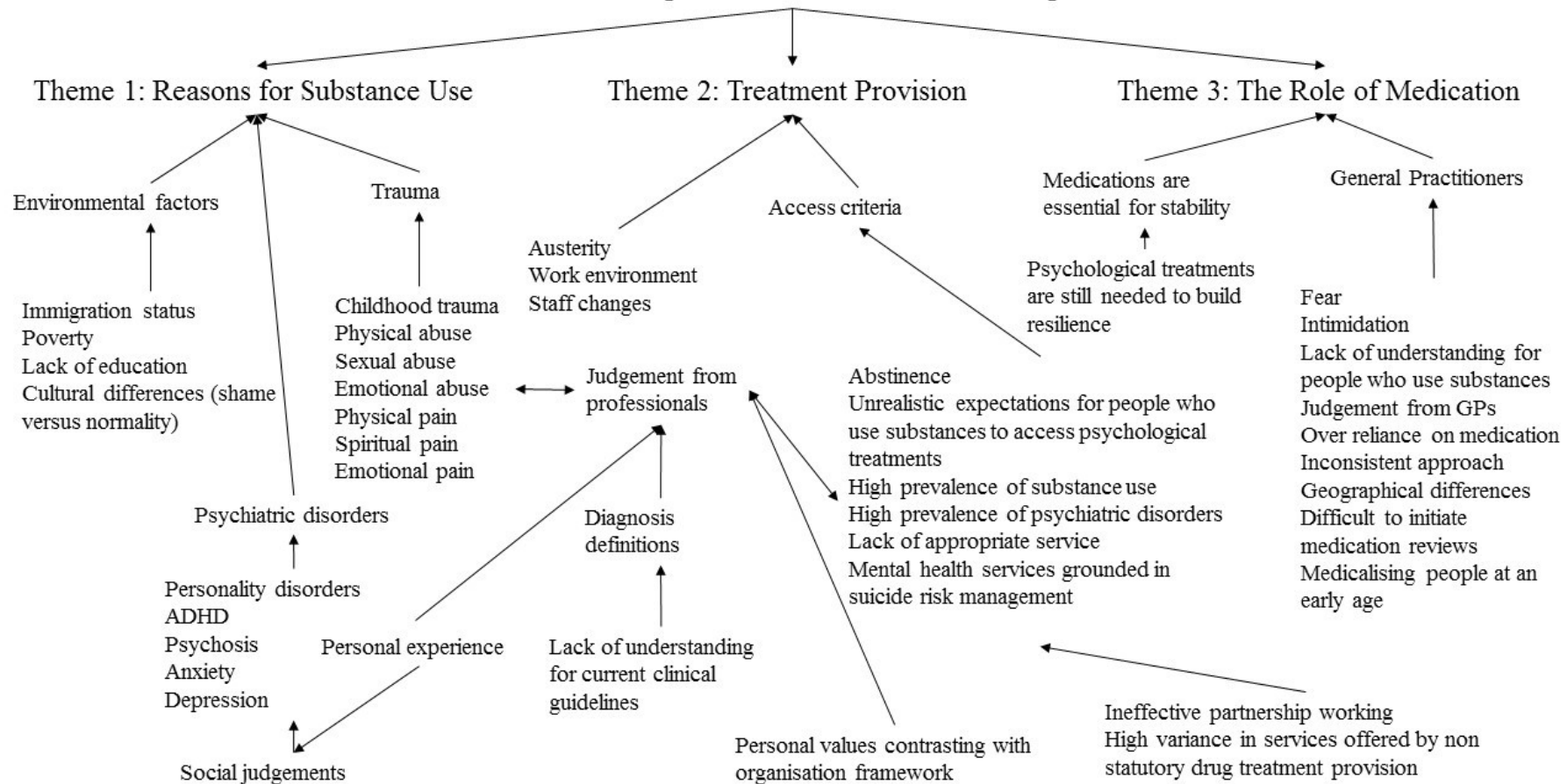


Figure 2.12: Coding tree of qualitative interviews (n=8)

Notes: Coding tree displaying major themes (Reasons for substance use, treatment provision and the role of medication) as well as minor themes identified by interviewees.

Reasons for Substance Use in People with Co-Existing Mental Health Problems

“We don’t exist in a vacuum there’s several things going on around us, all of those things are contributing to our sense of who we are, our identity, our desires and all those things shape how we see the world and I think mental health and mental illness is a response to that” (431-1, Clinical Psychologist, MHP)

Environmental factors such as immigration status, poverty, lack of education and cultural differences were reported by all DTP and one MHP as playing a role in the onset of substance use.

Childhood trauma was unanimously mentioned as a possible reason for initiation of substance use by DTPs however this opinion was not shared as distinctly with MHPs.

“...trauma seems to be the biggest underlying instigator of people picking up substances...I think it’s about what people experience and how they cope with what they experience. I think it triggers, trauma triggers a lot of mental health issues...yeah the way I see it trauma is a big, massive, underlying issue” (430-1, Community Drug Worker, DTP)

Personality disorders, attention deficit hyperactivity disorder, anxiety and depression were mentioned as pre-existing conditions people may use substances to cope with. Both DTPs and MHPs estimated high prevalence of co-existing psychiatric disorders with SUDs, estimating prevalence to be upwards of 80% of all service users. One female, black clinical psychologist was unsure why people use substances, alluding to spiritual and emotional pain whilst acknowledging self-medication theories but did not define any generalised root cause during interview.

“I see that person in a great deal of pain and they don’t know how else to soothe this pain and so that’s why they use the substances. It’s a way of escaping the pain, the turmoil, sometimes its spiritual pain, emotional turmoil, it could be physical pain” (431-1, Clinical Psychologist, MHP)

One female, white, late-twenties Community Drug Worker believed people who used substances were unfairly judged:

“I think people are judged very much. The same as mental health like 20 years ago or 30 years ago everyone was judged for having mental health like ‘oh you’re a nutter’, that’s moved on but substance misuse hasn’t” (430-4, Community Drug Worker, DTP)

Morality and judgement was detected:

“...people who are making life choices, and that’s their decision, but if they’re knocking on mental health doors in my opinion, well you need to address your substance use first...don’t come knocking on the door when you realise after you’ve been using crack and heroin for fifteen years and its completely destroyed your life. That’s my personal opinion” (431-2, Mental Health Nurse, MHP)

“the part that they have to play in the community is to take some responsibility for their own wellness in some shape or form and if that is not happening on a consistent basis we feel that’s over to other services” (430-2, Community Drug Worker, DTP)

Overall there was acceptance from both DTP and MHP for the complexity of people who use substances with one white, male mental health nurse stating other mental health professionals ‘struggled’ with them due to the ‘chaotic’ and ‘risky’ nature of the patients.

Treatment Provision

MHPs and DTPs identified relaxation of treatment criteria from Community Mental Health Teams (CMHT) as a change to be implemented. It was reported of all referrals to the mental health service across a four month period in 2017, only 3% went to CMHT and of those 2% were accepted. Acceptance means the patient would receive an opt-in letter and discharged if the patient made no further contact. There was unanimous agreement amongst all interviewees there is a service need for this patient cohort. Organisational barriers and stringent criteria for accessing existing treatment highlighted by DTPs was ratified by MHPs, stipulating current drug use would lead to automatic decline of referral unless the psychiatric disorder had been diagnosed prior to initiation of the substance use as per CMHT definition of dual diagnosis.

“if they’ve got a severe and enduring disorder that’s already established then they’re using drugs on top of that, that is dual diagnosis...Someone who’s had a traumatic upbringing, is very dysfunctional and using drugs is not going to meet their criteria”

(431-2, Mental Health Nurse. MHP)

“...a particular referral has taken almost 6-7 months before that persons got an appointment with a clinical psychologist. It’s just impossible for people to just be seen very quickly. For the crisis team for example, it’s very short, sharp interventions...the diagnosis is complex emotional personality disorder, emotional disorder so virtually no sort of coping mechanisms to deal with anything that can trigger an emotional reaction or response. That client is very dependent on alcohol...in and out of hospital for detoxes but because she comes out of her detox and goes straight back home, home is her trigger so she’ll pick up alcohol straight away after a detox...thereby making herself unable to receive the next level of care in mental health services, she’s very, very high risk of completing suicide but the crisis team are there providing those emergency interventions but that’s as far as it can go...the next stage, you have to be mentally robust in order to start, I’ve never quite understood that because it’s chicken and egg isn’t it? The criteria is a minimum of 3-5 months of sobriety from the problem substance so it’s chicken and egg” (430-2, Community Drug Worker, DTP)

Requirements for extended sobriety, typically a minimum of 3 months, were consistently reported by DTPs who cited a service user who, following 18 months sobriety, was told auditory hallucinations currently being experienced were alcohol related. Drug and alcohol use was reported to be prevalent in 70-80% of new referrals to community mental health services followed by problems related to benefits sanctions.

“drug and alcohol is the big one. It’s under-reported by the GPs...I assessed a client yesterday, she smokes cannabis every day, is that gonna be preventative for therapy? Therapeutic services in secondary care or primary care with Talking Therapies will say if a client is using crack, alcohol, abusing heroin or using cannabis or whatever then they’re not going to be eligible for therapy” (431-2, Mental Health Nurse, MHP)

One female, African Substance Misuse Nurse with qualifications and employment history in mental health nursing across multiple localities had seen treatment provision from the perspective of both drug treatment and mental health:

“when they are referred to mental health they just think whatever they’re using is causing the mental health issue whereas from the drugs area we think the mental health issue is the one that’s causing them to use the drugs so they don’t really get proper treatment. Wherever I’ve worked it’s just going back and forth with the mental health people, they will say ‘ask the person to stop using this then we can see them’. I think I

understand where they are coming from, the person who uses drugs aren't thinking clearly but they don't really get proper treatment in my own perspective" (430-3, Substance Misuse Nurse, DTP)

One white, male mental health nurse identified lack of an appropriate statutory service to refer in to whilst recognising escalating reports of suicidal intent:

"We assess them and nine times out of ten it's either refer it to the crisis team or signpost to drug and alcohol...if we were going to be really honest with these patients we'd say we're not offering you an assessment because there's nothing to offer you at the end of this assessment so we're giving them false hope... we're assessing them to make sure that we've done an assessment and said we've done an assessment" (431-2, Mental Health Nurse, MHP)

This experience was supported by DTPs.

"...there is a high level of people needing mental health services and they're under resourced however my experience is that they can be really dismissive and once a person is engaged with another agency, another service they feel they don't really have to do anything" (430-1, Community Drug Worker, DTP)

Organisational frameworks contrasted with the beliefs of one female, African Clinical Psychologist:

"I'm against these one size fits all rules, I think it depends on the person. If you have a substance misuse problem but you're able to engage in therapy... you can turn up to therapy sober and maybe be part of a therapeutic group... if you're able to make use of the therapy then why should you be denied treatment" (431-1, Clinical Psychologist, MHP)

In order to provide a level of psychological therapy support, DTPs operated an in house counselling service utilising student counsellors where long term abstinence was not a prerequisite to treatment. Conflicting with mental health team organisational belief that active substance use impedes ability to participate in treatment, engagement was reportedly positive:

"Clients just rave about their experience with the counsellors...not to say that they have stopped using or that they're not still relying on substances in some shape or form at

some level, it's not a cure but it is there to give clients a really good experience and build up there coping mechanisms" (430-2, Community Drug Worker, DTP)

DTPs were in favour of increased partnership working alongside each other as opposed to current methods of working which requires abstinence from substance use for a prolonged period before accessing psychological treatment. One DTP, a General Practitioner (GP), whose experience of specialist dual diagnosis workers across various locations was continued declining of specialist psychological intervention on the basis of current substance use. This was supported by one white, male mental health nurses experience with a colleague employed to undertake dual diagnosis assessments:

"she would say 'look, they're pretty pointless because at the end of the day we'd just be saying engage with drug and alcohol services' because there's not going to be a service for these people" (431-2, Mental Health Nurse, MHP)

MHPs felt drug treatment should be brought back to the NHS as non-statutory providers can differ significantly in services they offer, making partnership working more difficult. One DTP from the six interviewed knew the national guidance for working with co-existing mental health problems and substance use disorders but neither MHP knew what guidance directs. The role of the police was questioned by one MHP who queried what was being done to combat increases in illicit drug use.

The Role of Medication

Medication was viewed by both MHPs and DTPs as an aid for stability which may be essential for some conditions such as paranoid schizophrenia but generally should not be prescribed in isolation away from psychological therapy. DTPs felt psychological therapy was where service users would learn coping strategies for symptoms and resolve the historic issues that may trigger substance using behaviours.

"GPs don't help at all from what I've seen. They just overload them with a variety of drugs that they are using and then buying extra on the street in addition. Also they're getting medicated then selling them on without even using them themselves in some instances" (430-5, Prescribing Administrator, DTP)

"they might have had a diagnosis but they're still on the same medications for many years, when you know they might not need that level of medication" (430-2, Community Drug Worker, DTP)

GPs were thought to prescribe antidepressants without offering alternatives such as nutritional advice and counselling. One male, white, mental health nurse suggested GPs feel threatened, intimidated or pressured to prescribe medications. These patients are then referred to CMHT who then redirect to drug treatment services creating a perpetual loop. One white, male community drug worker who had worked in multiple localities identified differences in GP prescribing depending on geographical region:

“It seems here, whatever you want you’re gonna get even if you make stuff up...a lot of my clients on medication are on various types, all on the same script...one client over in <place>, mirtazapine, tramadol, oramorph, quetiapine and something else I can’t remember what that is. I think she’s on two kinds of antidepressant sertraline I think the other one was. Why? Do you know what I mean?” (430-6, Community Drug Worker, DTP)

Medication reviews for dose adjustment and contraindications of concurrent prescriptions were difficult to initiate despite patient requests. One female, Asian community drug worker cited lack of GP understanding for people who use substances and because of illicit use, ‘the shutters come down’. Another female, African substance misuse nurse stated:

“Theres still some judgemental attitude there. I remember working in GP shared care, all the doctors would do is just print the script and sign then you were like this person is due for medical review but it wasn’t a concern for them as much as someone who doesn’t use. For them it was like this person has put it on themselves” (430-3, Substance Misuse Nurse, DTP)

One white, male mental health nurse suggested medicalisation can begin during adolescence.

“there was one girl, she was 15 she had a diagnosis of ASD, conduct disorder, psychosis, you name it she had every diagnosis under the sun. She was 15 and she was on sodium valproate, diazepam, some really sedating medications, antipsychotics...she was 15. Like she’d been medicalised” (431-2, Mental Health Nurse, MHP)

2.3 Discussion

Opioid-related deaths increased between 2006-2015 across a period of socioeconomic change (benefits reform, change in drug policy) but the reasons for this are multivariate,

not least the change in coroner reporting homogenizing how deaths were recorded, meaning it is not possible to infer a single causation as to the increase. Prevalence of historic psychiatric problems in people known to use illicit drugs were vastly underreported. Excluding schizophrenia, depression and bi-polar, recorded historic psychiatric problems between 1st January 2006 and 31st December 2015 were lower than expected in opioid-related deaths involving known illicit drug users. Recorded historic psychiatric problems in people not known to use illicit drugs unexpectedly reflected prevalence rates in illicit opioid users and exceeded general population prevalence in all historic psychiatric problems except paranoia, PTSD and eating disorders. Interviews found that organisational barriers were thought to block access to psychological treatments for people who use opioids and together the findings suggested a bias for providing access to psychological therapies for people not known to use illicit drugs.

Prescription medications detected at post-mortem displayed an upward trend since 2006. Detection of opioid analgesic medications at post-mortem in people not known to use illicit drugs but with co-existing reported historic psychiatric problems decreased post 2013 but increased in known drug users irrespective of whether they had historic psychiatric problems or not. Psychiatric assessment and provision of evidence based treatments may be a protective factor against opioid analgesic medication use. In conjunction these findings suggest difficulties in access to psychiatric care for people who use opioids.

2.3.1 Mortality

Although average age of death for all opioid users has increased for the period 2006-2015 from 35 to 42 years old, this is unlikely to be the sole result of an aging population. The population in general is living longer so a gradual curve should be expected (Figure 2.1) however increases in mortality can be seen for the 35-44 and 45-54 age ranges from 2010 onwards. These spikes coincide with the new drug strategy (2010) and introduction of universal credit (2013) supporting studies regarding impact of policy change on mortality (Vandoros et al., 2015). The highest percentage of opioid-related deaths has been consistently within 35-44 year olds without variation across ten years. Therefore attributing opioid-related deaths unilaterally as a result of an aging population when the average age of mortality has increased by only a few months per age range across ten years would be misguided.

Within age range cohorts there is an increase in life expectancy for people with at least one historic psychiatric problem in the age ranges 15-24, 45-54 and 55-64 compared to people without (Figure 2.4) however overall life expectancy of those without historic psychiatric problems exceeds those with historic psychiatric problems. Caution should be applied to interpretation as the number of those with at least one historic psychiatric problem (n=1366) was almost double people without at least one historic psychiatric problem (n=784) and therefore is likely to show longer life expectancy in people with at least one historic psychiatric problem. The evidence base supports alternative reasoning though. In three cohorts where historic psychiatric problems were associated with shorter life expectancy rationale can be made for low representation of opioid users in 25-34 age range in drug treatment (Public Health England, 2017b) and therefore these people have less interaction with support services, further limiting the opportunity for identification for opioid use disorders or psychiatric problems. The 25-34 range was second highest percentage of all opioid-related deaths across 2006-2015 until 2013 when 45-54 year olds acutely increased for the remaining two years. People with opioid use disorder tend to present to drug and alcohol services for the first time at age 35 (European Monitoring Centre for Drugs and Drug Addiction, 2019) which may account for reduced life expectancy for 35-44 year olds with historic psychiatric problems where an opioid dependent lifestyle has already impacted on physical health (The Centre for Public Health, 2011). It is notable the difference in additional years of life (Figure 2.4) between the ranges 25-34 and 35-44 is reduced, further research outside the scope of this thesis may be warranted to examine individual case differences between these age groups. High comorbidities in the 65 and over age group could reasonably be expected to contribute to early mortality (Kester et al., 2017).

Deaths were controlled to remove suicide (Figure 2.2) because NPSAD includes non-drug-related suicide in this category with overdose recorded as 'drug poisoning' pre 2011. This is unlikely to skew results as the majority of drug-related deaths are a result of accidental poisoning (Office for National Statistics, 2018). There was an acute elevation in 2013 for suicides with at least one historic psychiatric problems (Figure 2.3), coinciding with an increase of anxiety/depression diagnoses in males and changes to the benefits system at the same time point supporting existing literature (Mental Health Foundation, 2016). Because the term 'drug-related death' was introduced in 2011 it is difficult to compare pre and post 2011 cause of death data. However the change in

available coroner verdicts may have led to homogenisation of cause of death reporting from 2011 onwards (Figure 2.2), indicated by decreases in suicide verdicts in people without historic psychiatric problems (Figure 2.3) found here. Alternatively the presence of an identified psychiatric problem may be a protective factor (when compared to people who use opioids without diagnosis) due to increased treatment support. It is also possible that the introduction of a generic definition of drug-related death has simply clouded cause of death interpretation and bloated mortality reporting overall but an individual reanalysis of each death was beyond the scope of this chapter.

2.3.2 The Prevalence of historic psychiatric problems

Low prevalence of PTSD as detected in this retrospective study is unexpected given trauma prevalence (Lawson et al., 2013) and usual co-existing schizophrenia (NICE, 2014) which was higher than expected. Paranoia may be recorded by GPs as a symptom rather than diagnosis which may explain low prevalence however under optimal levels of dosing of opiate substitution therapies such as methadone and buprenorphine may be a common problem in England (Advisory Council on the Misuse of Drugs, 2015) and would impede attempts to diagnose PTSD due to confounding symptoms with opioid withdrawal as discussed previously. Differences between number of recorded previous medical history with historic psychiatric problems (n=1366) and records without historic psychiatric problems (n=784) may indicate presence of novel information such as psychiatric diagnosis is more likely to be recorded than unremarkable medical histories. Presence of reported historic psychiatric problems and toxicology finding heroin at post-mortem in people not known to use illicit drugs suggest hidden opioid use disorders, potentially mitigated by implementation of GP risk assessment tools (Ducharme and Moore, 2019), or demonstrate that diagnosis is more readily available in perceived non-drug users (Section 2.2.4).

Female known illicit drug users were more likely than male to have historic psychiatric problems, until 2013 after which presence of psychiatric problems in opioid-related deaths in known illicit drug users and people not known to use illicit drugs began to decline (Figure 2.6) despite reporting of previous medical history increased in this period (Figure 2.5). Socioeconomic change may have triggered an increase in presentation to primary care by males between 2011 and 2013 (Malcolm et al., 2019). Although females face more barriers in accessing treatment for drug use (Arpa, 2017) they are more likely

than males to seek primary care treatment for psychiatric conditions (Green, 2006) and are more likely than males to receive treatment for anxiety or depressive disorder (Department of Health and Social Care, 2018). This may explain the high representation of female people not known to use illicit drugs with historic psychiatric problems as barriers to accessing drug treatment are unlikely to have prohibited presentation to primary care where they would receive diagnosis and treatment without referral to drug and alcohol treatment teams.

Mortality in people who were unemployed (Figure 2.7) and people who lived alone (Figure 2.8) were highest for people with and without historic psychiatric problems implying economic deprivation, loneliness and social isolation which are known risk factors for physical and mental health problems (Malcolm et al., 2019). It is also of note that deaths were lowest where people lived with their children perhaps suggesting a role for purpose in life as a protective factor against opioid-related death. This retrospective analysis of mortality is unable to confirm but the presence of individual purpose is in line with recovery capital theories of overcoming SUD (Best et al., 2020). Nevertheless the low prevalence of historic psychiatric problems in opioid-related deaths found in Table 2.1 is unexpected when socioeconomic risk factors feature prominently and consistently.

2.3.3 Prescription medications at post-mortem

Psychiatry has been debating the scientific meaning of diagnosis, preferring a symptom triggered approach to treatments arguing diagnosis results in a ‘disingenuous categorical system’ (Allsopp et al., 2019). Whilst diagnosis is key to receiving statutory psychological therapies, medications may be prescribed without a formal diagnosis to treat psychiatric symptoms.

Prescription medications detected at post-mortem (Figure 2.9) were examined to identify prevalence of prescription medications within opioid-related deaths but the increasing prescription medications found at post-mortem year by year cannot be assumed to indicate presence of psychiatric disorder due to the range of reasons medications are prescribed (Joint Formulary Committee, 2019). Antidepressants are recommended for use in moderate to severe depression but are also recommended within acute anxiety (NICE, 2014a) and PTSD treatment (NICE, 2018) to manage symptoms other than depression. Antidepressant medication alongside opioid use can increase risk of potentially fatal serotonin syndrome (Rickli et al., 2018) and opioid analgesic medications were found in

the majority of cases. Antipsychotics are recommended for treatment of psychosis, schizophrenia and bi-polar disorder (Joint Formulary Committee, 2019). Bi-polar prevalence was in line with expectations for illicit opioid users, see Table 2.1, but schizophrenia was notably higher and psychosis under-represented in both known illicit drug users and people not known to use illicit drugs. Antiepileptic escalation coincided with increased illicit use of gabapentinoids (classified by NPSAD as antiepileptic medications though prescribed for neuropathic pain usually) prior to reclassification in 2019 (Advisory Council on the Misuse of Drugs, 2016) due to their increasing presence in drug-related deaths where concomitant use alongside opioids can increase the effects of opioids (Lyndon et al., 2017).

It was beyond the scope of this chapter to analyse metabolites, prescription numbers, gender differences and other confounding variables required to assess the impact of drug-drug interactions or identify how many prescription medications were taken illicitly and so only opioid analgesics, as the focus of the data extraction (Figure 2.10), were analysed in context of cohort differences. Nevertheless, increases in medications found at post-mortem were higher than NHS prescribing trend increases between 2006 and 2015 (NHS Digital, 2017) where antidepressant items dispensed increased 0.98x, antiepileptics 1.33x, hypnotic/anxiolytics 0.0027x, psychosis and related disorders 0.51x and analgesics, which included non-steroidal anti-inflammatory drugs as well as opioids, increased 0.38x. Increasing volume of psychiatric medication and opioid analgesics found at post-mortem cannot be due solely to symptomatic GP prescribing.

Opiates such as heroin or methadone are recorded separately by NPSAD and were not included in the analysis meaning that the detected opioid analgesics (Figure 2.10, 2.11) were either prescribed, bought over the counter or prescriptions illicitly obtained. In people known to use drugs, opioid analgesic use may be due to the increasing use for managing emotional problems where psychiatric diagnosis has not been available, supporting self-medication theories (Cicero et al., 2017). In people not known to use drugs opioid analgesic use may be related to research showing increasing opioid prescribing correlation with opioid-related deaths (Taylor et al., 2019) and non-prescribed opioid analgesic recreational use (Yedinak et al., 2017). Figure 2.11 suggests that identification of opioid use disorders in people not known to use drugs may be missed by GPs when prescribing opioid analgesics as detection rates and deaths are almost equal in comparison to people known to use drugs. This could be improved through standardized

inclusion of screening tools by GPs such as the Opioid Risk Tool, a quick to administer and validated ten question assessment tool to identify risk of opioid abuse (Webster and Webster, 2005).

2.3.4 Commentary from health professionals

Organisational barriers were suggested to be produced by austerity affecting provision of services as demonstrated by difficulties in interviewing MHP. Interestingly recent analysis of disinvestment in 151 of 152 local authority commissioned UK drug and alcohol treatment services between 2013/14 and 2018/19 found that whilst local authority spending cuts were associated with fewer people accessing and completing treatment, spending cuts were not associated with deaths (Roscoe et al., 2022). Given that evidence shows that retention in drug treatment is a protective factor against mortality it is surprising that fewer people in treatment is not associated with the increase in mortality. This may suggest that whilst austerity has an impact on the ability of services to provide treatment, it is the quality and appropriateness of the treatment which has a greater influence on mortality. Austerity was further reflected in referrals to mental health support services as benefits sanctions were the second highest reason for referral to CMHT behind substance use (Figure 2.7, Theme 2) supporting evidence that socioeconomic change negatively effects mental health (Malcolm et al., 2019) and associated with the increase in historic psychiatric problems 2011-2013 (Figure 2.6).

The small sample size of MHPs prohibited exploration whether childhood trauma as a catalyst for substance use reported by DTPs would be supported by MHPs (Theme 1). Lack of trauma service signposting may be reflected in low prevalence of PTSD (Table 2). Requirements for abstinence prior to accessing psychological therapies mean it is not unreasonable to assume discussions around trauma are not routine and trauma informed care for substance users was not signposted by MHPs.

Perceived medication reliance (Theme 3) suggests opioid users may have been medicated without access to statutory psychological treatments (Figure 2.8). Year-on-year trends (Figure 2.8) show people not known to use illicit drugs with historic psychiatric problems were the only cohort where detection of opioid analgesics decreased post 2013 following benefits reform. Declining deaths in this cohort against the trend of increasing mortality (Figure 2.1) may be because self-reported substance use during referral for mental health services influences detection bias (Theme 2) in GPs and mental health professionals

prohibiting assessment. Lack of access to the evidence based treatments for substance users (World Drug Report, 2019) then contributes to increased opioid use and accidental overdose.

Although professionals agreed a specialist service was needed for people who use substances with co-existing psychiatric problems, services already exist in CMHT and trauma teams (NICE, 2016). Theme 2 demonstrated organisational criteria can hinder access to services in opposition to quality standards recommending substance use and severely intoxicated presentation should not be reason to exclude people from accessing these services (NICE, 2019). UK guidance recommends a proactive service led approach to engage this population in initiating treatment (NICE, 2016). The findings suggest guidance is not being followed.

2.3.5 Limitations

There are many limitations to using the NPSAD database. Firstly, the database relies on voluntary information from Coroners and there is a high degree of variance in completion and accuracy of submitted data. Secondly, seventy-nine percent of records were excluded when controlling for confirmation of previous medical history. Data cleansing was critical as it cannot be assumed that those without a previous medical history either had or did not have any historic psychiatric problems. This limitation meant caution must be applied to overall findings, specifically within comparing the analysed sample of people with historic psychiatric problems with population level data. Thirdly, the dataset does not indicate whether any attempts to access mental health services were made or whether a formal diagnosis was made. Fourthly, there is no information detailing when each historic psychiatric problem was recorded meaning psychiatric problems may not have been present at time of death or may have been in remission. Fifthly, information on treatment itself is not available and so it would be speculative as to what additional treatment a statutory diagnosis may have included or whether people without a recorded diagnosis had received non-statutory delivered psychological treatments. Sixthly, the NPSAD field 'known drug user' cannot be assumed to mean they were either known to drug treatment services or if they were currently using substances at time of death. Finally, direct comparison of mortality data pre and post socioeconomic changes (benefits welfare reform and introduction of a new drug strategy) was not possible due to changes in coroner reporting terms in 2011 when the socioeconomic change was introduced.

Interviews were undertaken with a small sample size across two localities and subject to self-selection bias. Data were self-reported and all accounts were taken at face value, representing the ‘truth’ for individuals at the time of interview, rather than universal ‘truth’. However detailed narratives echo globally identified barriers in accessing evidence based treatment (World Drug Report, 2019) and reflect estimates in prevalence of psychiatric disorders within drug treatment services (Guest and Holland, 2011). Larger qualitative studies to explore the perceptions of professionals working within care pathways and the experiences of people who use substances with co-existing psychiatric problems trying to access psychological treatments are warranted.

2.4 Conclusion

PTSD, anxiety, psychosis and eating disorders were considerably underdiagnosed in deaths involving known drug users where opiates were found at post-mortem in England between 2006 and 2015 during a period of socioeconomic change. It is unclear whether this was due to symptoms confounding diagnosis, detection bias, barriers to psychological treatment or combinations. Excluding paranoia, PTSD and eating disorders, psychiatric disorder recording in people not known to use drugs exceeded estimated general population prevalence which may indicate undetected risk of opioid use disorders. The increased detection of prescription medications and opioid analgesics which exceeds NHS prescribing data highlights (Section 2.3.3) increased recreational non-prescribed prescription use or self-medication where people are unable to access mental health treatment. There is an urgent need to reduce non-prescribed prescription medication use, specifically opioids, where presence at death exceeds NHS prescription data (Figure 2.9).

The qualitative analysis highlights professional views of a population asking for help but organisational barriers often mean psychological help is unavailable. The key differences between medication prescribed by professionals and illicit substances used to manage co-existing mental health problems are legal status and consequently the known purity of each substance. People who use substances are required to stop using the illicit substances which they know provide immediate relief for at least three months (Theme 2) prior to accessing psychological therapies which will not provide comparable, immediate relief of illicit substance use. Without normative coping skills this is unlikely to be an attractive proposition as people are being asked to stop doing the only thing that has worked for them in life to this point. From a behavioural-economic viewpoint, people who use

substances with psychiatric disorders then choose short-term gain (substance use) and long-term sacrifice (health implications, risk of overdose) (Rachlin, 2007). This seems irrational to people who do not use substances for relief but for people who do use substances to provide relief, this is the optimal choice where maladapted coping mechanisms exist (Theme 1), creating a vicious cycle of continued substance use that prohibits access to evidence based psychological therapies due to organisational barriers. By reducing opioid use the chances of accidental fatal overdose, the greatest cause of drug-related deaths (Office for National Statistics, 2018), will prominently diminish and lives can be saved.

Drug treatment professionals and mental health professionals share understanding of the complex interactions between substance use disorders and co-existing mental problems. Barriers to access psychological therapies are organisational in nature and result in reliance on medication to manage symptoms. This can be seen in national prescribing trends with escalating drug-related deaths (Taylor et al., 2019). Findings suggest that drug treatment and mental health services should review the pathways to psychological therapies ensuring they align with national guidance (NICE, 2016). Data from the quantitative analysis, supported by the qualitative experiences above indicates a treatment gap in identifying and managing co-existing psychiatric problems contributing to further increases in drug-related deaths. The evidence for oxytocin to reduce craving or consumption in addictive behaviours is systematically reviewed in the next chapter (Figure 2.13).

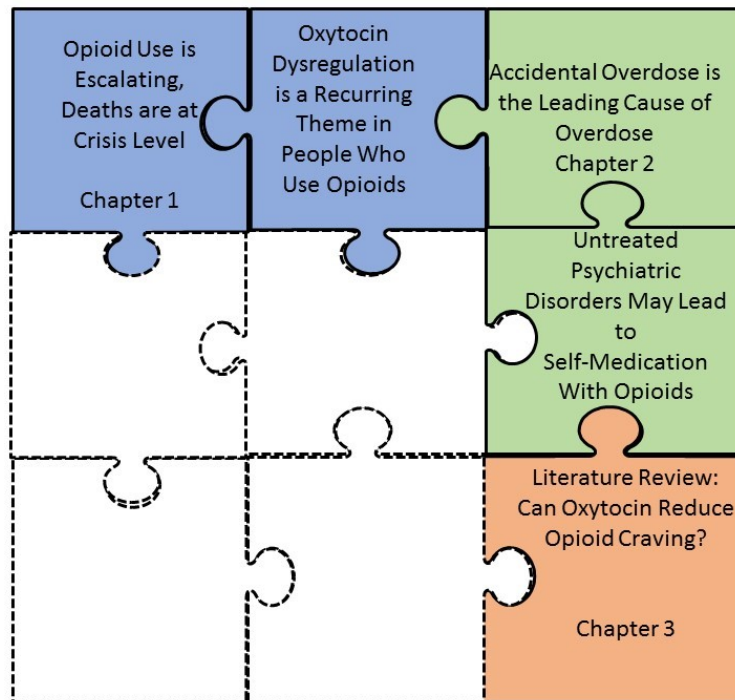


Figure 2.13: Key thesis findings by chapter up to chapter three

Notes: Chapter one outlined the extent of the opioid crisis with opioid-related deaths at crisis level. Chronic drug use dysregulates the endogenous oxytocin system and is highlighted in people who experience early life trauma and people with psychiatric disorders, both of which are highly prevalent in people who use opioids. Chapter two analysed the prevalence of psychiatric disorders in deaths where opioids were found at post-mortem and suggested that self-medication in the absence of psychological treatments may contribute to accidental overdose. The next chapter systematically reviews the evidence for nasal oxytocin to reduce craving.

Chapter Three

Can Nasal Oxytocin Reduce Craving in Automated Addictive Behaviours? A Systematic Review

‘Craving, not having, is the mother of a reckless giving of oneself’
– Eric Hoffer, American moral and social philosopher

Abstract

Existing pharmacotherapies for managing craving, a strong predictor of relapse in substance use disorders, are limited in efficacy and characterised by increased health risks associated with their pharmacological profile. Preclinical studies have identified oxytocin as a promising pharmacotherapy with anticraving properties. This chapter provides the first systematic review of 17 human studies ($n = 722$; 30% female) investigating the efficacy of nasal oxytocin to reduce craving or consumption in addictive behaviours. Findings support nasal oxytocin as a method that warrants further investigation regarding its capacity to decrease cue-induced, acute stress-induced or withdrawal-related craving and relapse related to alcohol, cannabis, opioids, cocaine or nicotine, including a potential role as ad hoc medication following exposure to drug-related cues. Future studies should investigate the role of factors such as treatment regimens and sample characteristics, including the role of the amygdala, which is proposed as part of a distinct mechanism mediating oxytocin's anticraving properties.

3. Introduction

As presented in section 1.2.1, craving is an established multifaceted antecedent predictor of automated addictive behaviours such as drug seeking behaviour (Tiffany et al., 2012), gambling disorder, internet gaming disorder, compulsive eating, exercise addiction, pornography addiction, and social network use disorder (Hormes, 2017). Many people who use substances describe drug seeking as feeling automatic and out of their control (Tiffany, 1990). This poses a significant challenge for relapse prevention following cessation of an unwanted behaviour. It follows that the ability to resist craving is vital to reducing the automaticity of looped addictive behaviour. Building on the idea that the subjective feeling of craving is just one symptom of the neurobiological mechanism (but not necessary to be present for the mechanism to be working), this thesis proposes that oxytocin dysregulation effectively freezes the craving mechanism (like stuck cogs in a broken watch) and ensures repetition of addictive behaviour in place (so the watch keeps telling the same time). The research underpinning this proposal is presented in 3.1.5. Administering oxytocin may unfreeze the craving mechanism.

This chapter will address the gap in current knowledge by systematically reviewing the evidence for nasal oxytocin to reduce craving or consumption in people with SUD. Animal studies were excluded from this review as preclinical reviews suggesting a role for oxytocin for initiation, continuation and cessation of substance use already exist and were presented in chapter one. Animal studies have paved the way for increasing numbers of human studies but to date no reviews of oxytocin's effect on drug craving or consumption in humans has taken place highlighting the novelty of this chapter. Beginning by expanding on the neurobiology influencing withdrawal-related and cue-induced craving (section 3.1.1 and 3.1.2), craving in relation to other addictive behaviours is then given an overview in section 3.1.3. Because of the effect that nasal oxytocin has on amygdala activity, the introduction progresses to investigate the amygdala's role in behaviour (section 3.1.4) and finally explains the novel mechanism of craving proposed by this thesis by which nasal oxytocin may work (section 3.1.5). The methods (section 3.2), results (section 3.3) and discussion (section 3.4) of the literature review are then presented.

3.1 The Neurobiology of Craving

This section will give an overview of the neurobiology behind withdrawal-related and cue-induced craving, highlighting the role of amygdala activity in both. The function and role of the amygdala is then discussed in depth providing the rationale for why hyperactivity rather than hypoactivity or volume may be the key component in mechanisms of opioid craving. Amygdala discussion continues with dual-route theory and amygdala hijack theory in order to interweave the novel mechanism of cue-induced craving suggested by this thesis which is tested in chapters four and five. For a current review of craving in opioid use disorder the reader is directed to Kakko et al. (2019) who discuss neurobiology and the implications of craving within clinical practice. Kakko et al. (2019) conclude that there is a clear need to increase understanding of opioid craving neurobiology as well as to identify novel strategies to manage craving, supporting the ideas presented in this thesis.

3.1.1 *Withdrawal-related craving*

Withdrawal-related craving refers to stress resulting from substance withdrawal (Shalev et al., 2002; Mantsch et al., 2016). Stress is defined as physiological changes in the body which activate the HPA axis (Koob, 2009). When activated corticotropin-releasing factor controls the release of adrenocorticotrophic hormone whose role is to regulate levels of the stress hormone cortisol (Koob, 2009). Cortisol is typically associated with negative, aversive states but effects are more complex than high cortisol meaning bad and low cortisol meaning good (Hoyt et al, 2016). Cortisol can also rise in response to perceived positive, exciting events and is associated with subsequent increases in alertness, activeness, relaxation as well as decreases in nervousness (Hoyt et al., 2016). The interaction between corticotropin-releasing factor, adrenocorticotrophic hormone and cortisol is linked to arousal states and pathological over activation of emotional systems (Koob, 2009) and the neuropharmacological action of corticotropin-releasing factor and noradrenaline within amygdala are key components of the system which manages emotional homeostasis (Koob, 2009). And so as a response to HPA axis over activation, and as a means to preserve homeostasis/find relief from the uncomfortable experience, people can use substances. Withdrawal-related reinstatement of substance use is not unique to opioids and is observed cross differing substances such as heroin, methamphetamine, alcohol, nicotine and cocaine (Mantsch et al., 2016). It is beyond the

scope of this thesis to review withdrawal-related craving in all substances and the reader is directed to Mantsch et al. 2016 for further information.

3.1.2 Cue-induced craving

Cue-induced drug craving is triggered when a person encounters something (people, places, things, emotions) that they relate to drug use (Jasinka et al., 2014). For example they may bump in to a friend they use drugs with, hear a song that reminds them of an event or moment they were using drugs or may experience an uncomfortable emotion which they know can be suppressed through drug use. It is important to understand that craving is always triggered by something unless the craving relates to withdrawal. As inconsistent doses of substitute opiates heighten the risk of accidental opioid overdose, substitute opiates are not suitable as a pharmacotherapy to manage cue-induced cravings and a therapeutic agent with a distinct mechanism of action from those currently available is needed. The mechanism for cue-induced drug craving will now be explained (Figure 3.1).

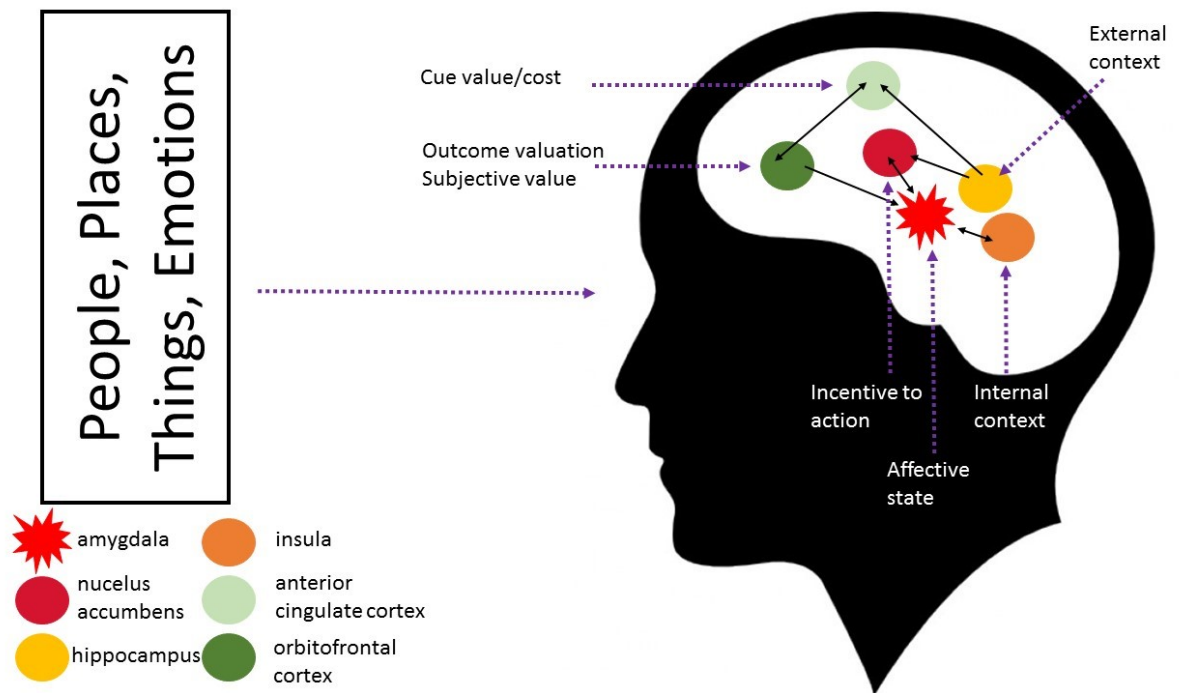


Figure 3.1: Neurobiology of cue-induced craving

Notes: When a drug-related cue is encountered the amygdala become hyperactive. The insula cortex confirms the association between the cue and past drug-use. The anterior cingulate then allocates attention towards the cue whilst stimulating memory recall of the benefits from drug using. The disrupted orbitofrontal cortex, which usually allows a person to reassess cues, is now inhibited leading to automated drug-seeking behaviour (Volkow et al, 2003; Goldtsein and Volkow 2011).

The mechanism is initiated when a cue triggers craving (Figure 3.1). The amygdala become hyperactive (Volkow et al., 2003) and with the rhinal cortex (part of the neural circuitry of explicit memory) shifts attention towards the drug by intensely recalling advantages, i.e. learnt positive or negative reinforcement, of using drugs rather than consequences of using (Bonson et al., 2002; Wise and Koob, 2014). The insula cortex (responsible for sensory processing, decision-making, and motor control) then confirms associations between the cue and past drug-use via the rhinal cortex. For a full review of the insula, the reader is directed to Ibrahim et al. (2019). The anterior cingulate then processes each cue allocating attention towards the drug whilst stimulating memory recall of the advantages of using drugs. Increased activity throughout amygdala, rhinal cortex and anterior cingulate is monitored by the orbitofrontal cortex which is normally involved in learning and reversing associations of stimuli (Rolls, 2004). The orbitofrontal cortex is located in the prefrontal cortex, the region which exerts inhibitory control over drug

reward saliency and decision making but becomes disrupted during drug cue-induced craving (Volkow et al., 2003). In the presence of drug-related cues, the orbitofrontal cortex becomes inhibited and the individual is unable to objectively consider the harms of each drug-related cue (Bonson et al., 2002). This prefrontal cortex disruption makes self-management of cue-induced craving even more challenging as behaviour becomes “automatic” (Goldstein and Volkow, 2011).

Within the above mechanism, the amygdala is important at the initial detection of drug-related cues but the anterior cingulate is equally important for its role in allocating attentional bias. The anterior cingulate cortex acts as a hub for neuronal circuits which connect both the ‘emotional’ limbic system and the ‘cognitive’ prefrontal cortex. These connections allow for the anterior cingulate cortex to be involved in decision-making, socially-driven interactions and empathy-related responses to stimuli (Lavin et al., 2013). There is an established functional link between the amygdala, anterior cingulate and both conscious and nonconscious attentional bias (Carlson et al., 2012; Carlson et al., 2013) and there is considerable evidence of a significant relationship between heightened amygdala activation and attentional bias towards drug-related cues in people who use substances (Hester and Luijten, 2014). Hyperactivity in the dorsal anterior cingulate cortex has also been seen as a predictor of relapse in newly detoxified people who used cocaine (Marhe et al., 2013). In people who use opioids, attentional bias has been found to be higher in an experimental study where heroin dependent people (n=68) currently undergoing methadone detoxification self-reported temptation to use heroin and that attentional bias was elevated in the one hour prior to self-reporting temptation to use heroin (Waters et al., 2012). This indicates that attentional bias may be a key component in the mechanism of craving and the reduction of attentional bias is hypothesised to be how nasal oxytocin exerts its effects on cue-induced craving.

Nasal oxytocin has been able to reduce attentional bias towards food in healthy controls and women with anorexia nervosa (Burmester et al., 2022; Leppanen et al., 2017; Kim et al., 2014) but not in women with bulimia nervosa or binge-eating disorder (Leslie et al., 2020), to normalise the difference in attention towards emotional faces between highly socially anxious males and healthy controls (Clark-Elford et al., 2015) and to increase attention to faces in people with autism spectrum disorders (Kanat et al., 2017). However the effect of nasal oxytocin on attentional bias to drug-related cues have not received the

same focus and to the best of our current knowledge there is no literature available to reference, adding to the novelty of this thesis.

Craving and attentional bias are not only present in SUDs. The next section briefly discusses evidence for craving and attentional bias in other automated addictive behaviours.

3.1.3 Other automated addictive behaviours

All experience involves brain mechanisms and in the case of automated addictive behaviours, this thesis suggests the craving *mechanism* which may or may not involve the subjective feeling of craving. Imagery is well known to induce craving in substance use disorders (McHugh et al., 2016) and can also induce craving in the use of social networking sites (Leng et al., 2019) and internet pornography (Pekal et al., 2018). In these examples, imagery triggers a process towards using social networks or sex/masturbation behaviour comparable with drug seeking behaviour. Whilst craving can be induced by imagery for use of social networking, *words* associated with social networking do not induce craving (Leng et al., 2019) just as drug-related words do not induce heroin craving (McHugh et al., 2016; Waters et al., 2012). Visual cues are consistent in inducing the neurobiological processes which govern automated behaviours.

The subjective craving experience is mirrored in both people with internet gaming disorder and people with substance use disorders. People describe negative feelings from not being able to play games, feelings of withdrawal when unable to access games and obsessing over ritualised aspects of playing games (Lopez-Fernandez, 2018). Craving in internet gaming also reflects ‘functional addiction’ typically associated with people who have an underlying alcohol use disorder. Functional addiction is the idea that someone is able to maintain a normal daily lifestyle of purpose whilst maintaining an addictive habit simultaneously. Craving to play video games has imitated this with video gaming having been observed to be kept hidden whilst daily lifestyle tasks were accomplished (Lopez-Fernandez, 2018). There are similarities between internet gaming disorder and substance use disorders regarding the strong desire to engage in the behaviour and negative feelings when the desire is not fulfilled.

Other automated addictive behaviours, as with substance use disorders, can also be linked to criminal behaviour. One Japanese study has shown gambling craving can predict

committing of criminal offences which give financial reward but not drug-related or violent-offences (Yokotani et al., 2019). This study concludes that gambling craving was linked to financial issues and not emotional or impulse control issues but it is reasonable to assume that a financial issue which resulted in crime is unlikely to have no emotional impact on the perpetrator. Similar to substance use disorders where people can continue using to chase past highs, gambling craving is associated with chasing past losses and continuing to gamble. Although problem gambling and SUDs may differ diagnostically, both behaviour outcomes are simply a need trying to be met stemming from previous beneficial experience i.e. recouping of losses, meeting financial demands or drug-related reward/relief.

Attentional bias is also present in automated addictive behaviours other than substance use disorders. Systematic review evidence has shown attentional bias in problem gambling (Hønsi et al., 2013) and interestingly one later study further suggests that attentional bias in low-risk gamblers is only present in those experiencing psychosocial stress – just as psychosocial factors are a risk factor for escalation of substance use disorders (McGrath et al., 2021). Individual studies where systematic reviews are not yet available confirm the presence of attentional biases in internet pornography disorder (Pekal et al., 2018) and internet gaming disorder (Jeromin et al., 2016; Kim et al., 2018). The presence of attentional bias towards social networking sites is less clear and fully powered studies have found conflicting results in similar samples, females, mean age of 20, though outcome measures differed between studies (Nikolaidou et al., 2019; Thomson et al., 2021). Nevertheless attentional biases appear to be present in all forms of automated addictive behaviours to some degree and further research is warranted.

Taken together these studies suggest mechanisms of craving leading to automated addictive behaviours share the components of craving as a subjective feeling and involuntary attentional biases as found in SUDs. Disrupting the neurobiological mechanism to create a window of opportunity for engagement in new behaviour would be beneficial across all addictive behaviours. Although there are neurobiological differences in withdrawal-related and cue-induced craving amygdala activation is present in both. The amygdala will now be discussed.

3.1.4 The role of the amygdala in behaviour

The amygdala are almond shaped masses of grey matter on each side of the brain which are best known for involvement in the ‘fight or flight’ response to threats (Roelofs, 2017) but also play an integrative role in responses to emotional/behavioural stimuli in humans (Rasia-Filho et al., 2000). Alongside emotion processing, the amygdala are involved in social behaviour response to stimuli and the process of reward learning. Allocating processing resources, such as attention, to stimuli which are perceived as being of prominence (Adolphs, 2010), the amygdala can be thought of as a storage device which associates Pavlovian conditioned stimuli with unconditioned stimuli (Fernando et al., 2013) i.e. the smell of baking bread alerting someone to the possibility of gaining pleasure by eating fresh bread or the smell of animal urine alerting animals that a predator is nearby. However this paints a far too simplistic picture as sex and cultural differences exist in left and right amygdala activation in response to the same stimuli (Derntl et al., 2012; Reber and Tranel, 2017). Full discussion of the differences in amygdala activation is too broad a topic to discuss in this thesis but generally the left amygdala is activated in processes which require focus without distraction, such as reading a book (Baeken et al., 2014) or tend-and-befriend processes (Gao et al., 2016). The right amygdala is activated when stimuli continually change requiring constant revaluation and response, such as negative emotion, alertness and hypervigilance (Baeken et al., 2014). Up to date generalised reviews of amygdala functioning are overdue but for further information the reader is directed to Brierley et al. (2002) and Rasia-Filho et al. (2000). Amygdala volume and amygdala activity in people with psychiatric disorders and people with substance use disorders is discussed next leading to an explanation of why the implications of amygdala activity is key to the mechanism of nasal oxytocin.

Evolutionary hypotheses for larger amygdala suggest that primate amygdala evolution occurred under the pressures of increasingly complex social interactions (Barton and Aggleton, 2000). Indeed larger amygdala volume is associated with size and complexity of social networks in male and female humans but does not correlate with social variables such as life satisfaction or social support (Bickart et al., 2011). Evidence of alterations in amygdala volume in people with psychiatric disorders are inconsistent. Whilst self-reported neglect and anxiety in boys aged 9-15 is positively associated with larger right amygdala volume (Roth et al., 2018) these results contrasted with meta-analyses of neuroimaging studies comparing adults with PTSD versus adults with trauma history but

no PTSD finding no significant difference in left/right amygdala size and volume (Woon and Hedges, 2009; Logue et al., 2018). Similar lack of difference can be seen in magnetic resonance imaging of people with bi-polar affective disorder type 1 versus healthy controls (Foland-Ross et al., 2012). Meta-analyses of thirteen studies comparing volumetric abnormalities in amygdala show a decrease in volume amongst people who have been depressed versus never-depressed people but this decrease was only evident in unmedicated individuals (Hamilton et al., 2008) and findings were replicated in later reviews of 18 studies looking at amygdala volume size in people with major depressive disorder (Nolan et al., 2020). In people receiving antidepressants, volume has been found to be larger indicating that antidepressants may facilitate neurogenesis beyond the size of healthy controls in the human amygdala (Hamilton et al., 2008; Nolan et al., 2020). Depression may be related to volumetric changes in amygdala but improved functioning in social networks as a byproduct of antidepressants or as a placebo effect of antidepressants may also encourage brain changes. Recent reviews of eighty-nine neuroimaging studies identifying structural and functional differences in generalised anxiety disorder found inconclusive results. Both enlarged and decreased volume of amygdala were seen but noted differences dependent on comorbid conditions and the action of medication (selective serotonin reuptake inhibitors versus benzodiazepines primarily). For more information the reader is directed to Madonna et al. (2019). Whether volumetric differences in amygdala exist as a result of psychiatric disorders is not clear as are any functional implications.

Alterations in amygdala volume are more consistently observed in people with SUDs. Increase of craving is associated with smaller amygdala volume in people who use marijuana (Padula et al., 2015), alcohol (Wrase et al., 2008) and cocaine (Makris et al., 2004) whilst daily administration of oral morphine has been found to reduce grey matter volume in the right amygdala (Lin et al., 2016). Evolutionary hypotheses (Barton and Aggleton, 2000) would infer smaller amygdala volume in substance users equates to decreased ability to process socioemotional cues and smaller volume may be linked to social isolation commonly seen in substance users (Hosseinbor et al., 2014), contributing to automated behaviours triggered by social cues due to impaired processing ability. The amygdala cannot be simultaneously bigger and smaller so the contrasting findings between amygdala volume for people with psychiatric disorders, highly prevalent

alongside SUDs, and people with SUDs may indicate that size is not as important as functional activity which is discussed next.

Hypoactivity of amygdala is defined as a lower than expected response in the amygdala when environmental stimuli are encountered. Amygdala hypoactivity following multiple-regression analysis in male and female youths aged 10-17 with callus-unemotional traits (low empathy, disregard for others) in response to emotional distress cues was associated with externalising proactive aggression (Lozier et al., 2014). This is consistent with theories suggesting callus-unemotional traits stem from deficiencies in empathic responses to distress and supports earlier studies in males with antisocial and conduct disorders, highly prevalent in SUDs, who also exhibited less right amygdala activity in response to fearful faces (Jones et al., 2009; Lozier et al., 2014), persisting in to adulthood (Hyde et al., 2014). One mixed sex fMRI study showed significant hypoactivity in right amygdala during a conflict control task in people with schizophrenia versus healthy controls as well as lower connectivity with the prefrontal cortex (Park et al., 2018). Hypoactivity in right amygdala translated to slower response times in the conflict control task supporting right amygdala involvement in dynamic stimuli detection (Baeken et al., 2014). However if amygdala hypoactivity was a protective factor against drug seeking behaviour then it would follow that people with antisocial personality traits would not use substances but this is not the case. Personality disorders, typically characterised by impulsive behaviour, are detected in up to 73% of people with SUDs (Parmar and Kalojiya, 2018) yet hyperactivity of the right amygdala is observed in people who use substances and engage in other addictive behaviours. There is an interesting conflict, beyond the limits of this thesis to fully investigate, between highly prevalent observable behaviour traits in people who use substances and neuroimaging of amygdala hypoactivity.

Hyperactivity of amygdala is defined as a heightened level of response in the amygdala when environmental stimuli are encountered. Hyperactivity of the amygdala is thought to be caused by pathological disruption of the GABAergic circuitry which regulates amygdala and is associated with behavioural disorders characterised by fear and anxiety, autism, Attention Deficit Hyperactivity Disorder, SUDs and neurotrauma such as PTSD (Sharp, 2017; Madonna et al., 2020). In drug users the amygdala become hyperactive in the presence of drug-related stimuli (Volkow et al., 2003) and hyperactivity is also observed following exposure to cues in behavioural addictions such as gambling

(Goudriaan et al., 2010), pornography, video games, shopping and food (Olsen, 2011). Modern addictions such as social networking are also susceptible to cue-induced craving (Niu et al., 2016) linked to amygdala hyperactivity (He et al., 2017). Opioid use (Vaughan et al., 1997), alcohol use (Banerjee, 2014) and cannabis use (Zehra et al., 2018) can all cause GABA signalling changes in amygdala but any relationship between hyperactivity, psychiatric comorbidities and substance use is unknown. The evidence suggests amygdala hyper/hypoactivity in response to cues is stimuli specific just as nasal oxytocins effects are perceptually selective (Bethlehem et al., 2013).

Amygdala activity is a more likely candidate than amygdala volume for cue-induced craving implications due to the observed hyperactive responses to drug-related cues. The ambiguous evidence for hyper/hypoactivity removes temptation for reverse inference which occurs when specific cognitive processes are attributed to be the result of observed brain activation (Hutzler, 2014). Evidence cannot support any assertion that behaviour is the exclusive result of neural activation due to unanswered questions and inconsistencies within findings. In addition amygdala do not possess the functional capability to process all sensory modalities alone but the evidence presented does support amygdala activation to be a cog in the wheel of a more complex neuropsychobiological mechanism. The mechanism proposed by this thesis, what happens when this mechanism breaks down and why oxytocin is a good candidate to modulate this mechanism is further elucidated in section 3.1.5.

3.1.5 Proposed modulatory role of oxytocin

One of the attractive properties of nasal oxytocin as a potential anticraving pharmacotherapeutic agent is its distinct mechanism of action compared to currently available anti-craving pharmacotherapy. Although the mechanism underlining the potential anticraving effect of oxytocin is not well understood, one possible mechanism involves the amygdala. Human neuroimaging studies have demonstrated that the suppression of activity in the amygdala is one of the most robust effects of nasal oxytocin, both in the resting human brain (Martins et al., 2020) and regarding the response of the amygdala to social emotional cues (Spengler et al., 2017). Consistent with human findings, suppression of amygdala activity by oxytocin has been reported in animal studies (Campbell-Smith et al., 2015). As such, the fact that amygdala hyperactivity is repeatedly seen as a precursor to driving automated addictive behaviours of a range of

different types of addictions, makes oxytocin an attractive anticraving potential therapeutic based on its unique amygdala suppressing properties.

Amygdala have also earlier been shown to play a key role in the evaluation of both positive and negative environmental stimuli (Cunningham et al., 2008). This section continues by introducing dual-route theories of amygdala and present the mechanism by which this thesis suggests nasal oxytocin exerts its anticraving effects.

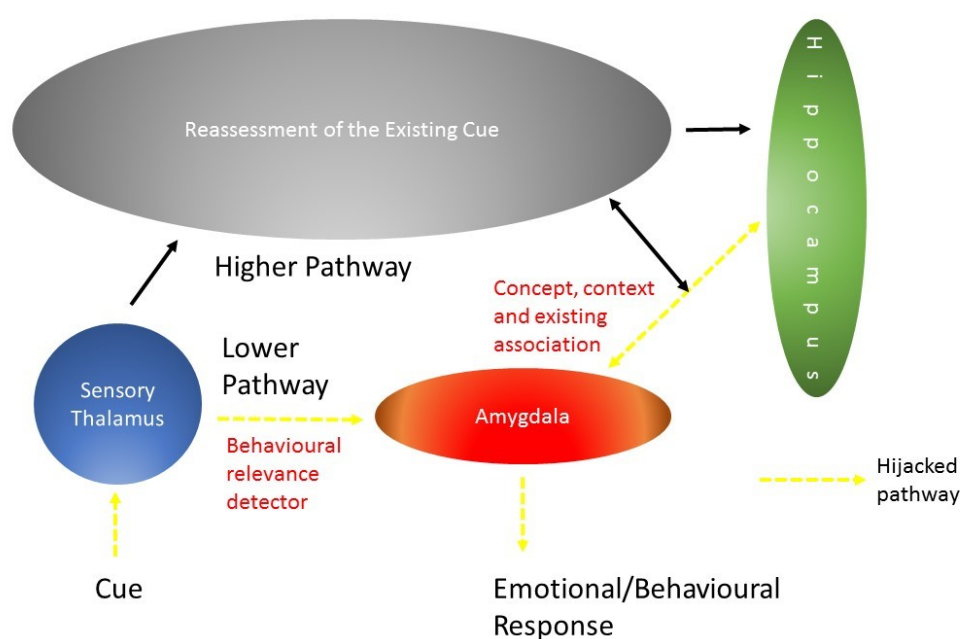


Figure 3.2: Proposed amygdala dual route pathways

Notes: The higher pathway allows for evaluation of all sensory input i.e. sounds, sights, smells etc, whilst interacting with the hippocampus to link with prior associations. When drawing on existing drug related memory associations the higher pathway gives pause for thought and reassessment of whether drug use is the best behaviour. In contrast, the lower pathway rapidly identifies and associates stimuli with existing associations and drives behaviour towards repetition of previous responses to the stimuli. When working in parallel the two pathways can rapidly detect environmental cues and reassess which behaviour is best to respond with. When the amygdala is hijacked the higher pathway is inhibited meaning old cue associations and behaviours (such as drug-related cues and drug-seeking behaviour) become looped and automated. Adapted from: https://thebrain.mcgill.ca/flash/a/a_04/a_04_cr/a_04_cr_peu/a_04_cr_peu.html

The dual-route theory (Garrido et al., 2012) suggests the existence of two distinct pathways mediating the response of the amygdala to external cues; the higher and the lower pathway (Figure 3.2). Whilst both pathways operate in parallel, numerous studies demonstrate the lower pathway offers fast evaluation of early sensory information and the higher pathway facilitates more considered reassessment of environmental cues (Garrido et al., 2012; McFadyen et al., 2017). It is suggested that the role of the lower pathway is that of a 'behavioural relevance detector' (an in-built early warning system) which identifies cues in the environment, allocates involuntary attention towards those cues (Pool et al., 2016), and quickly evaluates the benefits or harms associated with the cue in order to drive the behaviour response (Garrido et al., 2012; Garvert et al., 2014). This complex definition is otherwise known as the fight-or-flight response (Roelofs, 2017).

But as the fight-or-flight mechanism is normal and essential for human survival, what becomes hijacked? This thesis poses the question for future neuroimaging research and instead speculatively suggests that dysregulation of an allostatic oxytocin system hijacks the higher amygdala pathway, stopping reassessment of drug-related cues leading to looped behaviour. Cue detection which triggers fluctuations in peripheral oxytocin levels (Vrachnis et al., 2011; Churchland and Winkielman, 2012) could be the first stage in a larger 'craving' mechanism driving behaviour (Goldstein and Volkow, 2002). Part of this mechanism is activation of the prefrontal cortex, implicated in appraising the value of cues, and the anterior cingulate cortex which is implicated for salience (importance of a cue) signalling. Indeed fMRI studies which induced heroin craving in both short (23.6 ± 17.6 days) and long term abstinent (193.3 ± 42.7 days) people who were dependent on heroin found no change in self-reported craving scores and lower activity in the bilateral anterior cingulate cortex in the long term abstinent cohort compared to those in short term abstinence whose craving scores increased in response to heroin related cues and displayed higher activation of the bilateral anterior cingulate cortex (Li et al., 2013). These findings suggest increased susceptibility to craving and greater importance is attributed to heroin related cues in newly abstinent people where opioid-related cues continue to be strongly associated with providing reward or relief (Koob and Volkow, 2010). It is important to note that value and salience operate independently meaning that something of low value, such as opioids when a person decides to stop using them, can

remain of high importance. Salience may even be magnified in chance situations (such as randomly encountering an opioid-related cue) rather than controlled situations (Kahnt and Tobler, 2017). Once the amygdala become hyperactive following early detection of drug-related cues (Figure 3.1), hyperactivity is associated with an individual contextually-dependent dysfunction (meaning different people relate different cues to drugs) in the prefrontal cortex and results in reduced self-control (Wilson et al., 2004; Goldstein and Volkow, 2011). By now the higher amygdala pathway has become hijacked by the lower pathway and so reassessment of value and salience processing is inhibited by dysfunction of the endogenous oxytocin system. In keeping with allostatic theory of oxytocin, this means that rapid detection of opioid-related cues leads to the repetition of behaviours based on a prediction of beneficial reward/relief and the automated looped behaviour of opioid use (Wong et al., 2015; London et al., 2000). As repetition of the behaviour increases, the original motivation for these behaviours becomes immaterial and automaticity continues without conscious control (Ersche et al., 2017).

A healthy oxytocin system would usually regulate activity such as amygdala activation in the HPA axis but dysregulation of the oxytocin system may inhibit regulation. The continual observations of oxytocin dysregulation in people who use drugs (stemming from childhood trauma, chronic drug use, psychiatric disorders and genetic polymorphisms as discussed in chapter one) combined with amygdala suppression being one of the most robust findings from nasal oxytocin research suggests that the oxytocin system should be targeted for further investigation.

In summary an amygdala hijacking theory, as proposed in Figure 3.2, provides two explanations for the loop of drug using behaviour. According to this theory;

- 1) Drug-seeking behaviour coincides with exposure to drug-related cues and hyperactivity of amygdala, seizing up the flexibility to objectively assess situational salience (Figure 3.3)
- 2) Decreased inhibitory control of attentional bias contributes to drug seeking due to the inability to assess situational importance of drug-related environmental stimuli

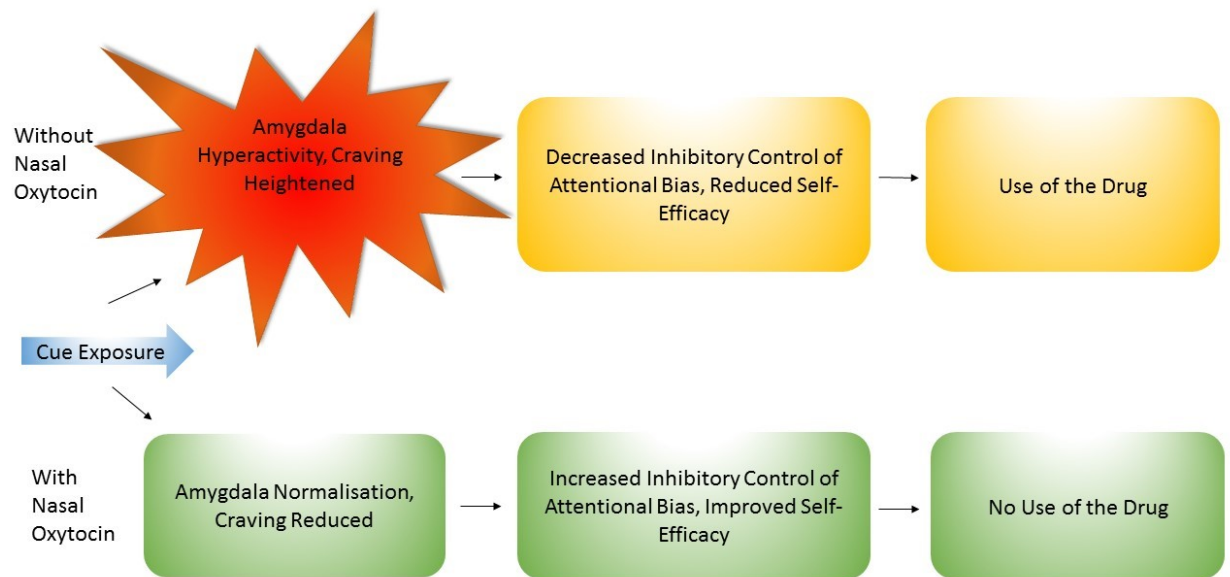


Figure 3.3: Proposed model of mechanism for cue-induced opioid craving

Notes: (Top) Under standard conditions, following exposure to drug related cues the amygdala becomes hyperactive, craving is heightened (Langleben et al, 2008; Mei et al, 2010; Langleben et al, 2014) and the salience of cues is increased. Self-control of attentional bias is decreased and this leads to relapse (Garland et al, 2014). **(Bottom)** Following the administration of nasal oxytocin, the amygdala response to drug-related cues is normalised, the salience of cues is decreased, self-control of attentional-bias is increased and relapse is avoided.

Based on Figure 3.3, this thesis posits that suppression of amygdala hyperactivity may create a short window of opportunity for the individual to make a new assessment to not to use drugs or to remove themselves from a high risk situation where they may be more tempted to use drugs as craving and attentional bias are reduced, leading to subsequent prevention of drug use. This chapter continues with the first systematic review aiming to synthesize evidence from human studies investigating the efficacy of nasal oxytocin as a pharmacotherapy to reduce craving in addictive behaviours, or its concomitant effects on the consumption of either licit or illicit substances, or on engagement in behavioural addictions.

The research question which this chapter seeks to address is: what is the effectiveness of nasal oxytocin to reduce craving and/or consumption in substance use disorders and other addictive behaviours?

3.2 Methods

Systematic reviews are the highest form of evidence and attempt to synthesize all available evidence around a specific research question. These are important in healthcare as they allow clinicians to have a conscientious, explicit and judicious evidence base to best inform treatment decisions for maximum efficacy.

Where possible in systematic reviews, meta-analyses are important to identify and statistically analyse patterns and trends amongst study results. This can be used to obtain increased understanding of how well a particular treatment or intervention works in differing settings.

This review complied with the 27 item checklist found as part of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Adopting definitions of Cochrane Collaboration, the PRISMA statement aims to help authors critically appraise, collect and analyse data to ensure transparent reporting of systematic reviews and meta-analyses (Page et al., 2021).

The study was conducted in accordance with the Declaration of Helsinki.

3.2.1 Literature search

This review identified peer-reviewed studies that investigated the effects of nasal oxytocin, compared to placebo, on craving induced by a cue paradigm, an acute stressor, or withdrawal related stress in humans. The following electronic databases were searched, from inception until July 2020: PubMed (Medline), Embase, Web of Science, Psycinfo and Google Scholar. These databases were chosen as this combination of databases results in 98.3% recall of available literature (Bramer et al., 2017). Google Scholar was included to improve the chance of returning documents outside of commercial publishers to reduce the risk of publication bias (Bramer et al., 2017). Google Scholar search reports were limited to the first 200 results within a topic search in line with recommendations for using Google Scholar as part of a systematic review (Haddaway et al., 2015). Google Scholar has high sensitivity and wide coverage meaning searching for a specific paper is a very different proposition to searching with a view to completing a systematic review

(Giustini and Boulos, 2013). This results in a vast amount of information returned per search. A major criticism of Google Scholar are search limitations of only basic Boolean operators available to utilise (Haddaway et al., 2015). This means academic thesis, government papers amongst other sources were included and bloated results. We used the following search terms (adapted according to the format required by each database): “oxytocin” AND (craving OR addictive behaviours OR pornography OR pathological gambling OR compulsive eating OR social networking sites OR internet addiction OR internet gaming).

3.2.2 Eligibility

We included studies meeting the following inclusion criteria: (a) peer-reviewed study, available in English; (b) used human adult volunteers; (c) compared the administration of nasal oxytocin to placebo; (d) focused on substance use disorders, compulsive eating, gambling addiction, pornography addiction, social network use disorder and gaming addiction as defined by DSM-IV, DSM-V or ICD11 (American Psychiatric Association, 2013; World Health Organisation, 2018). Disorders recognised by DSM-IV or V within the context of the review include substance use disorders and gambling. Compulsive sexual behavioural disorders which include pornography and sex addiction, gaming addiction and social network use disorder are recognised by ICD11 but not by DSM-V currently. Compulsive eating disorders have been recognised by both ICD11 and DSM-V, and we included Bulimia Nervosa or Binge Eating disorders, as binge eating has been conceptualised from a food addiction perspective (Treasure et al, 2018); (e) included one of the following measures of craving or consumption/engagement: validated self-report drug craving scale, oral fluid mouth swab drug screen and/or urine drug screen to provide objective measures of drug use, self-reported quantity and frequency of substance use. For food craving studies they were included if they used at least one of the following: validated self-report food craving scale, quantity of food or nutritive substance consumed. For gambling, porn, social network, gaming addictive behaviour studies, they were included if they measured at least one of the following: validated self-report craving scale, quantity of bets placed, quantity of pornographic material viewed, amount of time spent on social networking sites, time spent playing video games.

3.2.3 Data extraction

The following data were extracted from all papers independently by reviewers BH, AB and YP: first author, year of publication, country of origin, addictive behaviour, severity of substance use disorder, craving type, study design, sample size, dose administered, post-dosing measurement interval (single dose), administration regime (repeat dose), outcome measures related to craving or consumption, statistically significant effects of nasal oxytocin (compared to placebo) on each outcome measure. Any discrepancies were resolved through discussion. Information from included studies is presented in Table 3.1. A narrative summary of the included studies and reported significant results is provided. A meta-analysis was not possible due to substantial heterogeneity in study designs, addictive behaviours and outcome measures.

3.2.4 Risk of bias

One reviewer (BH) used the Cochrane Collaboration's risk of bias tool (Higgins et al., 2016) to conduct a quality assessment for methodological risk of bias. The following risk of bias criteria were applied for each study:

- Random sequence generation (selection bias). Methods used to generate allocation sequence recorded as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method not clearly stated); and high risk of bias (studies that included a biased randomisation procedure).
- Allocation concealment (selection bias). Methods used to conceal allocation to interventions from participants and/or researchers prior to assignment recorded as: low risk of bias (e.g. electronic or third party randomisation; consecutively numbered, sealed envelopes); unclear risk of bias (method not clearly stated); high risk of bias (no randomisation, participants and/or researchers were aware whether they received placebo or oxytocin).
- Blinding of outcome assessment (detection bias). Methods used to blind researchers from knowledge of which intervention a participant received. Methods recorded as: low risk of bias (study had a clear statement that outcome assessors were unaware of treatment allocation); unclear risk of bias (study stated that outcome assessors were blind to treatment allocation but lacked a clear

statement on how it was achieved); high risk of bias (study stated that outcome assessors were aware of treatment allocation).

- Incomplete outcome data (attrition bias). Incomplete data and incomplete explanation of incomplete data was recorded as: low risk (attrition fully reported and no differences between completers and non-completers); unclear risk of bias (attrition unclear or unclear differences between completers and non-completers); high risk of bias (attrition not reported or unaccounted for missing data).
- Selective reporting (reporting bias). Where all outcomes identified in methodology were reported within results this was recorded as low risk of bias; unclear risk of bias (outcomes reported descriptively without statistical analysis reporting); high risk of bias (missing outcome data).

3.3 Results

3.3.1 Study selection

The PRISMA chart can be found in Figure 3.4. We identified 516 records, and after duplicates were removed, 302 studies remained. Their titles and abstracts were screened by one reviewer (BH). We excluded 285 studies for not meeting one of more of the inclusion criteria. It was expected that results would return between 7% and 25% duplicate records based on a three database search (Qi et al., 2013) however this review returned greater duplication; Pubmed (20%), Embase (58%), World of Science (60%), Psychinfo (100%), Google Scholar (28%). We reviewed the full-text, and extracted data, from the remaining 17 publications (see Table 3.1).

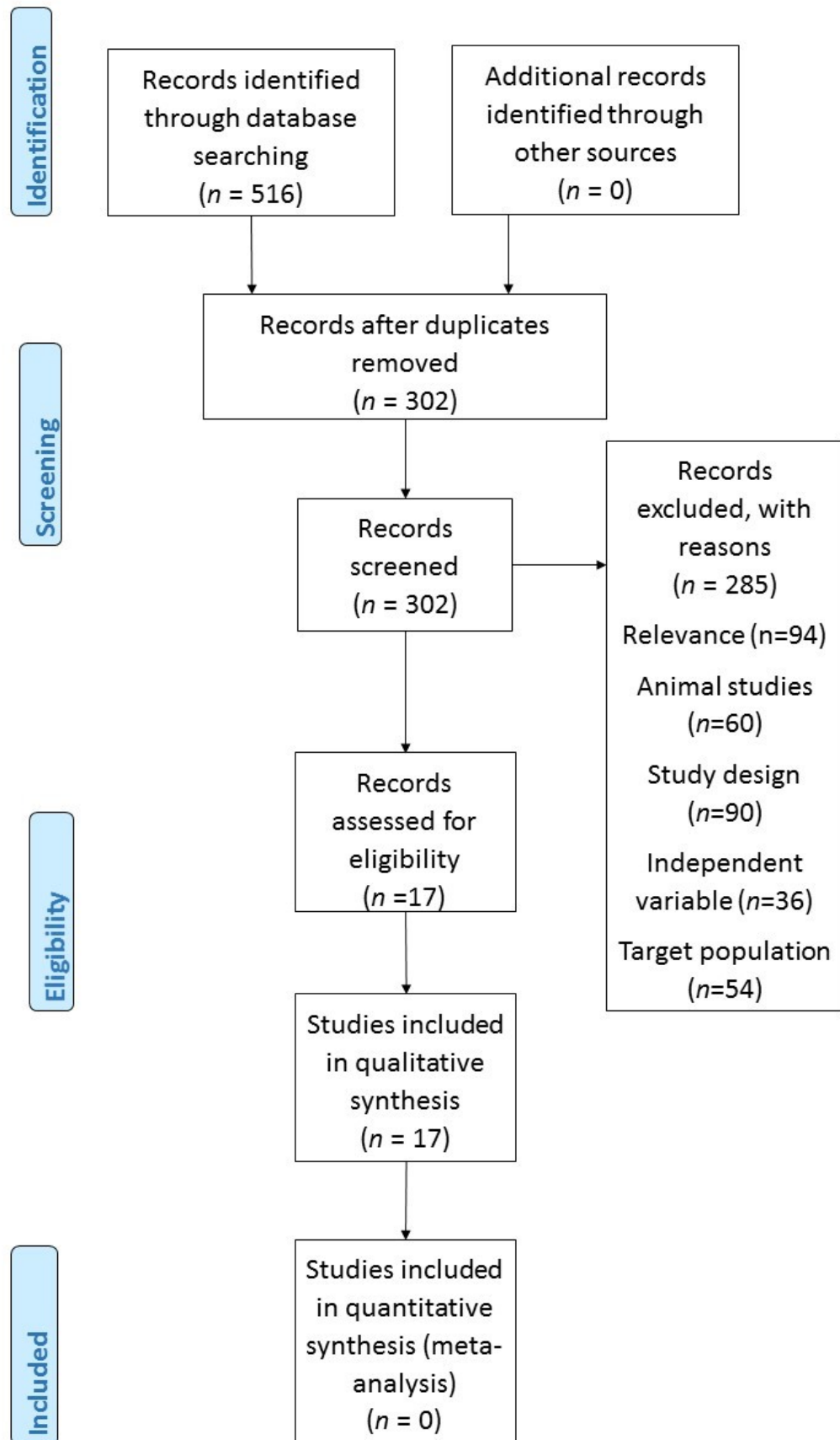


Figure 3.4: PRISMA diagram of search strategy

3.3.2 Study characteristics

Table 3.1 Data extracted from the 17 studies meeting our inclusion criteria

Study		Addictive Substance/Behaviour		Study Design			Intranasal Oxytocin Administration			Effects of Oxytocin vs Placebo		
First author & Date	Country of Origin	Substance/Behaviour	Diagnosis/Severity	Craving Type Measured	Design	Sample Size	Dose	Post Dosing Measurement Interval (Single Dose)	Regime (Repeat Dose)	Outcome Measures	Craving ratings/BOLD response	Consumption
Single dose oxytocin administration												
Bach et al, 2019 (same sample as Hansson et al 2017)	Germany	Alcohol	No diagnosis of SUD - social drinkers (including moderate/heavy social drinking; minimum alcohol consumption $\geq$ 1 standard drink, defined as 12g alcohol, on at least 2 days per week)	Cue-induced	RD, DB, W	13m	24IU	60 mins (onset of fMRI cue-induced craving paradigm)	N/A	fMRI BOLD connectivity response to cue-induced reactivity paradigm (OT vs. PL)	$\downarrow$ R NAc-R Cuneus $\beta=-0.14$; L Thalamus-R LOC $\beta=-0.12$ $\uparrow$ R PrCG-R PCG $\beta=0.16$	N/A

										Correlations between mean subjective alcohol cue-induced craving and OT vs. PL fMRI BOLD connectivity response	with R NAc-R Cuneus: ↑ Effect size: not reported with Thalamus-LOC: - Effect size: not reported with PrCG-PCG: - Effect size: not reported	N/A
Flanagan et al, 2019	USA	Alcohol	Alcohol Use Disorder (DSM V) and PTSD (at least 5 days abstinent, by self report)	Acute stress-induced (Trier Social Stress Task)	RD, DB, B	OT=32m PL=35m	40IU	60-120 mins (0-60 min post-stress induction)	N/A	study-specific subjective rating scale for craving (VAS)	- Effect size: not reported	N/A
Mitchell et al, 2016	USA	Alcohol	Alcohol Abuse (DSM IV - non physically dependent)	Cue-induced	RD, DB, W	32 (13f)	40IU	30 -90 mins	N/A	Alcohol Urge Questionnaire	- (main effect of OT); Effect size: not reported ↓ if high attachment anxiety; $\beta = -0.61$ ↑ if low attachment anxiety $\beta = 0.15$	N/A

Stauffer et al, 2019	USA	Alcohol	Alcohol Use Disorder (DSM V) and PTSD	Cue-induced	RD, DB, W	47m patients 36m controls	20IU, 40IU	75 mins (after water cue exposure) 85 mins (after alcohol cue exposure)	N/A	Single VAS ("How much are you currently craving alcohol?")	– $\beta=0.96$ (20IU) $\beta=-1.22$ (40IU)	N/A
McRae-Clark et al, 2013	USA	Cannabis	Marijuana Dependence (DSM-IV)	Acute stress-induced (Trier Social Stress Task)	RD, DB, B	OT=8 (1f) PL=8 (3f)	40IU	60-120 mins (pre-stressor, 0-, 5-, 35-, and 60-minutes post-stress induction)	N/A	Marijuana Craving Questionnaire (total score)	- (pre-stressor) $d=0.95$ ↓ (at 0- and 5-mins post-stressor) $d=1.23$ - (at 35- and 60- mins post-stressor) Effect size: not reported	N/A
Reed et al, 2019	USA	Cannabis	smoking between 2-18 cannabis cigarettes per week but not meet moderate to severe DSM-V criteria for Cannabis Use Disorder	Acute stress-induced (Trier Social Stress Task) vs no-stress task	RD, W	63 (32f)	40IU	30-360 mins	N/A	Cannabis self-administration 60-240 min post dosing (0-180 mins post-stressor)	N/A	– Effect size: not reported

										Drug craving (VAS) 30 min post-dosing (pre-stressor); 240min - 360min post-dosing (180min - 300min post-stressor)	— Effect size: not reported	N/A
Lee et al, 2014	USA	Cocaine (abstinent)	Cocaine dependence (DSM-IV-TR)	Withdrawal-related	RD, DB, W	23 (1f)	24IU	45mins	N/A	Urge to use VAS (baseline)	↑ Effect size: not reported	N/A
				Cue-Induced						Cue-induced urge to use plus 5 arousal related questions (all VAS, controlling for baseline)	↑ (excitement) Effect size: not reported — (urge/irritation, heart pounding) Effect size: not reported	N/A
McClure et al, 2019	USA	Nicotine	Smoke an average of 5 cigarettes/day for at least 6 months (abstained for 12 hours before laboratory session)	Acute stress-induced (Trier Social Stress Task)	RD, B	OT = 72 (45f); PL = 72 (46f)	40IU	75 and 95 mins (two assessments)	N/A	4 Item Craving Questionnaire (before dosing, 30/60/80/100, 120, 125, 150, 180 post dosing) (TSST 40-60 min post-dosing))	— Effect size: not reported	N/A

										latency to smoke (resistance task) & ad-libitum smoking (120-180 min post-dosing)	N/A	- $\eta^2 = 0.09$
Miller et al, 2016	USA	Nicotine	Daily smokers (abstained for 12 hours before laboratory session)	Withdrawal-related	RD, DB, W	17 (6f)	20IU	baseline and for 60 min (multiple assessments)	N/A	Short Tobacco Craving Questionnaire & Brief Questionnaire of Smoking Urges	- Effect size: not reported	N/A
				Cue-induced (30 min after top up)			top-up: 20IU (75 min after first dose)	120-210 min from first dose (multiple assessments)	N/A	(as above)	↓ $\eta^2 = 0.2$ (120 mins) $\eta^2 = 0.14$ (210 mins)	N/A
Van Hedger et al, 2018	USA	Nicotine	Daily smokers (abstained for 12 hours before laboratory session)	Withdrawal-related	RD, B & W	PL-PL= 16 (7f) OT-PL=16 (7f) PL-OT=16 (7f)	40IU	baseline, 20 min post-dosing	N/A	Short Tobacco Craving Questionnaire at baseline (withdrawal-related)	— Effect size: not reported	N/A
				Acute stress-induced (Trier Social Stress Task)				60m (immediately after TSST)		Short Tobacco Craving Questionnaire following Trier Social Stress Test	— Effect size: not reported	N/A

Van Hedger et al 2019	USA	Nicotine	Daily smokers (abstained for 18 hours before laboratory session)	Withdrawal-related	DB, W	35 (17f)	40IU	baseline, 30m, 120-180 min (every 20 min)	N/A	Short Tobacco Craving Questionnaire & Brief Questionnaire of Smoking Urges	↓ (desire to smoke) Effect size: not reported	N/A
				Withdrawal-related				30m		Demand for cigarettes	- Effect size: not reported	N/A
				Substance-induced				60-120 min		Desire to smoke	↓ (after first smoking opportunity) Effect size: not reported	N/A
								60-120 min		number of cigarettes smoked	N/A	↓ Effect size: not reported
Moeini et al, 2019	Iran	Opioids	Heroin dependence (DSM-IV) (Abstinent for 6-9 days)	Cue-induced	RD, DB, B	OT=29m PL=29m	40IU	45 mins	N/A	Desire for Drug Questionnaire (60 min post-dosing)	↓ $d=7.68$	N/A
										VAS (60 min post-dosing)	↓ $d=1.96$	N/A

Woolley et al, 2016	USA	Opioids	Heroin use, on substitute opiates and abstinent from all illicit drugs for 2 weeks prior to study enrolment	Cue-induced	RD, DB, W	33m	40IU	45 min	N/A	Craving & Urge to use (VAS) (before drug, directly before cue exposure, directly after cue exposure, 3 min following cue exposure, and again at the end of the study (135 min post-dosing)).	— Effect size: not reported	N/A
Repeated oxytocin administration												

Pedersen et al, 2013	USA	Alcohol	Alcohol dependent inpatients, average consumption of 8-30 standard drinks per day for at least 2 weeks prior to enrollment in the study, with history of severe withdrawal symptoms who undergo medical detoxification using symptom-driven administration of lorazepam	Withdrawal-related	RD, DB, B	OT=7 (1f) PL=4 (1f)	24IU, twice daily (48IU per day)	N/A	At 09:00 and 17:00 for 3 consecutive days	Penn Alcohol Craving Scale shortly after morning dose only on days 2 and 3	- $d=1.15$ (day 2) $d=0.03$ (day 3)	N/A
										Alcohol Craving Visual Analog Scale shortly after morning dose only on days 2 and 3	↓ $d=2.49$ (day 2) - $d=0.77$ (day 3)	N/A

Sherman et al, 2017	USA	Cannabis	Cannabis-dependent adults (DSM-IV)	-	RD, B	OT=8 (3f) PL=8 (3f)	40IU plus MET	OT administered 30 before first 2 out of 3 MET sessions in weeks 1, 2 and 4		Timeline Follow-Back test during study period	N/A	- $d=0.49$
Stauffer et al, 2016	USA	Cocaine, Opioids	Opioid use disorder (receiving methadone) and concurrent Cocaine use disorder (DSM-IV)	Cue-induced	RD, DB, B	OT=11 (5f) PL=11 (6f)	40IU, twice daily (80IU per day)	N/A	2 weeks, doses 8-10hrs apart	Self-reported drug use during treatment period	N/A	- $d=0.31$
										Urine sample measurement of benzoylecgonine(primary cocaine metabolite)	N/A	- $d=0.23$

									Cue-induced craving (VAS) for heroin/cocaine (before cue, after 1 min of drug cue video, after 3 min of neutral video), at day 1 (baseline), Day 15 (after 2 weeks of treatment), and Day 21 (after washout week)	- $d=0.29$ (cocaine, Day 15) $d=0.09$ (cocaine, Day 21) $d=0.71$ (heroin, Day 15) $d=0.77$ (heroin, Day 21)	N/A	
Agabio et al, 2016	Italy	Food	Binge eating disorder (DSM V); BMI>=30 (no current bulimia or anorexia)	Baseline craving	RD, DB, B	OT=8(7f) PL=9f	24IU, four times daily (96IU per day)	N/A	8 weeks (20mins prior to three meals and sleep)	Number of binge eating episodes (weeks 1, 4, 8 and once post treatment end)	N/A	- $d=1.75$
										Food craving (VAS; weeks 1, 4, 8 and once post treatment end)	- $d=0.15$	N/A

Notes: B = between subject design; CG: Cingulate gyrus; DB = double blind; M = males; F = females; FG: frontal gyrus; hipp = hippocampus; IFG=inferior frontal gyrus; IPL = inferior parietal lobule; IU = international units; L = left; MET = Motivational enhancement therapy; MGF=Middle frontal gyrus; N/A = not applicable; Not reported = effect size not reported and not enough data reported to calculate a standardised effect size; LOC: Lateral occipital cortex; NAc = Nucleus Accumbens; OG=occipital gyrus; OT = oxytocin; PL = placebo; PrCG = paracingulate gyrus; PCG = precentral gyrus; RD = randomised; R = right; SMA=supplementary motor area; SFG: Superior frontal gyrus; STG: superior temporal gyrus; W = within subject design; VAS = visual analog scale; * = not stated; Statistically significance defined as $P<0.05$; - = no effect for nasal versus placebo; ↓ = nasal oxytocin versus placebo reduced craving or consumption; ↑ = nasal oxytocin versus placebo increased craving or consumption.

The review identified a total of 17 studies meeting the inclusion criteria, originating in countries across the world (see Table 3.1). Of these, 13 studies reported the effects of a single dose of nasal oxytocin, compared to placebo, directly on outcome measures of craving or consumption for addictive behaviours related to alcohol (4 studies), cannabis (2 studies), cocaine (1 study), nicotine (4 studies), and opioids (2 studies). Most single-dose studies assessed only cue-induced or acute-stress induced craving (n=10; three of which assessed both cue-induced/acute stress-induced and withdrawal related craving), while 3 single-dose studies assessed both cue-induced craving and consumption. Four studies measured the effect of various regimes of repeated administration of nasal oxytocin, compared to placebo, directly on withdrawal-related craving for alcohol (one study), cue-induced craving for heroin/cocaine (one study), baseline craving for food (one study), or cannabis consumption (one study). There were no studies returned involving addictive behaviours beyond substance use disorders and food.

Of the 13 studies that investigated the effects of a single dose of nasal oxytocin administration on craving, most studies utilised study-specific visual analog scales (VAS) or validated craving measures (see Table 3.1). One study (Bach et al., 2019) did not report directly behavioural craving ratings, but the association between behavioural craving ratings during an fMRI cue-induction craving paradigm and connectivity between the blood oxygen level dependent (BOLD) response in specific brain regions. The studies varied substantially in the time they obtained measures of craving post dosing. Six single dose studies obtained single measures at intervals that ranged from 20 to 95 min post-dosing; while the remaining studies performed multiple assessments at intervals that varied from 0 – 360 minutes post-dosing.

All 3 studies that investigated the effects of a single dose of nasal oxytocin on consumption also measured cue-induced craving. These studies measured consumption over intervals that ranged from 60 – 240 minutes post-dosing. Of the 3 repeated oxytocin administration studies that measured consumption, one used self-report diaries (Agabio et al., 2016), and one used self-report measures and a urine drug screen test (Stauffer et al., 2016). The remaining study examined the potential for nasal oxytocin, compared to placebo, to enhance the effects of a psychotherapeutic intervention on cannabis consumption (Sherman et al., 2017).

3.3.3 Frequency of administration and dose

Doses in the studies that investigated the effects of a single dose of nasal oxytocin administration ranged from 20IU to 40IU. One study investigated two doses: 20IU and 40IU (Stauffer et al., 2019). Doses, daily frequency and duration of treatment varied substantially across the 3 repeated oxytocin administration studies, with daily doses ranging from 40IU – 96 IU.

3.3.4 Adverse effects

Most studies (11 out of 17) did not mention adverse effects, one study mentioned that there were no adverse effects reported (Stauffer et al., 2016), while three studies reported no significant differences in reported adverse effects between the oxytocin and placebo groups (Agabio et al., 2016; Mitchell et al., 2016; Stauffer et al., 2019). One study reported one case of nasal irritation and one case of headache in the placebo group, and one case of irritability and unpleasant taste in the mouth in the oxytocin group (McRae-Clark et al., 2013), while another study reported that 7 out of the 11 cases of reported adverse effects were in the oxytocin group, with mild/moderate headache and light-headedness being the most common effects (McClure et al., 2019).

3.3.5 Summary of results

Table 3.2 summarises the main effects of nasal oxytocin, compared to placebo, by addictive behaviour, regime of administration, outcome (statistical significance) and effect size (practical significance).

Table 3.2 Summary effects of nasal oxytocin, compared to placebo, on outcome measures of craving and consumption

Addictive behaviour	Behavioural craving ratings*			Consumption	
	N	Outcomes*****	Effect Sizes*****	Outcomes	Effect Sizes*****
Alcohol					
<i>Single dose</i>	3 (4)**	X / (↓↑)*** / X	4xNR		
<i>Repeated dose</i>	1	↓/ X/ X / X	2xL 1xM 1xS		
Cannabis					
<i>Single dose</i>	2	↓ / X	1xL 1xNR	X	1xNR
<i>Repeated dose</i>	1			X	1xM
Cocaine					
<i>Single dose</i>	1	↑ / ↑/ X	3xNR		
<i>Repeated dose (cocaine/opioids)</i>	1	X, X	2xS 2xM	X, X	2xS
Nicotine					
<i>Single dose</i>	4	↓ / ↓ / ↓ / X / X / X / X / X	1xL 7xNR	↓ / X	1xM 1xNR
<i>Repeated dose</i>	0				
Opioids					
<i>Single dose</i>	2	↓ / ↓ / X	2xL 1xNR		
<i>Repeated dose</i>	0				

Food					
<i>Single dose</i>	0				
<i>Repeated dose</i>	1	X	1xS	X	1xL
Total	16 (17)*				

Notes: X = no effect; ↓ = decrease; ↑ = increase; L = large; M = medium; N = number; NR = No effect size reported and not enough data reported to manually calculate any effect size; S = small

* Includes ratings in response to cue-induced, acute stress induced or withdrawal related craving. ** One study does not report directly behavioural craving ratings, but the association between behavioural craving ratings during an fMRI cue-induction craving paradigm and connectivity between the blood oxygen level dependent (BOLD) response in specific brain regions. *** No main effect; effect depended on attachment anxiety (increased rating if low attachment anxiety, decreased rating if high attachment anxiety). **** only Cohens *d*, partial ETA squared, effect-size *r* and standardised effect size interpretation included, regression coefficients excluded as they are unable to be grouped in to small, medium or large effect size. All individual values including regression coefficients can be found in Table 3.1. ***** Outcomes exceed number of studies where multiple outcomes of interest at differing time points were measured in the same study

Single dose oxytocin administration studies (craving)

Overall, for studies that included measures of craving, we observed an equal number of significant decreases and negative results for craving ratings related to cannabis, nicotine, or opioids. Regarding craving ratings for alcohol, none of the three studies reported a main effect of treatment, but one study reported that nasal oxytocin, compared to placebo, decreased cue-induced craving ratings for alcohol in those participants with high attachment anxiety, while it increased craving ratings in those participants with low attachment anxiety. An oxytocin induced (compared to placebo) increase in withdrawal-related craving for cocaine, and cue-induced ratings of excitement (but not urge to use, irritation or heart pounding) was also reported.

Repeated oxytocin administration studies (craving)

For addictive behaviours related to food or cocaine/opioids, neither of the two studies investigating the effect of repeated nasal oxytocin administration, compared to placebo, reported significant treatment effects regarding cue-induced craving. A single study reported though a significant decrease in withdrawal-related craving for alcohol following repeated treatment with nasal oxytocin, compared to placebo. No studies examined the effects of the repeated administration of nasal oxytocin on measures of craving for cannabis or nicotine.

Single dose oxytocin administration studies (consumption)

No significant decreases in measures of cue-induced or acute stress induced consumption of cannabis were observed. One study reported no significant effect of oxytocin treatment on acute stress induced nicotine consumption, while another study reported that a single dose of nasal oxytocin, compared to placebo, decreased the substance-induced nicotine consumption.

Repeated oxytocin administration studies (consumption)

Three studies examined the effects of the repeated administration of nasal oxytocin, compared to placebo, on consumption related to cocaine/opioids, cannabis (examining the potential enhancement of the effect of motivational enhancement therapy) and food; none of these studies reported a significant treatment effect. No studies examined the effects of the repeated administration of nasal oxytocin on consumption in relation to alcohol or nicotine.

3.3.6 Risk of bias

Random sequence generation

Sixteen out of the 17 studies were adjudged to be of low risk of bias. One study did not explicitly state whether randomization took place (Van Hedger et al., 2019).

Allocation concealment

Ten out of the 17 studies provided adequate descriptions of allocation concealment and were adjudged to have low risk of bias. Seven out of the 17 studies were unclear regarding the processes used to conceal allocation following randomisation (Bach et al., 2019; Flanagan et al., 2019; Lee et al., 2014; Miller et al., 2016; Reed et al., 2019; Sherman et al., 2017; Van Hedger et al., 2019).

Blinding of outcome assessment

Three studies were adjudged to have low risk of bias for blinding outcome assessors (Stauffer et al., 2019; Van Hedger et al., 2019; Woolley et al., 2016); the remaining fourteen studies were assessed as unclear.

Incomplete outcome data

Ten out of the 17 studies showed completeness of data collection. Three were listed as unclear risk of bias due to missing information on reported drop-outs (Moeini et al., 2019; Reed et al., 2019; Van Hedger et al., 2018); three were adjudged to be of high risk of attrition bias due to computer error losing data (Stauffer et al., 2016), lack of explanation for participants who were not retained (Bach et al., 2019) and missing outcome data (McClure et al., 2019).

Selective reporting

Fifteen studies reported data for all outcomes and were marked as low risk of bias. Two studies were adjudged to as unclear regarding reporting bias (McClure et al., 2019; Stauffer et al., 2016). McClure et al. (2019) provided complete data for participants who completed the study however 30 participants did not complete the study and no explanation was given for these. Stauffer et al. (2016) only reported cocaine consumption and did not report heroin consumption.

3.4 Discussion

This was the first systematic review aiming to synthesize evidence from 17 human studies investigating the efficacy of single dose or repeated nasal oxytocin administration as a pharmacotherapy to reduce craving in addictive behaviours, or reduce the consumption of either alcohol, cannabis, cocaine, opioids, nicotine, or food. Five out of 15 studies that investigated the effects of nasal oxytocin on self-report measures of craving reported a decrease in cue-induced craving, one study reported a decrease or increase depending on the participants' attachment style, one study reported an increase in craving, while the remaining eight studies found no effect. Regarding measures of consumption, only one out of seven studies involving the administration of nasal oxytocin reported a decrease in consumption, with the remaining six studies reporting no effect. The included studies were characterised by marked heterogeneity in terms of methodology, outcome measures, oxytocin dose and administration regime, sample characteristics, addiction severity, and some studies had notably small sample sizes, suggesting they did not have sufficient power to detect but the largest effect sizes, if an effect existed. Overall, the existing volume of work suggests that nasal oxytocin may affect self-reported craving for alcohol, cannabis, cocaine, nicotine and opioids, but not food (in populations with eating disorders), though no firm conclusions can be drawn at this stage. The findings warrant further investigation of nasal oxytocin as a method to decrease cue-induced, acute stress-induced, or withdrawal-related craving regarding addictive behaviours related to alcohol, cannabis, opioids, cocaine or nicotine.

Notably, the systematic analysis of all studies revealed a safe pharmacological profile for nasal oxytocin in populations with addictive behaviours. Most studies (15 out of 17 studies) either did not report adverse effects, or reported that there were no significant differences in the profile of effects between the oxytocin and placebo conditions. The remaining two studies reported mild effects that were observed in either the placebo (6 cases) or oxytocin (8 cases) groups. In addition, no issues were reported with respect to the tolerability of oxytocin in this population which adds to its attractiveness as a potential anticraving medication.

Future studies seeking to elucidate the potential of nasal oxytocin as a pharmacotherapy to reduce craving, and potentially relapse, need to systematically

investigate a number of factors related to treatment administration, study design and sample characteristics that are likely to impact efficacy. Below, the evidence related to the potential impact of factors in each of these three categories is discussed.

First, studies need to carefully investigate the effects of method of administration (Martins et al., 2020), dose (Spengler et al., 2017), and frequency of repeated administrations (Kou et al., 2020), as all three factors have been associated with differences in behaviour and central target engagement (e.g. the amygdala). Human studies assessing a range of different doses of nasal oxytocin on behavioural and neural outcomes have been scarce (Spengler et al., 2017; Quintana et al., 2018; Wynn et al., 2019; Lieberz et al., 2020) which is a serious limitation for the selection of the optimal dose which would exert maximal efficacy at a particular time point and brain region. With respect to craving, only one study (Stauffer et al., 2019) in this review compared two different doses (20IU and 40IU) of nasal oxytocin on the reduction of cue-induced alcohol craving, reporting no significant effect of either dose of nasal oxytocin versus placebo. The importance of establishing dose-response curves regarding the effects of nasal oxytocin on craving and central target engagement is highlighted by recent evidence that the effects of nasal oxytocin on social cognition in schizophrenia may follow a U-shaped dose response curve (Erdozain and Peñagarikano, 2020). Suboptimal treatment regimes are likely to result in inconsistent findings and missed opportunities to elucidate the role of nasal oxytocin as a pharmacotherapy to reduce craving.

Second, future studies need to systematically consider the timing of inducing craving and obtaining measures of craving post-dosing. Most studies involving the administration of a single dose of nasal oxytocin obtained ratings of craving either on a single or on multiple occasions over post-dosing intervals that ranged from a few minutes up to 360 minutes. The timing with respect to nasal oxytocin administration has been mainly driven by historical precedence (e.g. Born et al., 2002), while recent evidence suggests that nasal oxytocin may dampen activity in the amygdala as early as 15-32 minutes post-dosing (Martins et al., 2020). As suppression of amygdala hyperactivity is suggested to be one of the key mechanism by which oxytocin is thought to suppress cue-induced craving, it is likely that the optimal effect of oxytocin on cue-induced craving is induced at a much earlier time point following oxytocin administration. It is also important to take into account the time course of feelings of

craving post cue-induction. For example, with respect to optimal time of craving measurement following cue induction, studies have reported that the BOLD response in the amygdala following opioid-related cue-inducement peaks as early as 7 minutes and diminishes gradually over a period of 14 minutes (Murphy et al., 2018). Therefore, the assessment of the effect of nasal oxytocin on cue-induced or acute stress-induced cravings must be carefully planned to take into account not only the pharmacodynamics of nasal oxytocin but the time course of cue-induced feelings of craving. Sampling craving at suboptimal intervals is likely to result in inconsistent reports of efficacy across studies.

Currently, there is lack of clarity regarding the mechanisms mediating the effects of exogenous oxytocin on behaviour, and the mechanisms through which exogenous oxytocin may reach the brain, and this is an area of intense research currently. Exogenous oxytocin in systemic circulation is metabolised quickly (~ 1-5 minutes half-life in plasma), while the half-life of oxytocin in the cerebrospinal fluid is about 19 minutes (Mens et al., 1983). When administered nasally, oxytocin reaches systemic circulation (e.g. see Martins et al., 2020 for the pharmacokinetics of 40IU of nasal oxytocin in blood plasma in men over 115 min post-dosing). It is thought that oxytocin, as a large hydrophilic neuropeptide, does not cross the blood brain barrier in sufficient amounts (Ermisch et al., 1985), though recent evidence has identified mechanisms of active transport from the blood to the brain (Yamamoto et al., 2019). Nonetheless, there is also evidence to suggest that nasal oxytocin can directly reach the brain bypassing the blood brain barrier through nose-to-brain transportation (e.g. Martins et al., 2020). Once in the brain, the time course of the effects of oxytocin vary as a function of method of administration and point of entry, dosage, and target region (Martins et al., 2020). With respect to oxytocin's modulatory effect on the amygdala, recent studies have shown that nasally administered oxytocin (40IU) can decrease resting blood perfusion in the amygdala from 15 – 32 minutes post-dosing, whereas effects on other brain regions can be observed several minutes later (e.g. 87-95 minutes post-dosing for the anterior cingulate cortex) (Martins et al., 2020). Other studies investigating the BOLD response to emotional faces in the amygdala have shown dose dependent effects peaking 45-70 minutes post-dosing (Spengler et al., 2017). Taking these studies under consideration, the inconsistency among reports focusing on the efficacy of nasal oxytocin on craving is not surprising, and it is clear the further

research is required to elucidate the mechanisms and time-course of the effects of nasal oxytocin for a range of behaviours and targeted brain regions.

Third, future studies need to also carefully consider sample characteristics as potential moderating factors. For example, while there were more male participants than female participants in the studies included in this review, gender was not examined as a moderating factor (possibly due to the small sample sizes). It is well-known that the effects of nasal oxytocin on key brain structures (e.g. the amygdala), and its effects on anxiety, vary between men and women (Lieberz et al., 2020; Lynn et al. 2014; Xu et al., 2017; Spengler et al., 2017; Steinman et al., 2016). Interestingly, given the impact of drugs or addictive behaviours on reward saliency (Volkow et al., 2010), sexual dimorphic effects of nasal oxytocin have also been discussed in relation to amygdala function and salience processing (Gao et al., 2016). Additionally, one study showed that the effects of nasal oxytocin, compared to placebo, on cue-induced craving for alcohol depended on the participants' attachment style, specifically attachment anxiety (Mitchell et al., 2016). Attachment style is a risk factor for alcoholism and alcohol may provide a coping mechanism for insecurely attached individuals (Buckner et al., 2008; McNally et al., 2013), while it is known that nasal oxytocin has both anxiolytic properties (Neumann and Slattery, 2016; Yoon and Kim, 2020), plays a key role in separation related anxiety disorder (Schiele et al., 2020) and its effects can be moderated by attachment style (Bartz et al., 2011). Clearly, the role of relevant sample characteristics needs to be carefully considered in future, adequately powered studies.

Interestingly, the study investigating the effects of the repeated daily administration of nasal oxytocin on baseline craving for food or number of binge-eating episodes over a period of 8 weeks in a sample with binge-eating disorder (Agabio et al., 2016) did not report significant effects. This is partly consistent with studies with healthy volunteers, where nasal oxytocin, compared to placebo, is reported to be ineffective in modulating baseline, cue- or acute stress-induced craving for food, but contrasts the reported effect of nasal oxytocin in decreasing both energy intake after overnight fasting (Spetter et al., 2018), and reward related eating (Ott et al., 2013). The anorexigenic effects of oxytocin in humans are consistent with evidence from animal studies (Leslie et al., 2018). It is worth noting the study by Agabio et al. (2016) had a very small sample size (N=8-9 per treatment arm), which raises concerns regarding power. Additionally, it used a repeated administration regime, with a divided dose of

96IU delivered daily over 8 weeks whereas measuring time to binge-eating episode from nasal oxytocin self-administration may have been more appropriate because of susceptibility to environmental cues triggering binge-eating episodes, just as environmental cues can induce craving in substance use disorders (Iqbal and Rehman, 2020). The optimal pattern and dosage of oxytocin administration in repeated administration regimes are currently unclear, with certain administration regimes resulting in no effects or even opposite effects than those expected (Kou et al., 2020). This is not surprising, given that the effects of oxytocin on central intracellular signalling pathways are complex and can vary as a function of the amount of oxytocin that is available extracellularly (Chini et al., 2017). Future studies need to clarify the mechanisms mediating the anorexigenic effects of oxytocin in humans (Maejima et al., 2018), including its potential role, if any, in regulating food craving and feeding in eating disorders.

A number of recent papers have reviewed preclinical evidence regarding the role of oxytocin in addiction, including craving and drug consumption. Preclinical studies have certain distinct advantages compared to human studies, such as the direct central administration of oxytocin (Lee and Weerts, 2016; Bowen and Neumann, 2017), or simpler cue-conditioning in a controlled environment which is not confounded by individual differences in cue association reactivity with multiple different outcomes and expectancies (Bartz et al., 2011). In vivo studies also offer the opportunity to refine the molecular mechanisms underlining the effect of oxytocin on addictive behaviour which is something not always possible in human studies. As such, Bowen and Neumann (2017) reviewed the effects of oxytocin on the neural substrates of addiction, Zanos et al (2018) reviewed the effects of oxytocin on opioid addiction, King et al (2020) reviewed the role of oxytocin in alcohol and drug abuse, and Baracz et al (2020) reviewed the effect of early life stress on the central oxytocin system and susceptibility for drug addiction. The evidence from these reviews concurred on the idea that oxytocin may play an important role in the treatment of addiction, and the need for translational studies in humans to investigate the role of nasal oxytocin as a pharmacotherapy to reduce craving, at least in relation to alcohol, cannabis, cocaine, opioid, or food addiction.

3.4.1 Limitations

Apart from the factors discussed above, a number of further limitations should be acknowledged. First, there were considerable individual differences across participants and studies. For example, participants within studies differed considerably in terms of severity of drug or alcohol dependence. Future studies need to consider the possibility that the effects on craving may vary as a function of addiction severity. Second, the use of more than one drug concurrently is common among substance users, who use differing drugs to differing levels ranging from habitual to dependent use (European Monitoring Centre for Drugs and Drug Addiction, 2020). Therefore, it is not clear to what extent other drugs had or were currently being used by participants, to what degree and the impact of these on craving and consumption. Future studies should routinely perform urine drug screening to confirm self-report of abstinence from other drugs. Third, participants receiving substitute opiates were not adequately described. High dose methadone for instance is well known to suppress withdrawal-related craving (Clinical Guidelines on Drug Misuse and Dependence Update, 2017) and as such could mediate any reduction in withdrawal-related craving caused by nasal oxytocin administration. Fourth, the effect of nasal oxytocin versus placebo on cue-induced or withdrawal-related craving in alcohol or opioid dependent populations cannot be assumed to be the same as the effect on craving of daily nicotine or cannabis smokers due to the differing levels in reinforcement of each substance. Interestingly, one of the confounding factors which appears to limit the efficacy of nasal oxytocin in reducing craving is their motivation status with regards to seeking treatment for their substance use. McClure et al. (2019) and Lee et al (2014) recruited participants specifically who were non-treatment seeking for their substance use and none of these studies found nasal oxytocin was able to reduce craving or consumption. Not all studies stated the treatment seeking status of participants which prohibited further analysis but we propose that this is included in subsequent studies as it may influence the results. Failure to take into account variability in participant characteristics increases the likelihood of inconsistent or null results and limits our ability to draw any firm conclusions. Fifth, differing measures of craving were used across the studies reviewed here, adding to variability. Sixth, whilst consumption was measured together with craving in many studies, some studies were restricted to only craving. As consumption may occur independently of craving (Van Hedger et al., 2019), the

potential effect of nasal oxytocin to reduce substance use independent of changes in craving may have been missed. Finally, maybe the biggest limitation of the studies discussed in this review is the limited sample sizes. This is indeed acknowledged to be a limitation of nasal oxytocin studies in the field as a whole as recent evaluation of nasal oxytocin meta-analyses has found that designs are typically statistically underpowered to either detect or reject a wide range of effect sizes (Quintana, 2020). Larger, appropriately powered double blind, placebo-controlled human interventional studies assessing nasal oxytocin efficacy to reduce craving and consumption across all automated addictive behaviours are warranted.

3.5 Conclusions

Craving is an established predictor of automated addictive behaviours but current pharmacotherapies with anticraving properties have limited efficacy or are unsuitable to use due to poor compliance and aspects of their pharmacological profile such as side effects and risk of overdose when used for cue-induced craving. Overall, our findings, consistent with preclinical evidence, indicate that the investigation of nasal oxytocin as a method to decrease cue-induced, acute stress-induced or withdrawal-related craving regarding addictive behaviours related to alcohol, cannabis, opioids, cocaine, or nicotine warrants further attention. Combined with an excellent tolerability and safety profile, the distinct effect of nasal oxytocin on amygdala activity is unique amongst existing anticraving pharmacotherapies. This effect compliments its attractiveness as a potential ad-hoc medication to be administered following exposure to drug-related cues, as an asthmatic would use an asthma inhaler during an attack, to ultimately prevent relapse. Future studies should systematically investigate the role of a range of factors that might affect efficacy (e.g. treatment regimes and sample characteristics), and elucidate the neurobiological mechanisms underlying the effects of nasal oxytocin on cue-induced and withdrawal-related craving in adequately powered randomised controlled trials.

Chapter four continues exploring the role of oxytocin in opioid use disorder (Figure 3.5) by outlining the methods used in a novel proof-of-concept study which aimed to address some of the limitations found in this review. Notably by replicating how craving is induced in the real world through exposure to a cue and recording both subjective (self-report craving) and objective (attentional bias) measures across the

expected duration of a cue-induced opioid craving underpinned by neuroimaging evidence.

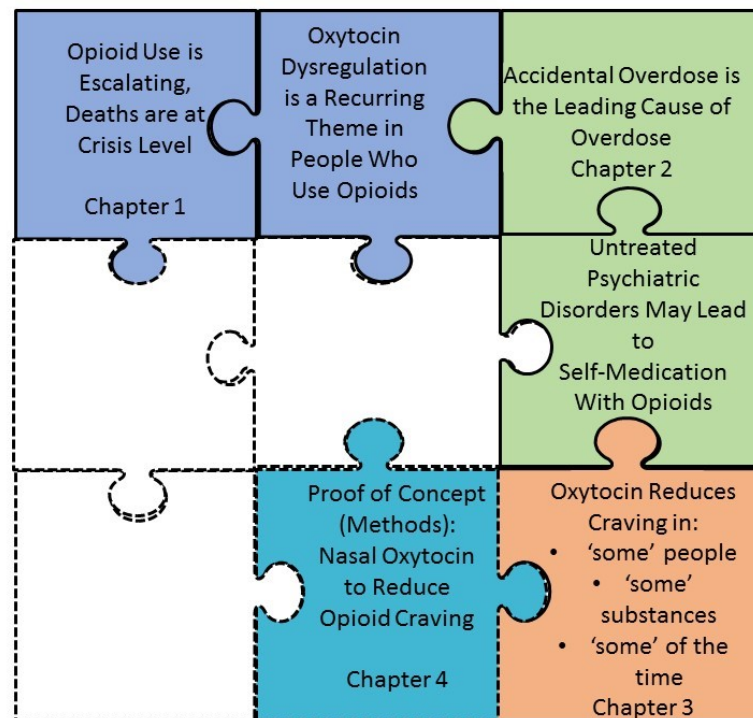


Figure 3.5: Key thesis findings by chapter up to chapter four

Notes: Chapter one outlined the extent of the opioid crisis with opioid-related deaths at crisis level. Chronic drug use dysregulates the endogenous oxytocin system and is highlighted in people who experience early life trauma and people with psychiatric disorders, both of which are highly prevalent in people who use opioids. Chapter two analysed the prevalence of psychiatric disorders in deaths where opioids were found at post-mortem and suggested that self-medication in the absence of psychological treatments may contribute to accidental overdose. Chapter three systematically reviewed human studies for nasal oxytocin to reduce craving or consumption in substance use disorders finding that nasal oxytocin works in some of the people, some of the time but variation throughout studies prohibits conclusive results. Chapter four presents the methods used in the proof-of-concept study to explore the mechanism of nasal oxytocin to reduce craving.

Chapter Four

Investigating The Mechanism Mediating The Effects Of Oxytocin On Opioid Craving: The Proof Of Concept (Study Methods)

‘While you are experimenting, do not remain content with the surface of things.’
– Ivan Pavlov, Russian Physiologist

Abstract

Chapter four outlines the methods used in a study which aimed to examine the effect of intranasal oxytocin on cue-induced opiate craving and attentional bias in males currently using heroin in addition to substitute opiates from four UK community drug treatment services. Recruitment took place during and post COVID-19 periods of social distancing. Caseworkers obtained consent to contact from service users before an initial telephone screen. Interested people were then scheduled for in-person screens typically within seven days of the initial telephone call. Subsequent visits took place within 30 days of the previous visit. Participants were required to attend four, one hour long clinic appointments. On three of these visits, opiate craving was induced by exposure to a video of a man preparing and injecting heroin. Participants were given oxytocin/placebo on two separate visits before the opioid craving scale (McHugh et al., 2014), and the addiction STROOP (Cox et al., 2006) outcome measures were taken over a 30 minute period post-exposure to the video. No spray was given at the first visit as this was a training visit to complete registration, obtain consent and walk-through study procedures. On the final visit participants were invited to an optional interview to explore their experiences of the study, craving management and to complete the Ravens brief cognitive task (Ravens, 2000) required to characterise the study. Participants received £20 in vouchers per clinic visit attended, totalling £80 and travel costs were reimbursed. The results are reported and discussed in chapters five and six respectively.

4. Introduction

Despite heterogeneity in existing research there is consensus over the anticraving properties of oxytocin but the mechanism underlining nasal oxytocin's influence on craving is poorly understood. This chapter sets out the rationale for the methods used to test the mechanism first proposed by this thesis in chapter three (Figure 3.3). I proposed that when in the presence of an opioid-related cue, hyperactivity of the amygdala inhibits the ability to reappraise cues leading to increased attentional bias towards the cue and automated behaviour i.e. relapse. Sections 4.1 to 4.8 inclusive describe the final study protocol as approved by the Brent NHS Research Ethics Service (20/LO/0758). Section 4.9 discusses all ethics amendments and deviations made to the original protocol. The results, discussion, limitations and conclusions of the study are presented and discussed in chapters five (quantitative results) and six (qualitative results). Methods, quantitative/qualitative results and discussion are not presented together in order to aid the reader rather than incorporate one large chapter.

4.1 Aim, Objectives and Hypotheses

Section 4.1 outlines the aims, objectives and hypotheses that underpin the study results reported and discussed in chapters five and six.

The main aim of this study was to investigate attentional bias as a potential mechanism underlining cue-induced craving and how this is influenced by nasal oxytocin in opioid dependent individuals in receipt of substitute opiates in UK community drug treatment. The rationale for this aim was that attentional bias is well documented in people who are dependent on opioids (Franken et al., 2000; Waters et al., 2012; Zhang et al., 2018; Zamani et al., 2014), can predict relapse to opioid use (Field et al., 2009; Garland et al., 2014) and occurs both rapidly and involuntarily if the reward/relief that the attentional bias is related to (in this case opioid use) has not recently been satiated (Pool et al., 2016). Craving can also predict relapse with meta-analyses finding higher self-report craving scores closest to time of use (Serre et al., 2015). If craving occurs when opioids have not been used recently then the rapid, involuntary increase in attentional bias may make it more difficult to not use opioids. The amygdala become hyperactive when craving is induced by exposure to drug-related cues (Volkow et al., 2003) and so immediate calming of the amygdala may delay the mechanism where attentional bias is heightened. Oxytocin dysregulation as a result of childhood trauma,

chronic drug use, psychiatric disorders, genetic polymorphisms or social inequalities may stop the brain from regulating amygdala hyperactivity leading to feelings of automated behaviour in response to attentional bias towards opioid-related cues. Similar to how a car without brake fluid will not be able to stop no matter how much the driver pushes the brake pedal and is aware of the dangers. Without access to imaging techniques the study is unable to provide evidence for the proposed reduction in amygdala activity following nasal oxytocin as part of this mechanism (Figure 3.3), nevertheless reduction in amygdala activity is one of the most robust findings of nasal oxytocin research (Martins et al., 2020) and so this study sought to provide insight to the correlation between attentional bias and craving.

4.1.1 Objectives

The study has four objectives:

- 1) To investigate the effect of nasal oxytocin administration compared to placebo on opioid related cue-induced subjective feeling of craving at 7, 15 and 30 minutes post exposure
- 2) To investigate the effect of nasal oxytocin administration compared to placebo on opioid related cue-induced attention bias at 7 and 30 minute post exposure
- 3) To assess whether under placebo, the change in opioid craving compared to baseline at 7, 15 and 30 min is associated with the change in attention bias following opioid related cue induction, compared to baseline, at 7 minutes post exposure
- 4) To assess whether the effect of nasal oxytocin administration compared to placebo on opioid related cue induced attention bias at min 7 predicts its effect on the subjective feeling of opioid craving compared to placebo at 15 and 30 minutes post-exposure

The study had a single exploratory objective:

- 1) Explore the experiences and perspectives of opioid users when managing opioid craving

4.1.2 Hypotheses

The null hypothesis was that there is no difference in attentional bias or cue-induced craving following exposure to a craving inducing video between nasal oxytocin and placebo administration and that the effect of oxytocin is not mediated by its effect on attentional bias. The alternative hypothesis was that there was a difference between the two groups:

Specifically we have the following hypotheses;

- 1) Nasal oxytocin administration compared to placebo decreases opioid related cue-induced subjective feeling of craving
- 2) Nasal oxytocin administration compared to placebo decreases opioid related cue-induced attentional bias
- 3) In the placebo condition, opioid-cue-induced changes in attentional bias at min 7 is associated with changes in subjective feelings of opioid craving at 7, 15 and 30 minutes post-exposure, relative to baseline
- 4) The effect of nasal oxytocin administration compared to placebo on cue induced subjective feeling of opioid craving at minutes 15 and 30 post exposure is predicted by its effect on attentional bias at minute 7.

The hypothesis proposed that the mechanism mediating the potential anti-craving effect of nasal oxytocin administration on cue-induced opioid craving involved an increased inhibitory control of attentional bias. The wider clinical benefits may then be to limit opioid use and prevent relapse. Clinical benefits were not testable in this proof of concept study but the data generated may support future funding applications for a larger study where clinical significance can be explored.

There was no hypothesis for the qualitative arm as this aspect of the study was hypothesis-generating (Sullivan et al., 2011).

4.2 Research Design

Section 4.2 explains the research design, randomisation procedures and the influence of patient and public involvement on the eventual design.

The study was a double-blind, placebo-controlled, randomized, and counterbalanced crossover design using a within-subjects design in opioid dependent males in receipt of substitution opioid therapy. The design was chosen because as participants act as their own controls, less participants are required to achieve statistical significance during data analysis if an effect is indeed present. The main disadvantage of this design was time burden on participants regarding clinic visits and the more complex statistical analysis required to account for carry-over effects (when the same participants are exposed to all experimental treatments and results are compared across different treatments), sequence effects (potential interactions among conditions of the experiment based on the sequences the treatments are presented) and period effects (changes that occur during the duration of the experimental stages). This was mitigated by ensuring clinic visit length was kept as close to a usual treatment visit where people receive structured psychosocial interventions as possible (approximately 45 minutes) and at the usual frequency (typically every two weeks and no longer than one month between visits).

Eligible male participants were invited to 4 visits. On visit 1 participants were completed baseline measures of the 11 point (0-10) Likert opioid craving scale (OCS) and attentional bias before exposure to a craving inducing video. The OCS was then administered at 7, 15 and 30 minutes post exposure and the attentional bias task was completed again at 8 and 31 minutes post exposure. Participants were trained in how clinic visits 2-4 would proceed, and provided baseline psychometric and sociodemographic measures. On visit 2 and 3, 7-30 days apart, participants completed baseline measures of the OCS and attentional bias. Participants then self-administered a single acute dose of nasal oxytocin (40IU, Syntocinon, Novartis) or matched placebo prior to exposure to a craving inducing video. Each participant then completed the OCS at 7, 15 and 30 minutes post exposure and the attentional bias task at 8 and 31 minutes post exposure. Clinic visit 4 was a safety follow up with an optional digitally recorded qualitative interview.

Each visit aimed to take place within 7-14 days of the preceding visit but to remain flexible and reduce participant burden, participants were able to attend up to 30 days from the previous visit before being excluded from the study. Participants were able to reenrol under the inclusion criteria.

Following the training visit (visit 1), participants received their first acute treatment (oxytocin or placebo on visit 2). After a 7-30 day washout period participants received the second treatment (e.g. on visit 3 they received placebo if they received oxytocin on the second visit or oxytocin if they received placebo on visit 2). Treatment order was counterbalanced across participants. Counterbalance was chosen to reduce the risk of confounders (fatigue, practice of the repeat measures, other effects outside the experiment) influencing the study results.

4.2.1 Randomisation

Randomisation is important to reduce selection bias and balance any known and unknown confounding variables which may impact the results. In this study where participants acted as their own controls but also received repeated measures, randomisation was also important to reduce any carry-over of learned effects from each clinic visit.

Participants were electronically randomised blind following visit 1 using www.sealedenvelope.com to one of two orders: AB or BA. The sprays were labelled A or B with the blinding list held by the principal investigators as they have no contact with any of the participants. As per standard counter-balancing procedures each group had an equal number of people, i.e. equal number of people have received the same treatment order. Active and placebo sprays were not identifiable by the research team (they will be contained in identical bottles without any distinctive marks), ensuring that both researchers and participants are blind regarding the treatment order in order to remove the potential for selection bias.

4.2.2 Patient and public involvement

Patient and public involvement in research means research that is conducted in collaboration ‘with’ people and not ‘on’ or ‘to’ them. Patient and public involvement at the design stage of research ensures the design is acceptable and relevant, improving recruitment and retention of participants. In this study, the patient and public

consultation was critical in helping evidence the need for research on craving reduction and acceptability within a vulnerable population to having craving induced. Involving relevant people (target populations, their families and support workers for example) means research is more likely to respect the rights, safety, dignity and wellbeing of participants which can then address any issues which may be identified by research ethics committees (discussed later in sections 4.7.3, 4.9).

The UK Standards for Public Involvement in Research provide a framework for researchers to adhere to in order to ensure that patients of services and members of the public are involved in the process of research (National Institute for Health Research, 2019). The six standards and how this study adhered to them are;

- **Inclusive opportunities;** Offer public involvement opportunities that are accessible and that reach people and groups according to research needs. Research to be informed by a diversity of public experience and insight, so that it leads to treatments and services which reflect these needs.

Informal discussions were held at a community drug treatment service in Reading, the original identified study location where I was previously employed, individually with 37 service users and community drug worker professionals in December 2017 prior to the official start of this PhD.

- **Working together;** Work together in a way that values all contributions, and that builds and sustains mutually respectful and productive relationships. Public involvement in research is better when people work together towards a common purpose, and different perspectives are respected.

Service users suggested being reimbursed for travel and this was included in the final design as well as voucher payment to reflect contributions of service users. No service users involved in the patient and public involvement exercise had concerns about inducing cravings with one white, female current heroin user concluding ‘if you’re using anyway it’s not like you’re destabilizing anyone’. During discussions all service users were asked if they would be interested in taking part in the study if funding was found and all said they would. Inclusion of a taught breathing, mindfulness exercise called ‘urge surfing’ (Bowen and Marlatt, 2009) to manage cravings was suggested by service users of a drug treatment provider however this was not included as part of

testing (visits 2 and 3) due to introducing a potential confounding variable. Instead, this was adapted and extended to form the topic guide (Appendix 2) for the qualitative interviews at clinic visit 4 due to suitability in design and reflecting service user input in design of the research.

- **Support and Learning;** We offer and promote support and learning that builds confidence and skills for public involvement in research. We seek to remove practical and social barriers that stop members of the public and research professionals from making the most of public involvement in research.

Service users from each study site and the patient and public involvement discussions were offered the opportunity to participate in the research as experts by experience. Roles were discussed and reassurance given that scientific training was not necessary though appropriate training would be given depending on the level of involvement for each service user.

- **Governance;** Involve the public in research management, regulation, leadership and decision making.

Public involvement in research governance can help research be more transparent and gain public trust.

One service user expressed interest in taking part in trial meetings as a designated expert-by-experience in November 2019. Their role was intended to be to attend study meetings and aid with public dissemination via social media, a dedicated website and service user forums. Time and travel would be reimbursed in line with INVOLVE recommend rates. Sadly this service user died during the coronavirus pandemic in 2020 prior to the start of recruitment and the role was not filled by another.

- **Communications;** Use plain language for well-timed and relevant communications, as part of involvement plans and activities. Communicate with a wider audience about public involvement and research, using a broad range of approaches that are accessible and appealing.

As well as the aforementioned service user interested in helping with governance of the study, another service user created a poster for use in each recruitment site (Appendix 3).

- **Impact;** Seek improvement by identifying and sharing the difference that public involvement makes to research. Understand the changes, benefits and learning gained from the insights and experiences of patients, carers and the public.

Dissemination events are planned across multiple localities where the study has taken place inviting members of the public, service users and professionals. These events will give service user representatives the opportunity of facilitating small group discussion as well as giving a small presentation to explain service user roles in this research. This is to introduce substance use research naive localities to the process and benefits of research as well as to act as patient and public involvement forums for the follow on fully powered randomized controlled trial which will build on the data generated by this study.

4.3 Participants

Section 4.3 will walk-through the study setting, the inclusion/exclusion criteria, the processes for participant recruitment and withdrawal and then finally how this data was reported in chapter five.

4.3.1 Setting

Although the original study site identified was in Reading and this was where the patient and public consultation took place, recommissioning of the proposed drug service prohibited further study involvement initially. Participants were initially recruited from one specialist drug community service in Chertsey offering opiate substitution therapy called i-Access NW which is located at the Abraham Cowley Unit in Chertsey and was operated by the study sponsor. The study sponsor was Surrey and Borders NHS Foundation Trust as the Chief Investigator was employed by them, providing clinical intervention as consultant addiction psychiatrist. The sponsor operated three drug treatment throughout Surrey and provided access to all of them. All three services provide satellite clinics located throughout Surrey at Elmbridge, Epsom and Ewell, Guildford, Mole Valley, Reigate and Banstead, Runnymede, Spelthorne, Surrey Heath, Tandridge, Waverley, Woking.

The site was selected due to service user demographic suitability for the study and existing relationships between the study team and the service providers. The existing

relationships meant that liaison with the research and development governance team was equally smooth. The sites agreed to support recruitment for the study and provided the anonymised data upon verbal request from clinical case notes to make the calculations for recruitment rate.

Further study sites were selected in November 2021. Study recruitment began in December 2020 and initially ended at the end of September 2021 when the oxytocin expired. At this stage ten participants had been recruited with one dropping out. Recruitment had been significantly impeded by the covid-19 pandemic which meant the specialist community drug service had far less contact with the target population and so opportunities to discuss the study were reduced. Following discussion the study team agreed to extend the recruitment period in order to reach the targeted sample size and strengthen statistical analysis. One specialist community drug service, Cranstoun, approached me with a view to supporting study recruitment however following review they were unable to provide help with recruitment due to other ongoing studies. The largest provider of specialist drug services in the UK, Change Grow Live, were then approached. The proposal was reviewed by their research department in November 2021 and three new sites were agreed, located in Luton, Newham and Reading. These sites were chosen as I have a long working relationship with the lead prescribing nurse in Luton, I was aware of the Newham service from my employment with a lived experience recovery organisation who provide weekend services at Newham and the Reading site was where the original patient and public involvement exercise took place and were now able to commit to involvement in the study.

All intervention took place at the Chertsey, Frimley, Luton, Newham or Reading community drug services with no lab component. The testing of participants for craving took place in a designated room to ensure privacy and minimize distractions.

4.3.2 Main criteria for inclusion/exclusion

The inclusion and exclusion criteria for the study were;

Inclusion criteria

- Primary diagnosis of opioid dependence as defined by current receipt of opiate substitution therapy (methadone or buprenorphine based products e.g. generic buprenorphine, Espranor, Subutex, Suboxone) for a minimum continuous period of 1 month
- Current use of heroin as defined by morphine or opiate positive drug screen at clinic visit 1 only
- Males aged 18-70 years
- Participants must be willing and able to give informed consent
- Participants must have understanding of English

Exclusion criteria

- Severe psychosis, Bipolar Affective Disorder I, severe depression (as defined by score >20 on PHQ-9 at clinic visit 1), suicidal ideation and intention, brain trauma or other severe neurological disorders as defined by GP medical summary provided as part of screening
- History of violence towards professionals in the previous 6 months
- History of severe kidney disease
- History of cardiovascular disease (heart disease, heart attacks, heart surgery)
- Nasal bleeding
- Attendance under the observable influence of substances at each clinic visit based on the clinicians assessment
- Attendance with observable or reported high temperature and/or continuous cough
- Use of heroin in the last 4 hours
- Any dose change of opiate substitution therapy between clinic visit 1 and 3
- Participants where craving is not induced during screening at clinic visit 1

In the event of a participant meeting the exclusion criteria between clinic visit 1 and clinic visit 3, participants were excluded and replaced.

Female people were excluded due to fluctuations in oxytocin levels during the menstrual cycle, the need for elimination of pregnancy risk and well documented gender differences in response to exogenous oxytocin administration between males and females (Lynn et al., 2014; Xu et al., 2017). FMRI studies have shown a significant sex-dependent difference in the mechanism for oxytocin's action on amygdala which influences salience and attractiveness of social attributes (Gao et al., 2016). The investigation of gender differences on the mechanism underlining the anti-craving effect of oxytocin is beyond the scope of this study and as such only males were included to reduce variability and enable the study to be adequately powered which is deemed to be feasible within the current parameters.

Male people aged 70 and over were excluded due to high risk of COVID-19 in line with NHS guidance. If participants presented with high temperature and/or continuous cough they were asked to self-isolate for 7 days in line with COVID-19 guidance and were given a new appointment within the 7-30 day window for testing. If the self-isolation period exceeded the testing window then participants were excluded and replaced.

4.3.3 Participant recruitment

The study aimed to recruit 34 male participants. The National Drug Treatment Monitoring System estimated 2966 opiate and crack cocaine users throughout Surrey in 2017/18 (Health and Wellbeing Surrey, 2019) meaning our recruitment target was 1% of the estimated available total population. The initial recruitment site, called i-Access, had an active caseload of 440 opioid dependent people.

The original recruitment target rate was 3 per month across a 10 month recruitment period with potential to extend for two further months if required. I was available one day per week due to full time employment commitments but availability was increased in February, March, May and August 2021 through the strategic use of annual leave. If required the participant was also available to attend evening appointments after his employment working day should participants be working and require flexible appointments. Care coordinators were presented with the participant information sheet initially and asked to discuss the study with potential participants who met the inclusion criteria. Care coordinators routinely discuss external opportunities with service users in appointments, representing no change to usual care. If service users

were interested then they were introduced to me and I explained the participant information sheet to them (Appendix 4). Service users were then offered an appointment for clinic visit 1 and clarified they were under no obligation to attend the appointment if they did not wish to take part in the study. If service users did not wish to book an appointment immediately they were given a minimum of 48 hours to think about the study and were then contacted by me. Two telephone calls, 1 text message and a message via the care coordinator was attempted before excluding the participant from further screening. Participants were free to change their mind at any stage and could enter the study at any point during the recruitment period provided they met the inclusion criteria.

Participant Information Sheets (Appendix 4) were also intended to be left in the reception area of the recruiting drug service. This was no deviation from usual practice as information leaflets are routinely distributed through drug service reception areas however covid infection control procedures prohibited this within the Chertsey and Frimley services. Posters (Appendix 3) were placed within the recruiting drug service signposting interested service users to more information about the study. This was no deviation from usual practice.

Two months before recruitment was initially expected to end (August 2021) the Chief Investigator and myself reviewed the electronic client notes of every male receiving substitute opiate treatment in the drug service. The purpose was to identify potential participants and to ensure that every effort was made to contact and recruit every potentially available participant. In line with ethical approvals the Chief Investigator first contacted the remaining eligible clients to receive consent to be contacted for the study before I attempted to make contact. At this stage we had recruited ten participants with one participant dropping out. There were no further participants recruited following this strategy underlining the difficulties of recruiting people who are currently using opioids to pharmacological research (Neale et al., 2018).

In November 2021 following confirmation of three new recruiting sites the recruitment rate was revised in line with study need. A further twenty-one participants were required to complete recruitment and ensure analysis would be fully powered. Due to PhD completion time constraints and my availability around full time employment, it was agreed that a minimum of fifteen more participants would be a

feasible recruitment target from the new sites. The National Drug Treatment Monitoring System estimated that in 2019-2020 there were 1,091 opiate users in Reading, 1,515 opiate users in Luton and 2,263 opiate users in Newham (Public Health England, 2020). Although only 50% are likely to be in treatment and even fewer not only meeting our inclusion criteria but willing to take part in the study, our experience with Surrey recruitment suggested that multiple services across differing localities would likely lead to more successful recruitment. The revised recruitment rate for 2022 equated to between five and seven per site over a maximum twelve month period due to the expiry date of the oxytocin.

The process walk-through for participant recruitment was:

- 1) Care coordinators identified eligible participants from existing service users
- 2) Care coordinators offered the study during routine appointments
- 3) I was introduced to interested service users and to discuss the participant information sheet (Appendix 4)
- 4) Service users were then given the option of signing the rear page of the participant information sheet (Appendix 4) giving consent to be followed up only
- 5) Service users were then given the option of booking clinic visit 1 immediately with no obligation to attend and I telephoned at least 48 hours later to confirm interest and answer any questions the potential participant may have had in deciding whether to participate or not
- 6) If I was unable to contact the potential participant then 2 telephone calls, 1 text message and a message via the care coordinator was attempted before excluding the participant from further screening. Participants were free to change their mind at any stage and could enter the study at any point during the recruitment period provided they met the inclusion criteria.

The study design reflected UK guidelines for improving recruitment to pharmacological studies for illicit opioid use (Neale et al., 2018) and included the following principles found here; reimbursement of travel costs, minimal study outcomes, short clinic visits, short total study duration, avoiding unnecessary toxicology screening, flexible attendance (within the 7-30 day washout period window), individual discussion with participants about the study, information and

provision of ‘rescue opioids’ i.e. Naloxone, a written consent contract, reimbursement of time for participation, coproduction with service users in the design of the study itself (through the patient and public involvement exercise already conducted), the availability of medical professionals at each study site, provision of a participant information sheet (Appendix 4), provision of data confidentiality assurances, demonstrate respect that some opioid users will take part for altruistic reasons rather than financial incentive, expression of thanks at each clinic visit.

4.3.4 Participant withdrawal

Participants were free to withdraw at any time without giving a reason.

In the case of participants who began the study but were unsure of continuing, all were assured that a decision to withdraw at any time, or a decision not to take part in the study, would not affect their current or future standard of care. Written informed consent and verbally affirmed at clinic visit 2, 3 and 4 was obtained prior to starting any procedures.

If participants withdrew from the study all identifiable information about them was destroyed. We retained and continued to use any data collected before such withdrawal of consent unless participants requested either verbally or in writing that they did not want us to use any data collected from them. Participants who dropped out were intended to be replaced until we completed the required sample size. The existing incomplete data from participants who dropped out was analysed.

In the unlikely event that a participant showed side or adverse effects to the nasal spray prior to clinic visit 3, the participant would be withdrawn from the study and a new participant would be recruited. The Chief Investigator or a delegate will have checked and monitored the participant until they were sure that they were safe to leave the premises. After testing, each participant was advised that they will receive a telephone call within 7 days. The Chief Investigator or a delegate telephoned the participant to check that all is well and report any side or adverse effects following the appropriate procedures. If deemed clinically relevant the Chief Investigator, was un-blinded regarding the nature of the compound the participant received in the specific visit (nasal oxytocin or placebo).

4.3.5 Trial population reporting

Section 4.3.5 outlines what is reported in chapter five regarding the trial population.

Screening data

The following summaries are presented for all screened patients: the number of days spent at the recruiting site, the number of people screened for eligibility, the number of participants recruited, the number of screened patients not recruited, and the reason for non-recruitment.

Eligibility

The number of ineligible patients screened were reported with reasons for ineligibility in the Consolidated Standards of Reporting Trials (CONSORT) diagram.

Recruitment

The flow of participants will be displayed in accordance with the CONSORT diagram. The diagram comprises of the number of people screened, eligible (with reasons for ineligibility), consented, randomised, each clinic visit (4 in total) and any participants withdrawing/lost to follow-up.

Withdrawal/ Follow-up

The number and proportion of patients who did not complete all four visits is reported (both withdrawals and drop outs) within the CONSORT diagram with numbers and reasons for withdrawal and/or drop out given at each clinic visit. All data up to and including the last attended visit from the date of randomisation was collected and reported.

Baseline patient demographics

Participants are described by age at informed consent, ethnicity, employment status, relationship status, type and dose of substitute opiate medication and presence of any co-existing psychiatric disorders summarized in a table. Categorical data is summarised by numbers and percentages. Continuous data is summarised by mean, standard deviation and range. There is no inferential analysis of demographics. Tests of statistical significance were not undertaken for baseline characteristics, rather the clinical importance of any imbalance is noted.

4.4 Investigational Medicinal Product

Section 4.4 gives details on the nasal spray of oxytocin including which dose was used, the rationale for that dose, where the oxytocin was obtained and how it was stored.

4.4.1 Dose

40IU Oxytocin or matched placebo was used. Ten insufflations, 5 per nostril. Administration was alternated between nostrils with a thirty second gap between administrations. I timed the self-administration and verbally informed each participant when to administer the next insufflation to ensure consistency. Participants were asked to remain still for thirty seconds at the end of the last insufflation with their head tilted back. 40IU was chosen as it has been shown to influence amygdala activity, central to the proposed mechanism, at 15 minutes post-administration (Martins et al., 2020).

4.4.2 Manufacturing

One spray bottle contained recanted Syntocinon (active ingredient: oxytocin), the other placebo (identical excipients except for oxytocin), manufactured by Guy's & St Thomas' NHS Foundation Trust, Pharmacy Manufacturing Unit and was delivered to each study site for storage and dispensing.

4.4.3 Storage

Both active sprays and placebos were safely stored under controlled conditions in a locked fridge accessible only by on-site clinicians and myself. They were stored between 2-8 degrees celcius as required by the manufacturer. The temperature was constantly monitored and recorded daily by on-site responsible staff.

4.5 Instruments

In order to measure craving the study needed reliable and validated subjective and objectives measures. Subjective measures were vital to understand the experience of the participants following cue-inducement and spray self-administration. Inclusion of an objective measure allowed the study to measure craving-related performance in an attention task irrespective of the subjective craving experience. Section 4.5 explains which primary and exploratory outcome measures were used, when and how they were administered and further detail on the validity of each measure.

4.5.1 Criteria for evaluation

Primary

Opioid Craving Scale (OCS). This is a validated tool to measure immediate subjective heroin craving (McHugh et al., 2014; McHugh et al., 2016) (Appendix 5). The OCS is a brief, 3-item measure used to measure opioid craving on a likert scale from 0 (no desire) – 10 (extremely strong). The questions asked were 1) How much do you currently crave heroin? 2) If you saw this in your everyday life, how much would you crave heroin? 3) How much did the video remind you of times that you have used heroin? The total score is calculated by averaging the score of all three items. Each participant was asked to point to the corresponding rating on the scale per question. During clinic visit 1 the complete OCS was presented post exposure to the cue-inducing video.

At clinic visits 2 and 3 the OCS was presented at 7 minutes, 15 minutes and 30 minutes post exposure to the cue-inducing video. Question 1 was also asked before cue-inducement at every clinic visit to measure the participant's baseline craving status before inducement. (Time duration of OCS self-administration: 1 minute)

Addiction STROOP test (Cox et al., 2006). This is a validated and widely used addiction STROOP test to objectively assess attentional bias towards drug-related cues. It measures a person's reaction times when asked to name the colour of drug-related words and neutral words that appear on a computer screen (Cox et al., 2006). The difference in correct reaction times between the two types of words provides a measure of attentional bias. Although performance on the addiction STROOP correlates with craving, the addiction STROOP does not induce craving (Field et al., 2009). The standard STROOP test and addiction STROOP test were also presented at baseline for training (visit 1), and then the addiction STROOP was used at 8 and 31 min post exposure to the cue-inducing video in visits 2 and 3. Both STROOP tasks were presented on a laptop and consisted of 40 trials. Words and colours within each trial were randomized by the STROOP program. Each word appeared for 500ms with a 2000ms delay between displaying each word where a fixation point was shown. Following discussion within the study team, no STROOP measurement was taken at 15 minutes to ease the burden on participants. The protocol to be used for the STROOP

test was based on well validated published protocols (Cox et al., 2006). See Table 4.1 for words used in the addiction STROOP task. (Time duration of Stroop: 5 minutes)

Neutral words	Heroin-related words
Was	Dope
Window	Brown
Invite	Needle
Lamp	Spoon
Key	Works
Shoe	Dark
House	Gouge
Carpet	Score
Floor	Cooker
Boots	Nod
Bulb	Foil
Read	Filter
Table	Medicine
Card	Snowball
Building	Dragon
Telephone	On

Table 4.1: Words used in the addiction STROOP task (Hamilton et al., 2011)

Notes: The STROOP effect is the delay in correct responses to the words listed in the column ‘Heroin-related words’ versus words listed in the column ‘Neutral words’. The words are shown in red, yellow, green or blue and each participant must press R, Y, G or B in accordance with the colour shown.

It was critical to the intended follow on study that the study was able to investigate the rapid effects of oxytocin on craving and attentional bias because the behaviour of a person becoming triggered, obtaining opioids and using opioids can happen quickly. The study was able to measure craving outcome at 7 mins post cue video exposure in line with existing evidence showing amygdala BOLD response to cue-induced craving and self-report peak timing of craving intensity post cue-exposure (Murphy et al., 2018). Immediately before spray administration, baseline measures of the OCS and Addiction STROOP were taken. Following spray administration there was a 6 minute delay until each participant is exposed to the same video excerpt to induce craving lasting 1 minute 59 seconds. The delay was because the earliest evidenced imaging shows nasal oxytocin effect 15 minutes post administration (Martins et al., 2020). Therefore timing of oxytocin administration, cue-inducement and outcome measures

(see Table 4.2) were aligned with expected peak of craving at a time when oxytocin was expected to affect amygdala (Murphy et al., 2018; Martins et al., 2020).

<i>post spray administration</i>	<i>post cue exposure</i>	<i>Outcome measure</i>
15 minutes	7 minutes	OCS
16 minutes	8 minutes	Addiction STROOP
23 minutes	15 minutes	OCS
38 minutes	30 minutes	OCS
39 minutes	31 minutes	Addiction STROOP

Table 4.2: Timing of outcome measures post spray administration and post cue exposure

Notes: Table showing the time of outcome measures (OCS or Addiction STROOP) in relation to cue exposure and spray administration. No STROOP measurement was taken at 15 minutes post cue exposure to ease the burden on participants. OCS = Opioid Craving Scale.

Exploratory

Qualitative interview. Current studies typically focus on initiation and cessation of drug use rather than understanding the experience of craving, awareness of attentional bias and how this might influence actively seeking and buying drugs. Greater understanding of this could inform the direction of future studies and immediately impact treatment provision. At clinic visit 4 participants were interviewed regarding their experience and perspective on craving self-management and obtaining illicit opioids. An interview schedule was produced which allowed for flexibility during interview (Appendix 2) (Time duration of interview: 30-40 minutes)

4.6 Procedure

Section 4.6 walks through each of the four clinic visits for the participants.

4.6.1 Visits and related activities

There were four site visits in total per participant. Clinic visits 1 and 4 could take place at any time of day. Clinic visits 2 and 3 were attempted between 13:00 – 15:00, each visit as close as possible to the previous visit with a 7-30 day washout period between visits. This was because the anticipated majority age range of participants (age 30-45)

will have lowest levels of natural oxytocin at this time (Forsling et al., 1998). However in order to facilitate participant requirements and reduce risk of drop out, this timing was flexible across the same day as close to the planned time of administration as was possible in line with participant availability to attend the recruiting site. Timings of all clinic visits were recorded.

I contacted all potential participants identified by care coordinators from the active caseload of each recruiting site to discuss the study, gave the participant information sheet and answered any initial questions. If the potential participant was interested then a time and date for visit 1 was arranged.

4.6.2 Screening visit (visit 1)

The process walk-through for clinic visit 1 was:

- 1) Participants were asked to wash their hands (<1 minute)
- 2) Written informed consent was completed (5 minutes)
- 3) Demographics completed (Appendix 5; 15 minutes)
- 4) PHQ9 (Kroenke et al., 2001) and IQ test (Ravens, 2000) completed (5 minutes)
- 5) TimeLine Followback (Appendix 6) conducted, as per standard care (3 minutes)
- 6) Urine drug screen was conducted, as per standard care (7 minutes)
- 7) Naloxone was offered to participants as per standard care (5 minutes)
- 8) The participant was trained in how to self-administer the nasal spray using a spray containing saline solution (5 minutes)
- 9) Baseline without exposure to cue-inducement video OCS was conducted (1 minute)
- 10) Baseline without exposure to cue-inducement video STROOP was conducted (5 minutes)
- 11) The participant was shown the opioid related cue video (duration of video: 1 minute 59 seconds)
- 12) Opioid Craving Scale was taken at 7, 15, 30 minutes following cue exposure. I asked three questions and the participant provided a verbal or non-verbal (i.e. finger pointing on the scale) response. I wrote the response on the OCS sheet. A new sheet was used per time point without verbal or non-verbal reference to previous scores. (1 minute per OCS application, 3 minutes in total)

- 13) STROOP was taken at 8 and 31 minutes following cue exposure (5 minutes per STROOP application, 10 minutes total)
- 14) Participants were invited to wait at the drug treatment centre for 45 minutes or until craving had subsided as a precautionary measure (45 minutes)
- 15) Participants were reimbursed for travel and given the date and time of their next appointment (1 minute)
- 16) I sent the participants GP a letter confirming entry in the trial (Appendix 7)

Total visit time per participant: between 68 minutes 59 seconds and 112 minutes 30 seconds dependent on time taken in step 14.

Detail step by step timeline (visit 1)

Written informed consent was taken and included access to medical and risk assessment to ensure eligibility if this had not been able to be checked previously by care coordinators. I reviewed all medical and risk assessment information to ensure each participant was suitable to enter the study.

Obtaining up to date medical records and keeping current risk assessments is routine practice for care coordinators working with opioid users in drug treatment. Ensuring medical records and risk assessments are available represented no further burden to the participant or was unnecessarily invasive as records were already available in order to initiate prescribing of substitute opiates. In the unlikely event that medical or risk assessment information was unable to be accessed by this time following participant recruitment, the visit was stopped and the participant rebooked for the next available opportunity to proceed. This was to ensure that eligible participants were not excluded unnecessarily due to a delay in obtaining information which ensured they met the inclusion criteria.

Demographics were completed (Appendix 8). Participants were given further opportunity to ask questions about the study and mental capacity was confirmed through verbally demonstrating understanding of the research study. The Patient Health Questionnaire-9 (PHQ9) is a reliable and valid nine point questionnaire measure of depression severity (Kroenke et al., 2001). Recommended for use in community drug treatment as part of routine assessment (Clinical Guidelines on Drug Misuse and Dependence Update, 2017), PHQ9 was used to ensure participants did not

meet exclusion criteria for severe depression as indicated by a score >20 . IQ was assessed using a brief Ravens Progressive Matrices, a validated and reliable test of general intelligence (Ravens, 2000). Ravens was included in order to characterise the sample and the brief version was decided in order to reduce the burden on participants. TimeLine Followback (Fals-Stewart et al., 2000; Appendix 6) was completed at this point with myself writing the information verbally given by each participant. Urine drug screen to confirm current opioid use, as defined by a positive screen for opiates or morphine, and eligibility was collected at this point. TimeLine Followback and urine drug screening are routine practice in drug treatment services representing no further burden on participants. Naloxone is a take away medication used to reverse opioid overdose and is routinely given by the drug service. Naloxone dispensing is considered good practice, precautionary only and represented no change from usual care or indication of an elevated risk (Strang et al., 2019). For familiarity and to provide baseline data without cue inducement, OCS and STROOP was then taken.

Participants were shown how to self-administer the nasal spray in accordance with published recommendations for the standardisation of oxytocin nasal administration (Guastella et al., 2013). Each participant was asked to self-administer saline spray using an individual spray. No sprays were reused on different participants in line with infection control procedures.

Each participant was then shown the cue inducement video in order to confirm eligibility. The presence of drug-related cues is well known to elevate craving for heroin users (McHugh et al., 2016) and in this study craving was induced via to exposure to 1 minute 59 seconds of documentary video footage (minutes 16:09-18:08) of 'Ben: Diary of a Heroin Addict' (Lambert, 2008) depicting the preparation and use of an intravenous groin injection of heroin, shown to induce heroin craving (Zhao et al., 2012). UK NHS ethically approved studies (REC number: 09/H1011/67) have induced opioid craving with video where opioid users self-reported that craving peaks at 7 minutes following video exposure and has dissipated by 15 minutes (Murphy et al., 2018). These timings and craving inducing methods were utilised when measuring this studies primary outcome.

Craving was measured using the OCS at 7, 15 and 30 minutes post-exposure to craving inducing video (Table 4.2). A single point score increase on the OCS (for example a rating from 5 to 6) is associated with 17% higher odds of using opioids in the following week (McHugh et al., 2016). For this reason, to progress to randomisation initially any score exceeding the baseline score for question 1 only on the OCS was taken as positive for having craving induced. This requirement was removed early in the study in order to include people who report to not feel craving but may still experience acute increases in attentional bias following exposure to opioid-related cues, see section 4.9.1.

Attentional bias was measured using the STROOP test at 8 and 31 minutes post-exposure to craving inducing video (Table 4.2). The study team decided not to measure attentional bias at the 16 minute time stamp alongside craving due to minimising the perceived burden on participants.

At least one clinician, either a nurse or a doctor, was on site and available on visit 1, 2 and 3 in case of adverse event. Naloxone was offered and participants invited to wait for 45 minutes or until craving has subsided before they leave the drug treatment service.

Participants were then reimbursed for travel.

4.6.3 Dosing & testing visit (visit 2)

The process walk-through for clinic visit 2 can be seen in Figure 4.1.

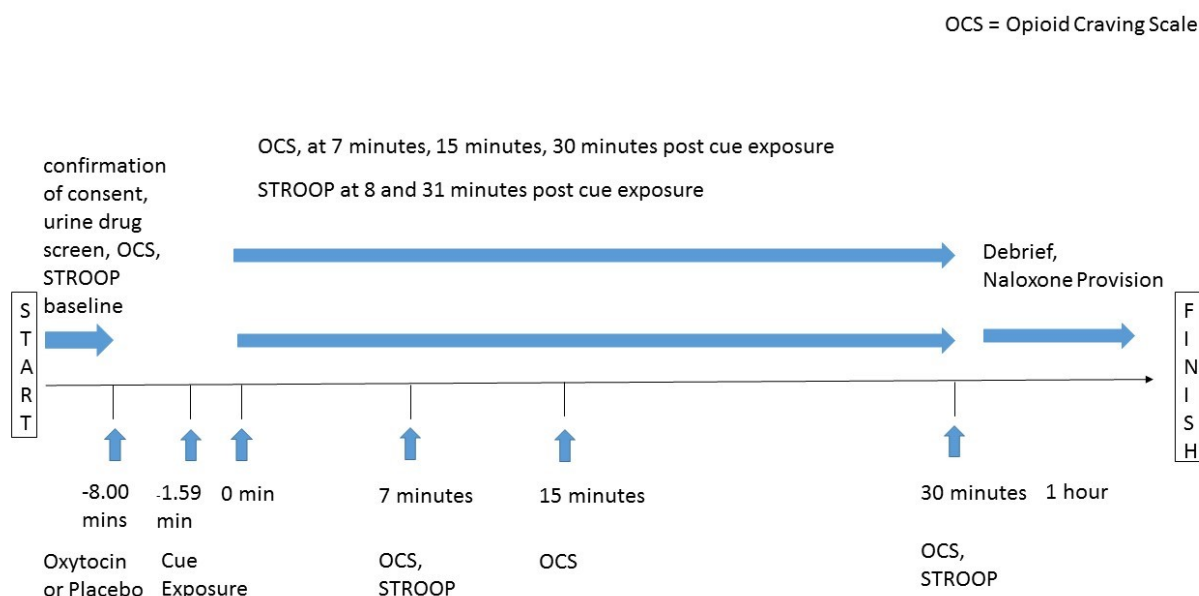


Figure 4.1: Walkthrough of clinic visits 2 and 3

Notes: Each participant begins clinic visit 2 and 3 with confirming verbal consent to continue followed by urine drug screening and baseline measures of the opioid craving scale and addiction STROOP. Nasal oxytocin is then self-administered and 6 minutes later a video exert of a man injecting heroin is shown lasting 1 minute 59 seconds. The end of this video is time zero. At 7, 15 and 30 minutes post exposure the opioid craving scale is administered. At 8 and 31 minutes post exposure the addiction STROOP is completed. The participant is then asked if they would like to stay on site until craving has fully subsided and Naloxone is given if the participant accepts the offer.

- 1) Participants were asked to wash their hands (<1 minute)
- 2) Confirm verbal consent to continue was taken (1 minute)
- 3) TimeLine Followback (Appendix 6) was conducted, as per standard care (3 minutes)
- 4) Urine drug screen was conducted, as per standard care (7 minutes)
- 5) Naloxone was offered to participants (5 minutes)
- 6) OCS was taken as per clinic visit 1 process (1 minute)
- 7) STROOP was taken as baseline measurement (5 minutes)

- 8) Participants were asked to score out of ten how blocked each nostril is (1 minute)
- 9) reminded participants how to use the nasal spray (2 minutes)
- 10) The participant was handed the spray (1 minute)
- 11) The participant self-administered the spray. Ten insufflations total, five per nostril (5 minutes)
- 12) The participant was shown the opioid related cue video six minutes from the last self-administrative insufflation of spray (duration of video: 1 minute 59 seconds)
- 13) OCS was taken at 7, 15, 30 minutes following cue exposure. I asked each question (total 3 questions) and the participant provided a verbal or non-verbal (i.e. finger pointing on the scale) response. I wrote the response on the opiate craving scale sheet. A new sheet was used per time point without verbal or non-verbal reference to previous scores. (1 minute per OCS application, 3 minutes total)
- 14) STROOP was taken at the 8 and 31 minute time points following OCS post cue exposure (5 minutes per STROOP application, 10 minutes total)
- 15) Following completion of the STROOP at 31 minutes during the debrief period, participants were asked to guess if they received oxytocin or placebo (1 minute)
- 16) Participants were invited to wait at the drug treatment centre for 45 minutes or until craving has subsided as a precautionary measure (45 minutes)
- 17) Participants were then reimbursed for travel and given the date and time of their next appointment (1 minute)

Total visit time per participant: between 47 minutes 30 seconds and 92 minutes 30 seconds, dependent on time taken in step 16.

Participants were asked to score out of 10 how blocked each nostril was prior to self-administration of the spray. This information was recorded and taken in to account for statistical analysis as a potential confounder.

This was followed by a 7-30 day washout period.

All case report form data was scanned and electronically stored on a General Data Protection Regulation compliant database. Paper copies of case report forms were kept in a folder, stored in a locked filing cabinet of a securely locked office at each study site.

Participants were then reimbursed for travel.

4.6.4 Dosing & testing visit (visit 3)

The process was as per clinic visit 2 (Figure 4.1) however the participant received the opposite spray (i.e. if they received spray A in visit 2, they received spray B in visit 3; if they received spray B in visit 2, participants received spray A in visit 3). This visit took place within 7-30 days at the same time of day as visit 2 or as close as possible.

Participants were then reimbursed for travel.

Telephone follow up (within 7 days post clinic visit 1, 2 and 3)

Every participant was followed up via telephone within 7 days of each clinic visit. Where the next appointment was 7 days later, an attempt was made 3 working days later which also acted as a reminder for the next appointment. Two attempts were made, if contact was unable to be made following the first attempt then each participant's assigned care coordinator at the recruiting site was contacted and informed. Following discussion each participant may be deemed either;

Green, no further contact by myself was required. This was appropriate if the keyworker has had contact since clinic visit 3 without adverse event reported.

Amber. No contact was made however this is not assessed by the care coordinator of the drug treatment service to be unusual behaviour for the participant. The care coordinator was asked to contact the client pharmacy to ensure participant has been collecting substitute opiates daily as per routine practice in assessing service user safety. If the participant had been seen by the pharmacy daily when collecting their substitute opiates, the second follow up telephone call will be attempted and the participant study involvement ended without adverse event.

Red, unable to contact and the participant had not been collecting from the pharmacy. A home visit would have been arranged, in line with recruiting site treatment as usual.

4.6.5 Safety monitoring and qualitative interview visit (visit 4)

The process walk-through for clinic visit 4 was:

- 1) Participants were asked to wash their hands (<1 minute)
- 2) Confirm verbal consent to continue (2 minutes)
- 3) Each participant was asked to detail any symptoms felt since the last visit as per usual telephone follow up procedure (undefined time length)
- 4) TimeLine Followback (Appendix 6) conducted, as per standard care (3 minutes)
- 5) Urine drug screen will be conducted, as per standard care (7 minutes)
- 6) PHQ9 was completed (2 minutes)
- 7) Ravens Progressive Matrices, a standardised IQ test was completed (10 minutes)
- 8) Qualitative interview was completed (up to 45 minutes, see appendix 8)

Participants were then reimbursed for travel and given up to £80 worth of vouchers (£20 per attended visit, see section 4.9.1).

Total visit time per participant: up to 69 minutes, dependent on step 3 and 7. In practice these timings were overestimations with clinic visit 4 lasting approximately 60 minutes.

Due to no administration of study drug, this visit could take place at any time of the day. Every effort was made to ensure this was within 7-30 days of clinic visit 3 however this was dependent on participant availability and may have occurred outside this window up until study end.

Every participant was asked to attend for face to face safety follow ups. Participants were offered the chance to have a medical review with the study site doctor booked as per routine practice every 12 weeks within community drug treatment. Each participant completed Timeline Followback, urine drug screening and PHQ9 (Kroenke et al., 2001) before proceeding to the qualitative interview.

Background rationale for the interview is discussed in depth in the introduction to chapter six. Interviews were conducted with myself (BH, white male) who had no relationship with the participants other than interaction at the previous three clinic visits and telephone safety follow ups. All interviews took place at clinic visit 4

between January 2021 and 17th October 2022. Interviews were privately digitally recorded with nobody else present. No participant had visibility of the semi-structured interview schedule (Appendix 2) prior to interview. Participants signed consent to be recorded as part of the initial study consent and in line with NHS ethics review, verbal consent to continue was confirmed at the start of visit 4 and participants were reminded that if they disclosed anything related to hurting themselves or others that the care coordinator would be informed as per standard safeguarding protocols. No participant asked to consider their involvement, one participant declined interview and one participant declined interview following confirmation of consent once the interview was underway. Interviews ranged between 02:50 and 30:30 minutes in length, no handwritten notes were made during the interviews and no interviews were repeated. All participants were offered visibility of their final transcript, one requested this and no amendments were made following review. Participants did not receive extra reimbursement for completing the interview and received vouchers for visit attendance as per previous visits.

Including the interview at clinic visit 4 and talking through the aspects of craving replicated ‘urge surfing’, a mindfulness technique used to reduce drug craving (Bowen and Marlatt, 2009) where service users are encouraged to talk through every aspect of drug use from anticipating using the drug, obtaining and using the drug then finally the feelings/impact post using the drug. Urge surfing is used in routine practice and no specialist training was required. Inclusion of this urge surfing format for the interview met the request made during the patient and public involvement phase of study design. I conducted each interview having had extensive experience using urge surfing with people who use opioids in my previous employment. Therefore the use of urge surfing as a template for interview constituted no increased burden on participants.

4.7 Monitoring of Side Effects

Section 4.7 begins with a definition of adverse events and reactions for the study and describes how they were reported. The section proceeds to explain the safety profile of oxytocin (subsection 4.7.2) and concludes with a comprehensive risk management plan for all risks and burdens that were anticipated in the study (subsection 4.7.3).

4.7.1 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Serious adverse event or serious adverse reaction defined as any adverse event or reaction that at any dose:

Results in death; or

- Is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death)
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition)
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the investigational medicinal product regardless of time of diagnosis).
- Or is another important medical condition

Important medical events that were not immediately life-threatening or result in death or hospitalisation but may have jeopardised the subject or may have required intervention to prevent one of the outcomes listed in the definition of serious were also considered serious.

For each SAE / SAR the following information was collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to drug / investigation), in the opinion of the investigator whether the event would be considered anticipated

All SAEs / SARs which occurred from the time of written informed consent (Appendix 3) until 7 days post cessation of the study protocol (following clinic visit 4) were recorded on the adverse event form and faxed to the sponsor within 24 hours of the research staff becoming aware of the event.

Once all resulting queries were resolved, I sent the sponsor the original form in order to notify the research ethics committee within 24 hours of the event happening. The original form was then posted to the sponsor and a copy retained on site.

Any change of condition or other follow-up information was faxed to the Sponsor as soon as it was available or at least within 24 hours of the information becoming available. Events were followed up until the event was resolved or a final outcome has been reached.

Adverse events were tabulated by oxytocin and placebo alongside a narrative description of each reported adverse event.

4.7.2 Safety profile

Oxytocin, the active substance, is part of a medicinal product licenced in the UK for intravenous use in induction of labour and as a nasal spray (Syntocinon, 40IU/ml) in EU countries. Nasal oxytocin was used off label which means oxytocin was used for a treatment outside of the licensed purpose.

A previous review of studies using nasal oxytocin on more than 1500 participants (79% male, 8% participants with mental health difficulties, dosage between 18IU and 40IU) reported no adverse effects associated with nasal oxytocin and dosages up to 40IU as used in experimental settings. Other recent research has investigated the safety and tolerability of nasal oxytocin in doses up to 72IU twice daily over the course of one week and has found no side-effect (Finger et al., 2015).

In any case, as an additional precaution, all participants were carefully monitored before, throughout and after each testing session. Participants received a telephone call within 7 days after each clinic visit to check that all is well and report any side effects. In case of an adverse effect I followed the required procedures to report it as outlined previously.

4.7.3 Identified study risks and burdens

The protocol identified a number of associated risks and burdens. Table 4.3 summarizes these, details how each risk/burden was managed and attributes a risk level of taking part in the study versus only receiving standard care following risk mitigation.

Identified Potential Risk or Burden to Participants	Mitigation	Risk Level versus Standard Care Post Mitigation (Low, Moderate, High)
Burden: Frequency and quantity of study visits	• Clinic visits were the same frequency and quantity as routine care with participants seeing keyworkers weekly, fortnightly or monthly • Study visits were on the same day as these, prior to routine care coordination appointments which could take place during the allocated time period waiting for any triggered craving to subside. • There was a voucher for participant reimbursement in line with good practice (Neale et al., 2018; Good practice for payment and recognition – things to consider, n.d.) • Participants were reimbursed for travel to the study site (Neale et al., 2018) • There was no extra burden to participants with frequency, only the length of appointment.	Medium
Burden: Urine drug screening	• Urine drug screens were part of routine care with screening taking place at each standard appointment. • There was no extra burden to participants.	Low
Burden: Completing TimeLine Followback at clinic visits	• Participants routinely self-report records of drug use over the previous 28 days to care coordinators. The TimeLine Followback method was less invasive than routine practice due to requiring less recollection (7 days in the study versus 28 days in routine practice) • There was no extra burden to participants.	Low
Burden: Dispensing of Naloxone	• Naloxone (Strang et al., 2019) is an anti-overdose drug given as part of routine care to all opioid users in a drug service. • There was no extra burden to participants.	Low

Burden: Ongoing care	• Participants received follow up telephone calls from the researcher within 7 days following each clinic visit • Participants continued to receive weekly or fortnightly appointments with care coordinators as per routine treatment • Side effect monitoring during each clinic visit is outlined in 4.7.1, 4.7.2	Low
Burden: Recruitment (care coordinators to identify potential participants)	• To reduce the burden on care coordinators to identify potential participants, a poster was created (Appendix 3) by one service user as part of the Patient and Public Involvement displayed in all recruitment sites • Participant Information Sheets were left at recruitment sites for participants to read whilst waiting for standard appointments. There is a space on the Participant Information Sheet where potential participants could consent to be contacted regarding the study without need for care coordinator identification • Risk was upgraded from low to high as covid-19 restrictions significantly increased the pressure on care coordinators in the recruiting service once recruitment began in December 2020. To counter this, one member of the drug and alcohol treatment team was assigned to support the research by calling every male participant receiving substitute opiates to request permission for myself to contact them about the study. This was required to ensure the study complied with the existing ethical approvals.	Low, later upgraded to high
Burden: Interview to talk about their experience	• The interview was estimated to last between 30 and 45 minutes and took place at visit 4 during safety follow ups from clinic visit 3. This represented no further time burden to participants in relation to the previous clinic visits. • Service users requested 'urge surfing' (Bowen and Marlatt, 2009) be included as part of the patient and public involvement activity. Urge surfing is a relapse prevention breathing exercise where people visualize and talk through the process of craving, obtaining drugs, using drugs and the feelings post drug use. The interview was an extended version of this and will likely aid reduction in future cravings.	Low

	Service users were able to decline the interview or specific questions within it.	
Risk: Inducing cravings which lead to increased use and overdose	- Our methodology for craving induction replicated one recent UK study, funded by the Medical Research Council (G0802663) which used video in the same way we propose to induce opioid cravings in abstinent heroin users and received NHS Research Ethics Committee approval (Murphy et al., 2018; REC 09/H1011/67) - Participants were invited to wait at the study site for 45 minutes to receive support from care coordinators and the study team or until they felt ok to leave. - There was an adverse event reporting governance structure which informed any sponsor decision to stop or amend the study. - The inclusion criteria required current use of illicit opioids therefore tolerance to different opioids (prescribed substitute and illicit i.e. heroin) has been established. No participant was destabilized from periods of not using illicit opioids. Destabilization and returning to using illicit opioids would increase the risk of overdose. - Opioid use was not expected to increase as a result of participation in the trial as no existing cue-induced craving of any illicit substance study which used nasal oxytocin has reported this. - All participants were offered take home Naloxone, a drug which reverses overdose and is already given as part of routine treatment by each drug treatment centre (Strang et al., 2019; Neale et al., 2018) - Inducing cravings is routine practice in drug trials	Low
Risk: Coerced involvement due to reimbursement	- The value of the voucher was not displayed on the participant information sheet, only that a voucher will be given - Vouchers are given due to good practice (Good practice for payment and recognition – things to consider, n.d.) and recommendations (Neale et al., 2018).	Low
Risk: Overdose of oxytocin	There is no evidence of euphoric effect, dependence, tolerance or withdrawal with nasal oxytocin.	Low

	• A previous review of studies using nasal oxytocin on more than 1500 participants (79% male, 8% participants with mental health difficulties, dosage between 18 IU and 40 IU) reported no adverse effects associated with nasal oxytocin and dosages up to 40IU as used in experimental settings (Macdonald and Feifel, 2013). • Oxytocin's potential to reverse morphine tolerance in animals (Sarnyai and Kovacs, 2014) has not been replicated in human trials giving no reason for concern in the safety profile for the study. • Tolerability without adverse event in opioid dependent people receiving methadone of up to 120mgs daily (n=64) without contraindication was found (Woolley et al., 2016). This was important for our study where participants received a range of methadone doses which did not exceed 120mgs daily.	
Risk: Recruitment and retention to the study	• The site was chosen due to having known populations in line with the inclusion criteria to minimise recruitment risk. • Members of the study team had existing relationships with the management for each trial site. • The Chief Investigator had strong links as consultant addictions psychiatrist for two NHS Foundation Trusts to ensure access to further sites if recruitment problems occur • The recruitment strategy was in line with UK research on improving recruitment and retention in opioid pharmacological trials (Neale et al., 2018) • Appointment frequency was in line with standard practice for drug treatment, there was no extra burden on participants. • The study design was received positively during the Public and Patient Involvement Consultation phase with all 37 service users stating they agreed with the proposed study and requirement to induce cravings. • Risk was upgraded from low to high as covid-19 restrictions on the drug treatment service when recruitment began meant a greater number of participants than initially estimated self-reported abstinence without the ability for the drug treatment service	Low, later upgraded to high

	to confirm. Face-to-face contacts were kept to a minimum and therefore reported abstinence made participants ineligible.	
Risk: Recruitment and retention to the study (COVID-19 specific)	• The infection rate was estimated to peak in May/June 2020 so recruitment will start in July as the infection decline was projected to be underway • The minimum time needed to complete the study per participant is 4 weeks and the maximum is 8 weeks. Our recruitment phase was 48 weeks in total, extendable to 52 weeks if required. • The study design meant participants unable to continue were replaced posing minimal threat to data collection • The study design ensured participants received vouchers up to the point they withdraw from the study ensuring no pressure to continue the study and minimal loss of benefit to the participant • Participants were required to wash their hands at the start of each clinic visit with an alcohol based hand rub in line with COVID-19 infection control guidance (Department of Health and Social Care et al., 2020) • The IT equipment was cleaned with a single use disinfectant wipe following each participant visit (Department of Health and Social Care et al., 2020) • I wore single use disposable gloves per clinic visit in line with COVID-19 infection control guidance (Department of Health and Social Care et al., 2020) • Each clinic visit was conducted on a one to one basis with no group work undertaken as per COVID-19 infection control guidance (Department of Health and Social Care et al., 2020) • Study criteria excluded people at higher risk of COVID-19 and potentially excluded people exhibiting symptoms of COVID-19 by ensuring they followed the recommended self-isolation phase before continuing with the study if possible. This is in line with COVID-19 infection control guidelines (Department of Health and Social Care et al., 2020) • As the primary contact in the study, I was a 42 year old, non-smoking male with no long term conditions and	High

	therefore not at high risk of COVID-19 • The recruitment and intervention site was located on hospital grounds	
Risk: Non-Disclosure of co-existing factors which may otherwise prohibit inclusion in the study and raise safety concerns	• Informed consent (Appendix 9) included access to medical records and drug treatment service risk assessments to ensure eligibility.	Low
Risk: Failure to protect personal data	• All paper records were kept on site in a lockable cupboard. • Participant identifiable records were separated from case report forms. • Data was anonymised and entered electronically to a secure, GDPR compliant database.	Low
Risk: Reliability of results	• All measurement tools used in the case report forms were validated for use in this population (Fals-Stewart et al., 2000; Cox et al., 2006; McHugh et al., 2014) and administered by trained, experienced professionals with up to date Good Clinical Practice for consistency. • I had 9 years experience working within a drug treatment service and had extensive experience engaging opioid users. I have completed qualitative interview training (2017) and was closely supervised by Professor Notley, a qualitative research expert.	Low
Risk: Oxytocin may increase aggression in males (Alcorn et al, 2015)	• History of violence towards professionals was included in the exclusion criteria and was assessed by each study sites risk assessment. • Should a participant become aggressive beyond usual presentation during the study they would have been excluded. • No study to date has reported heightened aggression in males as an adverse event.	Low

Table 4.3: Risk assessment of study safety and burden to participants

Notes: Depiction of identified risks and burdens to study completion, how they were mitigated and the risk scoring assigned to each. Covid-19 represented the greatest risk to study completion. Mitigation measures were led by government direction and NHS policies. Participant burden was the only medium threat and was mitigated by ensuring appointment frequency did not differ with current attendance times at the drug service. All other identified risks and burdens were assessed as low risk following mitigation measures. Low risk = highly unlikely to impact study completion, Medium risk = expected to impact but not prevent study completion, High risk = greatest risk to study completion.

4.8 Statistical Analysis Plan

Section 4.8 explains how the sample size was calculated, outlines the data analysis plan, confirms who had access to the data and finally aspects of data handling, quality assurance, finance and future publication policy. The results of the below analysis are reported and discussed in chapter five. The statistical analysis plan was pre-registered (<https://osf.io/pv75k/>) prior to commencing formal or informal analysis. In principle pre-registered studies ensure scientific integrity and are more reproducible as pre-registration ensures that data analysis is free influence by motivation, memory or reasoning biases. The evidence for this is conflicting however and for more information the reader is directed to Nosek et al. (2018).

4.8.1 Justification of sample size

Calculating a sample size is an important stage of designing a study to ensure the study is adequately powered. An underpowered study, such as when the sample size is too small, increases the risk of Type II errors (when the study results fail to reject the null hypothesis). Conversely when a sample size is too big, the chance of Type I error (when the study results wrongly support the hypothesis) is increased.

Our sample consisted of existing community based opioid dependent males in receipt of substitute opiates (methadone or buprenorphine based medications) who received both oxytocin and placebo on different visits (participants randomly allocated to treatment order). This was a proof of concept study and we used the GPower calculator (Version 3.1.9.6) to estimate the minimum required sample size for an a priori determined medium effect size ($f = 0.025$, corresponding to Cohen's $d = 0.050$) in a repeated measurements analysis of variance test, with power set at 80% (meaning that 80% of the time we would get a statistically significant result) and level of significance $\alpha = 0.05$ (meaning there is a 5% risk of finding a difference that does not really exist). The estimated required sample size was $N=34$.

4.8.2 Statistical interim analysis and stopping guidance

No formal statistical interim analysis was undertaken for the oxytocin vs placebo comparison.

4.8.3 Timing of final analysis

Final analysis for the oxytocin vs. placebo comparison took place once only. The first main report/publication of the study will be prepared for the oxytocin/placebo comparison when every participant has completed visit 3 and data for the primary endpoint has been received and cleaned (anticipated to be January 2023 or before).

4.8.4 Quantitative data analysis

In data analysis statistical significance can be misunderstood and miscommunicated as study results having no effect however absence of evidence is not evidence of absence (Sedgwick, 2014). Whilst statistical significance gives the researcher confidence that any results did not occur from chance alone it does not offer any insight as to clinical significance (the practical importance of an effect on everyday life) and so statistical significance based on an arbitrary number (typically <0.05 following a standardised equation) does not provide a good measure alone of evidence for supporting hypotheses (Amrhein et al., 2019). Results which achieve statistical significance are considered signposts to further enquiry and increase researcher confidence in the direction of their work. Absence of statistical significance does not mean results should be dismissed. Following the results of the systematic review (Chapter three) and in line with review of power in nasal oxytocin studies where sample sizes were mostly too small to detect or reject a range of effect sizes (Quintana, 2020), statistically significant results are reported in chapter five as p values alongside confidence intervals but all results are discussed irrespective of statistical significance.

Quantitative analysis methods

Order effects from each treatment (oxytocin/placebo or placebo/oxytocin)) will be mitigated by including treatment order as a between subjects variable of no theoretical interest in the analyses addressing each objective. If treatment order effects are not significant, this variable will be dropped from the final models.

There are two within subject independent variables; treatment and time points.

There is one between-subjects independent variable: treatment order.

There are two dependent variables; craving and attentional bias.

Adherence and protocol deviations

Adherence was defined as attending visits 1, 2 and 3 for the full duration. These visits constituted the full experimental phase. Visit 4 was not required for adherence because the interview was considered optional as per ethics recommendation. Compliance was calculated as a percentage of those randomised minus those who do not complete (withdrawal, drop out or meeting exclusion criteria) visit 3. This information is presented in the CONSORT diagram in chapter five with a descriptive summary of the percent compliance.

The following were pre-defined major protocol violations with direct implications on the primary outcome:

- 1) Meeting the exclusion criteria as defined within the protocol
- 2) Repeat administration at visit 3 of the same study spray administered at visit 2

Protocol deviations are summarised in narrative with adverse event data.

Analysis populations

The intention to treat population was all participants randomised. This population was used for analysis of all data in order to preserve the balance of randomization thereby minimising the risk of bias from comparing groups who differ in variables (McCoy, 2017; Mills et al., 2009).

Missing data

We anticipated minimal missing values, given that the study variables were determined during agreed clinic visits by trained researchers. Complete case analysis (statistical analysis that only includes participants where there is no missing data for the variables of interest) was used as the proportion of missing data was not above 5%. Missing data was reported narratively with reason for the missing data where necessary.

Craving definition

Craving (mean and SD) will be calculated using the opioid craving scale (McHugh et al., 2014) score at each collection time point (baseline, 7, 15, 30 minute post cue exposure) with baseline scores used as a covariant where required.

The OCS is an 11 point (0-10) Likert scale questionnaire and craving analysis will be completed twice. Firstly for the mean effect of all three questions asked in the opioid craving scale in line with validation of single use of the tool and secondly only analysis of the first question of the opioid craving scale (How much do you currently crave opiates? rated from not at all to extremely). This is because the answers to the final two questions (If you saw this in your everyday life, how much would you crave heroin? rated from no desire to extremely strong; How much did the video remind you of times that you have used heroin? rated from not at all to extremely) do not relate to the subjective feeling of craving which is our primary outcome. These questions were analysed and reported individually.

Attentional bias definition

Attentional bias (mean and SD) will be calculated using the mean STROOP effect scores in the addiction STROOP task (Cox et al., 2006) at visit 1 and at clinic visits 2 and 3 at each time collection point (baseline, 8 and 31 minutes post cue exposure).

Analysis methods

To confirm craving was induced at clinic visit 1 only, a paired samples t-test will be used to confirm that craving was induced between baseline measurement and 7 minutes post cue-exposure. The time point was chosen because craving is expected to peak at 7 minutes post cue-exposure in line with fMRI evidence (Murphy et al., 2018).

To confirm the induction of attentional bias at clinic visit 1, a paired samples t-test will be used to compare performance at baseline and 8 and 31 minutes post cue.

Objective one

This analysis evaluated the effects of the treatment on craving (OCS). A mixed ANCOVA was used with Treatment Order (Oxytocin session 2 vs. Oxytocin session 3) as the between subjects' variable and time (7 vs 15 vs 30), and treatment (Oxytocin vs Placebo) as the within subjects' variables. Baseline OCS scores for each treatment session were entered as covariates.

Data is visually presented as line charts with time point along the X axis, OCS score on the Y axis. Each data point represented mean $\pm$ SD of craving at baseline and 7, 15 and 30 minutes following placebo or oxytocin administration.

Objective two

This analysis evaluated the effects of the treatment on attention bias. A mixed ANCOVA was used with Treatment Order (Oxytocin session 2 vs. Oxytocin session 3) as the between subjects' variable and time (8 vs 31 min), and treatment (Oxytocin vs Placebo) as the within subjects' variables. Baseline STROOP effect scores for each treatment session were entered as covariates.

Objective three

To analyse objective 3 we ran three separate linear regression models. In each model, the cue-induced STROOP effect difference (STROOP effect Placebo timepoint - STROOP effect Placebo baseline) was regressed with craving change (from baseline) at each time point (7, 15 and 30 min) (placebo condition). Order of Oxytocin/placebo administration was added as a variable of no theoretical interest.

Objective four

To analyse objective 4 we ran two separate linear regression models. In each model, oxy-induced STROOP effect differences (STROOP effect Oxytocin_timepoint - STROOP effect placebo timepoint) was regressed with oxytocin-induced craving changes at 15 and 30 minutes (Oxytocin versus placebo). Order of Oxytocin/placebo administration was entered as a regressor of no theoretical interest.

Mediation analysis

Mediation analysis was undertaken to analyse whether craving score (OCS) is mediated by attentional bias (STROOP).

Statistical software

The analysis was carried out using SPSS version 28.

4.8.5 Qualitative data analysis

Interview recordings were transcribed verbatim and anonymized. For the qualitative analysis inductive content analysis (Elo and Kyngas, 2008) was undertaken due to the novelty of the phenomenon this study aims to capture. Three initial themes were preconceived by one white, male author (BH). These themes were early life experience, adolescent socialisation and psychiatric diagnosis as influenced by existing oxytocin dysregulation theory as outlined in chapter one. Interviews were read with an open mind and further themes emerged from coding and interpretation of the data. Interview coding was checked by one, white female author with no relationship to the participants (CN) and discussed where disagreements in coding were found. As the senior academic, CN decision was final. Analysis was conducted concurrently with data collection using Nvivo 12 software. Interviews were transcribed by hand without the use of digital transcription software by BH. Digital recordings of interviews were deleted immediately following transcribing.

The reporting of the qualitative component (see chapter six) complied with COREQ reporting standards (Tong et al., 2007).

4.8.6 Direct access to source data and documents

Direct access to data and other study documents was granted to authorised bodies for the purposes of inspection or audit as requested. Dr Bailey visited the recruiting site of the study sponsor once to inspect the trial procedures. The Sponsors research and development manager audited the medication log once in December 2021 prior to agreeing the addition of three new non-statutory recruitment sites.

4.8.7 Quality assurance, data handling, publication policy and finance

The members of the team were experienced researchers with a long track record of conducting sound experimental studies and actively supervised myself. The Chief Investigator, Dr Kouimtsidis, was a consultant addiction consultant with track record in conducting NIHR funded research in substance using populations (IRAS ID: 213086). Professor Duka, Dr Bailey and Dr Paloyelis, provided experience in conducting human studies involving nasal oxytocin in an opioid dependent population utilising cognitive experimental measures and had excellent understanding of the challenges involved (EudraCT Number: 2014-002708-26; Paloyelis et al., 2016; Davies et al., 2019; Leslie et al., 2020; Martins et al., 2020). Professor Notley provided expertise in producing qualitative research and led on supporting me with this design and analysis. All members of the team had experience in good clinical practice.

The Chief Investigator acted as custodian for the research data. All data was kept completely confidential, was anonymised and was only considered in relation to the project. Any information about participants' which left each study site had the name and address removed so that they could not be recognised from it. All audio recordings made were anonymised, securely stored in password protected computers and made accessible only to the investigators. Anonymous data was extracted from these recordings and the digital recordings were destroyed immediately following transcription.

Our findings will be disseminated at international conferences and in peer-reviewed scientific journals. Scientific papers will be submitted for publication in journals with open access options where possible. This study was funded through contributions from Dr Bailey (St Georges University of London) and Dr Paloyelis (Kings College London) research budgets only.

4.9 Ethics and Regulatory Approvals

Section 4.9 states which ethical approvals were met, which ethical amendments were submitted and why the ethical amendments were submitted.

This study was approved by the Brent NHS Research Ethics Committee in July 2020 (Ethics approval number 20/LO/0758). The core element of this study (video based craving induction in opioid users) was previously approved in research by the NHS Research Ethics committee (Ethics approval number: 09/H1011/67). Ethical approvals were sought as required by the Ethics Committee of Surrey and Borders NHS Foundation Trust.

The study was conducted in compliance with the principles of the Declaration of Helsinki and followed the principles of Good Clinical Practice.

4.9.1 Ethics amendments

Amendments to the study protocol were requested seven times. All amendments were agreed by NHS ethics committees. The changes and rationale for all amendments are detailed below.

Amendments one to three were submitted in November 2020 as recruitment began. Amendment one (20/LO/0758/1) was to allow me to screen participants using the electronic case notes maintained by the drug service. The rationale was to reduce burden on care coordinators to identify participants and allow for targeted recruitment. NHS ethics still required care coordinators to make the first contact with potential participants to ensure people did not feel obligated or pressured to take part in the study.

Amendment two (20/LO/0758/2) requested that an emotional STROOP task was used at clinic visit 1. The rationale was to aid understanding of the addiction STROOP results.

Amendment three (20/LO/0758/3) requested removal of the cognitive IQ task (Ravens measure) as part of the inclusion criteria and to be moved to the final visit 4 instead of at screening. Following review by the study team it was decided that this task was not necessary for inclusion, increased the time burden on participants and thereby could hinder recruitment.

Amendment four (20/LO/0758/4) was submitted in March 2021 and requested an amendment for the recruiting poster to include the research assistant contact details so participants could contact me directly. Local pharmacies were then contacted and asked to display posters where participants collected their prescriptions or used needle exchange services. This was to reduce burden on the care coordinators to identify participants as national Covid-19 restrictions were relaxed and treatment need was anticipated to increase.

Amendment five (20/LO/0758_INC) was submitted in April 2021 and requested permission to increase participant reimbursement from £10 per clinic visit to £20 per clinic visit (4 visits in total). The rationale was that the study team recognised the engagement being asked of participants who belong to vulnerable groups during the Covid-19 pandemic. With minimal research being conducted by universities there were finances available to increase reimbursement including retrospectively to the participants who have completed to date.

Amendment six (20/LO/0758) was submitted in April 2021 and requested for the inclusion criteria to remove 'A single-point score increase on opiate craving scale following our visual cue induction paradigm at clinic visit 1 to confirm that craving has been induced'. The rationale for this was because evidence shows not every person who uses opioids reports feeling cravings however our hypothesis is underpinned by an effect on attentional bias. The attentional bias is measured by STROOP test and may be present even without any change in self-reported craving. Removing this inclusion criteria ensured our sample is more inclusive and representative of the target population.

Amendment seven (20/LO/0758_new sites) was submitted in December 2021 and requested for the addition of three new recruiting sites located in Luton, Newham and Reading. The rationale for this amendment was that we had exhausted all potential participants available through Surrey & Borders NHS Foundation Trust at that time and to conclude the study would leave analysis underpowered. Further participants identified through Surrey and Borders NHS Foundation Trust were not excluded but were not explicitly targeted. This amendment also included a request to extend the study period until January 2023.

4.10 Conclusion

To summarise, this thesis has so far outlined how oxytocin dysregulation can be observed within multiple risk factors associated with opioid use and undertaken a literature review finding that nasal oxytocin may have utility in reducing drug craving (Figure 4.2). If craving can be reduced then accidental overdose, the leading cause of drug-related death, may be reduced but existing nasal oxytocin craving efficacy studies are limited by heterogeneity. Chapter four has outlined the methods used in designing and conducting a double-blind, placebo controlled study which investigated the effect of nasal oxytocin on attentional bias and cue-induced craving during the expected length of a cue-induced opioid craving in accordance with fMRI imaging evidence. The quantitative results are presented and discussed next in chapter five.

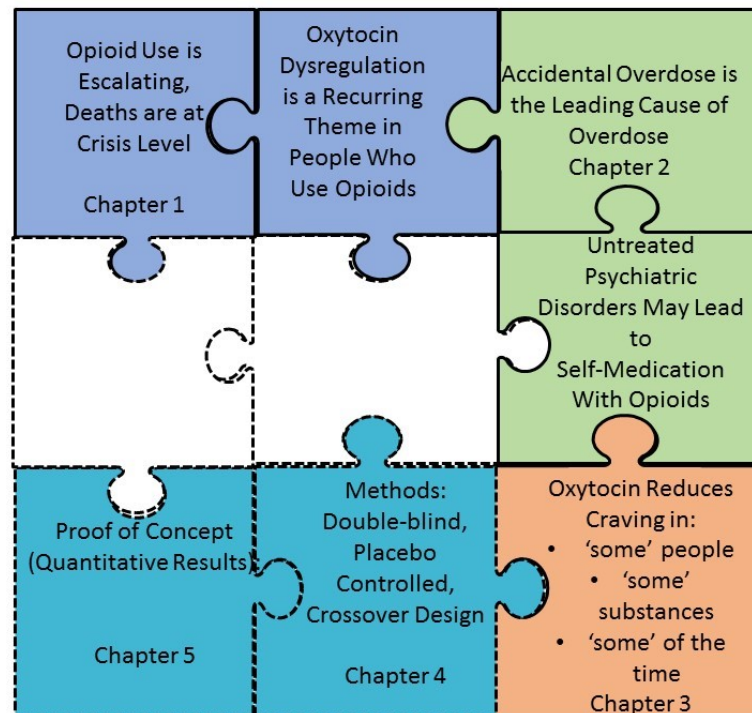


Figure 4.2: Key thesis findings by chapter up to chapter five

Notes: Chapter one outlined the extent of the opioid crisis with opioid-related deaths at crisis level. Chronic drug use dysregulates the endogenous oxytocin system and is highlighted in people who experience early life trauma and people with psychiatric disorders, both of which are highly prevalent in people who use opioids. Chapter two analysed the prevalence of psychiatric disorders in deaths where opioids were found at post-mortem and suggested that self-medication in the absence of psychological treatments may contribute to accidental overdose. Chapter three systematically reviewed human studies for nasal oxytocin to reduce craving or consumption in substance use disorders finding that nasal oxytocin works in some of the people, some of the time but variation throughout studies prohibits conclusive results. Chapter four explained the methods used throughout the proof-of-concept study which explored the mechanism of nasal oxytocin to reduce craving.

Chapter Five

Investigating The Mechanism Mediating The Effects Of Oxytocin On Opioid Craving: The Proof Of Concept (Quantitative Results)

“We have learned that the satisfaction of instincts cannot be the sole aim of our lives”
– Narcotics Anonymous, 12 Steps and 12 Traditions

Abstract

Chapter five presents the quantitative results of a randomized, double-blind, placebo-controlled, crossover, proof-of-concept study which explored the mechanism of nasal oxytocin (40 international units) on cue-induced craving as measured by the opioid craving scale and attentional bias as measured by the addiction STROOP task. Participants ($n=24$) were males using illicit heroin at least once in the last 7 days and in receipt of methadone or buprenorphine recruited from 4 UK community drug services.

Whilst there was a greater change from baseline in subjective craving under nasal oxytocin versus placebo there was no statistically significant effect of treatment ($F = 0.73$, $df=1$, $p=0.79$, $\eta^2=0.04$). The STROOP effect was 3x greater under nasal oxytocin versus placebo at 8 minutes and 2.5x greater under nasal oxytocin versus placebo at 31 minutes post exposure to the craving inducing video.

This single-dose crossover study did not find any significant difference for nasal oxytocin versus placebo to reduce cue-induced opioid craving although both placebo and oxytocin reduced craving compared to treatment as usual (no spray) in visit one. Effect sizes across the three component questions of the opioid craving scale were generally large suggesting practical significance in a heterogeneous population. It may be the only way to evaluate whether nasal oxytocin can be used ad-hoc to reduce opioid use is by performing trials where nasal oxytocin can be used pragmatically alongside community treatment.

5. Introduction

The methods reported in chapter four were used within a double blind, randomised, crossover design in a proof of concept study. The study aimed to examine the effect of a novel repurposed compound, nasal oxytocin (40IU), on cue-induced opioid craving and attentional bias in males currently using heroin in addition to prescribed substitute opiates from UK community drug treatment services (n=24). This cohort is generally considered the most unstable subgroup. Participants were required to attend four clinic appointments where on three of these visits, opioid craving was induced by exposure to a video of a man preparing and injecting heroin to his groin. Participants were given in a randomised sequence oxytocin/placebo on two separate visits before craving and attentional bias measures were taken over a 30 minute period post-exposure to the video. No spray was given at the first visit as this was a training visit to complete registration, obtain consent and walk-through study procedures. On the final visit participants were invited to an optional interview to explore their experiences of the study and craving management in general. These interviews are analysed and reported in Chapter six. Each visit lasted approximately one hour, had an agreed appointment time typically between 12:00 and 15:00, and could take place within a maximum of 30 days since the last visit in line with usual attendance at the drug service. Participants received £20 in vouchers per clinic visit attended, payable at the last session as well as travel costs reimbursed (Figure 5.1).

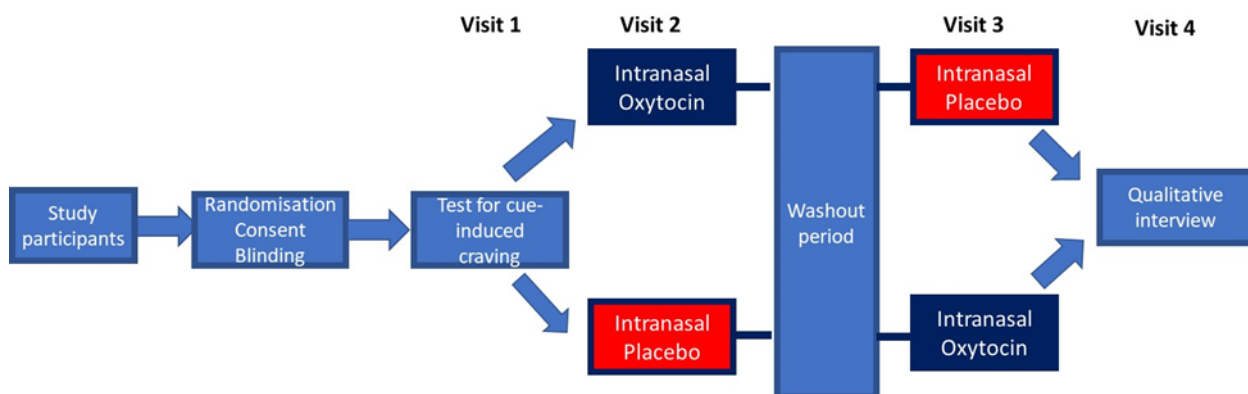


Figure 5.1: Walkthrough of four study visits

Notes: Following informed consent participants were randomised and blinded before completing visit one where study procedures were explained and participants were tested to confirm that craving was induced post exposure to the video cue. At visit 2 participants received either oxytocin or placebo before exposure to the craving inducing video and subsequent craving self-report at 7, 15 and 30 minutes post exposure. A washout period of between 7 and 30 days followed before visit 3 which repeated visit 2 but under the opposite treatment. Visit 4 was then completed and comprised of an optional qualitative interview focused on their experience of opioid craving.

Chapter five presents the quantitative results and discussion of this study. Section 5.1.1 reports the participant demographics, 5.1.3 then reports the results of objective one only. Section 5.2 then discusses the results and limitations before the chapter concludes.

5.1 Results

5.1.1 Demographics

The CONSORT diagram is presented in Figure 5.2. In total 113 males voluntarily in treatment for opioid use disorder consented to be contacted about the study. These people were screened to yield 41 people who were unable to be contacted and the exclusion criteria were met by; being female (n=4); abstinence from heroin use (n=17); psychiatric comorbidity (n=1); not being stable on their substitute opiates (n=4); out of area for recruitment (n=1) and being in custody prior to the first appointment (n=1) leaving 44 eligible people. Of the 44 people deemed eligible on the basis of exclusion criteria, further reasons for declining participation included; family members being upset at the idea of them taking part (n=1); unable to commit due to work (n=2); unable to commit to four appointments (n=5); anxiety about the study (n=3) and no reason

given (n=3) leaving 30 enrolled in the study across four recruitment sites. Reasons for withdrawal once randomized were dropping out of treatment (n=1); unable to contact post visit 1 (n=2); change in substitute opiate dose (n=1); randomized in error at screening (n=1) and one forced to withdraw due to study time constraints and being unable to confirm attendance within agreed parameters (n=1) leaving 24 to complete the study. The retention rate for all participants who started the study was 82%.

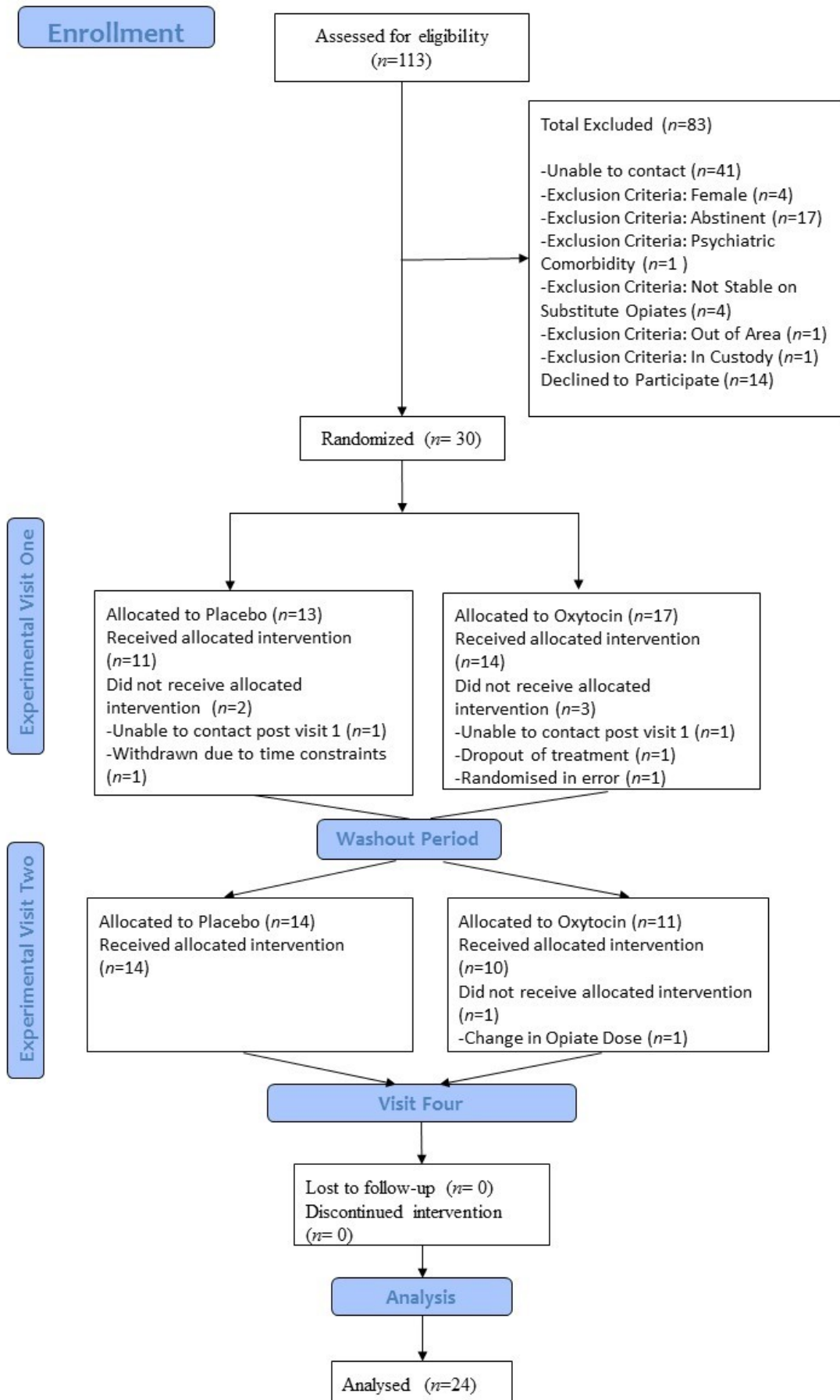


Figure 5.2: CONSORT diagram of study

The participant characteristics of the analysed sample (n=24) are presented in Table 5.1. Participants tended to be middle aged between 25 and 59 and were mostly of Caucasian ethnicity. All but two were in receipt of methadone. One participant was a non-native English speaker. There were no noteworthy differences in terms of characteristic information such as marital status, employment status and educational level.

	<i>mean</i>	<i>SD</i>			
Age	45.33	8.07	Current Mental Health Problems	<i>n</i>	%
			None	7	29
			Anxiety	12	50
Ethnicity	<i>n</i>	%	Psychosis	1	4
White British	21	88	Paranoia	0	0
Other White	1	4	Eating Disorder	0	0
Other Mixed	1	4	Depression	12	50
Pakistani	1	4	Bi-Polar	4	17
			PTSD	3	12
Education			Schizophrenia	2	8
Postgraduate Degree	1	4	Personality Disorder	3	12
Undergraduate Degree	2	8			
Diploma/BTEC	1	4	Current Medications		
A Level/NVQ	5	21	No other medications	7	29
O Level/GCSE	11	46	Amitriptyline	1	4
No Qualifications	4	17	Diazepam	2	8
			Dihydrocodeine	1	4
Employment			Fluoxetine	1	4
Full Time	2	8	Gabapentin	1	4
Part Time	1	4	Hydrocortizone	1	4
Sick >4 weeks	12	50	Ibuprofen	1	4
Unemployed	9	38	Inhalers	3	12
			Mirtazepine	7	29
Relationship			Olanzapine	1	4
Living Together	5	21	Pregabalin	4	17
Separated	2	8	Quetiapine	3	12
Single	17	71	Risperidone	1	4
			Rivaroxaban	1	4
Housing			Sertraline	1	4
Lives Alone	15	63	Sofosbuvir	1	4
With Partner	5	21	Tamazepam	1	4
With Mother and Father	1	4	Warfarin	1	4
With Mother Only	1	4			
In Shared Accommodation	2	8	Substitute Opiates		
			Methadone	22	92
Smoking Tobacco?			Buprenorphine	2	8
Yes	21	88		<i>mean</i>	<i>SD</i>
No	3	12	Methadone	60.95	17.43
			Buprenorphine	13	1.41
			Other Concurrent Substance Use	<i>n</i>	%
			Alcohol	2	8
			Cannabis	2	8
			Crack Cocaine	19	80
			No other use	1	4

Table 5.1: Participant characteristics (n=24)

Notes: Methadone and Buprenorphine doses in milligrams.

At visit one where no spray was administered the mean time from substitute opiate dose to start of clinic visit was 13.24 hours (SD = 12.22). Under placebo the mean time from substitute opiate dose to start of clinic visit was 14.64 hours (SD = 12.41) and under oxytocin was 13.33 hours (SD = 11.01). At visit one where no spray was administered the mean time from last use of heroin to start of clinic visit was 1.79 days (SD = 2.06). Under placebo the mean time from last use of heroin was 3.33 days (SD = 5.99) and under oxytocin the mean time was 1.91 days (SD = 3.25).

The mean Ravens-brief score was 9.76 (SD = 3.96) out of a maximum score of 30 with mean time taken to complete 10 minutes 12 seconds (SD = 0.32). Scores indicate participants were intellectually average. Two participants declined to complete Ravens scoring at visit 4.

5.1.2 Craving induction and blinding

Data was normally distributed allowing for use of parametric analyses. Craving was induced at visit one where no spray was administered following exposure to the video ($p < .001$, $\eta^2 = 0.44$). Only question one was used to assess craving as this question related specifically to the feeling of craving before and after exposure to the cue (Figure 5.3). Two participants did not have craving induced at clinic visit 1.

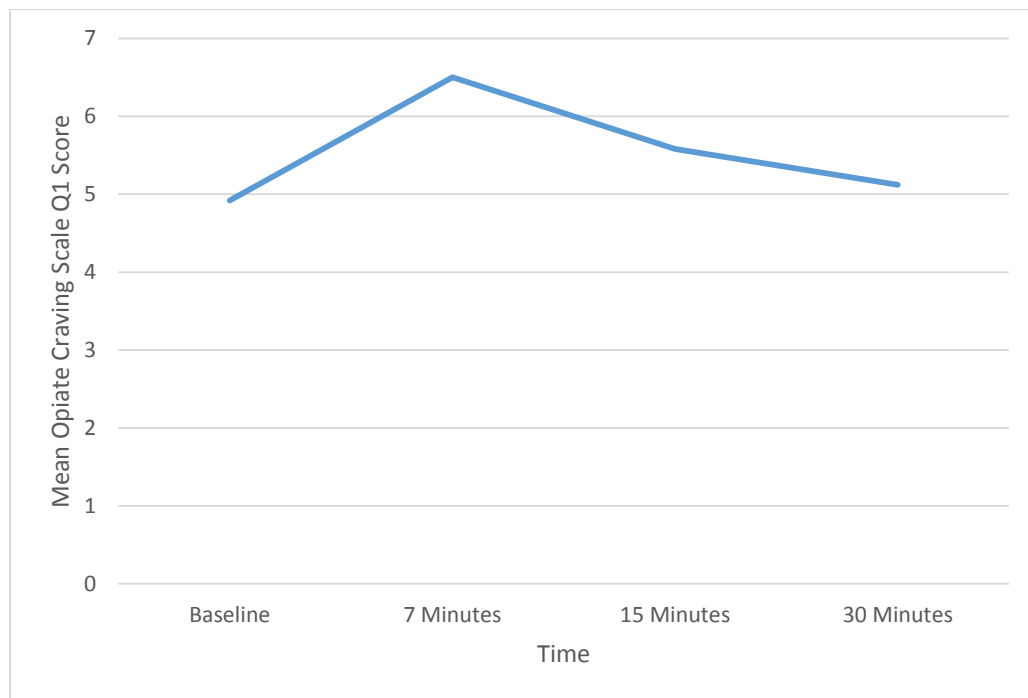


Figure 5.3: Mean scores of opiate craving scale question 1 (How much do you currently crave opiates?) at three different time points post cue exposure with no spray only

Notes: Opiate craving scale question one mean scores in response to exposure to craving inducing video with no spray treated participants (n=24). Craving was induced at 7 minutes post exposure to the video (p=<001 vs baseline, $\eta^2=0.44$, Bonferroni post hoc test).**

The likely Observer-Experimenter effect (Nichols and Maner, 2008; Holman et al., 2015) is where participant response is influenced by the presence of the researcher. This effect was evident under both oxytocin and placebo and combined with an expectation effect that craving would be reduced (Zhou et al., 2019), resulting in minimal increase in craving under placebo only (Figure 5.4) following exposure to the video.

Four people correctly guessed when they received placebo in subsequent visits (5 thought they received oxytocin, 14 were unsure) and eight people correctly guessed when they received oxytocin (3 thought they received placebo, 12 were unsure).

5.1.3 Objective one

Objective one was to investigate the effect of nasal oxytocin administration compared to placebo on opioid related cue-induced subjective feeling of craving at 7, 15 and 30 minutes post cue exposure. Craving was self-reported using the three question, eleven point Likert OCS (0-10).

Total scores

We deviated from the analysis plan (Chapter four, section 4.8) and total scores were not analysed because baseline measures for questions 2 and 3 were not taken. This was because they related to the cue-inducement video which participants had not yet been exposed to at baseline. Instead for questions two and three a 2-way repeated measures ANOVA was used for factors time and treatment. Order was used as a between subjects variable. Question one was analysed in accordance with the statistical analysis plan (Chapter four, section 4.8.4) with a mixed ANCOVA with Treatment Order (Oxytocin session 2 vs. Oxytocin session 3) as the between subjects' variable and time (7 vs 15 vs 30), and treatment (Oxytocin vs Placebo) as the within subjects' variables. Baseline OCS scores for each treatment session were entered as covariates.

Question 1- How much do you currently crave opiates?

Whilst both placebo and oxytocin reduced craving over time, analysis of the data shown in Figure 5.4 shows there was no statistically significant effect of treatment ($F = 0.73$, $df=1$, $p=0.79$, $\eta^2=0.04$), time ($F = 1.32$, $df=2$, $p=0.27$, $\eta^2=0.62$) or treatment*time ($F = 0.93$, $df=2$, $p=0.40$, $\eta^2=0.45$). There was no order effect on time ($F = 0.15$, $df=2$, $p=0.85$, $\eta^2=0.08$), treatment ($F = 0.00$, $df=1$, $p=0.97$, $\eta^2=0.00$) or treatment*time ($F = 0.62$, $df=2$, $p=0.49$, $\eta^2=0.30$).

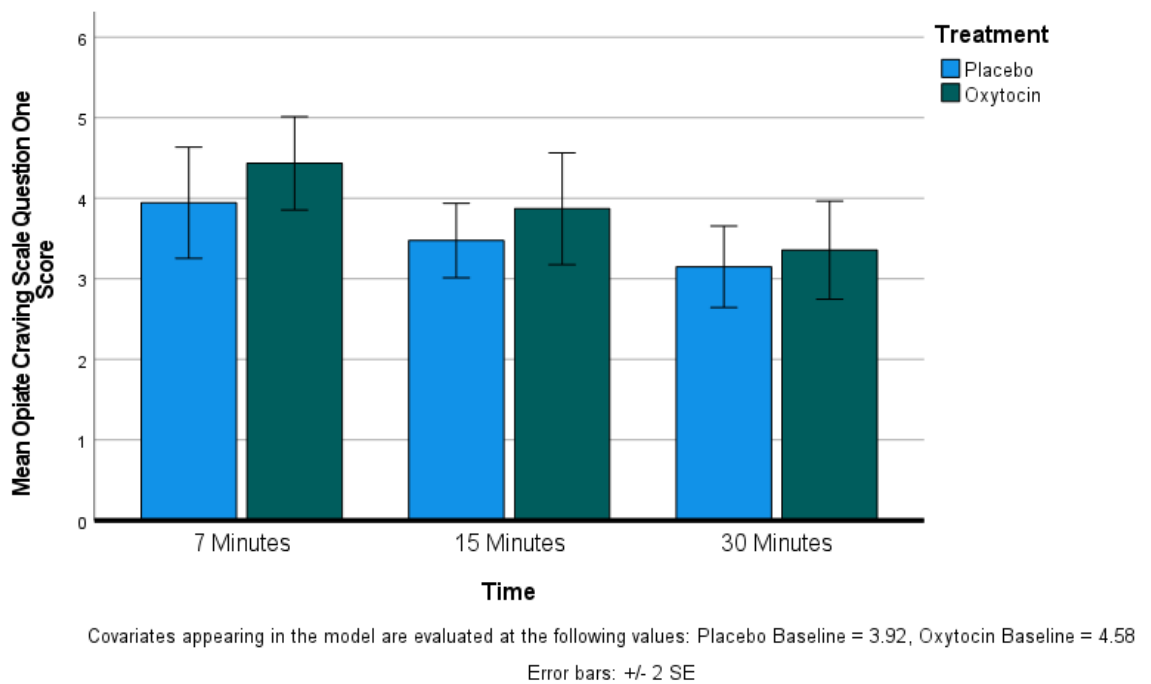


Figure 5.4: Mean scores of opiate craving scale question 1 (How much do you currently crave opiates?) at three different time points post cue exposure

Notes: Opiate craving scale question one mean scores in response to exposure to craving inducing video for oxytocin and placebo treated participants (n=24). Baseline scores reported as covariates. Error bars are standard error of the mean.

Under placebo baseline mean score was 3.92 (SD.=2.26), increasing by 2.04% compared to baseline at 7 minutes (M=4.00, SD.=2.23), then reducing by 9.69% compared to baseline at 15 minutes (M=3.54, SD.=2.04) and reducing again by 17.09% compared to baseline at 30 minutes (M=3.25, SD.=2.32). Under oxytocin baseline mean score was 4.58 (SD.=2.18), reducing by 1.74% compared to baseline at 7 minutes (M=4.50, SD.=2.14), continuing to reduce by 13.53% at 15 minutes compared to baseline (M=3.96, SD.=2.36) and reducing again by 25.32% at 30 minutes compared to baseline (M=3.42, SD.=1.93).

Figure 5.5 shows the change in craving score from baseline under both placebo and oxytocin

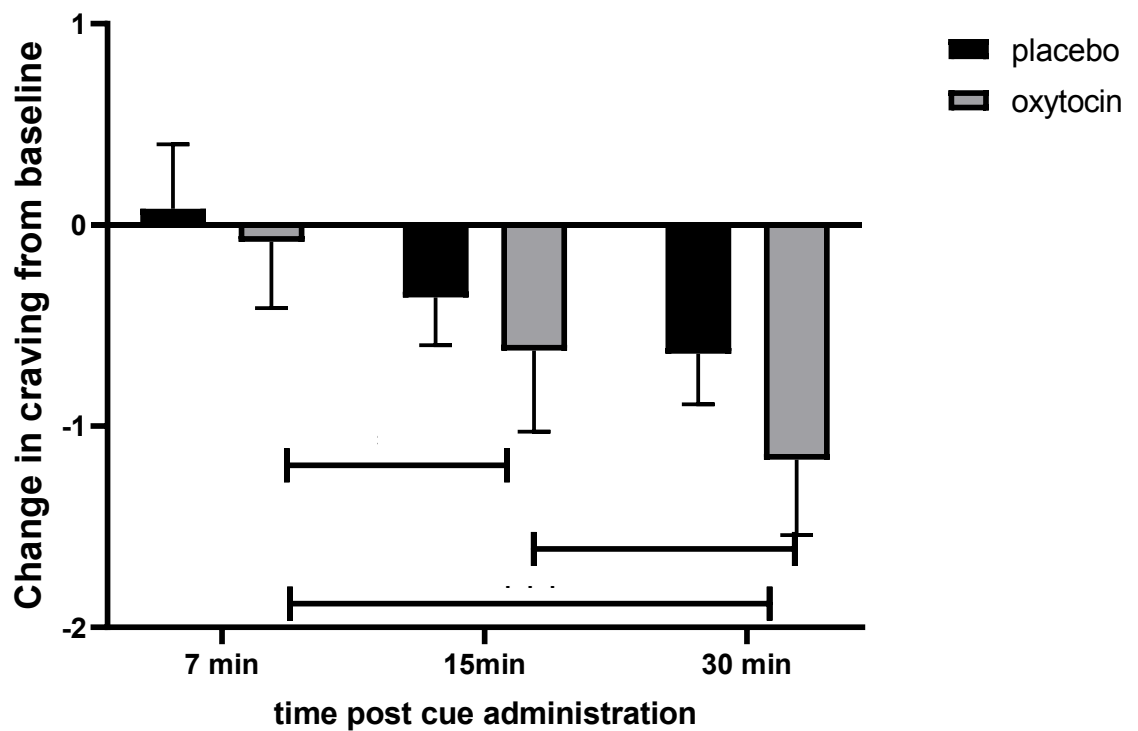


Figure 5.5: Change in craving from baseline of opiate craving scale question 1 (How much do you currently crave opiates?) at three different time points post cue exposure.

Data represents mean change of craving scores from baseline post cue exposure for oxytocin and placebo administration. Error bars represent SEM (n=24).

The distribution variance of question one scores may explain lack of significant difference between oxytocin and placebo. The distribution variance of question one scores for both oxytocin and placebo over three time points are displayed in Figure 5.6.

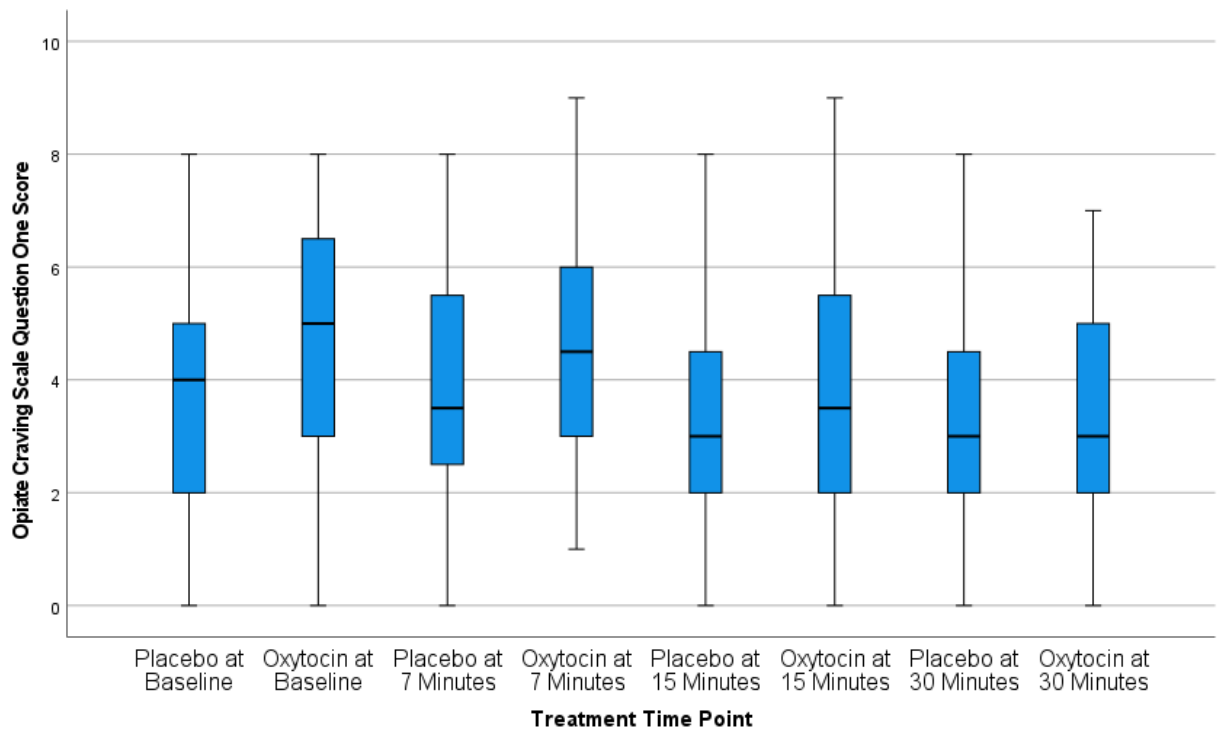


Figure 5.6: Opiate craving scale question 1 (How much do you currently crave opiates?) distribution variance for placebo and oxytocin

Notes: Opiate craving scale question one mean score distribution variance for oxytocin and placebo treated participants (n=24). There was greater variance in oxytocin scoring versus placebo at 15 and 30 minutes.

Question 2 - If you saw this in your everyday life, how much would you crave heroin?

Analysis of the data displayed in Figure 5.7 shows there was no statistically significant effect of treatment ($F = 2.83$, $df=1$, $p=0.10$, $\eta^2=0.11$), time ($F = 1.79$, $df=2$, $p=0.17$, $\eta^2=0.75$) or treatment*time ($F = 1.86$, $df=2$, $p=0.16$, $\eta^2=0.78$). There was no order effect on time ($F = 0.94$, $df=2$, $p=0.39$, $\eta^2=0.41$), treatment ($F = 0.00$, $df=1$, $p=0.99$, $\eta^2=0.00$) or treatment*time ($F = 0.15$, $df=2$, $p=0.86$, $\eta^2=0.00$).

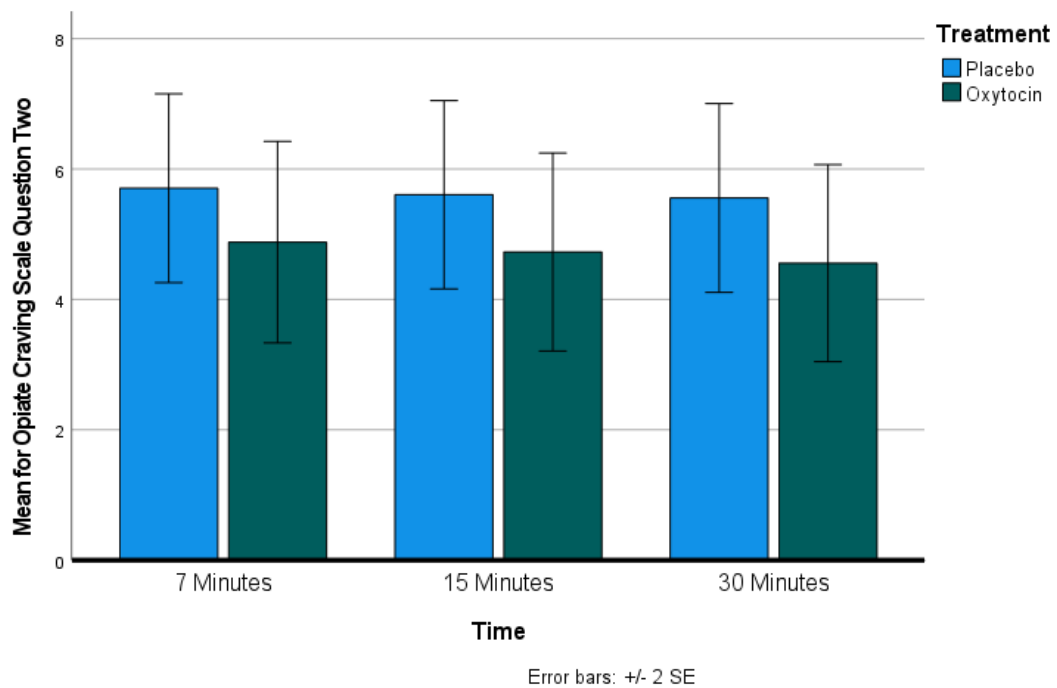


Figure 5.7: Mean scores of opiate craving scale question 2 (If you saw this in your everyday life, how much would you crave heroin?) at three different time points post cue exposure

Notes: Opiate craving scale question two mean scores in response to exposure to craving inducing video for oxytocin and placebo treated participants (n=24). Error bars are standard error of the mean.

Question 3 - How much did the video remind you of times that you have used heroin?

Analysis of the data shown in Figure 5.8 shows there was no statistically significant effect of treatment ($F = 0.00$, $df=1$, $p=0.95$, $\eta^2=0.00$), time ($F = 1.42$, $df=2$, $p=0.25$, $\eta^2=0.06$) or treatment*time ($F = 1.42$, $df=2$, $p=0.25$, $\eta^2=0.06$). There was no order effect on time ($F = 1.42$, $df=2$, $p=0.25$, $\eta^2=0.06$), treatment ($F = 0.50$, $df=1$, $p=0.48$, $\eta^2=0.23$) or treatment*time ($F = 1.42$, $df=2$, $p=0.25$, $\eta^2=0.06$).

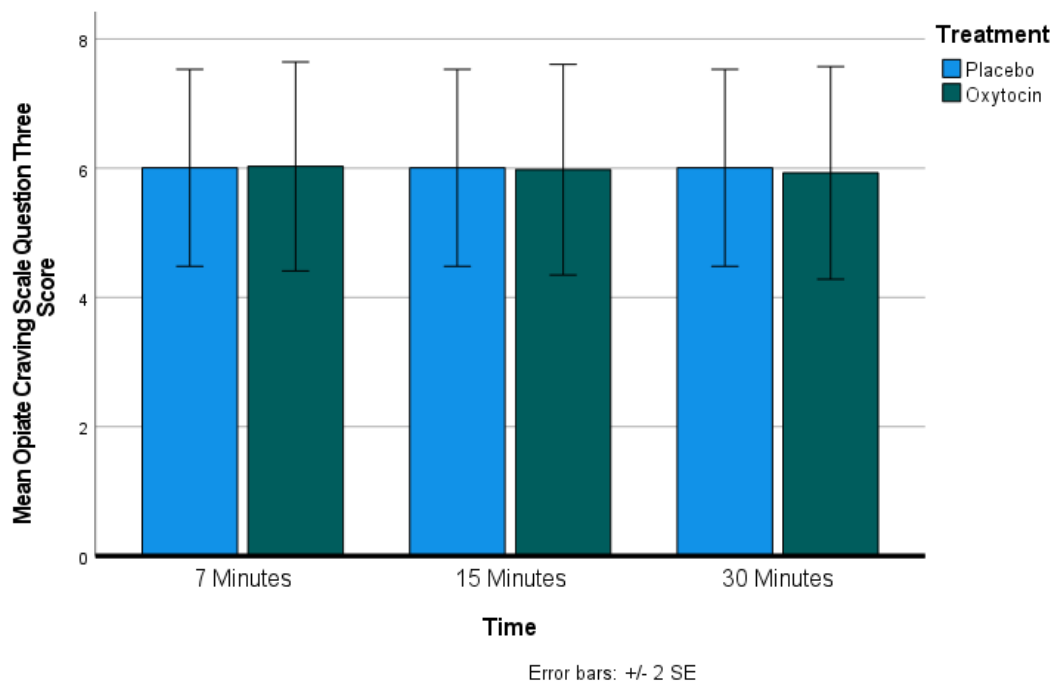


Figure 5.8: Mean scores of opiate craving scale question 3 (How much did the video remind you of times that you have used heroin?) at three different time points post cue exposure

Notes: Opiate craving scale question three mean scores in response to exposure to craving inducing video for oxytocin and placebo treated participants (n=24). Error bars are standard error of the mean.

5.1.4 Objective two

The STROOP results presented are from an initial analysis and are not valid as a technical error occurred, explained in detail in limitations (Section 5.2.1).

Objective two was to investigate the effect of nasal oxytocin administration compared to placebo on opioid related cue-induced attention bias at 7 and 30 minute post exposure.

One participant was removed due to response times below 150ms or above 2000ms (Jones et al., 2021). The raw data shows that the STROOP effect increased three-fold under oxytocin versus placebo at both 8 and 31 minutes post exposure to the opioid-related cue (Table 5.2).

	Neutral words mean response time in <i>ms</i> (SD)	Heroin words mean response time in <i>ms</i> (SD)	STROOP Effect in <i>ms</i> (SD)	Difference from baseline (%)
No spray (visit one)				
<i>Baseline</i>	1097 (196)	1115 (192)	18 (93)	N/A
<i>8 mins</i>	1016 (195)	1035 (193)	19 (65)	5.55
<i>31 mins</i>	971 (201)	974 (188)	3 (104)	-83.33
Placebo				
<i>Baseline</i>	971 (197)	984 (193)	13 (93)	N/A
<i>8 mins</i>	923 (195)	930 (190)	7 (64)	-46.15
<i>31 mins</i>	900 (197)	907 (185)	7 (104)	-46.15
Oxytocin				
<i>Baseline</i>	952 (195)	994 (191)	42 (94)	N/A
<i>8 mins</i>	899 (193)	927 (188)	28 (65)	-33.33
<i>31 mins</i>	870 (196)	888 (184)	18 (104)	-57.14

Table 5.2: Observed mean participant response time and average STROOP effect at baseline, 8 minutes and 31 minutes post exposure to opioid-related video cue

Notes: One participant was removed due to response times below 150ms or above 2000ms (Jones et al., 2021). Total participants included, 23. N/A, not applicable. *ms*, milliseconds. SD, standard deviation.

Analysis of the marginal mean data following repeated measures ANCOVA shown in Figure 5.9 shows there was no statistically significant effect of treatment ($F = 0.00$, $df=1$, $p=0.98$, $\eta^2=0.00$), time ($F = 0.08$, $df=1$, $p=0.77$, $\eta^2=0.00$) or treatment*time ($F = 0.21$, $df=1$, $p=0.64$, $\eta^2=0.11$). There was no order effect on time ($F = 1.87$, $df=1$, $p=1.87$, $\eta^2=0.09$), treatment ($F = 0.85$, $df=1$, $p=0.36$, $\eta^2=0.04$) or treatment*time ($F = 0.41$, $df=1$, $p=0.53$, $\eta^2=0.02$).

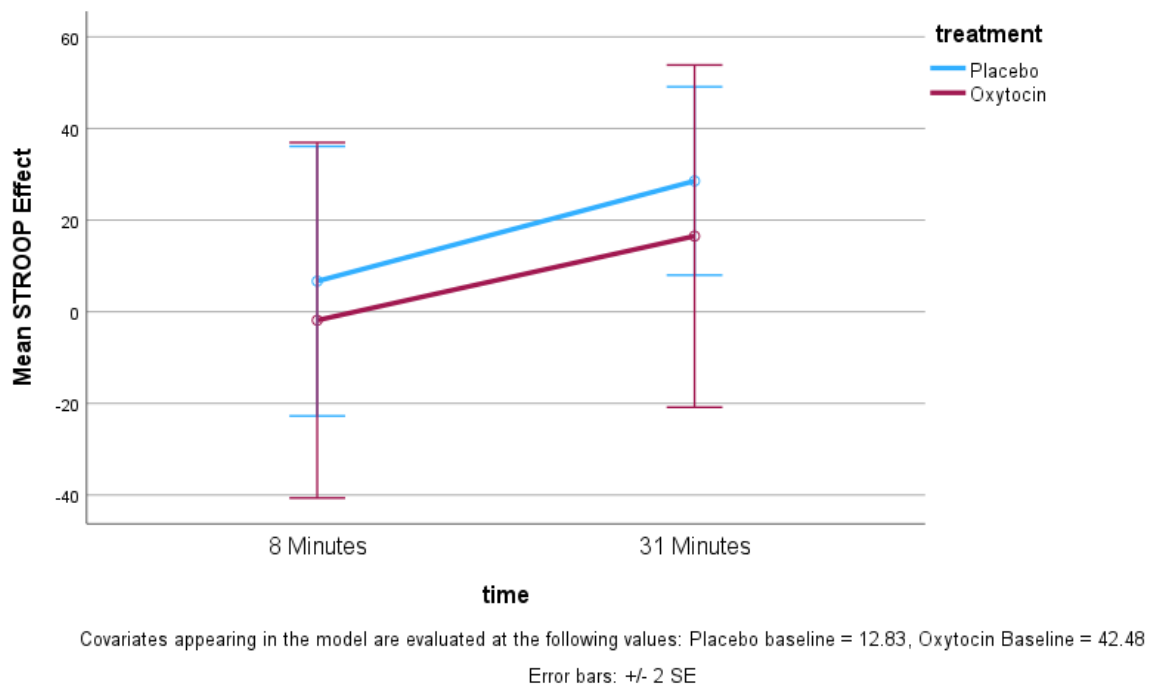


Figure 5.9: Marginal mean scores of Addiction STROOP effect at two different time points post cue exposure

Notes: Addiction STROOP marginal mean scores in response to exposure to craving inducing video for oxytocin and placebo treated participants (n=23). Error bars are standard error of the mean. Placebo baseline score 12.83, Oxytocin baseline score, 42.48

5.1.5 Objective three

Objective three was to assess whether under placebo, the change in opioid craving compared to baseline at 7, 15 and 30 min is associated with the change in attention bias following opioid related cue induction, compared to baseline and at 7 minutes post exposure.

There was a weak negative correlation which was not significant between craving at 7 minutes versus baseline and STROOP at 7 minutes versus baseline $r(1) = -0.27$, $p=0.45$. Craving scores were not associated with attentional bias $R^2 = 0.002$, $F(2, 20) = 0.23$, $p = .977$

There was a very weak positive correlation which was not significant between craving at 15 minutes versus baseline and STROOP at 7 minutes versus baseline $r(1) = 0.10$,

$p=0.32$. Craving scores were not associated with attentional bias $R^2 = 0.034$, $F(2, 20) = 0.34$, $p = .710$

There was a moderate negative correlation which was not significant between craving at 30 minutes versus baseline and STROOP at 7 minutes versus baseline $r(1) = -0.45$, $p=0.42$. Craving scores were not associated with attentional bias $R^2 = 0.103$, $F(2, 20) = 1.15$, $p = .336$

5.1.6 Objective four

Objective four was to assess whether the effect of nasal oxytocin administration compared to placebo on opioid related cue induced attentional bias at min 7 predicts its effect on the subjective feeling of opioid craving compared to placebo at 15 and 30 minutes post-exposure.

There was a weak positive correlation which was not significant between craving under placebo at 7 minutes versus craving under oxytocin at baseline and STROOP at 7 minutes versus baseline $r(2) = 0.12$, $p=0.28$. Craving scores did not predict attentional bias $R^2 = 0.015$, $F(1, 21) = 0.32$, $p = .577$

There was a weak positive correlation which was not significant between craving under placebo at 15 minutes versus craving under oxytocin at baseline and STROOP at 7 minutes versus baseline $r(2) = 0.25$, $p=0.11$. Craving scores did not predict attentional bias $R^2 = 0.066$, $F(1, 21) = 1.48$, $p = .236$

There was a weak positive correlation which was not significant between craving under placebo at 30 minutes versus craving under oxytocin at baseline and STROOP at 7 minutes versus baseline $r(2) = 0.27$, $p=0.10$. Craving scores did not predict attentional bias $R^2 = 0.077$, $F(1, 21) = 1.74$, $p = .200$

5.1.7 Observations

Post craving inducement at visits 1, 2 and 3 no participant waited at the treatment centre for craving to fully subside. Reasons given were participants confirmed they felt ok ($n=62$), partner/friend/family member was waiting ($n=4$), had to go to work ($n=1$), not stated ($n=1$), taxi was waiting ($n=3$), needed to leave in order to get buprenorphine from the pharmacy ($n=1$). Naloxone was offered a total of 72 times to participants and accepted a total of 3 times. Reasons given to decline Naloxone were

they already had it (n=57), Naloxone was not given by the drug service when the participant had previously requested (n=5), the participant perceived themselves as low risk of overdose due to smoking route of administration (n=4), the participant used heroin alone so felt it was pointless because nobody could use Naloxone on them if they overdosed (n=3).

5.1.8 Adverse events

There were no major protocol deviations and no adverse events to report. Self-administration of both placebo and oxytocin spray was well tolerated with no concerns reported.

5.2 Discussion

This double-blind, within-subjects crossover study is the first to examine the effects of nasal oxytocin (single dose; 40IU) on cue-induced opioid craving across three time points post craving induction. The time points were informed by fMRI evidence of opioid cue-induction demonstrating that amygdala activity peaks at 7 minutes post exposure to opioid-related cue and dissipates at 15 minutes (Murphy et al., 2018). Both placebo and oxytocin reduced cue-induced opioid craving in opioid dependent males receiving substitute opiates in community drug treatment who continue to use illicit heroin but there was no significant difference between the two groups. The lack of significance extended to acute subject craving feelings (as measured by Q1), craving associated with assessment of drug related cue value (as measured by Q2) and craving associated with memory of drug related cue (as measured by Q3). The overall effect of oxytocin on reducing the subjective feeling component of cue-induced craving was compounded by variance of distribution amongst other confounding variables and was further skewed by a large expectation effect where any spray clearly reduced craving making reliable interpretation of any oxytocin efficacy impossible. Effect sizes were encouraging to suggest practical significance for nasal oxytocin to reduce cue-induced craving and for an effect of nasal oxytocin on cue assessment which warrants further investigation. The results extend understanding for the design of studies which can reliably assess the role of nasal oxytocin as an anticraving opioid pharmacotherapy.

Data analysed in Figure 5.3 supports the fMRI studies which influenced the design used here (Murphy et al., 2018) to show a peak in cue-induced craving following

exposure to a novel cue at 7 minutes when no spray was administered. Baseline craving scores of 4-6 were lower than those previously found in opioid-dependent people ($M=6.9$, $n=360$) receiving buprenorphine-naloxone substitute opiate therapy (McHugh et al., 2014). The difference in craving may be due to substitute opiate medication where our participants were mostly prescribed methadone or in the participant characteristics where McHugh et al. (2014) recruited people dependent on prescription opioids only, excluding those with significant heroin use (defined as 5 or more days of heroin use in the previous 30 days, history of heroin injecting, or history of opioid dependence based on heroin use alone). It was notable in our study that craving was induced despite the prescribed doses of substitute opiates (Table 5.1), commonly reported to reduce all craving. When craving induction is rapid and intense without management, the response of buying and using opioids is easily initiated so accidental overdose can easily occur (Chapter six). When any spray was self-administered (but in front of the experimenter) there was a strong observer-experimenter effect which reduced self-reported craving (Figure 5.4). Observer-experimenter effects occur when the expectations of the observer influence the behaviour of participants (Holman et al., 2015). In this case the participants knew the key study outcome was reduction of cue-induced opioid craving and thereby reported lower craving scores following spray administration vs no spray day, irrespective of the content of the spray. Blinding is recommended to counter observer-experimenter effects and although this study was double-blinded, the effect may then have appeared because participants expected to find an effect of reduced cue-induced craving because that outcome was important to them (Zhou et al., 2019). The influence of participant expectations in clinical trials is not new. Between 2006 and 2017 90% of analgesic drug studies were not progressed beyond phase two and three trials due to failure to show superiority versus placebo, supporting findings from clinical trials related to treating depression and is an established problem within the emerging field of using psychedelics as treatment (Frisaldi et al., 2017; Curkovic and Kosec, 2019; Butler et al., 2022). Although participant expectation hindered the null hypothesis significance testing in this study, participant expectancy has been suggested elsewhere as being an important therapeutic outcome in clinical trials of this nature and should not be overlooked (Frisaldi et al., 2017).

There were many similarities between this study and the existing literature but also some key differences which may have affected the results. Our design differed from Moeini et al. (2019) and Woolley et al. (2016) who both used parallel designs as opposed to crossover, also used by Stauffer et al. (2016). Only Moeini et al. (2019) reported a reduction in craving versus placebo with the remainder finding no significant difference versus placebo. All studies were double-blind, placebo controlled recruiting similar participant characteristics. Moeini et al. (2019) and Woolley et al. (2016) also administered 40IU nasal oxytocin, recruited males only, utilised video or pictorial cues to induce craving and appointment times were broadly similar. Stauffer et al. (2016) used a repeated self-administration design in contrast to other studies and measured craving 1 minute post exposure to a pictorial cue. Moeini et al. (2019) participants had an average age of 33.8 years, Woolley et al. (2016) participants had an average age of 57.97 and Stauffer et al. (2016) recruited mainly African-Americans with an average age of 49.5 in comparison to the predominantly Caucasian males with an average age of 44.3 recruited in our study. Our participant characteristics reflected the in-treatment population for the UK (Adult Substance Misuse Treatment Statistics 2020 to 2021; Report, 2021), and as with Stauffer et al. (2016), our participants were also using concurrently using crack cocaine whereas Moeini et al. (2019) and Woolley et al. (2016) recruited abstinent participants with illicit drug use an exclusion criteria. There are likely differences in craving when people are actively using heroin and crack cocaine versus abstinent people. The inclusion of craving measures for crack cocaine alongside opioid craving measures should be considered in future studies. Methadone dose was not specified by Moeini et al. (2019) or Woolley et al. (2016) but Stauffer et al. (2016) reported an average dose of 101.4mg daily in comparison to 60.95mg daily in our study. Woolley et al. (2016) did confirm that study procedures took place 4 hours post methadone dosing in comparison to 13.24-14.64 hours in our study which meant that participants were experiencing the peak effects of methadone in Woolley et al. (2016) when undergoing procedures. Identifying the dose and timing of substitute opiate is important to identify whether nasal oxytocin can support existing pharmacotherapies when substitute opiates are past the expected peak plasma effects. The difference in time of methadone dosing is likely explained by study setting affecting control of the methadone variable (inpatient treatment in all other studies versus community treatment in this study).

Interestingly there was no difference in retention rate across all studies irrespective of setting (>85%). Only our study reported the current psychiatric disorders participants were diagnosed with and medications participants were currently prescribed. Both of these can impact cognitive function. Participant expectancy effects were not discussed by the existing literature but are not unexpected in trials of this nature and should be acknowledged (Zhou et al, 2019). It is encouraging that participant demographics, use of pictorial cues to induce opioid craving, tolerability and acceptability for nasal oxytocin sprays to reduce craving and participant retention rate (irrespective of treatment setting and concurrent opioid use) are becoming established in the literature. To progress nasal oxytocin studies much more detail is needed to be consistently reported in order to identify if there are specific subsets of the population for which nasal oxytocin may be more effective. This thesis recommends that participant characteristics are fully described such as oxytocin dose, participant age, time since last use of heroin, dose and time since substitute opiate dose, other concurrent substance use, presence of psychiatric disorders and concurrent medications by all studies of this nature to aid interpretation of the real world context for nasal oxytocin and opioid craving management.

Question one ‘How much do you currently crave opiates?’

Regarding ‘How much do you currently crave opiates?’ this was measured by the subjective feeling of opioid craving in real time. The reduction in craving under oxytocin versus placebo was greater but not statistically significant (Figure 5.4, Figure 5.5). There are ten key discussion points for failure to find significance of the effect. Firstly under oxytocin there was a higher baseline craving score. This resulted in the baseline oxytocin mean being 2 points higher than placebo on the eleven point Likert scale, a large difference albeit not significant. Secondly although OCS question one score distribution was overall parametric, the variability in distribution (Figure 5.6) could have confounded analysis in the sample. Thirdly, further caution should be applied to the reliability of the planned null hypothesis significance testing where no significant effect for time was found. This was surprising as the time period for data collection post cue-inducement reflected fMRI evidence which showed a reduction in brain activity across the same period (Murphy et al., 2018) and our participant self-report showed a return to baseline levels of craving (Figure 5.4). Fourthly, higher baseline craving under oxytocin (which more people received as the first treatment,

n=14) versus placebo suggests that participants could have become used to the cue, study conditions and perhaps were experiencing less anxiety (or confusing general study anxiety with craving at visit two) by the third visit. Fifthly the cue exposure video was not directly relevant to every participant with mean scores of 6/10 only (Figure 5.8). Had each cue exposure been individually relevant there may have been a greater effect on participant craving as suggested by participants during visit four. It was notable that when participants did not groin inject heroin as depicted by the video, participants remarked the audio narration of the person lying to his family and the family detailing their own feelings surrounding the person injecting brought about feelings of shame and identification which made them crave more than the act of groin injecting itself. Sixthly, although craving was measured at the evidenced peak time of brain activity following exposure to an opioid-related cue (Murphy et al., 2018), oxytocin was administered 15 minutes before the outcome measure was collected and, crucially, six minutes before the opioid-related cue was shown. Pragmatic studies will be needed where nasal oxytocin is administered when the opioid-related cue is first encountered and not before. Currently there is no evidence to show amygdala activity earlier than 15 minutes following nasal oxytocin administration and so our drug administration schedule reflected the available evidence. Eighthly, no other known study has used the OCS as a repeated measure in the same experimental visit and so reliability of the tool as a repeat measure cannot be assured. Ninthly, the dose may be inadequate where recent literature has shown that different doses (9, 18, 36IU) follow a dose response curve for regional cerebral blood flow in the amygdala at rest. In addition the subregion of the amygdala may also play a role but this was beyond the parameters of our study to explore (Martins et al., 2022). Finally people who use opioids have been found to have difficulty with interoceptive processing, the ability to identify changes in bodily sensations in response to external stimuli (Sübay and Sönmez, 2021). The difficulties with interoceptive processing and Alexithymia (the inability to identify and describe emotions experienced by oneself) associated with craving severity in males who use opioids (Gong et al., 2021) would make the internal monitoring of changes in craving difficult. Altered interoception and Alexithymia would provide additional explanation for why some people report to not feel craving (Drummond, 2001). Participant difficulties in identifying the feeling of opioid-craving and Alexithymia are supported in the narratives explored in Chapter six. Taken

together with the observer-experimenter effect seen under both oxytocin and placebo leading to a significant effect of treatment when comparisons were made with the non-spray craving, together with almost a third of participants reporting no difference in subjective craving, subjective feeling of craving may be a poor outcome measurement for this population. For that reason we had included an objective measure of increased emotional feelings following cue exposure: measurement of an emotional STROOP effect.

Of note is the possibility that the greater change from baseline in craving under oxytocin (Figure 5.5) could be the result of regression to the mean. Regression to the mean is a statistical phenomenon that happens when unusually large or small measurements, such as the higher baseline craving score under oxytocin versus placebo) are followed by repeated measurements which are closer to the real mean giving a false impression of change (Barnett et al., 2005). Common examples are from objective measures (blood pressure, height, birth weight, cholesterol) whereas our study required a subjective self-report of a bodily sensation our population have evidenced difficulties with as discussed above (Sübay and Sönmez, 2021). In addition there are a range of factors such as last use of heroin, time since methadone/buprenorphine dose and general anxiety which would have affected the self-report of the baseline measurement. Literature recommends protecting against regression to the mean at both the design and analysis stage. Multiple baseline measurements are recommended (Greender et al., 1992; Barnett et al., 2005) though again, due to the subjective nature of the craving measurement, it is difficult to see how baseline scores would have changed in this study. The inclusion of control groups is also recommended however our study utilised a crossover design where participants act as their own controls. Mean baseline scores on visit one where no spray was received (4.92, Figure 5.3) were closer to the oxytocin group (4.58) and so it may be that where fourteen people received oxytocin first versus ten for placebo, the lower baseline scores under placebo (3.92) were a simple carryover effect from the previous two visits with further reduction in craving scores rather than increasing to the mean a placebo effect of taking any spray. Analysing data with ANCOVA is also recommended to protecting against regression to the mean (Barnett et al., 2005) as in our study (Figure 5.4) which found no statistical significance for nasal oxytocin versus placebo to reduce craving.

The participant experience cannot be ignored entirely in favour of statistical significance and neither should statistical significance be discarded in favour of any other analysis that favours the hypothesis. All sources of evidence should be evaluated on their combined merit. Historically when this has not happened science dismissed patient reporting of antidepressant and antipsychotic withdrawal for decades leading to patient harm (Read, 2022; Hengartner et al., 2020; Guy et al., 2020). Within the realm of substance use disorders, there is a growing body of research to understand the effects of medicinal cannabis where patients report benefits yet the evidence base is at best mixed with high indications of placebo effects (Gedin et al., 2022). In the emerging area of using Psilocybin as a mental health and substance use disorder therapy early studies recruited small samples (albeit some were pilot studies and so appropriately small), many were open label and some did not include control groups (Henrique and Gama Marques, 2021). Expectancy effects are likely pronounced in these studies but without the self-report evidence from these studies then larger studies which have demonstrated efficacy utilising more rigorous methods, though the largest trial to date was still notably without a control group and likely influenced by participant expectancy, would not have been possible (Goodwin et al., 2022). Where trials have been placebo controlled, placebo could account for 40% of positive results (Hendrie and Pickles, 2016) at least in the early literature with some recent trials also showing no effect versus placebo (Szigeti et al., 2021; Marschall et al., 2022). Lack of statistical significant results do not mean there are no benefits to psychedelic treatments. Meta-analysis of placebo-controlled psychedelic assisted therapy have used effect sizes to determine direction of future research where p values did not approach significance but effect sizes were large (Luoma et al., 2020). It is recommended that oxytocin studies adopt a similar approach when evaluating oxytocin versus placebo for specific treatments given the evidence for expectancy effects where null hypothesis significance testing may otherwise halt future research of clinically significant treatments (Frisaldi et al., 2017; Curkovic and Kosec, 2019).

Question two 'If you saw this in your everyday life, how much would you crave heroin?'

Regarding 'If you saw this in your everyday life, how much would you crave heroin?' this question within the OCS related to an assessment of value towards the same cue which had been used to induce craving (Figure 5.4). No significant effect between

placebo and oxytocin was found on the assessment of whether exposure to this cue would lead to craving outside the clinical environment. The difference between processing question one and two is important. Question one (How much do you currently crave opiates?) required an identification of an internal momentary feeling whereas question two ('If you saw this in your everyday life, how much would you crave heroin?') required assessment of a cue to assign value, two different stages of the same neurological process when people encounter drug-related cues (Volkow et al., 2003; Goldstein and Volkow 2011; Figure 3.1). The larger reduction of craving under oxytocin may be due to the anxiolytic properties of oxytocin reducing amygdala activity and thus the value of the cue was diminished without an assessed need to fulfil (Figure 5.5).

Cue assessment is a critical part of opioid use and the interesting effect size of oxytocin on cue assessment is worthy of further research. For a cue to trigger craving then the cue must hold value i.e. each cue must be associated with a value linked belief. Value based decision making can involve economic value (decisions which provide benefit) and core values (motivational constructs and beliefs such as self-direction, stimulation, hedonism, achievement, power, security, conformity, tradition, benevolence and universalism about desirable end states which persist beyond changes to specific scenarios). Economic decisions have reliably been delineated to demonstrate activation in ventromedial prefrontal cortex/orbitofrontal cortex, ventral striatum, posterior cingulate cortex, amygdala, insula and posterior parietal cortex in studies where participants are offered a choice between rewarding and punishing stimuli as well as in studies where participants choose between a small reward now or a larger reward later known as delay gratification. The prefrontal cortex/orbitofrontal cortex has also shown activation in decision-making tasks involving core values indicating a common brain network across value based decision making (Brosch and Sander, 2013). One recent study measured value based decision making in people who use opioids that were twenty-four hours since their last dose of methadone. Findings showed that when people were experiencing withdrawal-related craving, people who used opioids were more likely to pay higher costs for consumer items and food more closely related to their opioid use than nonopioid-related but equally desirable options (Biernacki et al., 2022). This indicates withdrawal-related craving was driving a cognitive process where value of the stimuli was closely related to satiation of the need

(withdrawal). If oxytocin ameliorates the cue value assessment process then it follows opioid use would be reduced.

One as yet untested theory of value based decision making of people who use substances in early recovery suggests that there is an abundance of ‘noise’ surrounding cues which makes the cue-response difficult to suppress without finding alternative substance-free activities whose cues generate greater ‘noise’ (Field et al., 2020). ‘If you saw this in your everyday life, how much would you crave heroin?’ may speculatively indicate that in the presence of opioid-related cues when people are still actively using heroin, nasal oxytocin calms hyperactivity in the amygdala temporarily suppressing the cue ‘noise’, halting the anterior cingulate from assigning value to the cue and pausing the automaticity of cue-response (Volkow et al., 2003; Goldstein and Volkow 2011; Figure 3.1). Evidence has already shown that nasal oxytocin may help with impulsive cue response and cue reappraisal (Kapetaniou et al., 2021). Potentially in the immediate fifteen minute window of where amygdala activity is reduced following nasal oxytocin administration (Martins et al., 2020) is when the value of the cue may then be able to be reassessed allowing people to make a choice not to use opioids. Value based decision making within cue-induced cravings is then a natural target for inclusion in future models. For more information on value based decision making in addiction the reader is directed to Field et al. (2020).

Question three ‘How much did the video remind you of times that you have used heroin?’

Regarding ‘How much did the video remind you of times that you have used heroin?’ this question within the OCS related to the memory recall and association of the cue used to induce craving. Figures 5.8 showed there was no change across time or treatment in oxytocin, placebo or when no spray was administered. In contrast to question two there was also no difference in mean self-report between placebo and oxytocin. The reason may be that question one required identification of a momentary change in feeling, question two required a cue assessment and question three related to recall of a fixed point in memory. Given nasal oxytocins perceptual selectivity of cues differing between people (Bethlehem et al., 2013) there may have been a greater effect on question one if the cue was chosen based on an already conditioned association for each individual participant (Alaerts et al., 2021). Alternatively whilst

it is beyond the scope of this thesis to discuss memory retrieval processes, cued-recall is thought to evoke generate-recognise retrieval processes i.e. in the presence of cues firstly people generate a number of possible responses and then secondly each response is monitored for accuracy to the situation (Hunt et al., 2016). As nasal oxytocin may have impacted the cue assessment stage of opioid craving (Figure 5.7) then it may be that nasal oxytocin affects the generate-recognise process of cued memory recall. Although there was no significant effect for memory recall this does not necessarily conflict with the idea of oxytocin affecting cued memory recall if the process is staged i.e. accessing the memory is a stage before assessment of the cue and so recalling the association of the existing memory is not altered. Any oxytocin effect is unlikely to be a simple amplification of the positive or negative ‘recognise’ association to the cue or there would be greater variance in question two (‘if you saw this in your everyday life, how much would you crave heroin?’) under oxytocin rather than the reduction seen (Figure 5.8). The effect of nasal oxytocin on cue association and memory recall processes warrants further investigation.

Effect Sizes

Effect size may be a better indicator of superiority over placebo than null hypothesis significance testing for this population due to the number of confounding variables and high variance in the sample. Significance testing is limited by the assumption that a null hypothesis is always determinable, requiring near identical results which can mean that natural variance is misrecognised as error and that significance can be missed (Ialongo, 2016). Effect sizes occur independently of p value and report the size of any clinically significant effect, should an effect exist (Sullivan and Feinn, 2012). Whilst the study findings were unable to reject the null hypothesis, statistical significance does not define whether any effect exists. People who use opioids are likely to have multiple concurrent confounding variables (substitute opiate dose, concurrent medications, concurrent substance use, relevance of cue etc), so practical significance is of greater importance at this stage of research than statistical significance. The effect sizes found in our study are encouraging to suggest practical significance for oxytocin to reduce cue-induced craving (Table 5.3).

	<i>df</i>	<i>p</i>	η^2
Question one: How much do you currently crave opiates?			
<i>Treatment</i>	1	0.79	0.04
<i>Time</i>	2	0.27	0.62
<i>Treatment*Time</i>	2	0.40	0.45
Question two: If you saw this in your everyday life, how much would you crave heroin?			
<i>Treatment</i>	1	0.10	0.11
<i>Time</i>	2	0.16	0.78
<i>Treatment*Time</i>	2	0.16	0.78
Question three: How much did the video remind you of times that you have used heroin?			
<i>Treatment</i>	1	0.95	0.00
<i>Time</i>	2	0.25	0.06
<i>Treatment*Time</i>	2	0.25	0.06

Table 5.3: Significance and Partial ETA Squared effect sizes for craving scale questions one to three

Notes: Partial ETA Squared 0.01 = small effect, 0.06 = medium effect, 0.14 = large effect. *df*, degrees of freedom; *p*, significance; η^2 , effect size

Four out of nine analyses found large effect sizes with a further 3/9 finding moderate effect sizes. Comparisons of effect sizes with other nasal oxytocin for cue-induced opioid craving studies are difficult as effect sizes have not been routinely reported (Woolley et al., 2016; Moeini et al., 2019) however Stauffer et al. (2016) reported a medium to large effect size for oxytocin to reduce craving in their study where statistical significance was not found. Statistically significant differences between oxytocin and placebo were also not found by Stauffer et al. (2016) but their effect sizes supported those seen in our study (medium to large). To better understand the practical significance in nasal oxytocin studies it is vital that effect sizes are reported.

Attentional Bias

Prior to analysis of the attentional bias results it was required to first cleanse the data of any outliers in response times. In line with previous research any responses below 150ms or above 2000ms were identified as outliers to be removed (Jones et al., 2021). One participant was removed. In addition one systematic review of attentional bias in opioid use disorder suggested excluding any individual trials which were three standard deviations beyond the mean (Maclean et al., 2018). Following this no further participants were removed.

The observed mean data displayed an attentional bias of 18ms at baseline where no spray was administered for opioid related cues (Table 5.2) supporting systematic review evidence for attentional biases in the addiction STROOP for people who use opioids (Maclean et al., 2018; Table 5.4).

<i>Study</i>	<i>Participants</i>	<i>Last use of opioids</i>	<i>Opioid type</i>	<i>STROOP effect (ms)</i>
Fadardi and Ziacee (2010)	Opioid Users (n=53, 100% male) Healthy Controls (n=71, 54% male)	Last illicit use not reported, MMT daily	Heroin and Opium	Opioid users; 90 Healthy controls; 24
Franken et al (2000)*	Heroin dependent (n=21, 71% male) Healthy controls (n=30, 83% male)	>1 week	Heroin	Opioid users; Masked -5 Unmasked 64 Healthy controls; Masked 5 Unmasked 7
Franken et al. (2004)	Heroin dependent (n=17, 100% male)	>2 weeks	Heroin	Not reported
Lusher et al. (2009)	Heroin dependent (n=75, 85% male)	>1 day	Heroin	73
Marhe et al. (2013)	Heroin dependent (n=64, 85% male)	<1week, undergoing detoxification	Heroin	Relapsers; Temptation Assessments 159 Random Assessments 57 Non-Relapsers;

				Temptation Assessments 58 Random Assessments 36
Marissen et al. (2006)	Heroin dependent (n=110, 89% male)	>2 weeks, post detoxification	Heroin	Relapsers; 69 Non-Relapsers; 27
Waters et al. (2012)	Heroin dependent (n=63, 85% male)	<1 week, MMT daily during detoxification	Heroin	Temptation Assessments 64 Random Assessments 34
Yang et al. (2015)**	Heroin dependent (n=15, 100% male) Healthy Controls (n=15, 100% male)	>2 weeks, Partial MMT (n=2)	Heroin	No difference between groups

Table 5.4: Reported addiction STROOP effect in studies measuring attentional bias in people who use opioids

Notes: Franken et al. (2004) report a visual bar graph and p values of treatment versus placebo but no response times or STROOP effect, Yang et al. (2015) do not report STROOP effect. MMT, Methadone Maintenance Treatment; ms, milliseconds; * verbal response on STROOP; **modified emotional STROOP rather than validated addiction STROOP. Table adapted from Maclean et al. (2018).

There are no other studies which have investigated the effect of nasal oxytocin on attentional bias in people who use substances and so results cannot be compared. In contrast with our original model (Chapter three, figure 3.3) where we expected that nasal oxytocin's ability to calm the amygdala would allow for increased control over attentional bias, attentional bias was 3x higher under oxytocin at 8 minutes compared to placebo, decreasing from baseline by 33% under oxytocin compared to a decrease from baseline of 46% under placebo and 2.5x higher under oxytocin at 31minutes versus placebo albeit under oxytocin this was a reduction from baseline of 57% compared to 46% under placebo post exposure to the cue (Table 5.2). Our model proposed that attentional bias would acutely increase following exposure to a cue but these results suggest the opposite, although the observed reductions over time in STROOP effect could also be the result of learning.

In contrast to Field et al. (2009) meta-analysis, our study did not find that craving was associated with attentional bias and neither could craving scores predict attentional bias. Under placebo it was not expected to see negative correlations between craving and attentional bias at 7 and 30 minutes but a positive correlation at 15 minutes post exposure to the cue. This may suggest that at 7 minutes post exposure to an opioid-related cue, the peak time of brain activity following exposure to an opioid-related cue (Murphy et al. 2018), motor response can be rapid but slows 15 minutes post exposure when brain activity for craving is thought to have diminished. This does not explain why there was a further negative correlation at 30 minutes post exposure to the cue and is likely the result of the significant STROOP-related limitations as discussed in section 5.2.1. However, the STROOP results presented were from an initial analysis and were not valid as a technical error occurred, explained in detail in limitations (Section 5.2.1).

5.2.1 Limitations

There were a number of limitations to the overall study. First, the study focused on male participants due to sexual dimorphism in the oxytocin system and so findings cannot be extrapolated to females. Second, the study recruited people who had used heroin at least once in the last week, the majority had used within one day and so findings may not be consistent in people who are abstinent from heroin use. Third, concurrent psychiatric medications and concurrent use of alcohol, cannabis and crack cocaine can all impact performance in the experimental visits. The crossover design mitigated this to some degree. Whilst confounding variables diluted the analysis of statistical significance, practical significance was increased through greater representation of the target population. Fourthly, there was large variation in time since substitute opiate dose to treatment at the group level though individually the time from dose to treatment was consistent. Timing of substitute opiate dose is important in relation to ability to reduce craving. This study shows that males can be triggered to crave heroin by cues when optimal substitute opiates are outside 2-4 hours since consumption and therefore not at peak plasma levels (Figure 5.4; Clinical Guidelines on Drug Misuse and Dependence Update, 2017). Fifthly, for the subjective nature of craving, although not significant the higher baseline scores under oxytocin and greater variance in response under oxytocin are likely to have confounded analysis for question one (How much do you currently crave opiates?) of the OCS. Sixthly, the

crossover design may not have been optimal to reduce the participant expectancy effect as participants knew they would be receiving both oxytocin and placebo. In a parallel design participants would only have a 50% chance of receiving the treatment and so expectancy of an effect would be reduced. Seventhly it is possible that participants did not associate the novel cue with heroin use following exposure as they were denied of the opportunity to use heroin following the first craving induction. Finally, we had calculated 34 participants were required to be fully powered but were only able to recruit 24 participants meaning the study was likely underpowered. Larger cohorts will be necessary to confirm whether nasal oxytocin can reduce opioid craving however it may be that given the difficulties with identifying subjective opioid craving within this population, future studies will need to include objective measures (opioid use, change in attentional bias) as the primary outcome. Together these represent important limitations to the analysis. Exclusion criteria could remove concurrent psychiatric medications and concurrent substance use but the sample would then not be representative of the population and of very little practical significance.

The methodology specifically used to conduct the STROOP tests was also limited. Whilst I was analysing and trying to interpret the STROOP results I scrutinised the raw data and discovered that due to a major technical error in the automatic randomisation for the allocation per participant of each of the testing conditions the data could not be valid. Thus, although I am presenting here the initial analysis (before the error was discovered) the STROOP effects reported are not valid due to this error. The STROOP program randomized 40 trials but balanced trials per condition approximately 1:3 (neutral versus opioid related) and not in a homogenous way. Comparisons are then difficult to evaluate as participants received a higher number of opioid related words compared to neutral words (Table 5.5).

	<i>Neutral words</i>			<i>Opioid related words</i>		
	Baseline	8 Mins	31 Mins	Baseline	8 Mins	31Mins
<i>Clinic visit 1 (no spray)</i>	10	11	10	30	29	30
<i>Clinic visit 2 (Oxytocin)</i>	14	9	11	26	31	29
<i>Clinic visit 3 (Placebo)</i>	15	11	8	25	29	32

Table 5.5: Example of the Addiction Stroop trial randomization error for participant thirteen

Notes: Participant thirteen received an unbalanced number of trials for neutral and heroin-related words approximately 1:3 at each measurement point.

Cox et al. (2006) recommend the use of blocked stimuli presentation with a neutral filler word prior the presentation of a control word to reduce carryover effects rather than randomised. The stimulus words were part in line with recommendations made by Cox et al. (2006) in that they came from a validated source however one slang term for heroin, ‘brown’, is directly associated with a colour. ‘Brown’ was not omitted as this word is highly relevant to the sample. There are additional thoughts around the Stroop use to make it more relevant to the participants and more sensitive to drug effects. For instance, the opioid and neutral words could have been created as part of the patient and public involvement activities which would have removed any cultural differences where the word list used was American in origin. Generalised lists were chosen over individualised lists in order to ensure validity and also eliminated further individual differences in the sample where heterogeneity was already expected to exist during analysis. For therapeutic relevance this meant the results may not have been as precise as customising the words used as identified by participants (Cox et al., 2006). In line with Cox et al. (2006) four different responses were available to participants but these responses required solely a motor response rather than a verbal response. Responses were mapped to keys and no colour dots were placed on the relevant keys which increased the cognitive demand for participants to first read the word, then identify the colour and then press the correct key. Although a combination of vocal and manual responses are recommended as optimal for design (Cox et al., 2006), the

resource limitations of this study would not have allowed this to be incorporated. No participants reported problems with key mapping and so if this was a limitation then it was equal to all participants. This limitation may hinder comparison with other studies but aided validity of our study. One participant declined participation due to anxiety over dyslexia and his inability to complete the Stroop task and whilst participants questioned whether colour-blind people would fare differently, no participants were colour blind themselves.

5.3 Conclusion

This single-dose crossover study did not find any significant difference for nasal oxytocin versus placebo to reduce cue-induced opioid craving although both placebo and oxytocin reduced craving compared to treatment as usual (no spray) in visit one. Effect sizes, particularly regarding ‘If you saw this in your everyday life, how much would you crave heroin?’ which measured assessment of an opioid-related cue, were encouraging to suggest practical significance. Due to the expectancy effects where participants both identified with the problem and had a desire to find a solution, it may be the only way to evaluate whether nasal oxytocin can be used ad-hoc to reduce opioid use is by performing trials where nasal oxytocin can be used pragmatically alongside community treatment.

Figure 5.10 provides a visual representation of the thesis up until chapter six. Chapter six provides detailed narrative of the participant experience of craving which augment the quantitative results shown here.

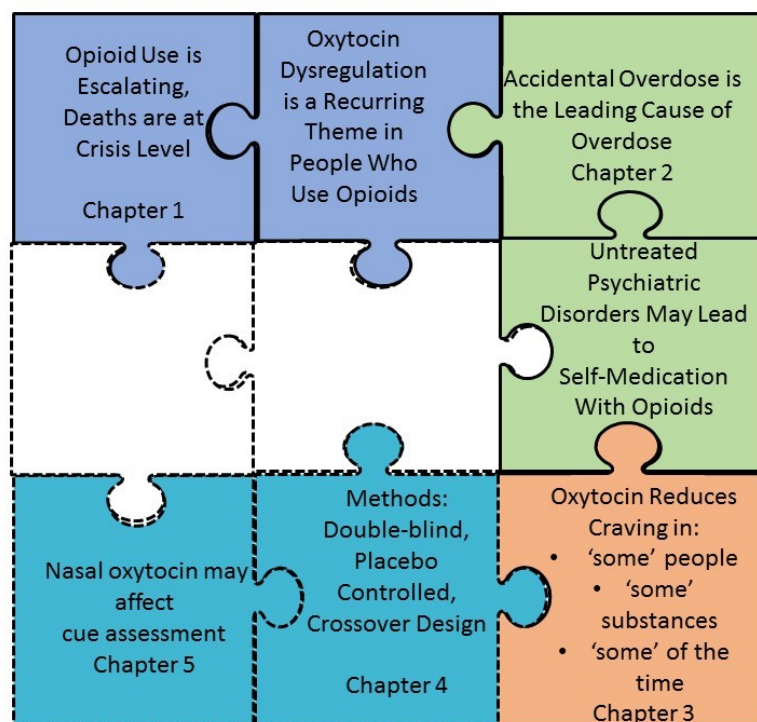


Figure 5.10: Key thesis findings by chapter up to chapter six

Notes: Chapter one outlined the extent of the opioid crisis with opioid-related deaths at crisis level. Chronic drug use dysregulates the endogenous oxytocin system and is highlighted in people who experience early life trauma and people with psychiatric disorders, both of which are highly prevalent in people who use opioids. Chapter two analysed the prevalence of psychiatric disorders in deaths where opioids were found at post-mortem and suggested that self-medication in the absence of psychological treatments may contribute to accidental overdose. Chapter three systematically reviewed human studies for nasal oxytocin to reduce craving or consumption in substance use disorders finding that nasal oxytocin works in some of the people, some of the time but variation throughout studies prohibits conclusive results. Chapter five showed that nasal oxytocin may play a larger role in the assessment of opioid-related cues. Chapter six presents results of the qualitative analysis.

Chapter Six

Exploring the Influences, Experiences and Perspectives of Opioid Seeking Behaviour in Dependent Opioid Users (Qualitative Results)

*‘The mentality, thought system and relationships that got you into addiction
will keep you there unless you disentangle yourself from them.’*

– Oche Otorkpa, The Night Before I killed Addiction

Abstract

There are strong social influences on the procurement of alcohol, cannabis, powder cocaine and ecstasy. Heroin is a drug typically thought of being used in isolation and there is a paucity of research exploring how social influences impact procuring heroin, particularly when people are trying to stop using heroin. To address this gap, this chapter explored external and internal determinants (triggers, craving management and the influence of others) which influence continuation of opioid use in males in UK community drug treatment who use illicit opioids alongside prescribed substitute opioids. The sample was self-selecting from the sample purposively recruited in chapter five. Using Janis (1972) eight symptoms of Groupthink as an a priori framework for analysis of the external determinants, the study method utilised qualitative interviews with fourteen men. Discussions were audio-recorded, transcribed verbatim, and analyzed thematically. Interviewees struggled to identify the feeling of craving, instead describing craving as continuous and intrusive thoughts. Evidence of Groupthink processes overall appeared in 13/14 interviews. *Peer pressure* was identified across 11/14 of the interviews followed by *rationale* (9/14). *Stereotypes* and *unanimity* appeared in 7/14 interviews with *invulnerability* and *morality* appearing in 6/14. The symptoms of *self-censorship* and *mind guards* did not appear. Interviews identified a shift in social networks from networks built on shared moments to networks built on transactional exchange. Individuals positioned themselves away from the heroin using group but were unable to break away fearing judgement from non-drug using society leaving them isolated. The greatest benefit to this network was mutual understanding though this created a cognitive dissonance when individuals wanted to stop using but continued to engage with group led transactional exchanges. The individual goal versus group goal conflict suggests that social network interventions may be more successful if delivered to cohorts of people who buy heroin together.

6. Introduction

Existing qualitative research primarily focuses on predictors of drug use and factors involved with cessation of drug use (McIntosh and McKeganey, 2001; Petterson et al., 2018). There is a lack of research focused on the experience and perspective of drug users who report powerlessness when craving opioids (Klein et al., 2022). Analysing the individual experiences of people who use opioids is as important as collecting quantitative data. One form of data is not privileged over another, all are equally valid and reveal different aspects of the behaviour and experience. Consistencies and contradictions between quantitative data and qualitative experience will provide those working in the field with a greater understanding of the barriers people face when trying to achieve abstinence. This chapter explores the individual experience of people who use heroin in order to contribute contextual knowledge to augment the quantitative data presented in chapter five.

People who use drugs report an internal conflict surrounding lack of self-control and momentary unawareness of the influence of cues. When drugs are used or the cue is removed people are then able to retrospectively link environmental cues to initiation of the cravings (Chaves et al., 2011; Yang et al., 2015; Klein et al., 2022). Examples of these cues include negative self-image, mood disturbance and striving for acceptance from others which occur in a staged process leading to relapse (Seyedfatemi et al., 2014). However cue-induced cravings are not limited to negative feelings as positive feelings can also elicit urges to experience highs once more (Chaves et al., 2011; Yang et al., 2015). In a study in Persian people who use opioids (n=36) it was found that craving was verbalised in eighty-nine different terms within nine categories encompassing stimulation and triggering, attention bias and obsession, decision making difficulty, information processing impairment, withdrawal induction, drug euphoric experience, mental urge, motor control problem and negative valancing and stigmatizing. Terms such as ‘thought of using’, ‘my brain is confused’, ‘wanting’, ‘I can’t think’ and ‘severe stimulation’ were frequently used by people (Maarefvand et al., 2013). Hendershot et al. (2011) had earlier suggested that applying learnt coping mechanisms for cravings is influenced by individual’s variables such as self-efficacy. Recent evidence supports this revealing that repeated relapse erodes people’s belief in their own self-efficacy to maintain abstinent based recovery where the diminished belief became greater the longer treatment was attempted and repeated relapse the

outcome (Klein et al., 2022). Interestingly despite low sexual desire in people who use opioids (Kheradmand et al., 2019) terms such as ‘slang for sexual desire’, ‘slang for ejaculation’, ‘I feel horny’, ‘horny’ and ‘turn on’ were mostly described during drug craving within the dimensions of drug euphoric experience, mental urge and motor control problem (Maarefvand et al., 2013) suggesting either an increased arousal state during opioid craving, alexithymia or altered interoceptive processing. Interoceptive processing is the way a person processes bodily sensation in relation to external stimulus to affect ongoing behaviour so altered processing may mean difficulty self-reporting the feeling of craving as previously indicated in people who use opioids (Paulus and Stewart, 2014; Stewart et al., 2020; Sübay and Sönmez, 2021). Combined, the above research provides insight to the difficulty in managing opioid cravings when triggered.

Self-control and awareness in the presence of opioid-related cues may be related to attentional bias influencing cognitive dissonance (Festinger, 1957). Cognitive dissonance is a social psychological theory which suggests that people seek consistency in their perceptions and mental conflict arises (dissonance) where a person’s behaviours and beliefs do not align. For example, believing that plastic is bad for the planet but continuing to buy plastic bags or, in the case of people who use opioids, the behaviour of opioid seeking versus the belief the person wants to abstain. The interviews here explored the internal conflict felt by participants as well as the influence of others during and in initiating this conflict.

It was important to explore the influence of others as heroin is typically a drug used in isolation unlike more socially acceptable illicit drugs such as cannabis, powder cocaine or ecstasy. However in drug use of all kinds there are social relationships required to procure drugs. There is strong evidence of peer pressure in adult UK consumers of alcohol (Morris et al., 2020) as well as in US consumers of alcohol and cannabis (Keysers et al, 2020). Conversely abstinent Belgians stated that central to recovery from powder cocaine was a difficult necessity of breaking away from old contacts in order to maintain abstinence and rebuild their lives (Dekkers et al., 2020). People who used MDMA in North America have described a tight-knit clubbing scene where quality assurance from dealers who relied on repeat custom was seen as a harm minimisation technique indicating a professional, transactional but no less social relationship (Palamar and Sönmez, 2022). There is a clear social influence of others

on acquiring some drugs but there is a paucity of research exploring in depth how heroin is procured, particularly when someone is trying to stop their heroin use.

In order to greater understand the complexity of social influences on obtaining heroin from an individual perspective, analysis used a framework of Groupthink (Janis, 1972) with the intention of findings acting as a precursor to future focus group research. Groupthink (Janis, 1972) describes when individuals in a small group accept a viewpoint thought to represent the whole group irrespective of whether the individual in the group accepts the viewpoint. There is no current literature that explores groupthink within people who use opioids. Groupthink is evidenced by eight symptoms; invulnerability (the group encourages risk-taking due to excessive optimism as a collective), rationale (ignoring advice and warnings from people in the out-group and instead continue with the in-group belief), morality (people ignore ethical or moral consequences of actions and believe unquestionably in the group morality), stereotypes (people view others who aren't part of the in-group as enemies), pressure (the group applies pressure to individuals within the group who go against the group ideas), self-censorship (members of the group censor themselves from speaking out against the group consensus), illusion of unanimity (members of the group assume every member of the group thinks the same), mind guards (members of the group intentionally hide information from the group which may contradict the group consensus).

This chapter presents the qualitative results from the proof-of-concept study presented in chapters four and five. Full details of the methods can be found in Chapter four and the interview schedule is located in appendix 2. In order to explore the internal conflict surrounding self-control during craving and the influence of others when triggered to crave heroin, interviews were undertaken with fourteen opioid dependent males in the final visit of the proof-of-concept study found in chapters four and five.

There were two primary aims for the qualitative study;

- 1) Firstly to gain further understanding regarding individual experiences of opioid cravings and how these are managed in real world settings
- 2) Secondly to explore of the experiences of people who use opioids to better understand the social process of procuring illicit opioids

There were five deductively derived themes used when coding each interview transcript. To better comprehend the real world experience of managing cravings, cravings were explored as the initial theme. Chapter one of this thesis introduced evidence from the existing oxytocin literature to suggest three elements of oxytocin dysregulation which can be linked to opioid use disorders; early childhood experiences, socialisation and psychiatric disorders. Although no central or peripheral oxytocin levels were measured in the participants of this study, these three elements formed a further three deductively derived themes for qualitative coding with the aim of linking real world experience to the already known oxytocin-related theory. The final deductive theme was that of Groupthink. Although interviews were conducted individually they represented an opportunity to explore the individual perspective of the influence of community when obtaining illicit opioids using the eight symptoms of Groupthink as a structure for analysis.

Section 6.1.1 reports the participant characteristics, 6.1.2 and 6.1.3 reports the results from the preconceived themes whilst 6.1.4 reports the new emerging themes. 6.2 discusses these findings before the chapter concludes in 6.3.

6.1 Results

6.1.1 Participant characteristics

Participant characteristics for the 14/24 participants who completed the interview can be found in Table 6.1. All 24 participants (Chapter five) were offered the opportunity to be interviewed however some declined as they were not comfortable with being recorded, one was intoxicated and it was deemed unethical to continue, another was too late to the appointment for the interview to take place. The sample was predominantly White British, representative of the treatment population in the UK. All but one participant was in receipt of methadone and all but three had at least one diagnosed co-existing psychiatric condition with anxiety and depression the most common. One interview (participant 09, interview length 10 minutes 44 seconds) was terminated early by the researcher as the participant became increasingly uncomfortable and one participant (participant 04, interview length 2 minutes 50 seconds) consented to be interviewed but then declined to answer.

Participant Number	Age	Ethnicity	Employment Status	Type of Substitute Opiates	Daily Dose	Diagnosed Psychiatric Problem 1	Diagnosed Psychiatric Problem 2	Diagnosed Psychiatric Problem 3
1	31	White British	Sick >4 weeks	MTD	100mg	Anxiety	Depression	None
2	43	White British	Full Time Employed	MTD	90mg	None	None	None
3	43	White British	Unemployed	MTD	50mg	Anxiety	Depression	None
4	45	White British	Sick >4 weeks	MTD	50mg	Anxiety	Depression	None
5	48	White British	Sick >4 weeks	MTD	60mg	Dissociative Identity Disorder	None	None
6	52	White British	Sick >4 weeks	MTD	60mg	Anxiety	None	None
7	25	White British	Full Time Employed	MTD	45mg	None	None	None
9	59	White British	Unemployed	BUP	14mg	Bi-Polar	PTSD	None
10	47	White British	Sick >4 weeks	MTD	36mg	Anxiety	Depression	Bi-Polar
12	44	White British	Unemployed	MTD	70mg	Anxiety	Depression	Borderline Personality Disorder
16	37	Asian Pakistani	Sick >4 weeks	MTD	50mg	Anxiety	Depression	None
17	54	White British	Unemployed	MTD	60mg	Psychosis	None	None
22	54	White British	Sick >4 weeks	MTD	60mg	None	None	None
26	40	White British	Sick >4 weeks	MTD	70mg	Anxiety	Depression	Personality Disorder (undefined)

Table 6.1: Participant characteristics

Notes: Table of the 14/24 participant demographics who completed the interview. BUP, buprenorphine; MTD, methadone; mg, milligrams.

6.1.2 Deductive themes

Figure 6.1 shows a summary of each deductive theme which affected self, followed by narrative description thereafter.

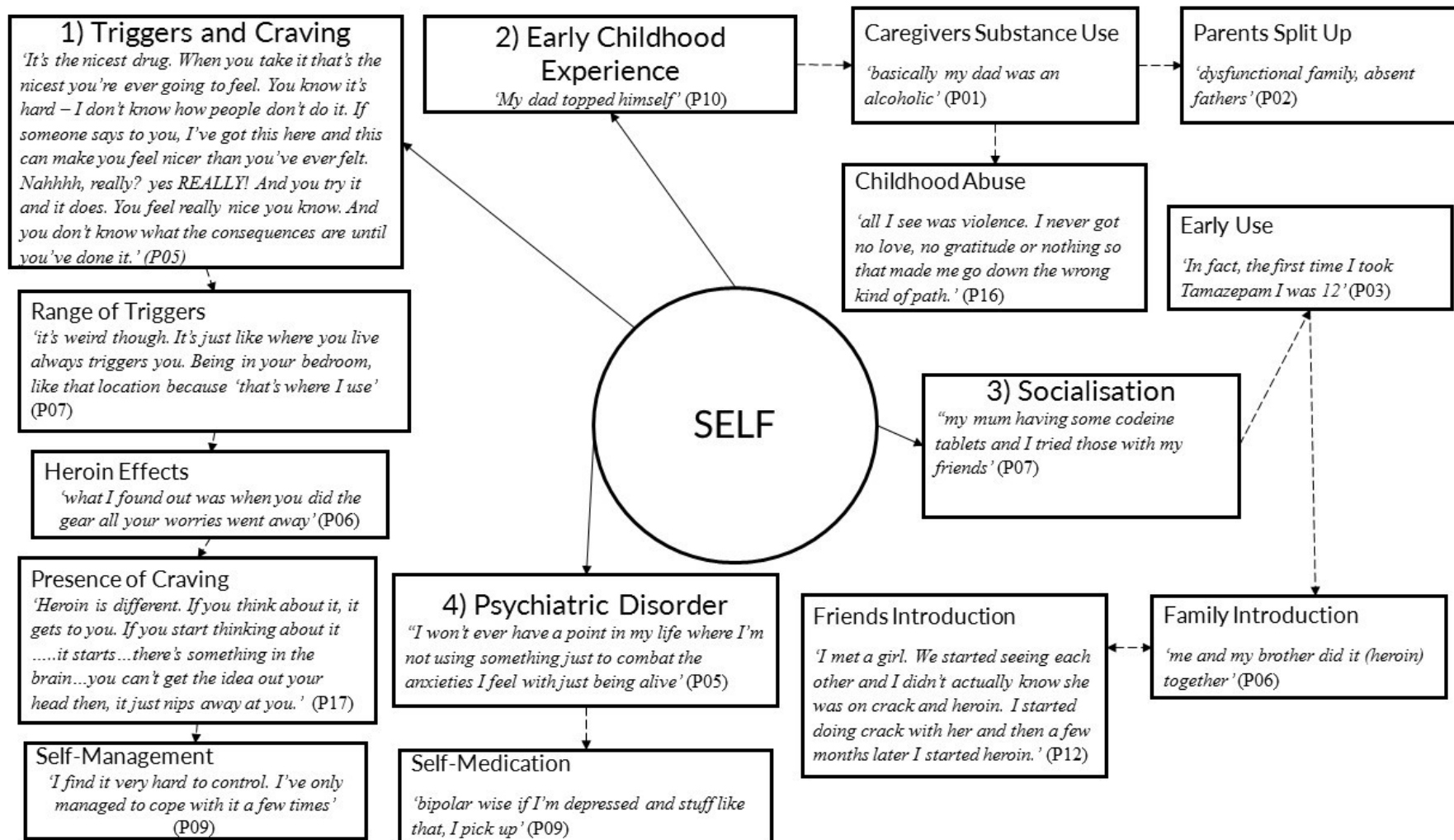


Figure 6.1: The deductive themes of heroin use which affected only the self

Notes: Figure depicting themes and linked subthemes for Triggers and Craving, Early Childhood Experience, Socialisation and Psychiatric Disorder. P#, participant number.

Triggers and Craving

Many emphasised that the biggest problem in managing triggers and cravings was that they enjoyed the feeling of using heroin. Participant five whose heroin use did not start until age 40 following the death of his brother but who uses heroin to manage his mental health stated,

‘you know there’s a certain feeling I get sometimes, maybe when I’ve used enough heroin or smoked enough weed when I’m feeling relaxed and I’m sitting down. It’s like your whole body is down where normally I’m sort of up, you know I only get those feelings every now and again, they’re very...I don’t get that feeling very often and sometimes it looks like everyone else gets that all the time’.

Although enjoyment of using heroin was acknowledged, there was also regret for using heroin unaware of the physical grip which heroin would take. Participant nine whose heroin use started at age 55 following a divorce stated,

‘I just seemed to cope better, or thought I did’

Participant three who started using Tamazepam aged 12 and then progressed to using stimulants throughout the rave music era of the 90s before being introduced to heroin shared a similar sentiment,

‘It’s such a sad thing and obviously I’ve been at points in my life where I’ve been at rock bottom, it’s a real detrimental thing to your life and I wish I’d realised you know, what it was going to cause me’

Participant sixteen was able to reflect on momentary changes in his beliefs that lead to regret immediately after using heroin,

‘I’ll probably find I feel more depressed afterwards. That’s what actually happens to be honest with you, nothing gets better.’

The data shown in Table 6.2 suggested a total immersion in the psychosocial experience with a full range of triggers identified by participants which fit within a predictor of substance craving psychosocial framework adapted from Gong et al. (2021). The range of triggers demonstrates how vast and sometimes seemingly insignificant drug-related triggers can be for people.

Life Events	Peer Drug Environment	General Environment	Psychological Security	Alexithymia
the time of the day	other people using heroin in front of them	everything being a trigger	boredom	emotions in general
belief that heroin use will make them better at work	other people who use heroin	the daily routine from waking up being a trigger	Poor mental health	difficult to manage emotions (anger, depression, injustice for example)
being around too many people (irrespective of whether they used heroin)	where people lived	toilets	loneliness	
receiving text messages from dealers	drug using environments in general	veins	knowing heroin would block out traumatic memories	
talking about heroin	other people asking you to score with them or if you know anyone who has any heroin	anything associated with drugs		
having money		depictions of heroin use on television		
arguments with loved ones				

Table 6.2: Triggers grouped by psychosocial factors

Notes: Triggers reported by participants grouped in to psychosocial factors. Table adapted from Gong et al. (2021) who identified the level of substance craving could be predicted by the psychosocial factors of life events, aggression behavior, positive psychological capital, interpersonal trust, psychological security, impulsivity, alexithymia, family intimacy, parental conflict, and deviant peers. Triggers listed were revealed from our study.

Participants struggled to define the feeling of craving unless it related to physical withdrawal-related craving. When cue-induced craving feelings were explored participants referred to recurring thoughts of heroin but thoughts of heroin were also identified as a potential trigger for craving itself. It would be difficult to identify if craving subsides when thoughts of heroin can reignite craving. This catch-22 described the constant battle many participants experienced but also may impact the accuracy of self-report craving measures such as those reported in the previous chapter.

When in withdrawal a small number of participants described withdrawal-related craving as a physical sensation that subsides when they take their methadone or use heroin. Participants did not make the differentiation between withdrawal and cue-induced craving. Participant ten whose methadone dose was under the recommended prescribing levels (meaning he was likely in a state of continued withdrawal) explained how this feeling can become exaggerated amongst other heroin users,

‘everyone’s afraid of the cluck and they all scare each other about it so you get something that’s a bit uncomfortable and it becomes dramatized and they’re terrified of the cluck, that’s what it is’

This was supported by participant four who was also prescribed methadone under recommended optimal levels,

‘Yeah, that’s the time when...because you know...normally I’m stable otherwise. It’s just when I haven’t got it that’s when I crave it. When I’m feeling ill you know, that’s what I don’t like, when you start to withdraw from it’

Otherwise craving was largely framed as a mental construct that was not a physical feeling but instead a recurring thought. Participant sixteen defined craving as,

‘a little thing in your head saying go and use, go and use, go and use’

whilst participant two’s heroin use was part of a daily routine whereby he would call his dealer during his work break at the same time every day to organise to buy heroin on a buy now, pay later arrangement because the dealer knew he had stable employment described an internal battle,

‘It’s that I’m so sick of fighting myself you know? Every day. It takes a big mental effort to just say ‘leave it for now, leave it for now’

Craving was denied by participant six who describes himself as 52 with emphysema and the lungs of an 80 year old. He smokes heroin as part of a routine, three times a week (Monday, Wednesday and Fridays) always bought from the same dealer and only when he had paid his bills such as rent, energy and food. He stated that he enjoys smoking heroin so is not triggered and doesn’t crave because his methadone dose is high enough for when he cannot use heroin,

‘I know where I stand with it, I know when I’m getting it, I know when I’m going without it’

Early childhood experiences

Participants were not explicitly asked about their relationship with their parents and so their presence in each narrative was unforced, organic and can be assumed as being significant parts of the story for each individual. Participant 3 explicitly stated he had a good childhood. Participant 22, who received emotional and physical abuse from his non-substance using mother as well as his absent father attempting to sleep with his then 16 year old girlfriend, had forgiven his mother stating she did the best she could with such a large family.

Only participant 1 and participant 10 clearly stated that their biological parents had used any substances. In both cases this was alcohol and in both cases neither participant drank alcohol themselves. Participant 16 was a Pakistani man who described his father joining him and his mother in this country at age 7 where he then witnessed and was subject to a lot of violence. He began using cannabis after his father would wrongfully accuse him of smoking it and subsequently assaulted him until participant 16 decided he may as well try. Then at age 17 he was introduced to heroin by a friend first followed soon after by crack cocaine when sitting in a car in a car park.

‘My mum basically fled from Pakistan to come here because she had a violent relationship with my father, obviously she had me in England so I was born in the UK and obviously when I was growing up I used to see people with dads and I was like ‘where’s my dad?’ so my mum must have felt ‘he needs his dad there, he needs a father figure’. So we started applying for his visa, we applied to a place called <name>, we used to go there and fill out his paperwork and he did come over. After that I thought things would be good with my dad and everything but no, all I see was violence. I never got no love, no gratitude or nothing so that made me go down the wrong kind of path.’

Despite his upbringing he still maintains respect for his parents and argues that it is Gods place to judge,

'I still have respect for my mum and dad. My mum I have no issue with but my dad it don't matter what he's done, he's still my dad. So yeah I have to respect him no matter what...Gods gonna judge who has done right or wrong so God will judge him and tell him where he went right or wrong'

Around half of all interviewed participants reported their parents were not together when they were children with very little narrative exploring this. No participant described this period as stable and instead reported a period of dysfunctional families inclusive of single parenting, step-parenting, the suicide of a parent, parental substance use and differing forms of emotional and physical abuse. Professional interpretation but not direct participant reporting reflects the widely accepted literature which describes the early life experiences of people who use opioids as traumatic (Lawson et al., 2013). Only participant two used the word trauma and that was to dismiss trauma as a reason for his substance use. Instead there was compassionate understanding and a normalization of turbulent early family life. One participant, participant three, expressly stated without prompt that he had a 'really good' childhood as if to reinforce that he had not been the victim of anything other than the free will of his own choice to try heroin. It is clear there is a discrepancy between what experiences professionals view as traumatic and the normalisation of these experiences by the people who adapt to life post exposure to them.

Socialisation

The use of heroin was described as a solo activity often underpinned by an embarrassment of other people seeing you physically and mentally impaired post-use, but the role of others in sourcing heroin and other drugs was a strong theme in all completed interviews. Typically, though not exclusively, friendships formed in early adolescence led to experimentation as part of a group with differing substances such as glue, solvents, nicotine, cannabis, alcohol and medications prescribed to parents such as benzodiazepines and opiate painkillers. Importantly this early use was not always linked to trauma and escape from difficult emotions but instead initial substance use was often an enjoyable group experience without regret. Participant 3 reminisced about the 90s rave music culture and how this was a bonding experience for him and his friends,

'We experienced a lot of stuff that a lot of youngsters nowadays will never. You know we went through a scene, a movement and it was a lot of fun and I did have good times...Then as I hit 19, one night we got back and we dropped a couple of Valium and stuff and then someone pulled out some heroin and put it on some foil. I was like 'no I'll never touch that stuff' and I stuck with that a while but I ended up in a moment of weakness. Another time we came back, smoked some and when I did it I was like 'whoah this is really nice' you know, I really enjoyed it.'

He then went on to explain that he began to isolate himself from his current social circle as his heroin use increased before someone 'regretfully' convinced him to use a needle on the promise that he would experience a greater sensation. Participant 6 shared a similar pathway to intravenous heroin use,

'yeah I started playing around with it, basically I went through the rave scene doing all the pills and the puff and having the odd pipe you know, crack pipe and all that, ketamine...you name it I did it. You know all through the rave scene in the late 80s, early nineties and then um started playing with heroin on the weekends. I was religious for a year – done it Friday, Saturday...heroin didn't come in to it until I was about 24. Before I was just doing pills, snowballs, dennis the menaces, red and yellows, all the ecstasy so yeah I had a good time. I had a bloody good time thinking of it!'

He continued by explaining how a friend first introduced him to smoking heroin despite being concerned that he would enjoy it too much. He then explained how his social network later prepared his first intravenous injection,

'I had a mate that was doing it and he said to me 'I've been frightened of introducing this to you because I know you'll love it' ...I think I'd been doing it about four months and everyone kept saying 'fuck me you never had a hit? you never had a hit?' and I goes no I'm alright smoking. That was it, they gave me this hit.'

Where family members were involved in the initial use of heroin and other drugs they typically belonged to the same social group. The exception was participant 12, a white British male diagnosed with anxiety, depression and borderline personality disorder who was introduced to powder cocaine aged 16 by his uncle in order to help him stay awake during the night shift at work. He described this as normal in his work place

amongst co-workers. This continued for ten to fifteen years where he states he lost family members, relationships, money and property before he went to rehab. After twelve years not using he met a woman who he did not realise used heroin and crack cocaine but they began a relationship culminating in him also beginning to use both drugs.

Psychiatric disorders

Despite high prevalence of psychiatric disorders within the interviewees, very few participants reported consciously using heroin to self-medicate. There may be some crossover with the range of emotions people described as triggers but these were not explicitly linked by participants to their mental health on the majority of occasions and so were not coded as such. Participant 9 did link his bi-polar to using heroin,

‘bipolar wise if I’m depressed and stuff like that I pick up’

But it was only participant 5, diagnosed with dissociative personality disorder, who explored the link between his internal mental state and the use of heroin to manage it. When discussing triggers and craving, he described a feeling like envy at how other people seemingly have a state of day to day calm which he can only achieve by using substances and queried whether he will ever have day to day mental calm naturally. Although he was prescribed medication for his mental health and appreciative of the support offered by services, his interview was candidly honest about his fears of stopping using heroin,

‘So I don’t feel comfortable all the time, now I’m going to give up heroin and life is suddenly scary because what is going to calm me down? I don’t want to be in a state all the time so I’m going to have to keep myself in some kind of calm area and not let life just zone me out.’

The experience of professionals attempting to refer to mental health services discussed in Chapter two was supported by the experience of Participant 26 who reported a long delay in receiving an initial appointment for psychological therapies,

‘There’s a lot I have to psychologically work out you know. But I’ve been waiting for this appointment that I thought was this morning, I’ve been waiting for that for nearly nine months.’

6.1.3 The Presence of Groupthink

Coding should be interpreted cautiously because some of the coding reflects the opposite definitions of each Groupthink symptom. This is likely due to the individual experiences explored and are better understood as individual perspectives of opioid using communities organised within the framework of Groupthink. In that sense these interviews provoke further research as to whether these perspectives would change when interviewed in a focus group of people who buy heroin together. Overall the interviews described an identity conflict caused by a reluctant belonging to a community which people wanted to move away from but whose members were the only people who accepted them and understood them without judgement. Belonging to this community appeared to cultivate ideological dilemmas and cognitive dissonance which enabled their own opioid use.

Figure 6.2 provides a graphical illustration of how prevalent each symptom of Groupthink was found to be within coding. Groupthink overall appeared in 13/14 interviews. Peer pressure as a symptom was identified across 11/14 of the interviews followed by rationale (9/14). Stereotypes and unanimity appeared in 7/14 interviews with the invulnerability and morality appearing in 6/14. The symptoms of self-censorship and mind guards did not appear. It is likely that both these would only become visible during coding of a group based discussion and comparison with individual interviews, certainly in the case of self-censorship.



Figure 6.2: The deductive Groupthink themes of heroin use and subthemes

Notes: Groupthink appeared in 13/14 interviews, Peer Pressure (11/14), Rationale (9/14), Stereotypes (7/14), Unanimity (7/14), Invulnerability (6/14), Morality (6/14). P#, participant number.

Participant 2 explained his rejection of the drug using community and seeming rejection of further communities to belong to,

‘this is the very thing I am striving not to become, a ‘one of them’... Trouble is, I don’t want to be part of no ‘us’ either. I’m me!’

The remainder of this section will explore each inference and counterview of Groupthink in turn.

Invulnerability

Participants described a minimised fear of overdose from heroin use, rationalised by other group members, on the basis of how they used i.e. smoking rather than injecting. Length of time using was also rationalised as less chance of overdose because they understood how much they were capable of using. No participant suggested individually or through warnings from other people that they may be vulnerable to overdose due to changes in purity or presence of adulterants. Whenever a change in drug, quantity of route of administration was made it was always within a social context where others initiated the change and minimised any safety aspects.

Participant 26 converted to Islam whilst in prison aged 15-19 and was introduced to crack cocaine and heroin at his prison release party. He had assumed that using crack cocaine and heroin was how people celebrated as his transition from adolescence to adulthood was not typical and he did not know any different. He since began to chase the feeling of overdosing which he recognised as a high risk strategy but linked his rationale to his need for attention and to know people cared about him,

‘back then I didn’t really have any...I’d heard of people overdosing but I didn’t think...you know when you’re younger there’s no fear. But then as I got older its weird cos I chase that very close level between going over and not going over... It’s something that I fear but I can’t wait to do again. I know when I’m there and everything’s going all fucked up and I think I’m on my way out...maybe it’s for people around me to see if they care? To say ‘are you alright’? Someone cares? To feel wanted, needed, loved, cared about?’

Rationale

Group encouragement and enablement regardless of when individuals positioned themselves as members of an out-group by attempting to stop using heroin was strongly implicated in participant experience. For example it was not uncommon for participants to explain how one person would help another person to buy heroin in exchange for a share but that they did not attempt to dissuade someone from using even if they knew they were trying to stop. This was described by participant 16,

'I think it was more for their vested interest. So obviously there's another person smoking gear so if he's on it we can go to him in the morning so if we can't got none then he'll have something. So it was their vested interest, you know what I mean?

They don't care if I'm off it, they would rather see me on it because it benefits them...I've tried stopping a lot of times and people don't really like to see, mainly people who use heroin they don't want you to stop. They try to say 'go on, have a little bit it'll make you feel better'

Participant 5 described a resentment for how he felt the community was self-serving and lacking interest in helping someone improve their situation,

'No-one will give you a chip. Won't give another person a bit of food but they'll kill him and give a cancer stick but not give him food. They'll say 'yeah you can suck on that cancer stick mate' and they've paid more money than they've even paid for their chips you know what I mean? and it's the whole thing that yeah you can die with me but I won't let you live with me...They'll let you die and they'll help you to die as long as you don't try and get out of where you're in'

But he also continued to say how being part of the group rationalised his own decision making indicating a conflict between his own beliefs and his beliefs when part of this community,

'if we both do it, it feels as if its right and it's not such a bad thing, such a terrible thing'

Morality

Despite enabling each other to use heroin which conflicts with individual goals and entering in to business-like exchanges as part of small groups in order to maintain heroin use, participants individually stated they would not push the idea of using on to other people as they recognised how hard it was to stop. Though as participant 1 stated,

‘I wouldn’t want to put the idea in their head. I’d leave them alone. If they came to me, that’s different...it’s hard to be around if you’re trying to stop but then everybody makes their own choices’

The influence of individual choice was mentioned by participant 12 who pressured his partner in to helping him first use heroin. Although she initially resisted he had the money to pay for heroin for both of them, consequentially her own moral standing changed and she introduced him to heroin,

‘She didn’t want me to because she said once you start you can’t stop, it’s hard but yeah she did warn me but I said no, I’ll give it a go.’

These narratives suggest that individual moral beliefs alter when group aims or needs can be met. By remaining a member of the group, even if a person achieves a period of abstinence, the opportunity for heroin use is unlikely to be denied as participant 5 continued to highlight,

‘you know other drug addicts would always pat you straight on the back and say ‘well done mate, I’m so proud of you’ but if you turn around and say ‘tell you what give me one more line’ they’ll go ‘yeah alright!’. They’re never going to turn round and argue’

Participant 3 described how the lifestyle eroded his identity and created a different version of himself which fuelled his negative self-image,

‘Your whole life becomes a lie. You become different people. It’s like being a schizophrenic. Two totally different personalities, it’s awful. Lying to people, almost believing your own bullshit. It’s terrible, absolutely horrific. That’s the one side of it that as I’ve got older I’ve tried to be as honest as I possibly can. Like now I wouldn’t ask someone for a lift, it would play on my mind too much. I’d just get on a train

now. On my own because I can't lie to people any more, I really hate it. That's the part of it that I really hate. And that's the part that caused so much heartache over the years, you know the fact that you just lie all the time. That's what people expect and say 'if you could just be honest with us it wouldn't be so bad'

Stereotypes

The subtheme of in-group bias underpinned narratives regarding judgements. Many participants felt judged by society though participant 12 separated judgement from understanding by confirming that he did not care if people understood his behaviour, before going on to detail an example of being targeted by strangers,

'people on the street or if I'm standing on the corner waiting then people driving past might shout out the window 'waiting for drugs' or people just stare at you sometimes'

Participant 16 also described a separation from being judged in relation to his friends rather than society on a wider scale,

'I think they wouldn't really understand because they haven't been there but they'd never judge me. They've always told me good things, told me to keep away from people who use and told me not to use'

Judgement from others within his religious community hindered participant 26 from engaging further with his religion due to the embarrassment he feels and stated that he felt 'dirty' because of his heroin use. The consistent belief amongst participants was that other people who use heroin understand them, making leaving this community difficult if it requires a period of social isolation. Participant 10 explained, 'If I don't smoke then I don't see no one. So it gets like a social thing'.

Peer pressure

Peer pressure was as prevalent within the rationalisation code. Participant 1 stated that although he would not push heroin use on anyone that he had 'seen some people keep hassling people who were trying to stop' whilst participant 12 stated he only gets influenced if someone calls him directly asking him to buy some. Despite understanding the role of peer pressure in their heroin use, participants held an equally strong belief that they are responsible for their own situation. Participant 2 explained,

‘should someone have saved me or whatever? <exhales> Maybe, maybe not, it’s my choice at the end of the day. It’s part of you... I could sit here and blame all the pain and trauma and everything but its nobody else fault that I’ve chosen that route to use....suffer or whatever you wanna call it as. I know what I’m doing to myself’

Illusion of unanimity

Unanimity was an undercurrent throughout all narratives when individuals spoke of interactions with others beginning with rejection of belonging to the group. Statements of ‘all in the same boat’ and ‘a problem shared’ were described by others when talking about stereotypes and judgement from others. There were no instances where people spoke of unanimity amongst the community in a positive way such as when attempting to stop heroin use. Any attempts to stop using where spoken about through self-isolation rather than group support, finding a new group to belong to or reconnecting with friends and family. This may indicate the lack of a positive shared goal amongst the heroin group members which may be present in other groups such as those who attend mutual aid meetings for example.

6.1.4 Inductive themes

The themes of ‘death’ and ‘relationship with dealers’ were identified whilst coding the interviews.

Death

The theme arose inductively in narratives as this was not a focus of the interview guide indicating the consistency, and passive acceptability, of early death as a life event in the lives of people who use heroin. In a minority of cases death was the catalyst for initial use of heroin but in the majority, interviewees knew many people who had died from overdose. No participant had received grief counselling for these deaths and participant 5 was not sure that the death of his brother – the event was triggered his initial pursuit of heroin from someone who also later died – was something he considered traumatic,

‘Like when my brother died they might be like ‘yeah I lost my dad, brother, kid on a certain day and it was so traumatic’ but you know yeah my brother died and it was sad but it weren’t traumatic. At least I don’t think it was’

Sadness or grief was not always the emotion expressed by participants. Participant 16 had earlier conveyed a non-judgemental attitude towards his father for the childhood violence he experienced but when asked about the death of people who introduced him to heroin he stated,

‘To be honest with you, I do feel bad for them but they should’ve known better’

This view was also conveyed by participant 1, ‘when he died I...didn’t feel as bad’ regarding the death of a friend’s brother who introduced him to heroin. The lack of empathy for some overdose deaths may further suggest a superficial emotional connection within the community akin to the perspectives found within the rationalisation, peer pressure, morality and illusion of unanimity codes.

Relationship with dealers

Far from the glamorised television image of drug dealers, the majority of participants across all interviews described a symbiotic network of ‘associates’ within the drug using community who they both bought from and bought heroin for. One person stated they had 72 phone numbers on their phone, another claimed to have 20, where they could get heroin from and explained that these numbers were often sold to dealers in exchange for heroin. This practice ensured that your phone number was continuously circulating within the community who could supply and to drug dealers further up the chain. This differed in three cases, participant 2 who would call his dealer from work at the same time every morning to arrange a delivery later that evening and often get it on a ‘use now, pay later’ arrangement. This was due to having used the same dealer for fifteen years and believed the relationship to be ‘professional’,

‘I don’t want to be their fucking mate you know what I mean <laugh> but there’s a modicum of respect that I think goes either way you know’

Participant 6 also described a long term relationship with a single dealer who he would call on a Monday to arrange his weeks supply. If the dealer does not have any or is out of the county then participant 6 would just use his prescribed methadone to ensure he does not go in to withdrawal. Under the guise of harm reduction participant 6 states he does not buy from another dealer who he would not know as he would be unable to trust regarding purity and contaminants. The ease of the relationship with his supplier, as with participant 2, is a factor in his continued use,

‘My mates <dealer> on about stopping, he wants to get out the country. He’s been saying it for a year now ‘I’ve had enough of this, this is stopping’ and I won’t play the county lines game so when he stops I’m going to stop. The day he goes ‘that’s it, it’s over’, I will try my damndest to not go anywhere to get anything. I am content on my juice but it’s the ease with him. He makes my life easy, I don’t have to go anywhere, I don’t have to go on the streets’

Participant 7 described how digital technologies were used by dealers now. He began using MDMA and powder cocaine aged 15 before trying his step-mother’s codeine tablets, a practice which continued throughout university. Having been aware of Reddit forums on the internet selling drugs since he was 16, he explored the darkweb and decided to try heroin. After moving to a new location he went to his doctor regarding codeine dependence and was referred in to his drug service where he made connections he wouldn’t normally have and his number was spread around there. Participant 7 does not speak to other people however, instead he uses an app called ‘wicca’ which is an encrypted messaging service where he has been added to various dealer groups. Ease of use was also a factor in participant 7’s continued use of the app. A similar lack of personal accountability to participant 6 was expressed in regards to wanting someone else control his access to heroin,

‘I would like to delete it all. I would like people to go but also now, because one of the people, there’s two or three dealers on there and one of them accidentally created a group of all his customers and now we’re all in there together and everyone’s talking about it and things. So I have kind of that now...which isn’t like a good thing. It would be nice if it all just kind of went. Kind of like if all the dealers weren’t on the app then I’d have no connections here...I’d rather someone just got rid of it for me, it’s easier that way. I don’t get involved in the messages. It’s just like inadvertently I’m in the chat because you get notifications but I don’t click on them. Occasionally I’ll click but I don’t participate or anything. So I literally go on there just to buy and then...’

6.2 Discussion

The role of communities in perpetuating heroin use was revealed in narratives which highlighted a symbiotic relationship with others that forms when people become physically dependent on heroin. Difficult early developmental years though did not exclusively describe trauma as the gateway in to heroin use in adolescence with many describing drug experimentation as an enjoyable period of lives albeit before they became dependent on heroin. From experimentation with recreational substances participant's expressed naivety and regret at initiation of heroin use which cultivated a desire to reject new superficial relationships which formed as a result. Fear of social isolation and the ease of availability to heroin enabled by these relationships made breaking these ties difficult.

In line with the evidence for people who use illicit heroin most participants described their early lives as one of instability and exposure to traumatic experiences. Notably participants discussed their stories with a calm normality rather than an emphasis on difference or regret. Often there was forgiveness and understanding for any physical or emotional abuse suffered from family members. These experiences are also thought to dysregulate the central oxytocin system as discussed in chapter one.

The influence of others on initiation of drug use was clear and unsurprising given the evidence base but the sense of belonging that was cultivated alongside the continued enjoyment of recreational use is not an area much explored by the literature. Belonging to a moment with others was important to people who used recreational drugs and those who ended up using heroin often gradually detached from the original social circle as they became physically dependent on heroin. People became outsiders looking in to their old selves who had a rich and varied social life but were now trapped within a smaller circle where the only shared interest was the sourcing and sharing of heroin. Despite this change participants held little ill feeling towards others for introducing them to heroin and accountability for their own choice was described throughout. The exception was when older family members or friends of friends, who were dependent on heroin themselves, were the ones to first suggest trying heroin. Participants then expressed resentment and betrayal believing they should have been protected from something they were naïve to.

New networks then formed with people who use heroin and lost the sense of belonging to a moment where drug use was supplementary, instead the enabling and encouragement of others to use heroin became central. Although this is in line with Social Identity Theory (Tajfel and Turner, 1986) where groups of people form based on shared interest, participants expressed a rejection of belonging to the group of people who use heroin and positioned themselves as different to the rest of the social network. For example there was a feeling throughout that others in the social group – but not the interviewee themselves - would prefer people to remain on heroin so that they could support their own habit. This was despite interviewees engaging in the same expectation of reciprocal heroin exchanges as others in the group. In many cases the new social group were described as ‘dealers’ but again, not the interviewee themselves. This reluctant attachment to the social group could support Jelic et al. (2009) finding that people with low personal self-esteem, as is seen with people who use opioids (Hendy et al., 2018), exhibit greater in-group bias when contributing to social groups to compensate for lack of self-worth.

Individual perspectives of people within these communities alluded to symptoms of Groupthink during decision making to use heroin which cannot be fully explored within the correct context. Judgement from society was a reason why people remain in the group as well as strong beliefs that people who don’t use heroin lacked empathy for them. Both perspectives were prevalent throughout narratives and contributes to understanding their ongoing interactions with a group they reject as individuals. Individuals said they preferred to stay away from people who used heroin, but heroin was readily available from others when they wanted it and contact with group members was maintained for this purpose. These narratives are underpinned by group based social exchange theory where individuals engage with others for the reward received (Brown et al., 2014).

Examples of triggers were wide ranging and highlighted the difficulty of managing them when every day events and objects can become associated with heroin. Importantly just the thought of heroin was enough to initiate a craving and cue-induced craving itself was difficult for people to describe. This indicates difficulties in identifying when individuals themselves may have been triggered. Lack of trigger and craving identification could contribute to the cognitive dissonance experienced by people using heroin when trying to stop.

A limited number of people suggested their use was linked to a co-existing psychiatric disorder. Those who did detailed a fear of not using any substance when they had been using heroin to feel 'normal' and delays in accessing professional psychological treatment services left only their heroin using social network for support. These new relationships were described as transactional in nature, again supporting a social exchange theory. Where relationships are experienced as superficial this could explain the ease of acceptance and normality of the high incidence of death within interviews. Although not explored here, both death and loss of social relationships are known to affect oxytocin levels contributing to an elevated risk of mood disorders (Hurlemann and Scheele, 2016; Bui et al., 2019) which themselves can elevate risk of opioid use disorder.

Johann Hari's 2015 TED talk claimed that 'the opposite of addiction is connection' (Tedx Talks, 2015) but these interviews show there is no shortage of connection during active heroin use. Supporting earlier qualitative research with people abstinent from problematic substance use for a minimum of five years (Pettersen et al., 2019) and recent systematic review of the role of social network support in treatment outcomes for medication of opioid use disorder outcomes (Kumar et al., 2021), it is the quality of those relationships and the focus of positive shared goals within social connections that is critical to people maintaining attempts to stop using heroin. Earlier research indicated that long term ties to other people who use heroin and judgement from professionals who have no experience of heroin use was reported to be a barrier to abstinence based recovery in people prescribed substitute opiates for five years or longer (Notley et al., 2015). The interviews coded here within the 'Socialisation' and 'Groupthink' themes add depth to the experienced difficulties people face where identity can become conflicted if people are torn between short term social isolation in order to make lifestyles changes and maintaining unhealthy connections which encourage heroin use.

These interviews were not without limitations. The sample was self-selecting and many people from the sample derived from the proof-of-concept study found in Chapter five declined to be interviewed meaning not all perspectives were able to be explored. Whilst this was a limitation it was also a strength in that those who did consent to be interviewed enabled in-depth exploration of their experiences. Our sample included males only and cannot be assumed to represent the experience of

women who use opioids. Simultaneously our sample was selected from three different geographical locations with males of differing ethnicity and religion. Interviews supported each other suggesting some consistency in the experience of males who use heroin. All interviews were taken at face value to represent the truth of the individual at that time rather than a universal truth.

The implications of this analysis highlight the importance of treatment which focuses on the social network as is currently recommend in the UK (HM Government, 2021). What has been revealed is that social network interventions may be more successful if delivered to cohorts of people who buy heroin together. Interventions could then challenge how individual's within those networks impact each other and highlight non-drug based similarities in individual interests in order to shift the reason for relationship wider than empathy for heroin use. It is the group psychology that needs to change rather than the individual who, according to these interviews, will often have conflicting goals to that of the social group. Where groups are resistant to treatment together or where individual people prefer to break away entirely from other people who use heroin, facilitating access to mutual aid or integration within local lived experience recovery organisations may be beneficial (Black, 2021). It is recommended that research is undertaken on groups of people who use heroin together in order to explore the idea of Groupthink further.

Incidence of trauma is well documented in the lives of people who use opioids but the impact of death less so. This is somewhat surprising given the escalating rates of opioid-related deaths and that exposure to unexpected death increases incidence of mood disorders and substance use (Keyes et al., 2015). Combined with evidence showing that circulating levels of oxytocin are elevated following the death of a loved one (Bui et al., 2019), the research implications from this analysis are to further explore how death is processed by people who use drugs; Is death truly experienced as casually as it is reported here, are there more subtle behavioural changes (lack of sleep, changes in family interactions or attempts to contact old networks for example), or emotional changes (guilt, blame, remorse for example), what is the meaning of elevated oxytocin levels and what is the effect on subsequent opioid use if grief counselling is provided immediately following exposure to death.

6.2.1 Reflections on researcher/interviewer influence

Conducting interviews at appointment four allowed participants to feel more relaxed and trusting of me but this also meant that some narrative that was discussed in appointments 1-3 was missed. Despite being more at ease, some participant's body language became observably stiffer as the relaxed conversation became an official recording. This may have impacted how much people were willing to disclose.

Although interviews were transcribed immediately, they were not coded typically until at least a week since the end of transcription. This was to ensure the narratives felt fresh to me and I would not code something based on what I thought I heard rather than what was actually said. The delay in coding also meant I was more careful in reviewing each narrative and this led to identification of differing codes.

I have extensive experience in delivering psychosocial interventions within a treatment setting to people who use opioids and had concerns that interviews which may read as unremarkable for me, may not be established in the existing literature and therefore be missed from reporting. To counter this I attempted to find another student, without the same employment experience, to review interviews and codes. There were some initial university ethical concerns over this such as exposing a potentially naïve student to difficult stories. When one appropriate student was found, it was not possible to train them in qualitative analysis in the time available.

Finally, I was aware of a potential reviewer bias in my belief that groupthink exists, stemming from my time employed in treatment. During coding there was an internal conflict when assigning codes to preconceived themes as to whether they really existed or whether I was led by my own bias. The identified reviewer bias was minimised by having a second analyst (supervisor CN) check my initial coding. During interviews there was a conscious effort made not to lead the participant. As someone with strong opinions I was very aware not to close the questions in order to obtain the 'right' answer which matched my Groupthink beliefs and when participants hesitated or asked for confirmation on what I meant, I took it as a sign to change direction of the interview so that each answer remained authentic. There was a similar effect in the analysis of each Groupthink symptom where I was aware I may be interpreting some narrative disingenuously. To counter this I accepted that these were individual experiences and that group answers would likely differ as per the theory of

Groupthink. This allowed me to code each narrative as a first stage of interview which would inform a later group discussion even if this was not part of the initial research plan. I would argue that within the readily acknowledged constraints of using a group based theory framework within individual interviews, the deductive theme was successful in identifying enough sub-themes to warrant further group based exploration. What was missing to progress the idea is any comparison of the same people being asked the same questions but within the groups they usually procure opioids with.

6.3 Conclusion

Far from becoming socially isolated when actively using heroin, interviews identified a shift in social networks from positive networks built on shared moments to networks built on a superficial, transactional exchange. Individuals positioned themselves away from the new group but found it difficult to break away fearing that the rest of the society judged them and they would be left isolated. Other people within the networks, but not the interviewee themselves, were viewed as hindering attempts to stop using heroin as people and the environments they used heroin in became heroin-associated cues for craving which was then difficult to self-manage. The greatest benefit of belonging to this network was that of mutual understanding. This exploration of individual perspectives on the community influence on using heroin adds novel contribution to the field by challenging the belief that people who use heroin are socially isolated which does not appear to be the case as reported here. Actively using heroin is a group experience and not an experience of isolation however the transition to abstinence can be isolating without a new social group to join.

Chapter seven concludes this thesis which has explored the potential role of oxytocin in opioid use disorder (Figure 6.3). Beginning with the key findings and continuing to a synthesis of the existing literature, chapter seven finishes with implications and future directions for oxytocin research within the addictions field.

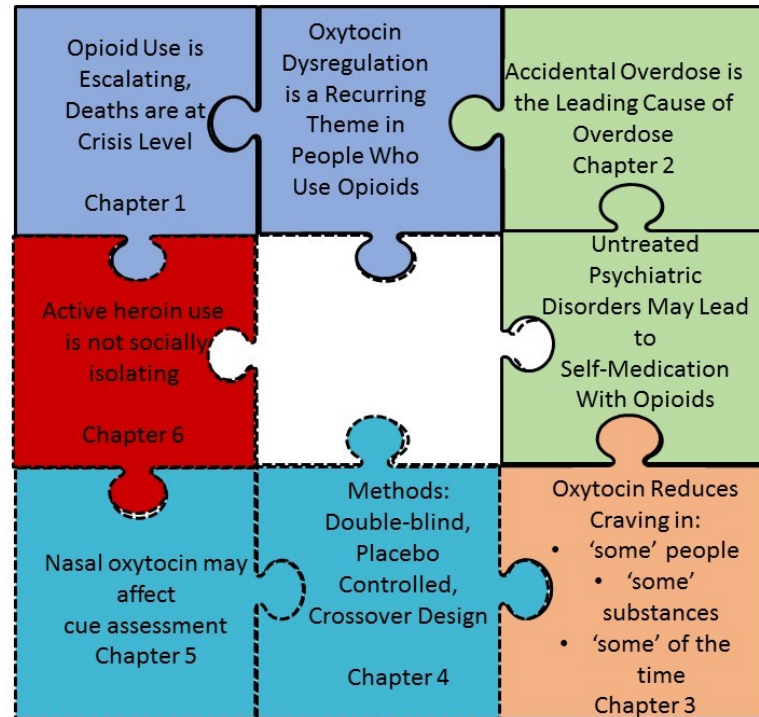


Figure 6.3: Key thesis findings by chapter up to chapter seven

Notes: Chapter one outlined the extent of the opioid crisis with opioid-related deaths at crisis level. Chronic drug use dysregulates the endogenous oxytocin system and is highlighted in people who experience early life trauma and people with psychiatric disorders, both of which are highly prevalent in people who use opioids. Chapter two analysed the prevalence of psychiatric disorders in deaths where opioids were found at post-mortem and suggested that self-medication in the absence of psychological treatments may contribute to accidental overdose. Chapter three systematically reviewed human studies for nasal oxytocin to reduce craving or consumption in substance use disorders finding that nasal oxytocin works in some of the people, some of the time but variation throughout studies prohibits conclusive results. Chapter five showed that nasal oxytocin may play a larger role in the assessment of opioid-related cues. Chapter six presents results of the qualitative analysis. Chapter six qualitatively analysed the experience of people who use heroin to show that there is not a lack of social connection during addiction but that the connection within groups is of a transactional nature.

Chapter Seven

Conclusions and Future Work

“Question everything. Learn something. Answer nothing”
-Euripides, Greek tragedian.

7. Introduction

This thesis set out to target opioid-related deaths through an analysis of the prevalence of psychiatric disorders in opioid-related deaths (Chapter two), explore the perspectives of professionals towards people with co-existing psychiatric disorders and substance use disorders (Chapter two), by reviewing the evidence base of a repurposed medication (oxytocin) as a possible anticraving medication (Chapter three), completing a proof-of-concept study for nasal oxytocin to reduce cue-induced opioid craving (Chapters four and five) and finally exploring the experiences of opioid dependent males who use illicit heroin when craving and procuring opioids (Chapter six). Although much evidence exists for the overall themes of mortality, craving, neuroscience and the individual experience of substance use disorders there is no single body of work which seeks to conceptualise the potential role of oxytocin within opioid use disorder. Throughout each chapter links to relevant oxytocin literature surrounding the themes of early life experience, socialisation and psychiatric disorders (Chapter one) were surmised (Figure 7.1).

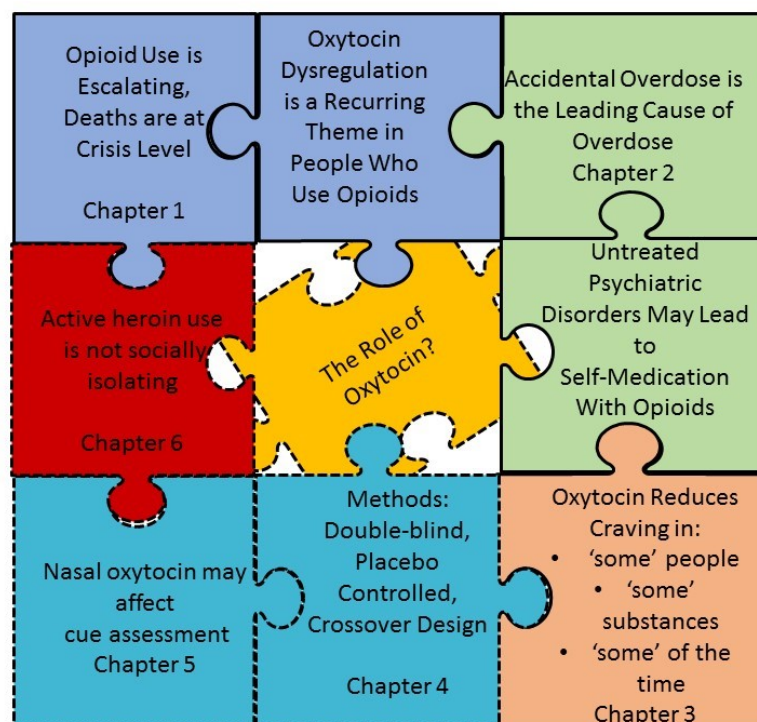


Figure 7.1: Complete key thesis findings

Notes: Chapter one outlined the extent of the opioid crisis with opioid-related deaths at crisis level. Chronic drug use dysregulates the endogenous oxytocin system and is highlighted in people who experience early life trauma and people with psychiatric disorders, both of which are highly prevalent in people who use opioids. Chapter two analysed the prevalence of psychiatric disorders in deaths where opioids were found at post-mortem and suggested that self-medication in the absence of psychological treatments may contribute to accidental overdose. Chapter three systematically reviewed human studies for nasal oxytocin to reduce craving or consumption in substance use disorders finding that nasal oxytocin works in some of the people, some of the time but variation throughout studies prohibits conclusive results. Chapter five showed that nasal oxytocin may play a larger role in the assessment of opioid-related cues. Chapter six qualitatively analysed the experience of people who use heroin to show that there is not a lack of social connection during addiction but that the connection within groups is of a transactional nature.

To fully explore the role of oxytocin within opioid use disorder is beyond the range of any single PhD thesis. Importantly this thesis has not sought to medicalise opioid use disorder or reduce opioid use to a simple dysregulated mechanism. Rather this thesis has acknowledged the impact that the environment plays on opioid use and discussed how oxytocin systems affected by environmental changes can influence opioid use. A

novel hypothesis for how a nasal spray of oxytocin may be able to reduce cue-induced opioid cravings was then tested. Four different methods were used (retrospective observational epidemiology, literature review, qualitative and crossover proof-of-concept) to research and theorise broad topics relating to opioid use disorder, the role of oxytocin therein. The key findings of each chapter are summarized in Table 7.1.

Study	Aims	Findings
Chapter 2: Mental Health Problems in Deaths Involving Opiates in England, 2006 – 2015: Prevalence and Perspectives	This study conducted a retrospective analysis of deaths in England between 2006 and 2015 where at least one opioid was found at post mortem as recorded in the NPSAD database. The aims were to: 1) Identify reported history of psychiatric problems in deaths where opiates were found at post-mortem which occurred between 2006-2015 in England 2) Identify prevalence of antidepressant, antiepileptic, antipsychotic, opioid analgesic and hypnotic/sedative medications found at post-mortem in all deaths within this period 3) Interview drug treatment and mental health professionals to contextualise findings within real world perspectives on psychiatric diagnosis.	(1) PTSD, anxiety, psychosis and eating disorders were under diagnosed in comparison to the estimated prevalence in people who use opioids in deaths involving people who were known to use illicit drugs. People not known to use drugs had higher recorded prevalence of anxiety, depression, bi-polar and eating disorders than people known to use drugs. Excluding paranoia, PTSD and eating disorders, people not known to use drugs who died with opiates found at post-mortem had higher recorded prevalence than expected for the general population for all psychiatric problems. In deaths where opiates were found at post-mortem, only people not known to use drugs with at least one diagnosed psychiatric problem declined from 2013 to 2015. All other cohorts (people not known to use drugs without at least one psychiatric problem, people known to use drugs with at least one psychiatric problem, people known to use drugs without at least one psychiatric problem) increased over the same period. (2) Detection of medications at post-mortem increased between 2006 and 2015; antidepressants 3.3x (2006 n=191, 2015 n=631), antiepileptics 8.9x (2006 n=27, 2015 n=242), antipsychotics 5.69x (2006 n=33, 2015 n=188), hypnotic/sedative 2.09x (2006 n=357, 2015 n=707) and opioid analgesic medications 2.3x (2006 n=378, 2015 n=884). This was higher than than NHS prescribing trend increases in England between 2006 and 2015 (NHS Digital, 2017) where antidepressant items dispensed increased 0.98x, antiepileptics 1.33x, hypnotic/anxiolytics 0.0027x, psychosis and related disorders 0.51x and analgesics, which included non-steroidal anti-inflammatory drugs as well as opioids, increased 0.38x. (3) Professionals identified barriers to accessing psychological therapies for people who use substances and a perceived

		reliance on medication prescribing to solely manage psychiatric disorders.
Chapter 3: Can Nasal Oxytocin Reduce Craving in Automated Addictive Behaviours? A Systematic Review	This systematic review used PRISMA guidelines to identify peer-reviewed studies that investigated the effects of nasal oxytocin, compared to placebo, on craving induced by a cue paradigm, an acute stressor, or withdrawal related stress in humans. The aim was to collate the evidence base for nasal oxytocin as a pharmacotherapy to reduce cravings which precede automated, addictive behaviours.	The review identified a total of 17 studies meeting the inclusion criteria, originating in countries across the world. Five out of 15 studies that investigated the effects of nasal oxytocin on self-report measures of craving reported a decrease in cue-induced craving, one study reported a decrease or increase depending on the participants' attachment style, one study reported an increase in craving, while the remaining eight studies found no effect. Regarding measures of consumption, only one out of seven studies involving the administration of nasal oxytocin reported a decrease in consumption, with the remaining six studies reporting no effect. There was heterogeneity across studies of dose levels, frequency of dosing, outcome measures, severity of addiction, length of participant abstinence, outcome reporting and population demographics. Poor methodological reporting was common with risk of detection bias, allocation concealment and risk of performance bias often unclear.
Chapter 5: Investigating The Mechanism Mediating The Effects Of Oxytocin On Opioid Craving: The Proof Of Concept (Quantitative Results)	The quantitative component of the study outlined in chapter four had four aims; 1) To explore whether nasal oxytocin administration compared to placebo decreases opioid related cue-induced subjective feeling of craving 2) To explore whether nasal oxytocin administration compared to placebo decreases opioid related cue-induced attentional bias 3) To explore whether in the placebo condition, opioid-cue-induced changes in attentional bias at min 7 are associated with changes in subjective feelings of opioid craving at 7, 15 and 30 minutes post-exposure, relative to baseline 4) To explore whether the effect of nasal oxytocin administration compared to placebo on cue induced subjective feeling of opioid craving at minutes 15 and 30	(1) There was no statistically significant difference between oxytocin and placebo to reduce cue-induced craving. Effect sizes suggested a clinically significant effect of oxytocin, specifically within the cue assessment component of cue-induced craving. (2) Contrary to our hypothesis, nasal oxytocin increased attentional bias 3 fold in comparison to placebo (3, 4) Changes in attentional bias were not related to changes in craving Note: During analysis of the raw data it emerged that the STROOP computer program did not balance randomisation across neutral/heroin-related conditions, a significant limitation in the attentional bias analysis

	post exposure is predicted by its effect on attentional bias at minute 7	
Chapter 6: Exploring the Influences, Experiences and Perspectives of Opioid Seeking Behaviour in Dependent Opioid Users (Qualitative Results)	The qualitative component of the study outlined in chapter four had two aims; 1) To gain further understanding regarding individual experiences of opioid cravings and how these are managed in real world settings 2) To explore of the experiences of people who use opioids to better understand the social process of procuring illicit opioids.	(1) Participants (n=14) described how triggers for heroin use became ingrained in every life. People struggled to define a physical sensation of craving and instead focused more on a continuous thought which itself acted as a trigger. Self-management of craving was an identified difficulty for all participants. (2) People described a reluctant belonging to a community built on the ability to support heroin use through superficial, transactional relationships.

Table 7.1: Summary of key findings from chapters two, three, five and six

Notes: Chapter one provided background information and chapter four described methods only and did not present findings.

7.1 Key Findings and Synthesis with Existing Literature

Section 7.1 reviews three key findings in the context of the current literature.

7.1.1 Moderate effect size for nasal oxytocin on opioid-related cue assessment

Previous literature has shown mixed results and large heterogeneity overall for nasal oxytocin to reduce cue-induced drug craving (Chapter three). Our study, which was unable to reject the null hypothesis, supported these findings (Chapter five). Where our study differed from existing literature for nasal oxytocin to reduce cue-induced craving was the identification of a cue assessment component of cue-induced opioid craving and reporting of the moderate effect size for self-reported reduced likelihood to use heroin following exposure to the cue. The neurobiological mechanism was not investigated in our study but randomised, double-blind, placebo controlled neuroimaging has already shown that nasal oxytocin decreases activation in the nucleus accumbens, anterior cingulate and insula during early pavlovian cue and context fear acquisition (Cavalli et al., 2017) which provides a starting point for future studies. In addition a growing body of research suggests that context is important to any effect of nasal oxytocin and that heterogeneous populations such as people with Schizophrenia, Autism Spectrum Disorders or perhaps SUD may see effects in sub-populations only (Ford and Young, 2022; Martins et al., 2022). Our study introduced a novel cue in a clinical environment where opportunity to use heroin immediately following exposure was denied and so arguably the cue was never conditioned to heroin use. Further research is necessary to better understand if our study parameters support Cavalli et al. (2017), to confirm any statistically significant effect of nasal oxytocin on opioid-related cue assessment, to examine any difference in setting (existing cue or novel cue only), any difference in context (clinical environment or real world environment) and in which populations.

7.1.2 Groupthink influences the cognitive conflict during attempts to stop heroin use

Chapter six supported elements of the existing research which found peer pressure, professional relationships with dealers influence procuring drugs other than opioids (Morris et al, 2020; Keysers et al., 2020; Palamar and Sönmez, 2022). There is much research regarding oxytocin and social processes. Early theory postulated that the effects of oxytocin were primarily the improvement of social cognitions and in

regulating prosocial behaviours (Bartz et al., 2011). As understanding has increased researchers are now more aware of the individual specificity of nasal oxytocin's effects, the limitations of known unknowns (optimal dosing, the meaning of any correlations between central and plasma oxytocin levels, genetic and endocrine biomarkers) and have evolved theory towards oxytocin as an allostatic regulatory peptide involved in much more than social cognitions and prosocial behaviour (Erdozain and Peñagarikano, 2020; Quintana and Guastella, 2020). Increased understanding of the complexity and sensitivity of oxytocin to environmental stimuli on an individual level helps to understand the effects on social cognitions and prosocial behaviours.

Group based decision making in healthy participants (n=123) has shown 24IU of nasal oxytocin facilitated the sharing and repetition of more unique information than people in the placebo group. This finding is important as it demonstrates an effect for nasal oxytocin to reduce conformity, and groupthink, in groups which typically only share commonly known information and do not share unique information (De Wilde et al., 2017). A link can be surmised that should nasal oxytocin be administered ad-hoc as suggested (Chapters three and five) then it may also interrupt groupthink when procuring opioids. Caution should be applied though as the evidence for nasal oxytocin's effects on group based decision making is not unequivocal. Nasal oxytocin has also been shown to increase in-group bias (De Dreu, Greer et al., 2011; De Dreu and Kret, 2016), increase dishonesty to benefit the in-group (Shalvi and De Dreu, 2014) and to increase gloating and envy (Shamay-Tsoory et al., 2009) in healthy populations. More research is needed to compare the effects of nasal oxytocin and placebo on group based social network interventions within existing cohorts of people who buy opioids together.

7.1.3 Under-diagnosis of psychiatric problems in opioid-related deaths 2006-2015

Our study was the first to specifically explore the prevalence of psychiatric disorders within opioid-related deaths and as such there is no directly comparative literature available. The Office for National Statistics do not routinely report this information in yearly bulletins and no further studies have been conducted by the NPSAD. However treatment statistics have recently begun to report the prevalence of people accessing in treatment who report a mental health need. According to the Office for Health

Improvement and Disparities (Adult substance misuse treatment statistics 2020 to 2021: report, 2021) 56.9% of people who use opioids who started treatment in 2020 to 2021 (n=21,307) had reported a mental health treatment need. Of these 50.5% (n=10,754) were receiving support through their GP, 13.4% (n=2,864) were already engaged with a mental health service, 1.2% (n=249) were receiving any NICE recommended psychosocial or pharmacological intervention provided for the treatment of a mental health problem in drug or alcohol services, 0.5% (n=100) were engaged with Improved Access to Psychological Therapy and 0.5% (n=106) had an identified space in a health-based place of safety for mental health crises. A treatment need was identified but no treatment was received or treatment was refused by 34.4% (n=7,340) of people who used opioids.

In contrast chapter two found that of all opioid-related deaths in people who had a confirmed medical history (n=2150), 63.53% (n=1366) had a historic psychiatric problem. Caution in comparison should be applied as our study refers to data from across a ten year period prior to 2020-2021 and relates to mortality rather than people undergoing treatment. When our data for 2015 is taken in isolation (n=374), the year where most previous medical was reported and therefore the year when most psychiatric diagnosis would be able to be confirmed, 63.90% (n=239) had a historic psychiatric problem. This perhaps indicates that psychiatric problems were more prevalent in mortality for people who use opioids than those in treatment however our study separated mortality between people known to use illicit drugs and people who were not known to use illicit drugs. Of those who were known to use illicit drugs in 2015 (n=279), 46.79% (n=175) had a historic psychiatric problem versus 67.36% (n=95) of people who were not known to use illicit drugs. Our study found higher prevalence of psychiatric disorders within people not known to use illicit drugs throughout the ten year period and above the expected prevalence of psychiatric disorders within the general population. A further limitation in the literature synthesis is that our study was unable to confirm what treatment people received, if any.

A comparison of our 2015 mortality data with the 2020-2021 in treatment data may indicate improved identification of psychiatric disorders amongst people known to use drugs but identification does not necessarily translate to improvements in treatment provision. The large number of people in treatment receiving help through their GP

(n=10,754) and the small number engaged with Improved Access to Psychological Therapy (n=106) suggests a medicalisation of psychiatric disorders which supports the escalation in prescription medication data found in chapter two (Section 2.3.3; Figure 2.9), barriers to accessing psychological treatments reported by professionals across two localities in chapter two (Section 2.2.4) and the experience of one service user from a different location as reported in chapter six (Section 6.1.2). For opioid-related deaths to reduce it is critical that people are able to access evidence based psychological therapies for the high prevalence of trauma experienced (Lawson et al., 2013) and not medicalised in isolation for associated symptoms.

The implications of this thesis and suggestions for future research are discussed in section 7.2.

7.2 Implications and Future Directions

This thesis balanced rigorous scientific enquiry with philosophical insights as to the role of oxytocin within opioid use disorders. Many of the ideas contained herein can be viewed as pre-theory, requiring development of hypotheses to then be tested. The biopsychosocial model of addiction argues that there is a constellation of factors both internal and external which increases and reduces risk of addiction (Marlatt & Baer, 1988) and the ideas presented in this thesis complement existing addiction theories when substance use disorders are viewed through a biopsychosocial lens (Figure 7.2).

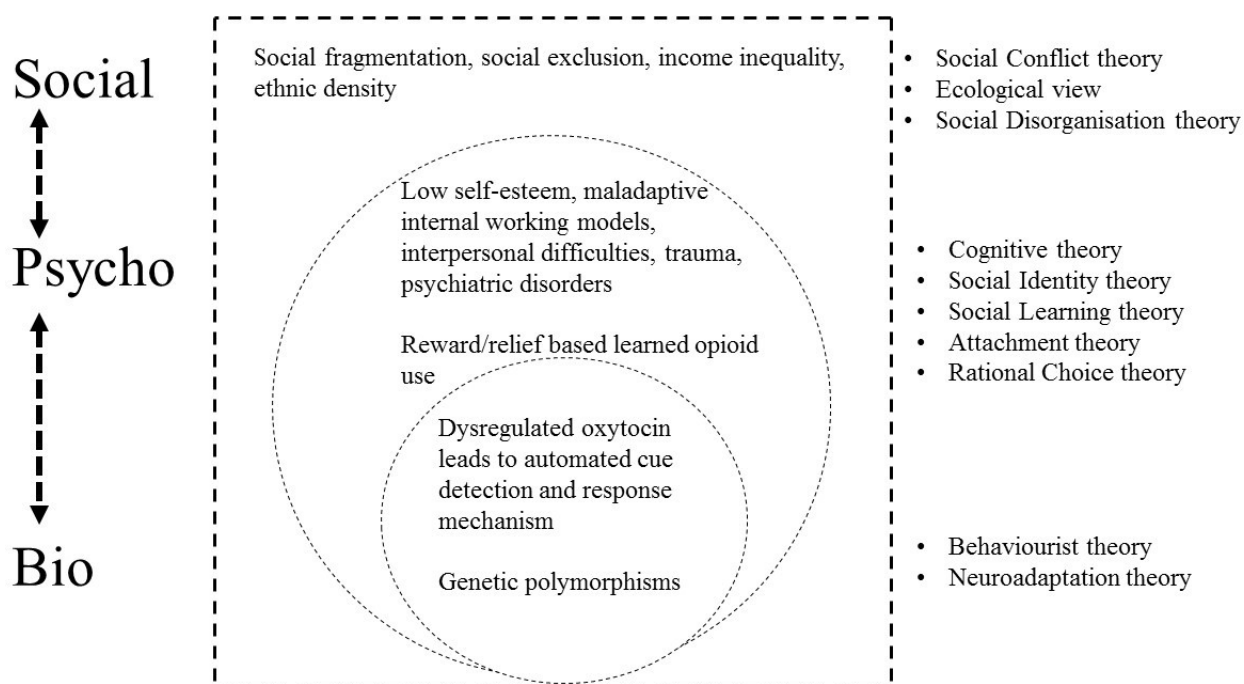


Figure 7.2: The biopsychosocial model for oxytocin dysregulation and opioid use disorder

Notes: The biological component of the model argues that dysregulation of the oxytocin system inhibits reassessment and response to opioid-related cues which leads to automated behaviour. The psychological component demonstrates how this dysregulation can be caused by trauma leading to difficulties with socialisation. The socioeconomic component shows how the conditions in which people live can alter the oxytocin system. Taken together, the impact of adaptations in the oxytocin system can be surmised in numerous theories of addiction suggesting a central role for the oxytocin system in opioid addiction.

Sections 7.2.1 to 7.2.3 inclusive will now discuss the implications and directions for oxytocin within each layer of the biopsychosocial model.

7.2.1 Implications and future directions for oxytocin within the biological component of a biopsychosocial model

The biological component (Figure 7.2) refers to genetics, neurotransmitters and associated neurological systems. These were presented as background literature in chapter one. Oxytocin dysregulation can be the result of adverse childhood experiences, genetic polymorphisms, chronic drug use or psychiatric disorders – all

highly prevalent in opioid use disorder (Chapter 1, Section 1.6). Oxytocin systems were linked to an allostatic theory meaning oxytocin is released in response to environmental cues as a predictor of bodily changes needed to meet the anticipated demands of the environment (Quintana & Guastella, 2020). The meaning of oxytocin dysregulation was theorised in chapter three and a novel mechanism researched in chapter five suggested that oxytocin dysregulation may hijack amygdala cue-response mechanisms locking the person in to patterns of looped behaviour. These chapters added to the hypothesis to suggest that biologically, oxytocin dysregulation may compliment existing behaviourist (substance use as a stimulus response such as cue conditioning), impulse-control disorders (substance use framed as the inability to control impulsive responses) and neuroadaptation (continued substance use resulting from changes which occur in the brain as a result of chronic substance use) theories of addiction.

In order to provide an evidenced foundation for the wider hypothesis of oxytocin dysregulation as a key component of opioid use disorder it is suggested that blood samples are taken nationally with the aim of mapping similarities and differences in plasma levels. By including oxytocin genes, through analysis of single nucleotide polymorphisms, amongst people with/without dependent opioid use substantial invaluable baseline data can be generated. Incorporating the definitions used by the National Drug Treatment Monitoring System and the Office of National Statistics for participant demographics (housing, employment, education for example) will enable correlation and regression analysis between multiple variables which could strengthen any theory of the influencing factors for oxytocin dysregulation in opioid use disorders.

7.2.2 Implications and future directions for oxytocin within the psychological component of a biopsychosocial model

The psychological component (Figure 7.2) refers to psychological composition (personality traits, psychiatric disorders, constructs such as self-esteem and the impact of events such as trauma on psychological state). Chapter one discussed how the biological component above may primarily affect socialisation. This thesis was unable to provide novel evidence for correlation or causation of oxytocin changes and psychological impact due to the limitations in the design of each included study.

However chapter two researched prevalence of psychiatric disorders, where oxytocin dysregulation has been consistently evidenced, in opioid related deaths. Chapter six researched the experience of people experiencing cravings finding themes which was reasonably linked to the introduction to oxytocin presented in chapter one. These chapters added to the wider ideas found in this thesis that suggest psychologically, oxytocin dysregulation may compliment cognitive theories (continued substance use due to functions such as learning, memory, attention, reasoning, and impulse control), social identity and social learning theory (substance use as learned behaviour influenced and reinforced by the social group's people associate with), attachment theory (substance use as self-medication to compensate for lacking attachment strategies) and rational choice theory of addiction (substance use as a costs-benefits decision).

Not everyone who is exposed to triggers will use heroin suggesting the involvement of other variables in the mechanism of heroin use. Chapter five postulated this variable may be a value based decision. The inclusion of a value based decision would sit well within rational choice theory of addiction. Rational Emotive Behavioural Therapy (Ellis, 1957) is a cognitive-behavioural model which can be simplified as the ABC of behaviour. This model proposes that an internal or external activating event (A) leads to a belief (B) and in turn the belief leads to a consequential behaviour (C). For example an opioid-related cue is linked to the belief that the cue will bring reward or relief and opioid use is the behaviour that follows. Ellis (1957) proposed that in order to change the behaviour, the belief must be changed. As beliefs and values are influenced largely by social construction (Ponizovskiy et al., 2019), and substance use is embedded with social experiences, future studies which investigate whether Rational Emotive Behavioural Therapy alone, Rational Behavioural Therapy plus oxytocin administered prior to the session or no treatment is effective in reducing opioid use. A similar approach has already been used by Sherman et al. (2017) whose parallel design randomized 8 people to oxytocin and 8 people to placebo prior to Motivational Enhancement Therapy, finding that those randomised to oxytocin in comparison to the placebo group reduced cannabis use over a four week study period.

The social cognition effects of nasal oxytocin have long been the focus of research though results are mixed and scepticism surrounding the efficacy of nasal oxytocin to

improve social cognition remains (Horta et al., 2021; Erdozain, and Peñagarikano, 2020). Research suggests that nasal oxytocin is involved in cue extinction as well as cue creation (Cavalli et al., 2017). This was supported recently by Kapetanidou et al. (2021) who found nasal oxytocin improved relearning of stimulus-outcome associations. A nasal spray of oxytocin when administered following exposure to opioid-related cues may, as part of interrupting the overall craving mechanism, allow revaluation of opioid-related cues by delaying euphoric recall which may be linked to the fear memory extinction effects of nasal oxytocin (Baldi et al., 2021). Reassessment could stimulate reverse learning of opioid-related cues, likely through repeat exposure and a continual change in behaviour making each future exposure to similar conditioned opioid-related cues easier to self-manage. As oxytocin is a facilitator of social learning rather than a cause of prosocial behaviour change, any reverse learning of opioid cues would require provision of psychosocial intervention alongside nasal oxytocin treatment (Ford and Young, 2022). Future research should seek to combine delay-gratification, reversal-learning, value based decision making and fear extinguishing in to a single crossover study exposing people to individually specific heroin-related cues and attempt to reverse the learning of those cues culminating in creation of a new conditioned response to the cue.

7.2.3 Implications and future directions for oxytocin within the social component of a biopsychosocial model

The social component (Figure 7.2) refers to the social environment (norms, cultural beliefs, expectancies, social approvals, accessibility and legality for example). Chapter one introduced evidence of oxytocin dysregulation as a result of socioeconomic differences which was further discussed in the conclusion of chapter two. Chapter six presented novel research highlighting the social influence and process of obtaining drugs overlapping with social psychological theories and added novelty by providing preliminary evidence of Groupthink (Janis, 1972) as a social mechanism for seeking illicit opioids. Together chapters one, two and six suggested that oxytocin dysregulation compliments social conflict theory (how structural factors in society affect substance use), ecological view of addiction (substance use as the result of the relationship between a person and their environment within the elements of place, time, physical features, activity, participant, and role) and social disorganisation

theory (substance use as a result of inequalities and heterogeneity in the characteristics of people living in social structures such as poverty, ethnicity and mobility).

Whether differing environments affect oxytocin levels, how long it takes for any changes to the oxytocin system to occur and whether these changes sustain if a person returns to a challenging environment are all targets for future research. Huang et al. (Manuscript submitted for publication) recently found a significant increase in serum oxytocin and oxytocin mRNA 30 days after leaving voluntary residential rehabilitation for methamphetamine addiction versus the plasma sample from the same people taken at rehabilitation entry. This suggests an effect of residential rehabilitation or of abstinence on the oxytocin system. At the time of writing, Huang et al. do not expand on treatment received during residential rehabilitation. The methods used by Huang et al. could be adapted to recruit people who use opioids before they go to residential rehabilitation and tracking their plasma oxytocin levels (as well as single nucleotide polymorphisms) through to either returning to the original environment or resettling to a new area. The period after leaving rehabilitation would be vital to monitor how long lasting these changes may be and provide valuable insight to relapse. In addition research should examine the effects of using a nasal spray of oxytocin prior to group based social network interventions as suggested previously (Section 7.1.2; Section 7.2.2). By incorporating mouth swab and urine drug screens (due to differences in detection time of last drug use) as well as self-report prior to the intervention this study would also be able to reliably identify changes in opioid using behaviour. Should oxytocin have the hypothesised effect of destabilising existing Groupthink within cohorts then this would be a further use for nasal oxytocin not only within clinical settings but potentially also as part of the proposed take-home ad-hoc pharmacotherapy postulated throughout this thesis and discussed further in section 7.2.4.

Section 7.2.4 discusses the implications and future directions for the role of nasal oxytocin as an anticraving pharmacotherapy to be used in treatment services.

7.2.4 Implications and future directions for nasal oxytocin as an anticraving pharmacotherapy

Chapter five has added to the evidence base for oxytocin as an anticraving pharmacotherapy by exploring three different components of cue-induced opioid craving. Mixed ANCOVA found no statistically significant effect of oxytocin versus placebo to reduce subjective craving on treatment ($F = 0.73$, $df=1$, $p=0.79$, $\eta^2=0.04$), time ($F = 1.32$, $df=2$, $p=0.27$, $\eta^2=0.62$) or treatment*time ($F = 0.93$, $df=2$, $p=0.40$, $\eta^2=0.45$). Subjective measures alone may not be reliable to assess the efficacy of craving reduction due to problems identifying internal emotional changes. For this reason we had intended to include an objective measure, attentional bias, with the hypothesis that attentional bias would acutely increase following exposure to opioid-related cues and that oxytocin would reduce the attentional bias, mediating the craving. Across all three questions of the craving measurement 4/9 analyses found large effect sizes and a further 3/9 found moderate effect sizes indicating practical significance. Only the question related to cue-related memory recall did not find large effect sizes. Effect sizes were largest for ‘if you saw this in your everyday life, how much would you crave heroin?’ Mixed ANCOVA found no statistically significant effect of treatment ($F = 2.83$, $df=1$, $p=0.10$, $\eta^2=0.11$), time ($F = 1.79$, $df=2$, $p=0.17$, $\eta^2=0.75$) or treatment*time ($F = 1.86$, $df=2$, $p=0.16$, $\eta^2=0.78$).

Our model proposed that an acute increase in attentional bias following exposure to opioid-related cues would drive opioid craving and that by reducing attentional bias a nasal spray of oxytocin could reduce opioid craving (Figure 3.3, p.142). Taking into account the limitations with our study design (Section 5.2.1, p.254), we saw an increase in attentional bias at 8 minutes post exposure to cue-induced craving 3x greater under oxytocin versus placebo but both reduced in comparison to baseline scoring. Contrary to existing evidence we also found no relationship between cue-induced opioid craving and attentional bias. This could be explained by nasal oxytocin’s known propensity to increase contextual salience to external cues (Shamay-Tsoory and Abu-Akel, 2016) but rather than theoretically increase craving as our model implied, craving scores under oxytocin reduced greater than under placebo albeit not significantly. Reducing the reduction in attentional bias versus baseline may be beneficial to controlling opioid use in people who have recently used heroin.

As the STROOP effect is a measure of response time a reduced attentional bias post exposure to a cue could indicate a rapid response whereas a larger attentional bias indicates a delayed response due to delays in cognitive processing. Speculatively reduced attentional bias may demonstrate a subconscious, automated response to opioid-related cues whereas creating an attentional bias would provide a brief window where other factors related to drug use such as value of the cue versus salience of the cue, knowing that both operate independently (Kahnt and Tobler, 2017), can be assessed. The effect sizes found in questions two of the opioid craving scale for likelihood to crave heroin may support this and any interplay between value of cue, salience of cue and craving scores warrant further investigation.

Value increases with probability of reward and decreases with probability of punishment whereas salience increases with probability of both reward and punishment (Kahnt and Tobler, 2017). Incentive-sensitization theory posits that drug use, especially when triggered by cues, is an amplification of ‘wanting’ rather than ‘liking’ the drug (Robinson and Berridge, 1993). This could be observed by the rapid response and declining STROOP effect meaning drug use is continued despite low value (less reward and anticipated post use punishment i.e. guilt, remorse, regret). However, central to Incentive-sensitization theory is an increase in release of dopamine following drug administration which is not yet confirmed in studies involving humans who use heroin (Nutt et al., 2015; Wise and Jordan, 2021; Millela et al., 2023). Possibly then the amplified ‘wanting’ rather than ‘liking’ posited by in Incentive-sensitization theory is caused by the loop of dysfunction proposed in Chapter three. In summary, endogenous oxytocin would usually regulate amygdala hyperactivity in the presence of stimuli (Uvnäs-Moberg et al., 2015). Endogenous oxytocin can be dysregulated by heroin use (Vuong et al., 2010), early life experiences (Baracz et al., 2020) and psychiatric disorders (Misrani et al., 2017; Winteron et al., 2021) which are all highly prevalent in people who use opioids. This means cue-induced amygdala hyperactivity is not attenuated and only existing opioid-related behaviours are automatically recalled by the hippocampus because the process of cue reassessment is inhibited and so the cycle of opioid use is continued (Figure 3.2, p.139). To reduce cue-induced opioid use it would then be necessary to create a delay

in cognitive processing such as through reducing the reduction in attentional bias and allowing for revaluation of likelihood to use opioids rather than rapid responses formed on previous knowledge of the cue.

From this perspective, our original idea that nasal oxytocin would increase inhibitory control of attentional bias may be supported albeit through a differing mechanism than first thought. Further studies are needed to investigate the effect of oxytocin on attentional bias in healthy controls, abstinent people with history of using heroin, abstinent people but maintained on substitute opiates and people currently using heroin with/without substitute opiates.

Due to the early stage of the proof-of-concept study the implications for practice are encouraging but theoretical at this stage. Oxytocin is only currently licensed to induce labour in the UK and there is much research to be conducted to confirm any efficacy in reducing opioid craving and opioid use.

The implications for research are far wider. Primarily the proof-of-concept study should be repeated with a robust attentional bias program in place in order to fully explore the hypothesis for how oxytocin may reduce cue-induced craving. Neuroimaging should be included in any follow up study. Whilst subjective craving may be a poor outcome measure due to problems with interoception and alexithymia, imaging may be a more reliable biomarker and would be able to confirm the neurobiological mechanism hypothesis for oxytocin to reduce cue-induced opioid craving. Secondly, it is vital that this research can be replicated in females in order to ensure nasal oxytocin can work in females as well as men. Females have higher levels of oxytocin than males naturally and together with the known differences in how nasal oxytocin works in females, it may be that dosing needs to be lower in females to elicit similar effects. Thirdly, the proof-of-concept study now has a protocol proven to be acceptable in recruitment to people currently using heroin which can be utilised across other substances and wider addictive behaviours (gambling, exercise, porn, gaming etc). Adjustments need only be made in the cue-inducement stimuli, time points for outcome measures and the outcome measures themselves, including participant expectancy as an important therapeutic outcome (Frisaldi et al., 2017). Cue-induced alcohol craving would be of particular interest as research has already shown that nasal

oxytocin can improve interoception in heavy alcohol users (Betka et al., 2018), a key barrier in assessing whether nasal oxytocin can reduce subjective craving in people who use opioids. Fourthly, the Stanford Expectations for Treatment Scale (Younger et al., 2012) should be used within collection of participant characteristics. This validated tool is used to assess participant expectancy effects in clinical trials to improve statistical sensitivity for detecting treatment differences. Finally the only way to properly test if nasal oxytocin is able to reduce opioid use is to conduct a fully powered randomised trial. Ideally as part of the plasma study outlined in section 7.2.1 and perhaps the psychological elements suggested in 7.2.2, this study would be required to allow participants to take nasal oxytocin away and self-record their own use. Participants would be asked to return empty sprays in order to receive new sprays which would allow for bottle weighing and support accurate recording of how much oxytocin people use as well as provide opportunity for objective measures of opioid use (saliva and urine drug screening). Although the safety profile of nasal oxytocin poses no cause for concern when administered clinically in a controlled environment there is the possibility that outside this environment people will try to inject it as with any drug. For females this could be particularly dangerous given oxytocin's current medical use for inducing labour but injecting will be a risk irrespective of female presence in the inclusion/exclusion criteria. Further consideration would also need to be given to the temperature required to store oxytocin. It would be difficult to endorse nasal oxytocin as an ad-hoc pharmacotherapy if participants could not carry it with them. One solution could be to give participants a small hot/cold thermal bag to keep each spray in and whilst there would be the risk of nonadherence, it may be the best solution for a randomised controlled trial if not the eventual solution. An alternative option would be to use the synthetic oxytocin analogue, carbetocin. Carbetocin, unlike oxytocin, is a functional selective oxytocin/Gq agonist and, again unlike oxytocin, is also a competitive antagonist of Vasopressin (Passoni et al., 2016). This markedly different pharmacological profile may mean further pilot studies are required to identify dose response or even to confirm that it acts in the same way on the amygdala as oxytocin to support the anticraving mechanism proposed by this thesis. Nevertheless, animal models have shown that carbetocin is able to attenuate stress induced reinstatement of opiate seeking in morphine abstinent mice (Zanos et al., 2014). Carbetocin may be also be superior to oxytocin for our proposed use as

carbetocin has been shown to maintain >95% purity of the peptide when stored at 30°C for three years, 6 months at 40°C, 3 months at 50°C and 1 month at 60°C (Malm al., 2018), combatting any limitation of oxytocins temperature requirements. The peripheral circulation half-life of carbetocin is also superior to oxytocin, carbetocin 85–100 min versus oxytocin 3.4 min (Passoni et al., 2016) meaning any anticraving effect may be prolonged. Although there is a concern that repeated administration of carbetocin could form tolerance because carbetocin does not induce oxytocin receptor recycling (Passoni et al., 2016), Prader-Willi syndrome studies in males ($n=53$) and females ($n=66$) aged 7-18 which have used nasal carbetocin 3xdaily for up to 52 weeks found no formation of tolerance and minimal side effects demonstrating safety in children and adolescents (Roof et al., 2023).

Section 7.2.5 next discusses the implications and future directions arising from this thesis for drug and alcohol treatment services.

7.2.5 Implications and future directions for drug and alcohol treatment services

Chapter two highlighted under-diagnosis of psychiatric problems in opioid-related deaths though diagnosis was higher in people who were not known to use illicit drugs. The follow up interviews suggested structural barriers to accessing psychological therapies which were not in line with UK national guidance. This was supported by participant experience in chapter six where a nine month delay in accessing an initial assessment for psychological therapy was reported. Judgemental attitudes from professionals were also identified as a barrier to accessing psychological therapies. If opioid-related deaths are to be reduced then treatment services must hold themselves accountable irrespective of financial austerity and take action to ensure service provision is in line with national guidance. One recommendation is that treatment services conduct an audit to identify how many people were referred for statutory psychological therapies, what the outcomes were and what the reasons for the outcomes were. By doing this, specific goals can be added to treatment plans to ensure people have realistic and actionable targets that allow them to receive the help they need. One further recommendation regards the detection of prescription medications at death. It would be preferable if people under the care of drug and alcohol services received all prescriptions solely from them. This would reduce the potential for over-prescribing and for drug-drug interactions which also contribute to opioid-related

deaths. The implications for drug and alcohol services arising from Chapter six were discussed in the relevant chapter.

Future directions for research in drug and alcohol treatment services are important in order to improve the care of people who use them. Previous research focused on occurrence of psychiatric disorders in opioid users and risk factors for opioid use disorders, the study presented in chapter two was the first to examine psychiatric disorders in opioid users posthumously. The limitations of NPSAD reporting prohibited confirmation of support for earlier UK comorbidity studies which concluded there had been a failure to detect co-existing mental health problems in opioid users (Weaver et al., 2003) but the rationale for this was suggested as being unidentified unmet needs by drug services. The qualitative interviews conducted in chapter 2 oppose this and suggest that psychiatric needs are identified by both drug services and mental health teams but that organisational gatekeeping frameworks are prohibitive to receiving psychological treatments. These findings progressed the discussion and support recent evidence reporting global barriers in accessing effective, evidence based treatment (World Drug Report, 2019). It is therefore recommended that the Weaver et al. (2003) study is updated using the same methods to provide current data from treatment services and subsequently that the posthumous study in Chapter two is repeated to substantiate findings. There is greater understanding of the NPSAD database limitations now. By working closely with the NPSAD data controllers at the outset to better define the parameters and restrictions prior to the data extraction, robust statistical analysis of the findings can be conducted. Expansion of the qualitative studies should seek to increase the number of healthcare professional interviews conducted across multiple sites and include the experiences of service users regarding attempts to receive psychological therapies for psychiatric distress.

7.3 General Limitations

Study-specific limitations have been critically evaluated in the corresponding chapters and will not be repeated here. Other limitations related to this thesis and specifically the role of oxytocin are discussed within this section.

The most important limitation is the known sexual dimorphic effects of nasal oxytocin. The mechanism for reduction of cue-induced craving postulated in Chapter three

(Figure 3.3, p.142) and tested in Chapter five is reliant on a reduction of amygdala hyperactivity in response to opioid-related cues following self-administration of oxytocin but nasal oxytocin can increase amygdala activity in response to socially positive cues in females. This may be because the doses used with females are too high where females have naturally higher levels of oxytocin in comparison to men. Less is more may be a more successful approach where females are concerned but much more dose-response research is required. Drawing any conclusion at this stage without focused research on females and also transgender people would be no more than speculation. A lack of evidence in these populations represents a significant limitation to progressing nasal oxytocin as a pharmacotherapy.

Another key limitation for the overarching idea of this thesis postulating that oxytocin dysregulation being central to opioid use disorder is the lack of understanding for what constitutes oxytocin dysregulation and what oxytocin dysregulation means for behaviour. Posttraumatic dysregulation alone could mean altered secretion, concentration, density of receptor sites or altered levels of the enzymes which metabolize oxytocin (Seng, 2010). There is high prevalence of adverse childhood experiences in people who use opioids and heroin use has been shown to inhibit oxytocin use (Vuong et al., 2010) but dysregulation caused by socioeconomic disparity and psychiatric disorders is more difficult to define. Plasma oxytocin levels are not a good barometer for dysregulation as studies which measure levels of plasma oxytocin have yielded inconsistent and contradictory results. Further it is unknown if or how differing causes of oxytocin dysregulation affect others. For example, do genetic polymorphisms heighten or reduce the chance of inconsistent parental care giving or does dysregulation caused by opioid use initiate epigenetic changes and would the social environment impact oxytocin plasma levels? Continuing from this limitation is how dysregulation affects males and females. Higher plasma levels in healthy women versus healthy males have been observed (Marazziti et al., 2019) but the relationship with central oxytocin in all sexes is largely unknown. Defined parameters of 'normal' oxytocin levels in males and females would first be required to be able to define dysregulated plasma levels. But setting biomarker parameters for oxytocin levels assumes that quantity of oxytocin is related to function of oxytocin in dysregulated systems. If nasal oxytocin effects were solely related to quantity then it

should be possible for male behaviour to replicate female behaviour just by increasing oxytocin and this is not the case. It is plausible that oxytocin acts like the oil in an engine and simply lubricates socially constructed behavioural mechanisms. Plasma quantity likely differs simply as a variance between the male and female engine without immediate consequence for function. Much investigation is needed to specify oxytocin dysregulation in order to corroborate any theory for the role of oxytocin in opioid user disorders.

7.4 Overall Conclusions

This thesis aimed to explore the potential role of oxytocin in opioid-related deaths primarily by testing whether a nasal spray of oxytocin was able to reduce cue-induced opioid craving. Much evidence herein has highlighted that oxytocin dysregulation can be caused by many of the risk factors associated with opioid use disorder. However the presented ideas are very early stage and require substantial further research to properly understand how oxytocin dysregulation can affect opioid use.

Based on the evidence discussed within the literature review, oxytocin could be efficacious in reducing opioid craving though the evidence base is hindered by heterogeneity. In our study 40IU of nasal oxytocin was able to reduce cue-induced craving 7, 15 and 30 minutes post exposure to a craving inducing video but so did placebo and no statistically significant difference between oxytocin and placebo was found. Participant expectations are well documented in clinical trials seeking to establish superiority of a treatment versus placebo and there was a large expectancy effect in this study which made analysis difficult. Sample size, distribution variance of oxytocin scores and whether a subjective measure of craving alone is reliable were all suggested as other reasons for not finding statistical significance. However effect sizes were encouraging to suggest clinical significance for nasal oxytocin and revealed a further avenue for exploration of the craving mechanism regarding assessment of opioid-related cues under nasal oxytocin. This thesis recommends that effect sizes and reporting of participant expectations are routinely reported in nasal oxytocin studies to provide wider insight to clinical significance.

Overall, the findings were unable to reject the null hypothesis for nasal oxytocin to reduce cue-induced opioid craving. Theoretical arguments, and data supporting nasal

oxytocin as being beneficial to reducing cue-induced opioid craving (effect sizes, qualitative data) have been put forward, but contradictory existing evidence cannot be ignored, suggesting the need for further research. The wider ideas linking oxytocin dysregulation and opioid use disorder suggested herein provide a rich, exciting pathway for future research. Increasing our understanding of how environments can shape development of the oxytocin system and consequently, how oxytocin dysregulation affects drug-related behaviours, could help save lives.

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*'The frontiers of a book are never clear-cut: beyond the title, the first lines,
and the last full stop, beyond its internal configuration and its autonomous form,
it is caught up in a system of references to other books,
other texts, other sentences: it is a node within a network'*
-Michel Foucault, French Philosopher

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Appendices

*“It is a very sad thing that nowadays there is so little useless
information”*

– Oscar Wilde, Irish Poet and Playwright

Appendix 1

Qualitative Study Interview Schedule

Aim: To explore the views and experiences of staff members involved in working with people who have substance use disorder(s), mental health problem(s) and people with co-existing substance use disorder(s) with mental health problem(s) to explore perceptions of situational, contextual, personal and organisational factors.

The order and exact content of the questions will be determined by the participant and on-going analysis. The following topics and prompts serve as an interview guide. Further prompts may be added following analysis and feedback from participant interviews

Introduction – Confirm consent to audio record.

Discuss anonymity and confidentiality and answer any questions

1. Background and role

Can you briefly explain your background and current role?

Prompts: personal background/experience, career path including but limited to academic training to current role

2. Study set up

Can you tell me about how your first became aware of this interview and any feelings you had about it?

Prompts: what were you curious about? What were you anxious about? Have you taken part in a study before? What are your expectations? Do you have any concerns?

3. People who use substances

- Do you have any thoughts, positive or negative, about people who use drugs and alcohol?

Interviewer Prompts: – choice or disease? Does It matter if the drug is legal i.e. tobacco? Difference with prescription drugs? Route of administration? Difference with gender? Social influences of drug use? What is recovery and is it possible?

4. People with mental health problems

- Do you have any thoughts, positive or negative, about people with mental health problems?

Interviewer Prompts: – social influence/impact on cause and recovery? Which problems are most prevalent on society? Why is that? Are some better or worse than others? Are mental health problems life long, is it possible to eliminate them or is the best that can happen management? What is the role of medication in mental health problems?

5. People who use substances who also have mental health problems

- Do you have any thoughts, positive or negative, about people who use drugs and alcohol but also have mental health problems?

Interviewer Prompts: – do you think many people use drugs/alcohol and have a mental health problem? are the two linked or does one create the other? Can one be treated without treating the other? Is recovery dependent on amount of drug/alcohol use, social factors or something else?

5. Treatment provision

- Do you have any thoughts, positive or negative, about treating people who use drugs/alcohol who also have mental health problems?

Interviewer Prompts: – role of medication, role of psychotherapy, difference in mental health diagnosis? Difference in substance used? Are you aware of any barriers organisationally that prohibit treatment? Are you aware of any facilitators of treatment organisationally?

6. Is there anything else you'd like to discuss about your involvement with these interviews?

Appendix 2

Qualitative Study Interview Schedule

Aim: To explore the views and experiences of service users regarding drug craving, awareness of attentional bias and obtaining illicit drugs.

The order and exact content of the questions will be determined by the participant and on-going analysis. The following topics and prompts serve as an interview guide. Further prompts may be added following analysis and feedback from participant interviews

Introduction – Confirm consent to audio record.

Discuss anonymity and confidentiality and answer any questions

1. Study set up

Can you tell me about how your first became aware of this study and any feelings you had about it?

Prompts: what were you curious about? What were you anxious about? Have you taken part in a study before? What are your expectations? Did you have any concerns?

2. Background

Can you briefly explain your background and when you started to use heroin?

Prompts: childhood experience, parents, experience of trauma, pathway of drug use, route of administration

3. Craving and attentional bias

Can you tell me how it feels to crave opioids or other drugs? How did you feel when you were completing the computer task?

Interviewer Prompts: – does it feel different for drugs and alcohol? what things trigger you to use? what kind of things do you do to manage the triggers? Did some words have a different effect on you than others?

4. The process of obtaining drugs

Can you talk me through what you do to obtain drugs?

Interviewer Prompts: – social influence? Conscious decision or automated? How does it feel, are there different feelings if you're alone or with friends? Do you use the same people to get drugs from, how do you meet dealers?

5. After using drugs

Can you tell me how you feel once you've used drugs?

Interviewer Prompts: – talk through the high, explore the after process, what are the impacts (good and bad), identify feelings and how they feel about those feelings

6. The end of the study

Now that the study is over, how do you feel about it?

Interviewer Prompts: – what went well, what would you change, has it been useful? number of site visits, payments, the computer task, how to encourage people to sign up

7. Is there anything else you'd like to discuss about your involvement with this study?

Appendix 3

Recruitment Poster

**Could a nasal spray
reduce your heroin
cravings?**

 **Currently using heroin?**

 **On a prescription of methadone or
buprenorphine?**

 **Male?**



**are you interested in taking
part in a 4 appointment
research study?**

**if you are then please ask your keyworker at iAccess
Chertsey, Frimley or Guildford for more details or
contact [redacted] (Tel: [redacted])**

				
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Appendix 4

Participant Information Sheet

Can and How a Nasal Spray Reduce Your Heroin Cravings?

Investigating the mechanism mediating the effects of oxytocin on opioid craving: A proof of concept study

You are being invited to take part in a research study. Before you decide whether you would like to take part or not, it is important that you understand why the research is being done and what it will involve. Please read this information sheet carefully and decide if you would like to take part or not.

What is the study about?



The aim of this study is to understand what happens to opioid cravings and attention when a nasal spray of a hormone called oxytocin is used. In total, about 30 people will take part in the study. Everyone will receive a nasal spray of both oxytocin and a placebo but nobody will know which one they receive first. The study will last between 4 and 8 weeks in total depending how often you want your appointments. You can choose weekly or fortnightly appointments.

Why have I been asked to take part in this study?

You have been invited to take part because your care team has identified that you are male, currently using heroin, stable of methadone or buprenorphine (including Espranor, Subutex and Suboxone) and may be interested. We're sorry but oxytocin works differently with females so we cannot invite females to take part in the research but females are more than welcome to help us tell people about the results if you would like.

What will happen to me if I take part?

- If you decide to take part, you will be asked to sign a consent form (you will be given a copy to keep along with this information sheet).

- You will be asked to attend four times in total. You can choose whether to have weekly or fortnightly appointments. Each visit will last between around 45 minutes to two hours, it depends on how long you want to stay afterwards.
- At your first visit you will complete a research assessment, which will involve answering some questions about your life (nationality, education, employment status etc). Craving and attention will also be measured.
- You will then be randomly allocated to receive either a nasal spray of oxytocin or placebo first. This will be done by computer and we won't know which one you have had until the study is finished. Random allocation means by chance, a bit like flipping a coin. This is to make sure the study is a fair test.
- On your second and third visits you will receive either a nasal spray of oxytocin or placebo (you will receive both during the study) and then tested for craving and attention in the same way as the first visit.
- At the fourth visit we would like to interview you about your experience and using heroin in general. This will be recorded digitally but will remain anonymous and confidential. Your care co-ordinator will not be informed of what you tell us.
- You have the right to withdraw from the study at any stage without having to explain your decision.

How will you test craving?



- We will show you a video of a man injecting heroin once and then ask you to tell us how it makes you feel using a rating scale. We will also test your attention using a computer program. We show the video once on visits one, two and three only. You will be asked to complete the craving test four times on visit one, two and three. Each craving test lasts for one minute. You will be asked to complete the attention test three times on visit one, two and three. Each test takes about 5 minutes. You will also continue to receive your usual care from your care team. Participating in the study will not interfere with the usual care you receive from your keyworker so you could have your study visits on the same

day as your keyworking visits so you don't have to attend any more than you normally do.

- At the end of each visit we will invite you to stay in the service until you feel you are ok to leave. This is why the visits could take up to one and a half hours but you are free to leave before this if you feel ok. We ask you to stay in case you continue to crave heroin and want to be in a safe place with support options. We will also give you a Naloxone pen.

Do I have to take part?

No. Participation is entirely voluntary, which means it is up to you whether you want to take part. *If you do decide to take part, but later change your mind, you are free to withdraw at any time without giving a reason. If you decide not to take part in the study, or later withdraw from the study, this will not in any way affect the normal care you receive.*

Will I be compensated for my time?

You will be compensated with shopping vouchers after visit four. There will be four visits in total. You will receive two vouchers per attended visit. For example if you only completed three visits then you would only receive six vouchers.

You will also have bus fare, or train fare from the surrounding area only, reimbursed for attendance at every clinic visit if you show us the receipt or ticket.

What are the possible disadvantages and risks of taking part?

The main disadvantage is that the video will make you crave heroin when you wouldn't have done normally. For the research assessments, there are no right or wrong answers and you do not have to answer any questions you do not want to. You are free to ask the interviewer to move on to another subject or to stop the session altogether if you find any of the questions upsetting.

What are the side-effects of nasal oxytocin and placebo?

There are no major side-effects known with nasal oxytocin and nasal oxytocin has been used on other studies with drug users without adverse event. Like all medications some people have bad reactions. You may experience mild light headedness/vertigo,

drowsiness, dry throat/mouth, nasal irritation, runny nose, abdominal/stomach pain, anxiety, euphoria, calm and headache. These are the same side-effects you may experience when you take the placebo and you have the same chance of experiencing them with both oxytocin and placebo.

If you experience any side-effects you can stay at the treatment centre until you feel better where trained staff will be available to support you. You can also withdraw from the study at any time.

What are the possible advantages or benefits of taking part?

The nasal spray used in this study is a new type of medication. For this reason we do not know whether or not it will be helpful. By taking part in the study you will be helping us to learn if this is helpful in reducing cravings and how it may work. This information will help us to prepare for a future bigger project that will give us a better idea whether the nasal spray is helpful or not, and if we should design a bigger study.

Will my responses be confidential?



Yes. All data collected will be kept confidential, and identified only by an anonymous identification code that will not personally identify you. No names will be used when the results of the study are published or talked about so your identity will never be revealed in any reports based on this study.



If you tell the research assistant something that makes them concerned for your safety, or the safety of others, they will have to share this information with your care team.

What will happen to the results of the research study?

The results of the study will be published in an academic journal and a lay summary of the findings will also be written. You are welcome to have a copy of the results of the study once it is completed, if you wish.



Who is organising and funding the research?

This research is being funded by St. Georges University of London and Kings College London. Surrey and Borders NHS Foundation Trust is the sponsor for the research.

Who has reviewed the study?

This research was reviewed and funded by St. Georges University of London and Kings College London. People with experience of using three different drug and alcohol services have provided advice on study procedures and documents so that the study will be carried out in the best possible way. All research in the NHS is also looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion (approved) by BRENT NHS Research Ethics Committee.

How will we use information about you?

We will need to use information from you, your drug and alcohol treatment records and your GP for this research project.

This information will include your:

- Full name
- Contact details
- Medical history including details of all medications currently prescribed
- Risk assessment created by the drug & alcohol service
- Pharmacy where you collect your methadone/buprenorphine/Espranor details
- Whether you have been in contact with your keyworker during the study period

People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to research@sabp.nhs.uk, or
- by ringing us on 01932 453000.

What should I do if I have questions or concerns about the research?



If you have any concern about any aspect of this study, you should ask to speak to the researcher who will do their best to answer your questions. If you would rather speak to someone else then you can contact Dr Christos Kouimtsidis at Surrey and Borders Partnership NHS Foundation Trust on 01932 453000. If you wish to complain formally, you can do this through the NHS Complaints Procedure. You can call the **Patient Advice and Liaison Service (PALS) freephone on 0800 731 2864 for information on how to do this.**

I would like to speak to the research assistant about taking part!

If you would like to speak to the research assistant about taking part you can either ask your keyworker to pass on the message or leave your name and contact number below then pass *this page only* back to reception who will give it to the research assistant. The research assistant will contact you by any of the ways you agree to be contacted then store this document in a folder in a locked cupboard to keep your details safe.

Please initial box

1. I give consent for you to contact me by telephone and you can get my number by looking at my case file

☐

2. I give consent for you to contact me by text message and you can get my phone number by looking at my case file

☐

3. I give consent for you to contact me at my pharmacy and you can get their number by looking at my case file.

☐

4. I give consent for you to contact me at my next keywork appointment and you can get this date by speaking to my keyworker.

☐

5. I understand I am under no obligation to enter the study, I would just like to know more

☐

Name of Participant

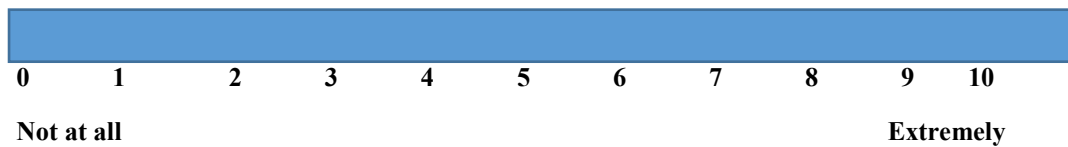
Date

Signature

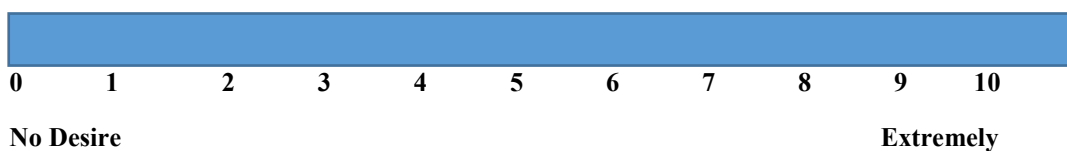
Appendix 5

Opiate Craving Scale

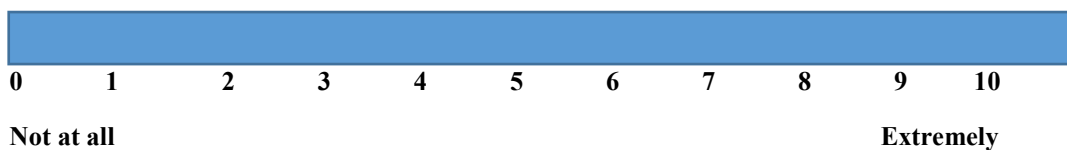
How much do you currently crave opiates? (rated from not at all to extremely)



If you saw this in your everyday life, how much would you crave heroin? (rated from no desire to extremely strong)



How much did the video remind you of times that you have used heroin? (rated from not at all to extremely)



Appendix 6

TimeLine FollowBack

Participant Number ____

Please complete by writing how many bags of heroin, if any, you have used on any of the days since you last saw the research assistant.

2020	SUN	MON	TUES	WED	THURS	FRI	SAT
	XX	XX	XX	XX	1	2	3
OCT	4	5	6	7	8	9	10
	11	12	13	14	15	16	17
	18	19	20	21	22	23	24
	25	26	27	28	29	30	31
NOV	1	2	3	4	5	6	7
	8	9	10	11	12	13	14
	15	16	17	18	19	20	21
	22	23	24	25	26	27	28
2020	29	30	1	2	3	4	5
DEC	6	7	8	9	10	11	12
	13	14	15	16	17	18	19
	20	21	22	23	24	25	26
	27	28	29	30	31		
2021						1	2
JAN	3	4	5	6	7	8	9
	10	11	12	13	14	15	16
	17	18	19	20	21	22	23
	24	25	26	27	28	29	30
FEB	31	1	2	3	4	5	6

	7	8	9	10	11	12	13
	14	15	16	17	18	19	20
	21	22	23	24	25	26	27
MAR	28	1	2	3	4	5	6
	7	8	9	10	11	12	13
	14	15	16	17	18	19	20
	21	22	23	24	25	26	27
	28	29	30	31	1	2	3
APR	4	5	6	7	8	9	10
	11	12	13	14	15	16	17
	18	19	20	21	22	23	24
	25	26	27	28	29	30	1
MAY	2	3	4	5	6	7	8
	9	10	11	12	13	14	15
	16	17	18	19	20	21	22
	23	24	25	26	27	28	29
JUN	30	31	1	2	3	4	5
	6	7	8	9	10	11	12
	13	14	15	16	17	18	19
	20	21	22	23	24	25	26
	27	28	29	30	1		

	SUN	MON	TUES	WED	THURS	FRI	SAT
						2	3
JUL	4	5	6	7	8	9	10
	11	12	13	14	15	16	17
	18	19	20	21	22	23	24
	25	26	27	28	29	30	31
	1	2	3	4	5	6	7
AUG	8	9	10	11	12	13	14
	15	16	17	18	19	20	21

	22	23	24	25	26	27	28
	29						

- Time to 1st opioid use (record as 0 if same day as TLFB, 99 if nil use since last TLFB)

Date of 1st day not using opioids:

DD/MMM/YYYY

Date of 1st opioid use since last TLFB
(if applicable):

DD/MMM/YYYY

Appendix 7

GP Letter

Date

Dear Doctor *Name*

RE: Investigating the mechanism mediating the effects of oxytocin on opioid craving: A proof of concept study

Patient Name and DOB

I am writing to inform you that your patient has agreed to participate in the above research study at (*recruiting site name*). The study is a randomized, double-blind crossover mechanistic proof-of-concept study. The study sponsor is Surrey & Borders NHS Foundation Trust.

The purpose of this study is to determine the effect of intranasal administration of the neuropeptide oxytocin on AB in opioid dependent individuals currently active in community drug treatment in a cue induced craving state; what the effects of intranasal administration of the neuropeptide oxytocin are on cue induced craving in opioid dependent individuals currently active in community drug treatment. The patient has been asked to participate as they are currently using illicit heroin on top of insert methadone or buprenorphine here. To take part in the study there will be four clinic visits. At clinic visit two or three the patient will have been randomized to receive a single dose of 40IU nasal oxytocin. A 7-30 day washout period will separate each clinic visit. Clinic visit 4 will be safety follow ups from visit 3 and a qualitative interview.

Contraindications

There are no expected contraindications with prescribed medications.

The main side effects to be aware of are detailed in the enclosed Participant Information Sheet.

I have enclosed a copy of the Participant Information Sheet for your reference, however if you have any queries or require further information please contact (*Insert site contact details including contact number and website*).

In the event of an emergency please call: Dr Christos Kouimtsidis on [REDACTED]

Yours Sincerely

Mr Ben Houghton

Research Assistant

(Insert Site Name)

Encs: Participant Information Sheet, version *(insert version number)* dated *(insert date)*

Appendix 8

Demographics

Participant Number ____

Age: ____

Gender: o Male o Female o Other

Is English your first language? Yes / No

Ethnic Background (Please tick one box):	
White:	Asian or Asian British:
British ☐	Indian ☐
Irish ☐	Pakistani ☐
Any other white background ☐	Bangladeshi ☐
	Any other Asian background ☐
Mixed:	Black and Black British:
White and Black Caribbean ☐	Caribbean ☐
White and Black African ☐	African ☐
White and Asian ☐	Any other Black background ☐
Any other Mixed background ☐	
	Chinese or other ethnic group:
	Chinese ☐
	Any other ethnic group ☐

Did you migrate from another country to live in the UK? Yes ☐ No ☐

What is the highest level of education you achieved? (tick one)

- | | |
|---|---|
| ☐ No qualifications | ☐ University Degree |
| ☐ O Level / GCSE | ☐ Postgraduate Degree |
| ☐ A Level / NVQ | ☐ Other (please specify)..... |
| ☐ Diploma / BTEC | |

What is your current employment status? (tick one)

- ☐ Full time ☐ Retired ☐ Part time ☐ Sick leave >4 weeks
- ☐ Unemployed ☐ House-wife ☐ Student ☐ Other (please specify).....

What best describes your current relationship status? (tick one)

- ☐ Married ☐ Divorced ☐ Separated ☐ Living together
- ☐ Single ☐ Widowed ☐ In a relationship but not living together

Do you have any children under 18? ☐ Yes ☐ No

If you do, how many are living with you?

Who else lives in your household with you? (e.g., mum, brother, 2 friends)

.....

Do you currently smoke tobacco?

Yes ☐ No ☐

Have you ever been diagnosed with any of the following mental health conditions?

	Yes	No	Professional or Self-Diagnosed
Anxiety			
Psychosis			
Paranoia			
Eating Disorder			
Depression			

Bi-Polar			
PTSD			
Schizophrenia			
Personality Disorder (please specify)			

(type of personality disorder).....

Are you currently taking any medication (s)?

Yes ☐ No ☐

	Medication name	Dose	When started MM/YYYY
Opiate Substitution Therapy			
Medication 2			
Medication 3			
Medication 4			
Medication 5			

Please continue on additional paper if necessary

Appendix 9

Informed Consent



IRAS ID: 281656

Centre Number:

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Investigating the mechanism mediating the effects of oxytocin on opioid craving: A proof of concept study

Please initial box

1. I confirm that I have read the information sheet dated.....
(version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care, ongoing treatment or legal rights being affected. ☐
3. I understand that if I withdraw, my data collected to that point will be used anonymously. If I do not wish for any of my data to be used I should initial this box. ☐
4. I agree for my voice to be digitally recorded when I am interviewed and that anonymised quotes may be used in the research reports produced. ☐

5. I agree to provide urine drug screens for the study. I understand my care coordinator will not be informed of the results of these and that the results will be anonymised for the purposes of the research only. ☐
6. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from St Georges University, Cranmer Terrace, London, SW17 0RE, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. ☐
7. I agree to my General Practitioner being informed of my participation in the study. I agree to my General Practitioner being involved in the study, including any necessary exchange of information about me between my GP and the research team. ☐
8. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature

_____	_____	_____
Name of Research Assistant	Date	Signature

When completed: 1 for participant, 1 for researcher site file

