Comparing the Effects of Ketamine and Lidocaine on Mood, Subjective Drug Effects, and Pain

Matt Knox

D.Clin.Psy. thesis (Volume 1), 2018
University College London

UCL Doctorate in Clinical Psychology

Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Name: Matthew Iain Knox

Date: 09.07.2018

Overview

This thesis investigates the effects of the drug ketamine in both clinical and recreational populations. Part one presents a literature review investigating the effects of long-term ketamine use on cognition. The results indicated that long-term ketamine use impairs episodic memory. However, this was not found across all tasks reviewed. Evidence looking at working memory and executive functioning provided an inconsistent picture. This is in line with previous research where some studies have found these domains to be impaired in long-term ketamine users and other studies have found no impairments. Methodological issues were considered, including the impact of poly-substance use, the presence of mood disorders and the lack of consistency in cognitive tasks employed to measure functioning.

Part two presents an empirical paper exploring the effects of ketamine in comparison to lidocaine on mood, subjective drug effects and pain outcomes for treating patients with chronic neuropathic pain. Both drugs reduced scores on pain measures during the infusion and at a one-week follow-up. No antidepressant like effects were observed in either group. The ketamine group reported feeling more intense drug effects, feeling higher and liking the drug more than the lidocaine group. However, both drug groups had low ratings for wanting more of the drug, suggesting that ketamine is unlikely to be sought outside the pain clinic for its reinforcing effects.

Part three provides a critical appraisal of the research. It describes the process of conducting the research, alongside providing reflections on working with patients who have chronic pain. This was a joint project with a fellow DClinPsy student, Catherine Trotman (Trotman, 2018). Will Lawn (Post-Doc) was also involved in the data collection. See Appendix 1. for a breakdown of contributions.

Impact Statement

Chronic neuropathic pain is a significant worldwide health concern. Treatment for chronic neuropathic pain is varied, and only 30-40% of patients report adequate pain relief in response to first-line treatments. Additionally, depression and depressive-like symptoms are often found co-morbidly in people who have chronic pain. The presence of depression at baseline has been linked to poorer outcomes in chronic pain populations. The current study investigated the effect of the drug ketamine, a treatment shown to produce sustained analgesia in this population, and rapid-acting antidepressant effects in treatment-resistant depressed populations. Patients being treated with ketamine were compared with those being treated with the drug lidocaine. Measures used were indices of pain, mood, and subjective reinforcing effects of the drug.

Both ketamine and lidocaine participants showed significant pain relief at the one-week follow-up when compared to scores at baseline. Further, the study found that patients being treated with ketamine felt significantly more intense drug effects, feeling higher and liking the effects of the drug more than those who were treated with lidocaine. However, ketamine patients' ratings showed they did not want more of the drug. Further, ketamine does not have a significant anti-depressant effect on patients with chronic pain.

The current study adds to the evidence base for the use of ketamine in treating chronic neuropathic pain in that significant reductions in pain measures were achieved. Currently, there are no standardized protocols in clinical practice for what dose of ketamine or treatment frequency should be used in treating chronic pain. These results will add to the growing literature which will inform this process.

The study also indicated that the chronic pain population may show a different response to healthy volunteers regarding the subjective drug effects. The ketamine group reported greater acute reinforcing drug effects than the lidocaine group (feeling high, liking the drug), but ketamine participants did not want more of the drug. This is a significant finding, as it may indicate a low abuse potential in the chronic pain population. This is significant when considering the use of ketamine as a treatment in clinical practice and will add to the literature that will inform the use of ketamine in future treatments.

Ketamine did not show any specific anti-depressant effects in our participants. Therefore further research is needed to investigate ketamine's anti-depressant properties across different patient groups.

These results will be disseminated locally to the pain clinic as well as through publication to inform academics and clinical practitioners.

Table of Contents

Tables and Figures

Part 1: Literature Review

Part 2: Empirical Paper

Acknowledgements

With special appreciation and thanks to my supervisors, Prof. H. Valerie Curran and Dr Sunjeev Kamboj, for their support, encouragement and availability.

My gratitude also to PhD candidate, Will Lawn, for his enthusiasm and continual support throughout all stages of the project.

Special thanks to my family and friends, particularly to Fay Davies for her support and care during the last few months.

This study was supported by grants from:

Research Department of Clinical, Educational and Health Psychology, University College London

and

Graduate School, University College London

Part 1: Literature Review

Effects of Chronic Ketamine Use on Cognitive function

Abstract

Aim: The recreational use of ketamine has been increasing over the past decade. Literature shows that ketamine, in acute doses, robustly impairs a number of cognitive functions. However, literature examining the effects of chronic ketamine use has been less conclusive. This review provides a narrative synthesis of evidence examining the effects of chronic ketamine use on cognition.

Method: A systematic review of case-control studies investigating the effects of chronic ketamine use on cognition in humans was performed through electronic database searches. Articles were selected from peer-reviewed journals published between January 2008 and April 2018. The Newcastle-Ottawa Scale was used to assess the methodological quality of the studies included.

Results: 11 studies met the inclusion criteria for the current review. All studies scored either high (6) or medium (5) on the quality assessment. Nine studies employed drug naïve control groups, six studies employed other drug using groups and four studies employed ex-ketamine using controls. Results were considered across four cognitive domains: Declarative Memory, Working Memory, Executive Functions and Component Processes. The evidence suggests that chronic ketamine use most robustly impairs episodic memory functions. Impairments were inconsistently reported across studies in the domains of working memory, executive functions and component processes.

Conclusion: This review provides preliminary support for the existence of impairments in episodic memory function in chronic ketamine users. Findings in other cognitive domains are inconclusive. This review highlights the need for replication studies and the methodological issues that need to be considered when using naturalistic populations of drug users. Future research should examine the

impact of drug use patterns (frequency, average amount used per session, lifetime usage, poly-drug use) on cognitive functioning.

Introduction

Ketamine is a non-competitive N-Methyl-D-Aspartate Receptor (NMDA-R) antagonist which affects the action of the amino acid class of neurotransmitters. Ketamine was originally designed as a less powerful analogue of the anaesthetic drug phencyclidine (PCP) which was known to induce psychotomimetic symptoms. Ketamine has been used in anaesthesia for over 50 years and has a well-established safety profile, especially because it does not repress the respiratory system. Thus, ketamine can be used in situations where sophisticated resuscitation equipment is not available, including field/war scenarios. Indeed, ketamine is on the World Health Organisation's list of essential medicines. Furthermore, ketamine, at sub-anaesthetic doses, has also been shown to produce good analgesia in patients experiencing neuropathic pain (Lynch et al., 2005), a condition that is particularly hard to treat effectively with other agents. In addition to this, recent evidence has shown intravenous and intranasal ketamine administration to produce rapid antidepressant effects in populations of depressed patients that have not responded to other treatments for depression (Krystal 2007; Salvadore and Singh, 2013; Young, 2013).

Emergence Phenomena

Patients being treated with ketamine have often reported experiencing a range of psychedelic symptoms while recovering from ketamine anaesthesia. These reported symptoms have been labelled 'emergence phenomena' and include, hallucinations, delusions, confusion, out-of-body experiences and 'near-death' experiences. These have limited the use of ketamine in adult humans. However, these same effects have contributed to the use of acute ketamine as a pharmacological way of modelling psychosis in human and animal studies. Both

anecdotal reports and evidence from controlled studies have demonstrated that in acute doses ketamine induces reliable, yet reversible, dose-related positive and negative schizophrenia-like symptoms (e.g. Jansen, 1990; Krystal et al., 1994; Morgan, Rossell et al., 2006). In addition to this, research indicates that ketamine mimics the symptoms of schizophrenia more closely than any other drug (Newcomer & Krystal, 2001).

Acute Effects of Ketamine on Memory and Cognition

Indeed, in acute doses, ketamine has the potential to significantly impact cognitive and psychological functioning via the dense population of NMDA-R located within the cerebral cortex and hippocampus (Aalto et al., 2002; Breier et al., 1997). Furthermore, The NMDA-R is thought to be important in long-term potentiation, a form of synaptic plasticity which is central to learning and memory (Harris et al., 1984). Thus, given that ketamine's principal action is at the NMDA-R, the effects of acute ketamine use on cognition have been of interest to researchers. Acutely, ketamine produces transitory, dose-dependent memory impairment in healthy volunteers. These transitory impairments have been found in the domains of working memory (Krystal et al. 2005, Morgan et al. 2004a) and declarative memory (Morgan et al. 2004a, 2004b, Parwani et al. 2005, Rowland et al. 2005). However, research investigating ketamine's acute effects on executive functioning has produced an inconsistent picture. For instance, performance was found to be intact on the Stroop Task (Parwani et al. 2005) and Trail Making Task (Morgan et al. 2004a) but impaired on the Hayling Test (Morgan et al. 2004b) and Wisconsin Card Sorting Test (Krystal et al. 1999, 2000).

Recreational Use

Ketamine is also used widely as a recreational drug, in part because of the psychotomimetic effects described above. Recreational use has become more mainstream over the past decade, with the drug moving from being used predominantly as a 'club drug', in specific sub-cultures, to its broader use as a party drug across many populations. Ketamine's recreational use has been reported in 59 countries including Australia, UK, USA and Hong Kong (United Nations Office on Drug Control, 2016). Recent lifetime prevalence statistics are 2.6% in 16-24-year-olds in the UK, 1.5 % in 12th-grade students in the USA and 1.7% in 14 years and older youth in Australia (United Nations Office on Drug Control, 2016). Further to this, ketamine users are more likely than those who use other illicit drugs to report poly-substance use. Hoare (2010) reported that only 3% of ketamine users surveyed in their study reported only using ketamine, and not any other illicit substances, over the past year.

Abuse

Ketamine abuse is reported as a worldwide public health concern (Liao et al., 2017). Indeed, ketamine was reportedly the second most commonly abused drug in Hong Kong in 2014 (Narcotics Division, Security Bureau, 2015). Long-term ketamine use can lead to serious side effects, including bladder and renal complications, such as ketamine-induced ulcerative cystitis and stomach ulcers. These can lead to severe complications with long-term consequences (Morgan & Curran, 2012). The evidence is not clear with regards to whether ketamine results in physical dependence (Critchlow 2006; Ricaurte & McCann, 2005). However, research shows that the psychological properties that ketamine posses, especially the

high which is experienced, lead to its abuse potential (Krystal et al., 1999). Further to this, due to ketamine's short half-life (180 mins) (Celmens et al., 1982), it tends to result in only mild 'hangovers' which may increase the likelihood of its abuse. Evidence also suggests that long-term ketamine use impacts cognitive functioning (Morgan & Curran, 2012).

Methodological Considerations in Chronic Ketamine Use Research

Given ketamine is a drug that is only given in controlled doses, in medical environments, and has been shown to have significant physiological and cognitive impacts, it is not ethical to conduct controlled studies on the effects of repeated dosing in study populations. Thus, to study the effects of chronic ketamine use, naturalistic populations (i.e. populations who self-administer recreationally) are the only way to investigate the effects of chronic ketamine use on humans. Further, as discussed above those who use drugs recreationally generally use other substances as well. Thus, isolating the effects of 'pure' ketamine use can be challenging to achieve.

Chronic Ketamine Use and its Effects on Cognition

The majority of studies to date have utilised recreational ketamine users to examine the cognitive effects of chronic ketamine use. However, reports on how long-term ketamine use effects cognition have been sparse and inconsistent. For instance, in a recent review (Morgan and Curran, 2012) only three publications on cognitive impairment in long-term ketamine use were identified. Morgan and Curran's (2006) review, of the acute and chronic effects of ketamine use on memory, reported that chronic ketamine use had specific yet wide-ranging effects on memory systems. In general, the findings seem to corroborate those found in research looking

into the acute effects of ketamine on healthy volunteers. Episodic memory was found to be impaired in ketamine users across a range of paradigms. Further to this, long-term ketamine use may cause a greater degree of impairment, in this domain, than those that have been reported after acute doses of ketamine in healthy volunteers. However, measures of working memory, attention and executive functioning have shown less consistent results. Overall, previous research indicates that acute ketamine use impairs working memory (Curran & Monaghan, 2001; Curran and Morgan, 2000; Morgan, Monaghan et al., 2004) but longer-term effects are inconclusive. Findings for executive functioning and attention paradigms have also yielded mixed results with some studies finding impairment (Curran and Morgan, 2000; Morgan et al., 2009) but some studies finding these domains to be intact (Morgan et al., 2004b). Thus, given that ketamine is now used widely as a 'club drug', and frequent use is rising across the world, it is important to review the most recent evidence examining the effects of chronic ketamine use.

Objective of the Current Review

To the best of the author's knowledge, there has been no systematic review of the literature examining the effects of chronic ketamine use in the last 10-years. The current review, therefore, aims to update the chronic use sections of Morgan and Curran's (2006 and 2012) papers and expand on these by examining recent research into the impact of chronic ketamine use on cognition. This will be addressed with a review of studies from the past ten years (2008-18).

Methods

Search Strategy

A systematic literature search was carried out using three electronic databases (PsycINFO), EMBASE and MEDLINE). Search terms related to ketamine were combined with terms associated with cognitive functioning and chronic drug use (see table 1 for details). The focus of this review was specific to neuropsychological/cognitive studies. However, the initial search strategy was designed to be as exhaustive as possible. Once duplicate citations were removed 983 citations remained. The abstracts of these articles were then assessed with the following criteria in mind:

1) The target population included adults (over 18) who reported long-term-frequent ketamine use

2) The study reported results from tests of cognitive functioning

3) The study was published in a peer reviewed journal

4) The study was reported in English

5) The study was published between January 2008 and April 2018

6) The study did not use case studies

7) A comparison (control) group was used

Studies that appeared to meet these criteria were then subject to a more detailed evaluation. 11 articles were found to meet the inclusion criteria. One paper was excluded on the basis that its focus was on a highly specific aspect of learning (associative blocking to reward-predicting cues), thus would not have been comparable with the others studies included in this review which focused of broader aspects of cognitive functioning. This search is summarised in Figure 1.

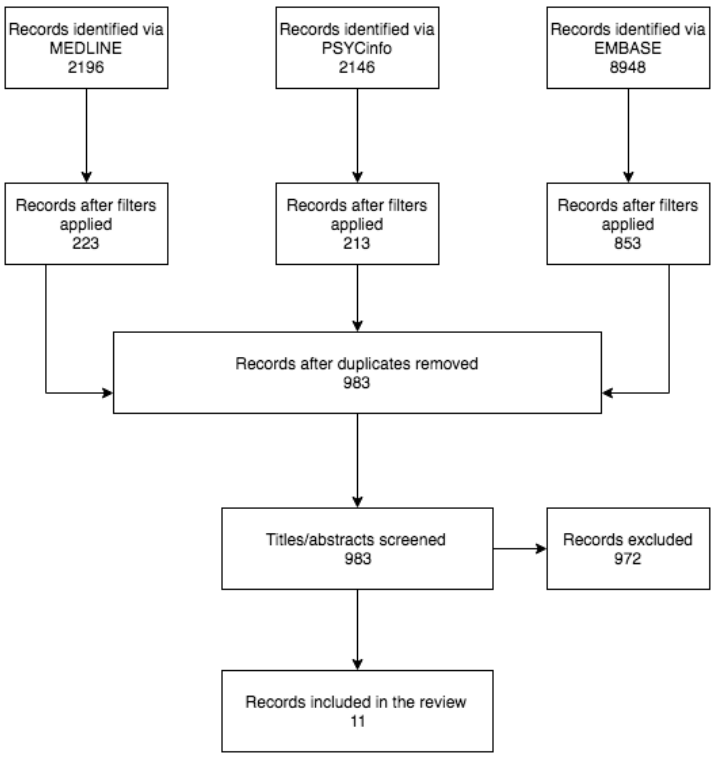
Data Extraction

For each study, the sole reviewer extracted age, gender, ketamine use data, cognitive domains investigated, experimental tasks employed and key cognitive findings. The primary results of interest were group differences in performance on cognitive tasks and group differences in the extent of ketamine use.

Table 1: Summary of Systematic Review Search Terms

Key concepts	Ketamine	Cognitive effect	Chronic use
Alternative terms	"ketamine" "ketalar" "NMDA receptor antagonist" "ketanest" "keta*" "esketamine"	"cognition" "cognitive dysfunction" "cognitive impairment" "executive function" "information processing" processing speed" "reaction time" "learning" "memory" "dissociat*" "k-hole" "positive symptom*" "negative symptom" "priming" "decision making" "judgement"	"substance*" "drug*" "misuse" " dependen*" "abuse" "chronic" "addict*" "addiction"

Figure 1: *Literature Search Results, Figures and Selection Strategy*



Quality and Relevance Assessment

A quality and relevance assessment of the studies was carried out. All studies included in this review employed a cross-sectional design. Thus, the Newcastle-Ottawa Scale (NOS), (Wells et al., 2004), a tool to aid researchers conducting systematic reviews and meta-analyses, in assessing the quality of non-randomised studies, was utilised. The NOS utilises a star rating system to evaluate the studies across three broad categories: the selection procedure for study groups; how comparable the groups are; the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. An overall rating system of quality for the current review was developed based on the NOS star ratings. Studies scoring seven or more stars were rated as high in both relevance and quality, studies scoring five to six stars were rated as medium in quality and studies scoring less than four stars were rated as low.

Six studies fell into the high category and five studies in the medium category as depicted in table 2 below.

Table 2: Summary of Quality and Relevance Assessment

Study	Year	Selection	Control	Outcome	Overall Rating
Chan et al.,	2013	**	*	**	**Medium**
Cheng et al.,	2018	**	**	***	**High**
Liang et al.,	2013	***	*	**	**Medium**
Minseung Kim et al.,	2016	*	*	***	**Medium**
Morgan et al.	2009	****	**	***	**High**
Morgan et al.,	2010	****	**	***	**High**
Morgan, Duffin et al.,	2012	***	**	***	**High**
Stefanovic et al.	2009	****	**	***	**High**
Tang et. al.,	2013	***	*	**	**Medium**
Zeng et al.,	2016	**	*	***	**Medium**
Zhang et al.,	2018	****	**	***	**High**

Results

A summary of studies entered into the review is provided in table 3. Table 4 provides a summary of ketamine use across the studies.

Table 3 Summary of Results and Study Characteristics

Study, Year and reference	Country	Type of Study	Sample Size and Characteristics	Other Controls/Measures reported	Cognitive Test	Cognitive Domain	Main results
Chan, et al 2013	China	Case-Control	55 Participants. **Ketamine Users:** n=25, M:F=11:14. Mean age = 19.84±3.53. **Control:** n=30, M:F=11,19. Mean age = 18.90±2.86.	To control for poly-drug use, the study included ketamine users who have no more than monthly use of cannabis and/or weekly use of cocaine, ecstasy, and methamphetamine.	Stroop Test. Verbal Fluency Test. Ruff Figural Fluency Test. Symbol Digit Modalities Test. Digit Vigilance Test. Chinese Auditory-Verbal Learning Test. Continuous Visual Memory Test.	Executive Function. Psychomotor Function. Attention. Declarative Memory.	Impairments in verbal fluency, cognitive processing speed and verbal learning were observed in the frequent ketamine user group. Furthermore, correlation analysis showed a negative association between between longer life time usage and verbal learning performance.
Cheng et al., 2018	China	Case-Control	130 Participants. **Ketamine users (KNP):** n=51, M:F=36:15. Mean age = 30.00±6.20. **Ketamine Users with Persistent Psychotic Symptoms (KPP)** n=23, M:F=18:5. Mean age = 30.30±7.10. **Schizophrenic Patients (SZ):** n=75, M:F=38:37. Mean age = 39.50 ± 8.10.	Urine Testing to confirm group membership.	Groton Maze Learning Task. Social Emotional Cognition Task. One Back Task. Detection Task. Identification Task. International shopping List Task and Delayed Recall Task.	Social Cognition. Working Memory. Attention/Vigilance. Declarative Memory.	Chronic heavy ketamine abusers with persistent psychotic symptoms beyond ketamine discontinuation (KPP) showed a higher degree of impairment in verbal memory and spatial problem solving than the group of ketamine users who displayed no psychotic symptoms (KNP). Secondly, the study reported that participants with diagnoses of schizophrenia (SZ) showed significantly more cognitive impairment than the KNP group. However, the KPP group showed a similar cognitive profile to the SZ group.

Liang et al., 2013	China	Case-Control	196 Participants. **Current Users:** n=32, M:F=19:13. Mean age = 20.7±4.1. **Former Users:** n=64, M:F=36:28. Mean age = 20.1±3.6. **Control:** n=100, M:F=58:42. Mean age = 20.6±3.6.	Univariate General Linear Model (GLM) was used to control for the potentially confounding factors including age, sex, years of education and BDI[3] score as covariates.	Stroop Test. Modified Verbal Fluency Test. Wisconsin Card Sorting Test. Digit Span Backwards. Short Form of the Wechsler Adult Intelligence Test. WMS[4]: Logical Memory. WMS: Word List. Rey–Osterrieth Complex Figure.	Executive Function. Working Memory. General IQ. Declarative Memory.	Verbal and visual memory impairments were found in the ketamine with poly-drug use group and the ex-ketamine user group.
Minseung Kim et al., 2016	Korea	Case-Control	30 Participants. **Long-term Frequent Ketamine Treatment:** n=14, M:F=12:2. Mean age = 38.57±8.36. **Non-Long-term Frequent Ketamine Treatment:** n=16, M:F=8:8. Mean age = 37.50±9.30.	None Stated	Stroop Colour Test. Trail Making Test. Digit Symbol. Digit Span. Controlled Oral Word Association Test (COWAT).	Executive Function. Psychomotor Function. Working Memory. Declarative Memory.	Impairments in working memory, processing speed and tests of executive functioning were found in the long-term frequent ketamine infusion group. These impairments were not observed in the control group.
Morgan et al.,2009	U.K.	Case-Control	150 Participants. **Frequent Ketamine:** n=30, M:F=19:11. Mean age = 25.87±9.23. **Infrequent Ketamine:** n=30, (M:F=24:6)**.** Mean age =27.37 ±6.73	Hair samples analysed for drug use confirmation. Pre-morbid IQ. Years in Education. Family History of mental illness.	Fluency. Semantic and phonological tasks Stockings of Cambridge (SOC). Spot the word. CANTAB[1]: Spatial working memory. CANTAB: Pattern recognition memory.	Executive Function. Pre-morbid IQ. Working Memory. Declarative Memory.	Impairments in working memory, episodic memory, aspects of executive functional and reduced psychological wellbeing were found in long-term frequent ketamine users. No impairments were found in recreational ketamine users.

			Ex-Ketamine: n=30, M:F=20:10. Mean age = 27.3±5.31. **Poly-drug control:** n=30, M:F=22:10. Mean age = 29.63±9.27. **Non-Drug Control:** n=30**,** M:F=21:9. Mean age = 24.8±5.83.		Source memory task. Prose recall subtest of RBMT[2.] Hayling.		
Morgan et al., 2012	U.K.	Case-Control	130 Participants. **Ketamine users:** n=21, M:F=12:9. Mean age = 25.05±7.61. **Cannabis users:** n=29, M:F=20:9. Mean age = 20.86±3.71. **Cocaine users:** n=22, M:F=15:7. Mean age = 35.32±7.33. **Recreational Poly Drug users:** n=28, M:F=10:18. Mean age = 28.07±7.38. **Drug Naïve Controls:** n=30, M:F=18:12. Mean age = 29.83±11.49.	None reported.	Spot the Word. Digit Span. Prose Recall RBMT.	Pre-morbid IQ. Working Memory. Declarative Memory.	Ketamine and cannabis groups showed the greatest impairment on attentional aspects of tasks. The authors highlight that the cognitive profile of dependent ketamine users is similar to that of prodromal individuals who transitioned to psychosis.

Morgan et al.,2010	U.K.	Longitudinal	120 Participants. **Frequent Ketamine:** n=25, M:F=15:10. Mean age = 25.87±9.23. **Infrequent Ketamine:** n=26, M:F=21:5**.** Mean age =27.5 ±6.98. **Ex-Ketamine:** n=23, M:F=15:8. Mean age = 27.26±3.84. **Poly-drug Control:** n=25, M:F=17:7. Mean age = 31.29±9.47. **Non-Drug Control:** n=21, M:F=14:7. Mean age = 25.05±6.67.	Hair samples analysed for drug use confirmation. Pre-morbid IQ. Years in Education. Family History of mental illness.	Fluency. Semantic and phonological tasks Stockings of Cambridge (SOC). Spot the word CANTAB: Spatial working memory. CANTAB: Pattern recognition memory. Source memory task. Prose recall subtest of RBMT. Hayling.	Executive Function. Pre-morbid IQ. Working Memory. Declarative Memory.	At the 12-month follow-up results showed that the cognitive deficits observed in long-term frequent ketamine users were still present. A correlation was found where an increase in ketamine use was negatively associated with performance on spatial working memory and pattern recognition tasks.
Stefanovic, et al, 2009	UK	Case-Control	96 Participants. **Ketamine users:** n=22, M:F=19:3. Mean age = 21.00±2.24. **Recreational Poly Drug users:** n=26, M:F=18:8. Mean age = 21.00±1.03. **Drug Naïve Controls:** n=48, M:F=26:22. Mean age = 20.15±2.01.	Urine Testing to confirm group membership.	Semantic Priming Paradigm.	Semantic Memory.	No differences in semantic priming were found between the ketamine user group and the non-drug using control group.

Tang et al., 2013	China	Case Control	200 Participants. **Current Users:** n=51, M:F=29:22. Mean age = 22.80±4.3. **Former Users:** n=49, M:F=24:25. Mean age = 22.0±4.0. **Control:** n=100, M:F=58:42. Mean age = 20.6±3.6.	Cognitive functions were adjusted for age, gender, and education using ANCOVA[6].	Stroop Test. Modified Verbal Fluency Test . Digit Symbol Coding. Digit Span. Arithmetic WAIS III[7]. Logical Memory. Rey-Osterrieth Complex Figure.	Executive Function. Psychomotor Function. Working Memory. Declarative Memory.	Frequent ketamine users showed impaired in mental and motor speed, visual and verbal memory, and executive functions. Frequent ketamine users also displayed a higher number of depressive symptoms. Significant correlations between depressive scores and working memory were found.
Zeng et al., 2016	China	Case-Control	170 Participants. **Ketamine Users:** n=51, M:F=29:22. Mean age = 25.72±5.83. **Methadone Users:** n=60, M:F=36:23. Mean age = 42.48±5.09. **Control:** n=60, M:F=30:30. Mean age = 23.25±3.47.	Urine Testing to confirm group membership.	Stroop Test. Stop Signal. Iowa Gambling Task. Raven's Progressive Matrices. 2-Back. Barratt's Impulsivity Scale.	Executive Function. Decision Making. General IQ. Working Memory. Impulsivity.	Ketamine and methadone users showed significantly higher levels of self=reported impulsivity and antisocial traits than the non drug using control group. The ketamine group showed significantly poorer performance on working memory tasks than either the methadone or control groups. Both ketamine and methadone users showed impairments on the response inhibition task.
Zhang et al., 2018	China	Case-Control	200 Participants. **Ketamine (non heavy other drug) users[8]:** n=286, M:F=186:100. Mean age = 25.3±4.8. **Ketamine (heavy other drug) users[9]:** n=279, M:F188:91. Mean age = 24.0±5.0.	Cognitive task scores were analysed with a univariate general linear model with age, sex, education and BDI scores as covariates.	Stroop Test. Wisconsin Card Sorting Test. Digit Span. Logical Memory. Rey-Osterrieth Complex Figure.	Executive Function. Working Memory. Declarative Memory.	Both the non-heavy other drug user and heavy other drug user ketamine groups showed impairments tasks of verbal and visual memory. Both groups showed no impairment on task of working memory and executive functioning. Furthermore, no significant differences, in terms of task performance, were found between the two ketamine user

	Control: n=261, M:F=128:133. Mean age = 22.9±5.1.	groups. However, a higher average amount of ketamine used per session was negatively associated with performance in the short-term verbal memory for the heaving other drug using ketamine group.

[1] CANTAB: Cambridge Neuropsychological Test Automated Battery, [2] RBMT: Rivermead behavioural memory test, [3] BDI: Beck Depression Inventory, [4] WMS: Wechsler Memory Scale, [5] CRPS: Complex Regional Pain Syndrome, [6] ANCOVA: Analysis of covariance, [7] WAIS III: Wechsler Adult Intelligence Scale, [8] Ketamine (non heavy other drug) users: Used ketamine and a low frequency of other drugs, [9] Ketamine (heavy other drug) users: Used ketamine and a high frequency of other drug i.e. used other recreational drugs more than 24 times over 6 months within the past 2 years in addition to ketamine, [10] PANSS: Positive and Negative Syndrome Scale.

Table 4 Summary of Ketamine Use Across Studies Selected for Review

Study, Year and reference	Country	Type of Study	Sample Size and Characteristics	Ketamine use	Length of Ketamine Use	Current Amount per Session (Grams)	Days since last use
Chan, et al 2013	China	Case-Control	55 Participants. **Ketamine Users:** n=25, M:F=11:14. Mean age = 19.84±3.53. **Control:** n=30, M:F=11,19. Mean age = 18.90±2.86.	**Reported Frequency:** Ketamine Users: Not stated but users were recruited on basis that they reported using ketamine at least once a month for the past 2 years.	**Reported Time:** Ketamine users had been using > 2 years.	**Not Reported.**	All participants that entered the study were required to abstain from all drugs and alcohol for 48 hours.
Cheng et al., 2018	China	Case-Control	130 Participants. **Ketamine users (KNP):** n=51, M:F=36:15. Mean age = 30.00±6.20. **Ketamine Users with Persistent Psychotic Symptoms (KPP)** n=23, M:F=18:5. Mean age = 30.30±7.10. **Schizophrenic Patients (SZ):** n=75, M:F=38:37. Mean age = 39.50 ± 8.10.	**Reported Frequency:** Days Per Month **Ketamine users:** 26.9 ± 8.2. **Ketamine Users with PPS:** 24.6 ± 10.3.	**Reported Time:** Years**. Ketamine users:** 7.5 ± 4.3. **Ketamine Users with PPS:** 6.0 ± 3.8.	**Ketamine users:** 4.3 ± 2.7. **Ketamine Users with PPS**: 2.4 ± 2.1.	Participants were required to have been abstinent for at least 10 days prior to study participation.
Liang et al., 2013	China	Case-Control	196 Participants. **Current Users:** n=32, M:F=19:13. Mean age = 20.7±4.1. **Former Users:** n=64, M:F=36:28. Mean age = 20.1±3.6.	**Reported Frequency:** Days Per Month. **Current Users:** 4.1 ± 8.9.	**Reported Time:** Months. **Current Users:** 43.1 ± 48.0.	**Not reported.**	**Current Users:** 10.3 ± 10.9. **Former Users:** 213.2 ± 151.4 .

			Control: n=100, M:F=58:42. Mean age = 20.6±3.6.				
Minseung Kim et al., 2016	Korea	Case-Control	30 Participants. **Long-term Frequent Ketamine Treatment:** n=14, M:F=12:2. Mean age = 38.57±8.36. **Non-Long-term Frequent Ketamine Treatment:** n=16, M:F=8:8. Mean age = 37.50±9.30.	**Reported Frequency:** Days of use over a 6-month period **Long-term Frequent Ketamine Treatment:** 41.7 ± 13.7. **Non-Long-term Frequent Ketamine Treatment**: 2.9 ± 3.3.	**Reported Time:** Years. **Long-term Frequent Ketamine Treatment:**3.82 ± 1.3. **Non-Long-term Frequent Ketamine Treatment:** 1.86 ± 2.2.	**Not Reported.**	**Not reported.**
Morgan et al.,2009	U.K.	Case-Control	150 Participants. **Frequent Ketamine:** n=30, M:F=19:11. Mean age = 25.87±9.23. **Infrequent Ketamine:** n=30, (M:F=24:6**).** Mean age =27.37 ±6.73. **Ex-Ketamine:** n=30, M:F=20:10. Mean age = 27.3±5.31. **Poly-drug control:** n=30, M:F=22:10. Mean age = 29.63±9.27. **Non-Drug Control:** n=30**,** M:F=21:9. Mean age = 24.8±5.83.	**Reported Frequency:** Days Per Month. **Frequent Ketamine:** 20.13 ± 2.36. **Infrequent Ketamine:** 3.25 ± 2.55.	**Reported Time:** Years **Frequent Ketamine:** 6.07 ± 4.89. **Infrequent Ketamine:** 4.20 ± 2.20 . **Ex-Ketamine:** 7.63 ± 2.63.	**Frequent Ketamine:** 3.80 ± 2.36. **Infrequent Ketamine:** 1.28 ± 1.13.	**Frequent Ketamine:** 1.6 ± 1.27. **Infrequent Ketamine:** 11.3 ± 9.36. **Ex-Ketamine:** 344.43 ± 624.72.

Morgan et al., 2012	U.K.	Case-Control	130 Participants. **Ketamine users:** n=21, M:F=12:9. Mean age = 25.05±7.61. **Cannabis users:** n=29, M:F=20:9. Mean age = 20.86±3.71. **Cocaine users:** n=22, M:F=15:7. Mean age = 35.32±7.33. **Recreational Poly Drug users:** n=28, M:F=10:18. Mean age = 28.07±7.38. **Drug Naïve Controls:** n=30, M:F=18:12. Mean age = 29.83±11.49.	**Reported Frequency:** Days Per Month **Ketamine users**: 30.00 ± 0. **Cannabis users:** 0.17 (0.76). **Cocaine users:** 0.00 (0.00)**.** **Recreational Poly Drug users:** 4.93 (5.78)	**Reported Time:** Years. **Ketamine users:** 5.65 ± 3.48. **Cannabis users:** 0.02 ± 0.09. **Cocaine users:** 0.19 ± 0.85. **Recreational Poly Drug users:** 4.30 ± 3.54.	**Ketamine users:** 3.32 ± 2.13. **Cannabis users:** 0.02 ± 0.06. **Cocaine users:** 0.00± 0.00. **Recreational Poly Drug users:** 1.13 ± 1.46.	**Not Reported.**
Morgan et al.,2010	U.K.	Longitudinal	120 Participants. **Frequent Ketamine:** n=25, M:F=15:10. Mean age = 25.87±9.23. **Infrequent Ketamine:** n=26, M:F=21:5**.** Mean age =27.5 ±6.98. **Ex-Ketamine:** n=23, M:F=15:8. Mean age = 27.26±3.84. **Poly-drug Control:** n=25, M:F=17:7. Mean age = 31.29±9.47. **Non-Drug Control:** n=21, M:F=14:7. Mean age = 25.05±6.67.	**Reported Frequency:** Days Per Month. **Frequent Ketamine:** 16.0 ± 10.01. **Infrequent Ketamine:** 4.70 ± 6.48.	**Reported Time:** Years. **Frequent Ketamine:** 6.07 ± 4.89. **Infrequent Ketamine:** 4.20 ± 2.20 3.69. **Ex-Ketamine:** 7.63 ± 2.63.	**Frequent Ketamine:** 2.18 ± 1.82. **Infrequent Ketamine:** 1.11 ± 1.06.	**Frequent Ketamine:** 35.44 ± 94.59. **Infrequent Ketamine:** 26.46 ± 61.82. **Ex-Ketamine:** 34.71 ± 50.49.

Stefanovic, et al, 2009	UK	Case-Control	96 Participants. **Ketamine users:** n=22, M:F=19:3. Mean age = 21.00±2.24. **Recreational Poly Drug users:** n=26, M:F=18:8. Mean age = 21.00±1.03. **Drug Naïve Controls:** n=48, M:F=26:22. Mean age = 20.15±2.01.	**Reported Frequency:** Days Per Month **Ketamine users:** 17.79 ± 11.05.	**Reported Time:** Years **Ketamine users:** 3.30 ± 2.92.	**Ketamine users:** 0.99 ± 0.85.	**Ketamine users:** 3.74 ± 5.10.
Tang et al., 2013	China	Case Control	200 Participants. **Current Users:** n=51, M:F=29:22. Mean age = 22.80±4.3. **Former Users:** n=49, M:F=24:25. Mean age = 22.0±4.0. **Control:** n=100, M:F=58:42. Mean age = 20.6±3.6.	**Reported Frequency:** Days Per Month **Current Users:** 17.4 ± 10.9.	**Reported Time:** Years **Current Users:** 5.3 ± 2.8. **Former Users:** 4.7 ± 3.0.	**Not Reported.**	**Current Users:** 2.7 ± 6.8. **Former Users:** 189 ± 163.
Zeng et al., 2016	China	Case-Control	170 Participants. **Ketamine Users:** n=51, M:F=29:22. Mean age = 25.72±5.83. **Methadone Users:** n=60, M:F=36:23. Mean age = 42.48±5.09. **Control:** n=60, M:F=30:30. Mean age = 23.25±3.47.	**Reported Frequency:** Days Per Week. **Ketamine Users**: 6.09 ± 1.60.	**Not Reported.**	**Ketamine Users**: 2.06 ±1.75.	Participants self-reported abstinence for at least 24 hours prior to study.

Zhang et al., 2018	China	Case-Control	200 Participants. **Ketamine (non heavy other drug) users[8]:** n=286, M:F=186:100. Mean age = 25.3±4.8. **Ketamine (heavy other drug) users[9]:** n=279, M:F188:91. Mean age = 24.0±5.0. **Control:** n=261, M:F=128:133. Mean age = 22.9±5.1.	**Reported Frequency:** Days Per Month. **Ketamine (non heavy other drug) users:** 9.10 ± 10.72. **Ketamine (heavy other drug) users:** 6.82 ± 9.69.	**Reported Time:** Months. **Ketamine (non heavy other drug) users:** 77.68 ± 44.05. **Ketamine (heavy other drug) users:** 81.35 ± 45.83.	**Ketamine (non heavy other drug) users:** 3.47 ± 3.30. **Ketamine (heavy other drug) users:** 3.49 ± 3.87.	**Not reported.**

Memory is a complex domain, which encompasses a wide range of processes. There are a wide variety of tests employed to measure different aspects of memory. For this review, data from memory tasks will be broken down into declarative and working memory sections.

Declarative Memory

Declarative memory can be defined as memories that are consciously accessible for facts and events which have either personal or general relevance (Gazzaniga et al., 2002). Declarative memory, therefore, includes both episodic (memory for personally experienced events in their context) and semantic memory (memory for general information outside a personal context) (Tulving et al. 1998). These memories can be verbally reported and are also referred to as explicit memory (Gazzaniga et al., 2002). The cognitive tasks included in this review, which will be reported, are those that tap verbal learning and episodic memory, visual learning and episodic memory and semantic memory.

Verbal Learning and Episodic Memory

To assess verbal learning and episodic memory, studies most often utilise word list learning tasks (e.g. Rey Auditory Verbal Learning Test (RAVLT)) or a prose recall task (e.g. Prose recall subtest of the Rivermead Behavioural Memory Test) with immediate and delayed recall trails. Nine out of the 11 studies reviewed used measures of verbal learning to assess episodic memory (Chan, et al 2013; Cheng et al., 2018; Liang et al., 2013; Minseung Kim et al., 2016; Morgan et al., 2009, 2010, 2012; Tang et al., 2013; Zhang et al., 2018) and eight studies reported an impairment in chronic ketamine users. Seven of these studies used drug naïve control

groups. Four of the studies used poly-drug user control groups. Four studies used ex-ketamine user control groups (see table 3. for details).

Six studies reported impairments in verbal learning and memory in chronic ketamine users when compared to drug naïve controls (Chan, et al. 2013; Liang et al., 2013; Morgan et al., 2010, 2012; Tang et al., 2013; Zhang et al., 2018). Furthermore, Liang et al. (2013) reported persisting impairments in ex-ketamine users. This was not found in all other studies employing ex-ketamine user controls (Morgan et al., 2009; 2010; Tang et al. 2013). Cheng et al., (2018) found that chronic ketamine users showed a similar level of impairment, on a word recall task, to a group of participants with a diagnosis of schizophrenia. Chan et al. (2013) reported a strong negative association with lifetime usage of ketamine (no. of years using ketamine) and performance on a task of verbal learning and episodic memory. Morgan et al., (2010) and Zhang et al., (2018) also reported that higher average doses of ketamine were related to poorer performance on a prose recall task. Thus, highlighting the possible impact that the degree of drug use has on cognitive impairment. Interestingly, both Zhang et al., (2018) and Morgan et al., (2012), reported a non-specific drug effect on verbal learning and memory. That is, impairments in verbal learning and memory were seen across other drug-using groups. Thus, highlighting the possible impact of other drug use in this domain and the problematic nature of using naturalistic populations. For instance, the difficulty attributing observed impairments to the drug ketamine when users frequently use other substances which may also impair this domain. In contrast to the above, Morgan et al., (2009), reported that frequent ketamine users showed no impairment on a task of prose recall.

Morgan et al., (2009; 2010) also used a Source Memory Task as an index of episodic memory, i.e. the awareness of when and where a stimulus was encoded. Both studies found no impairment in frequent ketamine users' performance on source memory in comparison to controls. That is, if frequent ketamine users recognised a word on the task, they were able to remember the contextual information surrounding it. However, in Morgan et al. 's (2009) study they reported that frequent ketamine users recognised fewer words on the Source Memory Task. This correlated with the spot the word scores (a measure of pre-morbid IQ) in frequent ketamine users. Thus, possibly suggesting that these deficits may, in part, be related to lower levels of pre-morbid IQ in the frequent ketamine user group studied.

Visual Learning and Episodic Memory

Seven out of the 11 studies reviewed used measures of visual learning to assess episodic memory (Chan, et al 2013; Cheng et al., 2018; Liang et al., 2013; Morgan et al., 2009, 2010; Tang et al., 2013; Zhang et al., 2018). Studies most often utilise figure tasks (e.g. Rey-Osterrieth Complex Figure) with immediate and delayed recall trails. In accordance with the data on verbal learning and episodic memory, six out of the seven studies using visual learning tasks found impairments in ketamine users (Cheng et al., 2018; Liang et al., 2013; Morgan et al., 2009, 2010; Tang et al., 2013; Zhang et al., 2018). Zhang et al., (2018) reported that shorter periods of abstinence from ketamine were associated with poorer performance on visual learning tasks. Thus, highlighting the need to investigate how abstinence affects performance in chronic ketamine users further. Conversely, Chan et al., (2013) found that their sample of ketamine users, although impaired on verbal learning and memory, were not significantly impaired on visual learning and memory. The

authors highlight that earlier literature in rats suggests that chronic exposure to NMDA-R antagonists affects verbal, but not visual learning and memory (Morris, Anderson, Lynch, & Baudry, 1986). However, another consideration are the differing levels of ketamine use that may be present across study populations. Indeed, Chan et al., (2013) required all participants to abstain from ketamine use 48 hours before study participation. One possible implication of these findings is that impairments observed may be the result of acute residual effects of ketamine use. However, further study is warranted to explore this.

Semantic Memory

Meanings of words, knowledge and ideas are thought to be stored within the semantic memory system. Experimental methods which tap this memory often use semantic priming. Findings have shown that healthy individuals will generally show faster response times to target words (e.g. lemon) when they are followed by a prime word which is semantically related (e.g. orange). However, when a prime word that is not related (e.g. bin) follows the target word individuals generally show slower reaction times. The observed effect on reaction times is termed the semantic priming effect.

Stefanovic et al., (2009) reported that long-term ketamine users did not differ from non-drug users in the semantic priming task. Furthermore, their study also reported that long-term ketamine users showed increased semantic priming (faster reaction times to related words) overall compared with the poly-drug user control group. However, the authors suggest that this mainly reflected the very low priming levels in the poly-drug control group. The authors highlight that these results do not replicate previous research which indicated impairment in long-term ketamine users

semantic priming performance. Interestingly, participants in Stefanovic et al., (2009) on average used just under a gram of ketamine per session (0.99 g). However, all other studies in this review, that reported average amount of ketamine used per session, stated, on average, participants used several grams. One possible interpretation of this may be that although participants in the current study were long-term users of ketamine, they may need to take higher doses of the drug to see the same impairments reported in previous studies.

Interim Summary

In summary, the studies included in this review present a varied picture. Studies looking at verbal and visual learning with episodic memory are in line with previous research, with the majority of studies finding impairments in long-term ketamine users. However, these findings were not found in a task of semantic memory or the source memory task. Indeed, there was a general inconsistency in the tasks used across studies to measure these domains. The use of the prose recall task has been critiqued for its use in investigating episodic memory. Morgan & Riccelli et al., (2004) state that the task only requires participants to recall learnt information, and there is no component which requires participants to recall information specific to the encoding context. Thus, the different tasks employed may be measuring different component processes involved in declarative memory. Furthermore, several of the studies highlighted associations between drug use behaviour (frequency, abstinence, lifetime usage etc.) and performance on tasks. Patterns of drug use and how they relate to impairment warrant further investigation. Moreover, two studies reported non-specific drug impairments. Thus, highlighting the difficulty in

attributing observed effects to ketamine use when the population of users frequently use other illicit substances.

Working Memory

Working memory can be conceptualised as a system with the capacity to retain a limited amount of information over the short-term (maintenance) and the ability to perform mental operations on the information which is being stored (manipulation) (Gazzaniga et al., 2002). To date, working memory impairment in chronic ketamine users has been inconsistently reported. Nine of the reviewed studies considered working memory in the context of chronic ketamine use (Cheng et al., 2018; Liang et al., 2013; Minseung Kim et al., 2016; Morgan et al., 2009, 2010, 2012; Tang et al., 2013; Zeng et al., 2016; Zhang et al., 2018). Eight studies included drug naïve control groups. Five studies used poly-drug user control groups. Four studies used ex-ketamine user control groups. Six of the nine studies considered here showed an impairment in chronic ketamine users as compared to the control groups (Minseung Kim et al., 2016; Morgan et al., 2009, 2010, 2012; Tang et al., 2013; Zeng et al., 2016).

Three of the studies reviewed (Morgan et al., 2009; Morgan et al., 2010; Tang et al., 2013) reported that working memory deficits were specific to frequent ketamine users. Morgan et al. 's., (2010) one-year longitudinal study reported that, for the frequent ketamine user group, increases in self-reported ketamine use, over the year, were associated with an increase in errors on the spatial working memory task. The authors highlight that that there was no impairment in this task with healthy volunteers following an acute dose of ketamine (Morgan et al., 2010). Thus

indicating that this may be an effect which is confined to the frequent use of ketamine.

Interestingly, Morgan et al., (2012) reported that chronic ketamine users and recreational poly-drug (including ketamine use) controls only showed impairment on the digit span backwards task and not the forwards part of the task (when compared to cannabis users, cocaine users and drug naïve controls). Thus, suggesting in this study that ketamine users specifically showed difficulties with manipulating (rather than merely storing) information in working memory, a problem which is also seen following acute ketamine use (Honey et al., 2004). Thus maintenance of information in the working memory appears to be intact.

Cheng et al., (2018) found that ketamine users, with persisting psychotic symptoms, performed similarly to a group of participants who had a diagnosis of schizophrenia across tasks of working memory. The authors suggest that this finding supports previous hypotheses that chronic ketamine users have a similar profile of cognitive impairments to individuals with diagnoses of schizophrenia (Morgan and Curran, 2006).

Working memory functions were found to be intact in chronic ketamine users in three out of the nine studies considered (Cheng et al., 2018; Liang et al., 2018; Zhang et al., 2018). Liang et al., (2013) suggest one possible explanation for this inconstancy may be the differing levels of ketamine use across studies. Indeed, Liang et al., (2013) reported that the ketamine users who participated in their study had relatively longer periods of abstinence and less median ketamine use per-month than Morgan et al., (2009). However, Zhang et al., (2018) reported that participants in their study showed comparative usage data (average quantity per session, lifetime usage) to the population in Morgan et al., (2009), but had significantly less median

use per month. Thus, perhaps indicating that days used per month may be negatively associated with the effects of long-term ketamine use on cognition.

Tang et al., (2013) reported that depressive symptoms were modestly correlated with working memory in current ketamine users. Indeed, depressive symptomatology has been widely reported in chronic, daily ketamine users (Chan et al., 2013; Morgan et al., 2010; Morgan et al., 2009; Zhang et al., 2018). Given that depression has been related to implicit learning in poly-substance users (Stevens et al., 2007) and cognitive impairment is also widely found in depression (lee et al., 2012) it is important to consider this as a possible confounding factor on cognitive performance.

Interim Summary II

In summary, the review has provided inconsistent results with regards to working memory. Six of the nine studies reviewed have shown that chronic ketamine use is associated with deficits in working memory. Interestingly, both Liang et al., (2013) and Zhang et al., (2018), who found intact working memory functioning, reported that participants in their studies had a reduced level of ketamine use (monthly use and average amount of drug used per session) compared to the majority of studies that reported impairment. Indeed, level of drug use is likely an important factor in possible impairment. Given the naturalistic nature of the study sample, this is difficult to control. Further to this, there was an array of tasks used to assess working memory. Thus, differences in task difficulty may also impact study findings. Furthermore, only five of the nine studies utilised poly-drug user control groups. Thus, given the high level of poly-substance use in the ketamine using population, other drug use may have an impact on any observed impairments.

Executive Function

Executive function comprises a broad range of cognitive processes that allows us to use our perceptions, our knowledge and task-orientated goals to inform the selection of actions and thoughts from a wide range of possibilities. Thus, giving us cognitive flexibility and letting us think, plan and act in ways that allow us to achieve goals and problem solve. A variety of standardized instruments are used to measure aspects of executive functioning. These include the Wisconsin Card Sorting Test, Stroop Test, and measures of verbal fluency. These tests assess specific components of executive functioning rather than executive functioning as a whole. Because of the broad range of processes involved in executive functioning, some measures will predominantly tap the planning component, such as the Stockings of Cambridge, or another measure may tap predominantly inhibition such as the Go/No-Go task or the Hayling task.

Fluency

Five studies reported in this review used measures of verbal fluency (Chan et al., 2013; Liang et al., 2013; Morgan et al., 2009; Morgan et al., 2010; Tang et al., 2013). All five of these studies used drug naïve control groups, three of the studies used ex-ketamine user comparison groups to assess post-abstinence effects, and two studies used poly-drug user control groups.

Three out of the five studies reported impairment in verbal fluency in comparison to drug naïve controls (Chan et al., 2013; Morgan et al., 2010; Tang et al., 2013). Morgan et al. 's (2010) 1-year longitudinal study reported a decline in semantic fluency over the course of the year. However, this decline was found in

both frequent and abstinent ketamine users. The authors note that this decline in performance was not correlated with a change in ketamine use and comment that it is unclear if this decline is being mediated by other factors, such as an increase in depressive symptoms across the two groups.

Chan et al., (2013) reported that they found impairment in a task of verbal fluency, however not in a task of figural fluency (non-verbal tasks where persons are required to generate as many nonsense drawings or figures as possible within a limited time). The authors suggest that impairment in verbal fluency may be, in part, related to ketamine-induced damage to the left frontal cortex (Liao et al., 2011). Chan et al., (2013) continue to suggest, that the specific impairment in verbal fluency, and not figural fluency, reported in their study may be related to selective impairment of semantic memory as opposed to a general dysexecutive function.

Two studies reported no impairments in chronic ketamine users in comparison to healthy drug control groups (Liang et al., 2013; Morgan et al., 2009). Again, Liang et al. 's., (2013) study utilised a group of participants who used less ketamine in an average session and took ketamine less frequently per month when compared to the other studies reviewed in this section. Thus, this may indicate dose-related differences in performance on tasks of fluency.

All studies reported in this section varied considerably in average days since last use of ketamine reported by the participants. For example, Chan et al. (2013) required participants to be abstinent for 48 hours before participating, whereas no other studies employed these controls. Thus, variations in performance, across this review, may also be impacted by a number of factors regarding drug use (e.g. period of abstinence, poly-substance use etc.)

Inhibition, Response Initiation and Selective Attention

Response inhibition can be thought of as an executive function which involves managing behaviour, thoughts, attention and/or emotions to inhibit a strong, internal predisposition to respond to an external stimulus (Diamond, 2013). Measures of inhibition are derived from tests such as the Go/No-Go, Stop-Signal tasks, The Stroop Test and the Hayling test. However, it is important to note that these tests also tap other domains such as processing speed and verbal initiation. Thus, impairment on tasks may be the result of a component process, rather than the intended domain to be measured.

Seven studies reported in this review used measures of inhibition (Chan et al., 2013; Liang et al., 2013; Minseung Kim et al., 2016; Morgan et al., 2009; Tang et al., 2013; Zeng et al., 2016; Zhang et al., 2018). Six of the studies used drug naïve control groups, three of the studies used ex-ketamine user control groups, and two studies used poly-drug user control groups.

The findings present a mixed picture. Three studies reported impairments in the domain of inhibition (Minseung Kim et al., 2016; Tang et al., 2013; Zeng et al., 2016). Zeng et al., (2016) reported that Ketamine users performed worse than the drug naïve control group on the stop-signal-go task (errors condition). Furthermore, ketamine users also performed significantly poorer than both methadone users and drug naïve controls in all conditions of the Stroop task.

Tang et al., (2013) reported that ketamine users showed slower reaction time on the Stroop task in comparison to ex-ketamine users and drug naïve controls. Interestingly, impairment on the Stroop task was also found in a group of chronic pain patients who were being frequently treated with ketamine when compared to a group of patients who were not receiving long-term frequent- ketamine treatment

(Minseung Kim et al., 2016). However, it is important to note that Minseung Kim et al., (2016) recruited participants from a medical population of chronic pain patients. Further to this, the effects of other drug use were not considered in this study. Thus, the results of the study should be considered with caution.

Four studies found no impairments on either the Stroop task (Chan et al., 2013; Liang et al., 2013; Zhang et al., 2018) or the Hayling Task (Morgan et al., 2009). Chan et al., (2013), Liang et al., (2013), and Zhang et al., (2018) all reported that ketamine users in their studies use the drug, on average, fewer days a month, than both Tang et al., (2013) and Zeng et al., (2016) (see table 3). Although, amount of ketamine used per session was similar between ketamine users in the majority of studies discussed in this section (Chan et al., 2013; Morgan et al., 2009; Tang et al., 2013; Zeng et al., 2016; Zhang et al., 2018). Thus, perhaps indicating that frequency of use per month may have a greater impact on inhibition, initiation and selective attention than the amount used per session.

Planning, Reasoning and Problem Solving

Two of the studies considered in this review used the Wisconsin Card Sorting Test to assess set-shifting (Liang et al., 2013; Zhang et al., 2018) i.e. the measurement of how a person can flexibly switch tasks while being given changing schedules of reinforcement (Monchi et al., 2001). Both studies found no impairment in set shifting in frequent ketamine users.

Two studies in this review used the Stockings of Cambridge (SOC). Based on the Tower of London task, this assesses spatial planning and provides an index of frontal lobe functioning (Morgan et al., 2009; 2010). Interestingly, Morgan et al. (2009) reported that the frequent ketamine user group were less likely to solve the

problems in the minimum number of moves when compared to all other groups in their study (infrequent ketamine users, ex-ketamine users, poly-drug control, drug naïve control). However, in their follow-up study, Morgan et al., (2010) found that frequent ketamine user's performance had improved on the SOC Task. The authors suggest that these results may reflect practice effects, as the test only has one version. Furthermore, as the frequent ketamine user group performed particularly badly at bassline, they had a much greater potential to show improvement than the other groups who were observed in the study.

Decision Making

Substance misuse is often associated with impulsive decision making. Theoretically, this is because individuals who display impulsive traits may expect and also experience a higher level of reinforcement from substance use (Gullo et al., 2014). This is further compounded by a diminished ability to limit substance use regardless of future negative consequences (Gullo et al., 2014). Risky and impulsive decision making is often measured using tasks such as the Iowa Gambling Task (IGT), delay discounting tasks, and behavioural risk-taking tasks including the Balloon Analogue Risk Task (BART).

To date, research looking into the impulsivity of ketamine users is lacking. Out of the 12 studies reviewed, one study (Zeng et al., 2016) investigated this. The study used a case-control design to look at the differences in impulsivity and decision making across three groups: chronic ketamine users, chronic methadone users and drug naïve controls. The study used the Iowa Gambling Task (IGT) & Barratt's Impulsivity Scale to measure decision making and impulsivity respectively. The authors reported that methadone and ketamine users displayed scores indicating

high impulsivity on the Barratt's Impulsivity Scale compared to the drug naïve control group. The authors highlight that these results replicate research on opioid user's self-reported impulsivity. Furthermore, evidence from longitudinal studies has suggested that impulsivity is a key factor in the early development of substance abuse (Sher et al., 1991; Finn, 2002). The authors suggest this may partially explain why ketamine users display continued patterns of use, however, often without displaying other signs of addiction.

No significant differences were found between any groups on the Iowa Gambling Task (assessing decision making). The authors highlight that this finding is not consistent with some of the previous literature examining Iowa Gambling Task (Mukherjee and Kable, 2014) and suggest that studies investigating component processes which are utilised in the Iowa Gambling Task performance may highlight possible differences in ketamine users (Yechiam et al., 2005).

Interim Summary III

Executive functions perhaps pose one of the greatest challenges in measuring the impact of chronic ketamine use on cognition, due to the wide range of processes that make up the construct and the large number of tests that are used to assess it. This review has broken down executive function into four areas: planning, reasoning, problem-solving; inhibition, initiation, selective attention; fluency; and decision making. Across all four areas, there has been a wide range of inconsistencies in the findings. This may be, in part, a result of the range of tests employed to measure executive functions and the multiple domains tapped by each test. Thus, with a broad range of tests, the possibility of differing levels of difficulty is introduced. Additionally, it may also be partly explained by varying drug use across the

populations. Indeed, this is one of the most significant challenges when assessing this evidence. Given that there are many aspects of drug use (frequency, the amount used per session, lifetime usage etc.) comparing results across diverse samples presents many issues. Thus, further research examining these factors is warranted.

Component Processes: Attentional Function and Processing Speed

This section addresses the tasks used by researchers to look specifically at attentional function and processing speed. However, it is important to note that the functions measured by these tests are also important components to many of the other cognitive tests reviewed in this paper (e.g. to complete the Stroop test both attention and processing speed are important functions). Thus, highlighting the limited nature of considering these tests in isolated domains.

Three of the tests included in this section of the review utilised Digit Symbol tasks as a measure of processing speed (Chan et al., 2013; Minseung Kim et al., 2016; Tang et al., 2013). Two of the three studies reported that frequent ketamine users showed impaired processing speed in comparison to control groups (Chan et al., 2013; Tang et al., 2013). Two of the studies reviewed used cognitive tests that tap sustained attention (Digit Vigilance test & Identification Task). Minseung Kim et al., (2016) reported that patients being treated in a long-term frequent ketamine group performed significantly worse on a measure of sustained attention (Controlled Oral Word Association Test) than the control group. In contrast to this, Chan et al., (2013) reported that there was no difference between sustained or selective attention (Digit Vigilance Test) in a group of current ketamine users when compared to drug naïve controls.

Interim Summary IV

Tasks of general information processing were lacking in the studies considered in this review. However, it is important to note, that many of the tasks used to tap other domains, such as working memory, will also tap aspects of processing speed and attention. Indeed, this is a general consideration that needs to be taken into account across all sections of this review.

Discussion

Declarative Memory

The body of work that has been examined in the current review has broadly mirrored previous research into the effects of chronic ketamine use on cognition. Cognitive testing in the domain of episodic memory generally indicated that chronic exposure to ketamine causes impairments in tasks of both verbal and visual learning on episodic memory. Further to this, it also mirrors the evidence provided in acute ketamine studies, which have been able to robustly show impairment in episodic memory functions following single doses of ketamine. One possible explanation for these findings comes from imaging studies. Evidence from structural magnetic resonance imaging (MRI) studies have indicated that, in chronic ketamine users, there is a significant reduction in the grey matter volume of the dorsal prefrontal cortex (PFC) (Liao et al., 2011), which has been suggested to potentially be, in part, a contributing factor in the impairment of episodic memory performance. Additionally, ketamine has been shown to cause neuronal death, which leads to a reduction in the grey matter volume in the PFC which can further explain the impairment seen in performance on memory tasks (Lebedev et al., 2004). However, the impairments discussed in this paragraph were not reported in a task of semantic

memory or a source memory task. This may highlight varying degrees of difficulty across tasks or that tasks may be tapping different aspects of memory function. Thus, further study is needed to continue exploring these domains.

Working Memory and Executive Functions

The body of work reviewed here presented an inconsistent picture regarding working memory and executive functions. This inconsistency in findings is in line with previous literature with some studies reporting impairments in working memory and executive functioning (e.g. Morgan, Mofeez, Brander, Bromley & Curran, 2004) and other studies finding no impairments (e.g. Newcomer et al., 1999). There are a number of proposed reasons for these inconsistencies. Morgan and Curran (2006) suggested that one reason may be due to the wide range of tests employed to measure these domains and thus potential differences in task difficulty. Another explanation is that both working memory and executive functions may be particularly sensitive to the residual effects of acute ketamine use. Thus, the number of days that ketamine has been used in the previous month, and time since the last dose, may be significant factors which impact the performance of participants (Morgan et al., 2009). After a significant period of repeated, high doses of ketamine, NMDA receptor toxicity can occur. This may lead to a withdrawal state in these users which may, in part, explain variability in performance observed in the literature. That is, users may be in varying levels of withdrawal due to highly variable levels of drug use (e.g. frequency, the amount used per session etc.), which may then impact on their performance in tasks tapping working memory and executive functions.

The papers included in this review have somewhat neglected both the domains of decision making and impulsivity. Given the links between impulsive

decision making and drug abuse, it would be important that this be taken up by future research in the context of examining a more comprehensive cognitive profile.

Impairments in Ex-Ketamine Users

Only one study out of four using ex-ketamine controls found persisting episodic memory impairments in ex-ketamine users (Liang et al., 2013). Indeed, previous research has yielded mixed results. A three-year longitudinal study found that semantic memory deficits were reversible in their study population (Morgan et al., 2006). However, episodic memory and attention deficits were not (Morgan et al., 2006). Tang et al., (2013) suggested that the observed reversibility of cognitive impairment may be partly explained by evidence from animal models which have demonstrated the reversible neurotoxicity of NMDA-R antagonists (Jevtovic-Todorovic et al., 2001). However, given that research to date is still conflicting it is essential that the consideration of other confounds be taken into consideration when assessing enduring impairments (e.g. effects of poly-drug use, the presence of depressed mood etc.).

Methodological Issues

Substance Use: The majority of studies included in this review reported on other drug use within their sample population. Several studies also used poly-drug user (without ketamine use) control groups. However, across the studies, there was a great deal of variation with regards to inclusion and exclusion criteria for poly-drug user groups. Three studies used urine samples to confirm group membership and two studies utilised hair samples to perform the same task. The remainder of the studies relied on self-reports from the study participants. It is likely that this method of data

collection will have a degree of measurement error which will reduce the reliability of information obtained. Given that 'pure ketamine-only' users are rare, i.e. most ketamine users also use other illicit substances, it is crucial that future research continues to control for poly-drug use. The use of biological analysis to confirm drug use appears to be the most effective way of achieving this at present.

Studies included in this review reported varying levels of ketamine use among participants. Furthermore, findings indicated that longer lifetime usage (Chan et al., 2013), decreased length of abstinence before participation (Zhang et al., 2018) and increased dosage of ketamine (Morgan et al., 2010; Zhang et al., 2018) all negatively impacted performance on declarative memory tasks. Thus, the way people use ketamine (frequency, dosage, length of abstinence before the study, and lifetime use) and how this impacts on cognitive functioning are essential factors to explore in future research.

Independent Group Design: A number of studies included in this review utilised independent group designs. Thus, researchers have attempted to create participant groups which are matched on a number of variables (e.g. educational attainment, pre-morbid IQ, drug use, age etc.). This is carried out for two primary purposes. Firstly, to treat groups as equivalents. Secondly, as an attempt to isolate the effect of the independent variable and reduce any effects of confounding variables. However, given the issues described regarding substance use, matching groups on this variable can be problematic. Indeed, using demographic details such as educational attainment may also be problematic in matching groups.

Depressed Mood: Depression is also commonly associated with illicit substance use (Davis et al., 2008), including ketamine (Morgan and Curran, 2012). In the current review, nine out of the eleven papers reviewed included self-report

measures of depression (e.g. Beck Depression Inventory). Eight of the papers reported that frequent ketamine users have a higher level of depressive symptoms than control groups. Associations between illicit substance use and depression are most often explained by a causal relationship or shared etiological factors, such as genetic predisposition, which contribute to a pre-disposition to both disorders (Swendsen and Merikangas, 2000). However, studies exploring the relationship between long-term ketamine use and depression are lacking. Furthermore, depression in young adults has been shown to be associated with impairment in a range of cognitive domains (Castaneda et al., 2008). This includes executive dysfunction (Smith et al., 2006), attentional deficits (Mahurin et al., 2006) and short-term working memory impairments (Hill et al., 2004). Thus, it is essential that future research continues to consider the possible impact of depressed mood on any cognitive impairments observed in chronic ketamine users.

Limitations of the Review Process: The main limitation of the review process relates to the process of dividing neuropsychological tests into specific cognitive domains. Although, given the diversity and breadth of data this was essential to allow a coherent description and comparison of research. It is important to consider that while any given cognitive assessment task may be designed to focus on one cognitive domain, any task will generally tap a number of systems which may reach across multiple cognitive domains (Wheeler et al., 1997). Further to this, the various component process involved in the execution of tasks will also be shared across tests measuring different aspects of cognitive functioning (e.g. attention, reaction speed). Thus, isolating the effects of chronic ketamine use within single cognitive domains can be problematic. When looking at results on an individual (case by case basis), it is important to look at all tests of cognitive functioning in the broader context of the

whole battery of tests and any background information that you have on that individual. This is not possible when reviewing multiple studies.

Clinical Implications

This review has highlighted that chronic ketamine use has a number of long-term effects on cognition which may not be reversible after cessation of ketamine use. Given the increasing use of the drug worldwide it is important that users can access information about the possible risks and harms that chronic use may bring. Furthermore, it is essential that dissemination of this information is done in a practical and accessible manner. Indeed, it is important that relevant healthcare professionals have access to this information so that they can provide accurate and relevant information to those that request it.

Future Research

As has been outlined in this review, research into the long-term effects of chronic ketamine use is still lacking. Numerous methodological complications make it difficult to generalise results across populations and findings are often inconsistent with previous literature. Thus, it is essential that there are continued longitudinal studies that will assess the effects of differing levels of ketamine use. In particular, studies should focus on the longevity of any observed impairments and whether observed impairments are reversible.

Conclusions

In conclusion, this review highlights that further research is needed to continue investigating the effects of chronic ketamine use on cognition. The papers

in this review suggest that chronic ketamine use may impair episodic memory which is in line with previous research. Studies looking at executive functioning and working memory have also mirrored previous research yielding inconsistent results. There are a number of methodological limitations when studying drug using populations which should be considered when designing future research. Thus, replication of findings is required alongside the continued development of research paradigms which investigate how drug use patterns impact cognition.

References

Aalto, S., Hirvonen, J., Kajander, J., Scheinin, H., Någren, K., Vilkman, H., ... & Hietala, J. (2002). Ketamine does not decrease striatal dopamine D 2 receptor binding in man. *Psychopharmacology, 164*, 401-406.

Ballard, E. D., Ionescu, D. F., Voort, J. L. V., Niciu, M. J., Richards, E. M., Luckenbaugh, D. A., & Zarate Jr, C. A. (2014). Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. *Journal of Psychiatric Research*, *58*, 161-166.

Breier, A., Malhotra, A. K., Pinals, D. A., Weisenfeld, N. I., & Pickar, D. (1997). Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in healthy volunteers. *The American Journal of Psychiatry*, *154*, 805.

Castaneda, A. E., Tuulio-Henriksson, A., Marttunen, M., Suvisaari, J., & Lönnqvist, J. (2008). A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *Journal of Affective Disorders, 106,* 1–27.

Clements, J. A., Nimmo, W. S., & Grant, I. S. (1982). Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. *Journal of Pharmaceutical Sciences*, *71*, 539-542.

Correll, G. E., Maleki, J., Gracely, E. J., Muir, J. J., & Harbut, R. E. (2004). Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. *Pain Medicine*, *5*, 263-275.

Davis, L., Uezato, A., Newell, J. M., & Frazier, E. (2008). Major depression and comorbid substance use disorders. *Current Opinion in Psychiatry, 21,* 14–18.

Diamond, A. (2013). Executive functions. *Annual Review of Psychology*, *64*, 135-168.

Finn, P.R.,2002. Motivation, working memory, and decision making: a cognitive motivational theory of personality vulnerability to alcoholism. *Behavioral Cognitive Neuroscience Review, 1*, 183–205.

Gazzaniga, M. S., Ivry, R. B., & Mangun, G. R. (2002). The methods of cognitive neuroscience. *Cognitive Neuroscience: The Biology of Mind*, *2*, 96-147.

Gullo, M. J., Loxton, N. J., & Dawe, S. (2014). Impulsivity: Four ways five factors are not basic to addiction. *Addictive Behaviours*, *39*, 1547-1556.

Harris, E. W., Ganong, A. H., & Cotman, C. W. (1984). Long-term potentiation in the hippocampus involves activation of N-methyl-D-aspartate receptors. *Brain Research, 323,* 132-137.

Hill, S. K., Keshavan, M. S., Thase, M. E., & Sweeney, J. A. (2004). Neuro-

psychological dysfunction in antipsychotic-naive first-episode unipolar psychotic depression. *American Journal of Psychiatry, 161,* 996–1003.

Honey, R. A., Honey, G. D., O'loughlin, C., Sharar, S. R., Kumaran, D., Bullmore, E. T., ... & Fletcher, P. C. (2004). Acute ketamine administration alters the brain responses to executive demands in a verbal working memory task: an FMRI study. *Neuropsychopharmacology*, *29*, 1203.

Jansen, K. L. (1990). Ketamine–can chronic use impair memory. *International Journal of the Addictions*, *25*, 133-139.

Jevtovic-Todorovic, V., Wozniak, D. F., Benshoff, N. D., & Olney, J. W. (2001). A comparative evaluation of the neurotoxic properties of ketamine and nitrous oxide. *Brain Research*, *895*, 264-267.

Krystal, J. H. (2007). Ketamine and the potential role for rapid-acting antidepressant medications. *Swiss Medical Weekly*, *137*, 215-216.

Krystal, J. H., D'Souza, D. C., Karper, L. P., Bennett, A., Abi-Dargham, A., Abi-Saab, D., ... & Charney, D. S. (1999). Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. *Psychopharmacology*, *145*, 193-204.

Krystal, J. H., Karper, L. P., Seibyl, J. P., Freeman, G. K., Delaney, R., Bremner, J. & Charney, D. S. (1994). Subanesthetic effects of the noncompetitive NMDA

antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Archives of General Psychiatry*, *51*, 199-214.

Lapidus, K. A., Levitch, C. F., Perez, A. M., Brallier, J. W., Parides, M. K., Soleimani, L., ... & Murrough, J. W. (2014). A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biological Psychiatry*, *76*, 970-976.

Lee, R. S., Hermens, D. F., Porter, M. A., & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode major depressive disorder. *Journal of Affective Disorders, 140*, 113–124.

Liao, Y., Tang, J., Corlett, P. R., Wang, X., Yang, M., Chen, H., et al. (2011). Reduced dorsal prefrontal gray matter after chronic ketamine use. *Biological Psychiatry, 69,* 42–48.

Liao, Y., Tang, Y. L., & Hao, W. (2017). Ketamine and international regulations. *The American Journal of Drug and Alcohol Abuse*, *43*, 495-504.

Lynch, M. E., Clark, A. J., Sawynok, J., & Sullivan, M. J. (2005). Topical amitriptyline and ketamine in neuropathic pain syndromes: an open-label study. *The Journal of Pain*, *6*, 644-649.

Mahurin, R. K., Velligan, D. I., Hazleton, B., Davis, J. M., Eckert, S., & Miller, A. L. (2006). Trail making test errors and executive function in schizophrenia and depression. *The Clinical Neuropsychologist, 20,* 271–288.

Monchi, O., Petrides, M. Petre, V., Worsley, K., & Dagher, A. (2001). Wisconsin card sorting revisited: Distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *The Journal of Neuroscience, 21,* 7733-7741.

Moore, K. (2004). A commitment to clubbing. *Peace Review*, *16*, 459-465.

Morgan, C. J., Curran, H. V., & Independent Scientific Committee on Drugs (ISCD). (2012). Ketamine use: a review. *Addiction*, *107*, 27-38.

Morgan, C. J., Mofeez, A., Brandner, B., Bromley, L., & Curran, H. V. (2004). Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. *Neuropsychopharmacology, 29*, 208.

Morgan, C. J., Riccelli, M., Maitland, C. H., & Curran, H. V. (2004). Long-term effects of ketamine: evidence for a persisting impairment of source memory in recreational users. *Drug & Alcohol Dependence*, *75*, 301-308.

Morgan, C. J., Rossell, S. L., Pepper, F., Smart, J., Blackburn, J., Brandner, B., & Curran, H. V. (2006). Semantic priming after ketamine acutely in healthy volunteers and following chronic self-administration in substance users. *Biological Psychiatry*, *59*, 265-272.

Morris, R. G. M., Anderson, E., Lynch, G. A., & Baudry, M. (1986). Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. *Nature*, *319*, 774.

Mukherjee, D., & Kable, J. W. (2014). Value-based decision making in mental illness: a meta-analysis. *Clinical Psychological Science*, *2*, 767-782.

Newcomer, J. W., & Krystal, J. H. (2001). NMDA receptor regulation of memory and behavior in humans. *Hippocampus*, *11*, 529-542.

Newcomer, J. W., Farber, N. B., Jevtovic-Todorovic, V., Selke, G., Melson, A. K., Hershey, T.,& Olney, J. W. (1999). Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology*, *20*, 106-118

Salvadore, G., & Singh, J. B. (2013). Ketamine as a fast acting antidepressant: current knowledge and open questions. *CNS Neuroscience & Therapeutics*, *19*, 428-436.

Sher, K. J., Walitzer, K. S., Wood, P. K., & Brent, E. E. (1991). Characteristics of children of alcoholics: putative risk factors, substance use and abuse, and psychopathology. *Journal of Abnormal Psychology*, *100*, 427.

Smith, D. J., Muir, W. J., & Blackwood, D. H. R. (2006). Neurocognitive impairment in euthymic young adults with bipolar spectrum disorder and recurrent

major depressive disorder. *Bipolar Disorders, 8,* 40–46.

Stevens, A., Peschk, I., & Schwarz, J. (2007). Implicit learning, executive function and hedonic activity in chronic polydrug abusers, currently abstinent polydrug abusers and controls. *Addiction*, *102*, 937-946.

Sunder, R. A., Toshniwal, G., & Dureja, G. P. (2008). Ketamine as an adjuvant in sympathetic blocks for management of central sensitization following peripheral nerve injury. *Journal of Brachial Plexus and Peripheral Nerve Injury*, *3*, 22.

Swendsen, J. D., & Merikangas, K. R. (2000). The comorbidity of depression and substance use disorders. *Clinical Psychology Review, 20,* 173–189.

Thakurta, R. G., Ray, P., Kanji, D., Das, R., Bisui, B., & Singh, O. P. (2012). Rapid antidepressant response with ketamine: is it the solution to resistant depression?. *Indian Journal of Psychological Medicine*, *34*, 56.

Tulving, E. (1998). Neurocognitive processes of human memory. *Wenner Gren International Series*, *70*, 263-283.

United Nations Office on Drug Control, 2016. World Report 2016. United Nations, New York. Retrieved from: https://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf.

Verdejo-García, A., Lawrence, A. J., & Clark, L. (2008). Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. *Neuroscience & Biobehavioral Reviews*, *32*, 777-810.

Wheeler, M. A., Stuss, D. T., & Tulving, E. (1997). Toward a theory of episodic memory: the frontal lobes and autonoetic consciousness. *Psychological bulletin*, *121*, 331.

Yechiam, E., Busemeyer, J. R., Stout, J. C., & Bechara, A. (2005). Using cognitive models to map relations between neuropsychological disorders and human decision-making deficits. *Psychological Science*, *16*, 973-978.

Young, S. N. (2013). Single treatments that have lasting effects: some thoughts on the antidepressant effects of ketamine and botulinum toxin and the anxiolytic effect of psilocybin. *Journal of Psychiatry & Neuroscience*, *38*, 78.

Zarate, C. A., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., & Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry*, *63*, 856-864.

Part 2: Empirical Paper

Comparing the Effects of Ketamine and Lidocaine on Mood, Subjective Drug Effects, and Pain

Abstract

Aim: To explore the effects of sub-anaesthetic intravenous infusions of ketamine compared to lidocaine in chronic neuropathic pain patients. The study examined the effects of ketamine treatment on mood, subjective drug effects and pain. The association between pain and mood was also evaluated.

Method: A between subject's design was used to compare patients receiving ketamine treatment (n=24) with a control group receiving lidocaine treatment (n=34) over four-time points (baseline, mid-infusion, post-infusion and one-week follow-up). Mood was assessed using the Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire-2 (PHQ-2) and an 11-point Numerical Rating Scale (NRS). Pain was assessed over three indices (intensity, distress and interference) using 11-point NRS and similar scales were used for patient ratings of subjective drug effects.

Results: Both ketamine and lidocaine treatments yielded similar reductions in pain intensity at the one-week follow-up. Ketamine provided a greater reduction in pain intensity during the infusion. Subjective drug effect scales indicated that the ketamine treatment group felt significantly higher, felt a stronger sensation of drug effect, and liked the drug effect more than the lidocaine group. Data from mood measures were inconclusive. PHQ-2 and depression NRS showed reductions in scores of depression at the one-week follow-up for both treatment groups. However, HADS depression scores showed no significant differences. HADS anxiety data indicated that both ketamine and lidocaine groups showed significant reductions in anxiety at one-week follow-up. Further correlational analysis indicated a relationship between a reduction in both pain intensity and interference scores (baseline and one-

week follow-up) with a reduction in HADS anxiety scores for the ketamine treatment group.

Conclusion: The findings support previous literature showing the efficacy of ketamine treatment for chronic neuropathic pain. Results indicated that participants experienced the acute reinforcing effects of ketamine (feeling high and liking the drug effect) but did not want more of the drug. This may indicate a reduced abuse potential in the chronic pain population. Findings also indicated that ketamine did not produce anti-depressant effects in patients with chronic neuropathic pain. Therefore, that the rapid-acting anti-depressant effects found in populations of treatment-resistant depressed patients may not extend to those with chronic pain.

1. Introduction

1.1 Overview

Chronic neuropathic pain diagnoses have been increasing over the past three decades (Fayaz et al., 2016). Neuropathic pain is the result of lesions or damage to the somatosensory nervous system (Treede et al., 2008). This damage can cause alterations in the structure and/or function of the nervous system which may lead to pain occurring spontaneously or in response to innocuous stimuli (Niesters et al., 2014). A number of neurochemical processes are thought to underlie the development and maintenance of neuropathic pain causing peripheral and central sensitization (Treede et al., 2008). Symptoms include an increase in painful response to ordinarily innocuous and normally painful stimuli, enhanced temporal summation and spontaneous pain. Treatment for neuropathic pain is varied and generally involves a trial and error approach. Anti-depressants and anti-epileptics are used as first-line drugs. However, treatment efficacy ('adequate' pain relief) for these medications is limited with only 30-40% of patients responding. The remainder of patients either show very limited or no response (Dworkin et al., 2010, Finnerup et al., 2005).

1.2 The N-Methyl-D-Aspartate receptor

Recent research has implicated the N-Methyl-D-Aspartate receptor (NMDA-R) in the development and maintenance of chronic pain. During chronic pain states, the NMDA-R is activated and up-regulated in the spinal cord (central sensitization) (Schwartzman et al., 2001). This causes an increased responsiveness in the pain pathways within the central nervous system leading to the symptoms of neuropathic pain described above (Sigtermans et al., 2009). Considering this relationship,

NMDA-R antagonists could theoretically have an important role in the treatment and management of neuropathic pain.

1.3 Ketamine's Analgesic and Anaesthetic Use

Ketamine, a potent NMDA-R antagonist, produces strong analgesia in patients with neuropathic pain states when given at sub-anaesthetic doses. This effect is presumed to work via the direct inhibition of NMDA-Rs. However, other mechanisms, such as increases in descending inhibition or anti-inflammatory effects at central sites, may also contribute. NMDA-R antagonists such as ketamine may also reverse central sensitization and alter neuroplasticity (Azari et al. 2012). There is now a growing body of evidence that suggests ketamine is efficacious in the treatment of both neuropathic pain and post-operative pain (Hocking & Cousins, 2003; Nourozi et al. 2010; Finch et al., 2009).

Ketamine has a long history of use as an approved anaesthetic agent in children and adults for both diagnostic and surgical procedures (Lanning and Harmel, 1975). In anaesthesia, ketamine is usually administered intravenously. However, administration of the drug may also be carried out subcutaneously, intramuscularly, intradermally, intranasally, intrarectally, or orally. Although dissociative reactions have been associated with its use in anaesthesia, ketamine continues to be an advantageous anaesthetic because of its short half-life (approx. 180 mins) and lack of respiratory depression (Celmens et al., 1982). Single infusions of ketamine are well tolerated. However, transient side effects of ketamine in clinical studies include psychotomimetic symptoms (e.g. hallucinations, delusions), memory deficits, panic attacks, nausea, and somnolence. These effects typically reduce once infusions have stopped and completely subside within two hours (Aan Het Rot et al.,

2012, Blier et al., 2012). For the last half-century, ketamine has been shown to have a robust safety profile and has been administered, in clinical practice, to millions of people worldwide. (Lahti et al., 2001; Corrsen et al., 1988; Reich and Silvay, 1989; White et al., 1982). Indeed, ketamine is on the WHO's list of essential medicines.

1.4 Assessment of Pain in Research

Several guidelines exist with regards to measuring the efficacy and safety of a drug in the management of chronic pain. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) aims to aid the implementation of clinical trials via the development of reviews and guidelines that focus on the design and execution of research in the field. IMMPACT guidelines recommend when assessing the efficacy of treatment for chronic pain that six core outcome domains are considered: pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition (Turk et al., 2003). These guidelines have been taken into consideration while designing the current study.

1.5 Recreational Use of Ketamine

A different population using the drug ketamine do so 'recreationally' because they value its psychotomimetic and other effects. This population is varied, with a minority using the drug daily and a majority using much less often, for example, only at music festivals. Recreational use of ketamine has increased since the turn of the century (Moore, 2004) and an additional number of reported risks have come to light as a result. Heavy use of the drug is associated with bladder and renal complications as well as memory deficits. It is important to note that due to the repeated exposure

to large doses of ketamine and the high frequency of abuse of other substances in this population it is not possible to directly extrapolate these risks to clinical (pain management) populations. In clinical settings, ketamine has proven to be well tolerated by patients. Furthermore, heavy recreational users of ketamine often use grams of the drug every day. However, in medical settings milligrams are used more commonly once a month.

1.6 Ketamine's Reinforcing Properties

Research examining the reinforcing or dependence-forming properties of ketamine is currently limited. Pre-clinical findings, across a number of behavioural paradigms, indicate that ketamine may share a number of properties with other dependence-forming substances. Studies have shown that ketamine produces conditioned place preference (Layer et al. 1993), and is self-administered by rats and primates (Marquis et al.1989; Winger et al. 1989). Ketamine substitutes for ethanol in drug discrimination paradigms with rats (Shelton, 2004 & Harrison et al. 1998) and alcohol-dependent humans show enhanced NMDA function (Krystal et al. 2011). Further, Ketamine has been shown to produce similar subjective drug effects to ethanol in recently detoxified alcoholics (Krystal et al., 1998). Morgan et al. (2004) found an inverted U-shaped dose-response curve when healthy, ketamine-naïve volunteers were asked to rate how much they 'liked' the drug and wanted more of it when sub-anaesthetic doses (0.4mg/kg and 0.8mg) or placebo was infused intravenously. Results showed that both groups given ketamine liked the drug effects and wanted more of both doses in the early phase of the infusion. However, for the high dose group, these ratings showed a significant reduction towards the end of the

infusion. Conversely, the low dose group continued to report liking the drug effects and wanting more of the drug.

1.7 Ketamine's Antidepressant Properties

Recent evidence suggests that ketamine also possesses potent antidepressant properties (see Abdallah et al. 2015 for review). Major depressive disorder (MDD) is a significant global health concern, affecting millions of people and thus having severe socioeconomic and health consequences (Kessler et al., 2003). Currently, the use of antidepressant treatment in patients with MDD has proven to be unsatisfactory for a significant proportion (around a third) of those treated. Indeed, relapses, low remission rates and continuing low-level symptomatology are common and can lead to persistent functional impairment. Further, there is a wide acceptance that both tricyclic and SSRI antidepressant medications require a lag period of several weeks before any improvement in mood and well-being are experienced. Thus, there is a clear need for a treatment that has rapid-acting antidepressant properties. Ketamine has been of particular interest because of its rapid antidepressant effects (Berman et al., 2000). Berman et al. (2000) found that treatment refractory MDD patients showed a robust antidepressant effect within 4 hours of a sub-anaesthetic dose of ketamine which subsided within one-to-two weeks of the initial infusion. These antidepressant properties of ketamine have been replicated several times (see Abdallah et al. 2015 for a review) including randomized controlled trials (RCTs) (Berman et al., 2000; Murrough et al., 2013; Zarate et al., 2006; Valentine et al., 2011). Furthermore, meta-analyses have shown the rapid antidepressant effects of ketamine to be robust relative to saline controls. Additionally, ketamine has been found to be more effective than control placebo treatments with active side-effect

profiles in order to make the blinding component of the study more robust (Newpoer et al., 2015; Caddy et al., 2014; Fond et al., 2014; McGirr et al., 2015; Romeo et al., 2015).

1.8 Co-Morbid Depression and Chronic Pain

Depression and depressive-like symptoms are often found co-morbidly in people who have chronic pain (Banks and Kerns, 1996). There are a number of theories that have attempted to explain the co-occurrence of chronic pain and depression, yet the relationship between the two remains unclear. Some theories conceptualize the two as distinct, unrelated conditions, while other theories have suggested that regarding psychology or biology they are closely linked. Early theories suggested that chronic pain may be the result of a conversion of conscious or unconscious psychological distress into pain (psychosomatic) (e.g. Blumer and Heilbronn 1982). However, research demonstrating changes in the central nervous system of those with chronic pain has provided clear evidence against this model (Tracey and Mantyh 2007; Turk and Salovey 1984; Crombez et al., 2009). Bank's and Kern's (1996) diathesis-stress model postulates that some individuals may be more likely to develop depression due to an increased sensitivity to particular stressors. This increased sensitivity may be the result of genetic vulnerability or environmental factors. Thus, this model predicts that chronic pain would be a stressor which increases the likelihood of an individual developing depression. More recently, evidence from the field of neuroscience has highlighted the efficacy of an emotion regulation model. Linton and Bergbom's (2011) model considers the interaction of pain and depression in relation to other cognitive factors such as catastrophizing and emotion regulation. Firstly, the authors highlight the central role

of catastrophizing in models of both pain and depression thus signifying an important link. Secondly, how depression and pain both act as significant emotional stressors. The model states that episodes of pain induce catastrophic thinking which leads to an increased strain on an individual's emotional regulation system. Successful regulation of this leads to coping, while negative behavioural emotional regulation leads to increased negative affect, pain, and mood-related disability. However, current theories still contend with integrating neuroscience and psychological theories of co-morbid pain and depression. Indeed, there is a risk of not representing the extent to which the common pathways and neurotransmitter systems impact on the experience and development of chronic pain and depression.

Williams and Schafer (2016) conducted a review of longitudinal studies looking at the relationship between pain and depression. This highlighted evidence which suggests the presence of depression at baseline testing leads to worse outcomes in chronic pain. Thus, the detection of depression and treatment of any mood disorder alongside pain management may substantially enhance outcomes. However, reliable evidence for existing models of chronic pain and depression are lacking (Williams and Schafer, 2016). Indeed, assessing the emotional functioning of patients who present with chronic pain has proven difficult because of the overlap between symptoms of depression (fatigue, memory and concentration deficits, libido, appetite or weight changes) and those of chronic pain and or the associated side effects of some of the medications used to treat chronic pain. Further to this, many measures used to screen or diagnose depression may have poor validity within the chronic pain population (e.g. Pincus and Williams, 1999; Morley et al., 2002; Shafer, 2006).

1.9 Rationale for the Current Study

Given ketamine's efficacy as a treatment for chronic pain, alongside its rapid-acting anti-depressant effects, we are interested in ketamine's effects on mood in the chronic neuropathic pain population. If patients treated with ketamine show significant improvements, relative to controls, on measures of mood, this might tentatively indicate that ketamine's anti-depressant properties extend to chronic neuropathic pain patients. Furthermore, in both healthy volunteer and animal studies, ketamine has been shown to share a number of properties with other dependence-forming drugs. Thus, we hope to gain an insight into how a chronic pain population responds to the drug, how well tolerated it is at the doses given and how much the patients enjoy or want more of the drug. This is important, concerning its use clinically, as it may indicate abuse potential, the practicality of use, and adverse effects in this population. Through this research, we also hope to add to the growing evidence base in the use of ketamine in a chronic pain setting.

1.10 Hypotheses

Based on the literature regarding ketamine's anti-depressant properties (see Abdallah et al., 2015 for review), and the strong link between depression and chronic pain (Banks and Kerns, 1996), we predict that patients receiving ketamine treatment will show a greater improvement on measures of depressed mood than the lidocaine group.

Based on previous research we predicted that the ketamine group would experience more subjective drug effects than the lidocaine group. In particular, they will have higher ratings of perceptual distortions, feeling high, wanting more of the drug, and intensity of drug effect (Morgan et al., 2004).

With regards to chronic pain, based on the work discussed above (Hocking & Cousins, 2003; Nourozi et al., 2010 and Finch et al., 2009) we predicted that we will observe a reduction in pain both at the acute stage (during treatment) and at the one-week follow-up stage for both ketamine and control group patients treated with lidocaine.

Further exploratory within-group correlations for pain measures and mood measures will be carried out looking for correlations between pain relief and change in depression.

1.11 Aims

This, primarily exploratory study had three aims. First, it sought to explore the effects of sub-anaesthetic doses of intravenous (IV) ketamine on the mood of patients with chronic neuropathic pain. Second, was to assess the acute effects of low sub-anaesthetic IV ketamine on subjective drug effects such as enjoyment, wanting more of the drug and feeling high. Third, it aimed to observe the effect of ketamine on pain both acutely and at a one-week follow-up.

2. Method

2.1 Power Analysis

Power analysis for this study was informed by Coyle and Laws (2015). This meta-analysis found large effect sizes for the acute effects of single infusions of ketamine on depressed mood. Assuming equal group sizes, the power calculation was carried out on "G*Power 3" computer program (Faul, Erdfelder, Land, Buchner, 2007), specifying alpha=5% and desired power =80%. The effect size was

conservatively estimated down from large to medium and with a predicted sample size of 40 (per-group) we calculated a total power of 0.87.

2.2 Joint Thesis

This thesis is part of a joint research project and was completed together with a fellow trainee clinical psychologist, Catherine Trotman (Trotman, 2018). See appendix 1. for further details of contributions made by each trainee.

2.3 Ethics

The study was approved by the South Central Berkshire NHS Research Ethics committee (see appendix 2). All participants provided written informed consent (see appendix 3.).

2.4 Participants and Design and Study Site

A between-within subjects quasi-experimental design was used to compare patients receiving ketamine treatment with those receiving the sodium channel blocker lignocaine. Lignocaine was chosen as a comparison drug for several reasons. Firstly, it has a well-documented efficacy and safety profile within the chronic pain population (Hocking & Cousins, 2003; Nourozi et al., 2010; Finch et al., 2009). Secondly, patients at the UCLH pain management centre are regularly treated with lignocaine for the management of chronic neuropathic pain, thus provide an easy group to recruit from in a natural experiment. Thirdly, lignocaine has not been shown to have antidepressant properties in populations of depressed patients. Thus, it would provide a good comparison to ketamine with regards to its effects on depressive symptomatology within the chronic pain population. Fourthly, lignocaine is not

abused recreationally, thus would provide a good comparison for the reinforcing effects of ketamine.

A convenience sample of participants was identified using the database from the study site. Researchers attempted to contact patients receiving ketamine or lidocaine infusions between February 2018 and May 2018. Those who were interested in participating were emailed a participant information sheet (see appendix 4.). Those who agreed to participate in the study were then scheduled for testing at the same time as their infusion of ketamine or lidocaine. All participants provided written informed consent.

Inclusion criteria were men and women aged 18-70 years who were native English speakers. Participants had moderate to severe chronic neuropathic pain and had been deemed by their consultant to require IV lignocaine or ketamine to manage their pain. Patients were excluded if they had a suspected allergy to ketamine, diagnosis of psychiatric illnesses, a record of serious head injury, a record of learning disability, were pregnant or breastfeeding, or were unable to provide informed consent.

The study site is a nationally recognised centre of excellence for people with acute chronic pain. The service comprises of a multi-disciplinary team of doctors, nurses, physiotherapists and psychologists. The service receives nationwide referrals for patients who have been unable to manage their pain locally alongside providing services locally. The service is one of several centres nationwide that prescribes ketamine to manage chronic pain and also provides other specialist interventions including systemic drug treatment, intravenous drug infusions, peripheral and central nerve blocks, radio frequency lesioning and spinal implants. They also also provide information and access to TENS machines and acupuncture.

2.5 Measures

2.5.1 Mood

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) was employed as the primary measure of depression. Additionally, the 2-item Patient Health Questionnaire depression module (PHQ-2) and a depression Numerical Rating Scale (NRS) (described in 2.5.3) were chosen because of their past use in studies exploring the antidepressant and reinforcing effects of ketamine. Further, both of these measures were brief (<2 items) and did not include items that report on somatic symptoms.

The HADS is a self-report measure developed to identify depression and anxiety in non-psychiatric hospital settings (see appendix 5). The measure contains seven items in an anxiety subscale and seven items in a depression subscale. The HADS does not include items measuring somatic symptoms, such as insomnia, common in many other questionnaires measuring anxiety and depression. The HADS has been studied rigorously across a wide range of populations. Bjelland, Dahl, Haug and Neckelmann (2002) conducted a review of 747 studies to assess the validity of the HADS. They reported that alphas for the internal reliability of the anxiety subscale were within the range of 0.68 to 0.92 (mean 0.83). With regards to the depression subscale, the alphas ranged from 0.76 to 0.90 (mean 0.82). Their review also demonstrated that the HADS had a similar sensitivity to other widely used measures which assess mood and anxiety, such as the Beck Depression Inventory and the General Health Questionnaire. Thus, the reviewers concluded that the concurrent validity of the HADS is good to very good.

The PHQ-2 (see appendix 5.) is a brief version of the 9-item Patient Health

Questionnaire depression module (PHQ-9). The PHQ-2 asks recipients to report on the frequency of depressed mood and anhedonia over the past two weeks scoring each as 0 ("not at all") to 3 ("nearly every day"). Kroenke et al. (2003) conducted a study on the validity of the PHQ-2 on a sample of 6000 patients. The short-form General Health Survey in conjunction with participant reported sick leave and symptom-related impact of day-to-day functioning was used to assess construct validity. An independent structured mental health professional interview, in a sample of 580 patients, was used to assess criterion validity. The study found that a PHQ-2 score of >3 had a sensitivity of 83% and a specificity of 92% for major depressive disorder. The researchers concluded that overall the construct and criterion validity of the PHQ-2 make it a good measure of depression screening.

The PHQ-2 was adapted in this study to ask participants to report the frequency of depressed mood over the past week, rather than two weeks in the original (Kroenke et al., 2003). This change was implemented to ensure that participants were only reporting on the period between their infusion and the 1-week follow-up.

2.5.2 Pain Intensity, Pain Distress and Pain Interference

Participants will be asked to rate their pain on three 11-point (0-10) NRS (see appendix 6.). The pain intensity scale asked ‘how intense is your pain right now' with 0 being anchored with the label of no pain and 10 being anchored with the label extremely intense pain. Participants would then circle the appropriate number on the numbered line using a pen. Alternatively, participants could also verbally report their response to the researcher. Similar 11-point scales were used to measure pain distress, with the anchor of 0 being ‘not distressing' and the anchor of 10 being

‘extremely distressing'. The anchors for the 11-point pain interference scale were 0 ‘does not interfere' and 10 ‘interferes with everything'. As above, participants either circled the appropriate answer or responded verbally which was followed by the researcher recording their answer. 11-point NRS were chosen as research suggests that they are as reliable and valid for pain ratings as Visual Analogue Scales (VAS), 11-point box scales and 101-point numerical rating scales for both acute and chronic pain (Jensen, Karoly, & Braver, 1986; Jensen, Karoly, O’Riordan, Bland, & Burns, 1989). In addition to this, research has suggested that individuals prefer NRS over VAS (Price, Patel, Robinson, & Staud, 2008). Furthermore, NRS have been shown to have similar sensitivity to VAS (Bolton & Wilkinson, 1998; Bone et al., 2002; Breivik et al., 2000; Changues et al., 2010). It is not possible to determine internal consistency for these NRS as they are single item measures.

2.5.3 Subjective Rating Scales

A subjective drug effects scale containing 11 items consisting of an 11-point NRS (Curran & Morgan, 2000) was employed (see appendix 7.). Effects were split into four broad categories: i) Bodily Symptoms (dizziness, drowsiness, nausea), ii) Cognitive/Mood Symptoms (mental confusion, depression), iii) Perceptual Symptoms (visual distortions, out of body experience) and iv) Reinforcing Drug Effects (liking the drug, disliking the drug, feeling high, feeling a drug effect). All were measured using 11-point NRS with the anchor of 0 labelled ‘not at all', and the anchor of 10 labelled ‘extremely'. Participants would then either circle the appropriate number on the numbered line using a pen or verbally report their response to the researcher who would then record it.

2.5.4 Alcohol Use

The Alcohol Use Disorders Identification Test (AUDIT) was used to index the participant's alcohol use (see appendix 8.). The AUDIT is a 10-item, self-administered questionnaire that was developed to detect patterns of heavy alcohol use (Babor et al., 2001). Items are rated on a five-point Likert scale (0-4) with higher scores reflecting hazardous alcohol use. The AUDIT employs a cut-off score off eight which indicates hazardous alcohol use. The AUDIT has good reliability and validity (Babor et al., 2001).

2.5.6 Demographic Details

Participant age and gender were recorded (see appendix 8.). Participants were also asked to state the highest level of education they had attained: GCSE or age 16 equivalent, A-Level or age 18 equivalent, undergraduate or equivalent, post-graduate or equivalent.

2.6 Procedure

2.6.1 Baseline

When participants arrived at the pain clinic for their appointment, they were greeted by researchers and asked to provide informed consent. Participants were asked to complete initial baseline measures about current depressive symptomatology (HADS and PHQ-2, depression NRS), three NRS assessing different indices of pain (intensity, degree of distress, and degree of interference in functioning caused by the pain). Participants were also asked to complete the subjective effects NRS bodily symptoms (dizziness, drowsiness, nausea), cognitive/mood symptoms (mental confusion, depression), and perceptual symptoms

(visual distortions, out of body experience). Participants were not asked to complete the reinforcing drug effects NRS at baseline. Following completion of these measures, researchers informed the medical staff that the patient was ready for their infusion and participants were admitted to the ward for treatment.

2.6.2 Infusion

Ketamine infusions typically lasted for around 30 minutes, while lidocaine infusions lasted between one to three hours. Participant's mid-infusion time-point and treatment dosage were calculated at the beginning of each infusion. Protocols for treatment dose at the study site were 0.5mg per kg of body weight for ketamine and 2-to-3mg per kg of body weight for lidocaine. A number of factors dictate whether a patient is prescribed lidocaine or ketamine including the patient's medical history and current medications being used. Lidocaine is typically used as the first line infusion treatment at the study site. If patients show no or limited response to lidocaine they will then be prescribed ketamine. However, if patients have any history of heart disease, cardiac arrhythmias, recent myocardial infarction or are deemed to be high risk for cardiac complications they would not be eligible for lidocaine treatment and would be prescribed ketamine in the first instance.

2.6.3 Mid-infusion

At the mid-point of their infusion participants were asked them to complete the three pain NRS (intensity, distress and interference) and the full subjective effects NRS battery.

2.6.4 Post-Infusion

Immediately after infusions were finished participants completed the three pain NRS, full subjective effects NRS battery, AUDIT and the highest level of education attained questionnaire. They were then given the opportunity to ask any further questions and a time was arranged to carry out the one-week follow-up phone call.

2.6.5 One-Week Follow-Up

One-week following each participant's infusion they were contacted by telephone. Participants were given the opportunity to answer any questions, and then the same set of measures completed at baseline were repeated remotely. See table 1. for a summary of the procedure.

Table 1 Summary of Procedure Depicting Which Tests Were Carried out at Each Time-Point

Prior to infusion/baseline	**Infusion**	**Mid-infusion**	**Post-infusion**	**1-week follow-up**
Pain NRS	n/a	Pain NRS	Pain NRS	Pain NRS
HADS	n/a	HADS	HADS	HADS
PHQ	n/a	PHQ	PHQ	PHQ
Subjective effects NRS ([1]without reinforcing drug effects)	n/a	Subjective effects NRS ([2]with reinforcing drug effects)	Subjective effects NRS (with reinforcing drug effects)	Depression NRS only
	n/a	-	AUDIT	-

[1] This was a partial battery measuring i) Bodily Symptoms (dizziness, drowsiness, nausea), ii) Cognitive/Mood Symptoms (mental confusion, depression), iii) Perceptual Symptoms (visual distortions, out of body experience) only. [2] This was the full subjective effects battery including all reinforcing drug effects questions (liking the drug, disliking the drug, feeling high, feeling a drug effect, wanting more of the drug)

2.7 Statistical Analyses

Statistical Package for Social Sciences (SPSS Version 25) was used to perform all analyses. Group differences for categorical variables (gender and educational levels) were examined with chi-square tests, and t-tests were used for the

continuous variable of age. Mann-Whitney U tests were used to compare the groups on AUDIT scores as this variable violated the assumption of normality.

Distribution of data was assessed using, skewness and kurtosis data, histograms, p-p plots and the Kolmogorov–Smirnov test. Where these tests indicated that the assumptions of normality had been violated the decision was made to continue carrying out mixed ANOVAs. The rationale for this was based on Field (2013) where he noted that in samples of 40 or more with no outliers, the sampling distribution is usually normal according to central limit theorem. Furthermore, it is preferable to use a robust measure, such as an F-test, where possible. After performing ANOVAs, the distribution of the residuals was examined. Where a violation of the assumption of normality was indicated, a secondary non-parametric analysis, using Mann-Whitney U tests of change scores was conducted to confirm findings. Secondary Mann-Whitney U tests are reported in appendix 9.

The primary analysis aimed to examine the difference between the ketamine and lidocaine groups on measures of pain and mood over two timeframes: acutely (baseline, mid-infusion and post-infusion) and longer-term (baseline and one-week follow-up). 2(group: ketamine; lidocaine) x 3 (Time: baseline, mid-infusion and post-infusion) mixed ANOVAs were undertaken for the acute scores and 2 (group: Ketamine; Lidocaine) x 2 (baseline and one-week follow-up) mixed ANOVAs were undertaken for the follow-up scores.

For the analysis exploring the subjective effects, 2(group: ketamine; lidocaine) x 3 (Time: baseline, mid-infusion and post-infusion) mixed ANOVAs were carried out. Where data was only collected at mid-infusion and post-infusion, 2 (group: Ketamine; Lidocaine) x 2 (mid-infusion and post-infusion) mixed ANOVAs were carried out.

Assumptions of sphericity were assessed using Mauchley's test and where this assumption was violated the Greenhouse-Geisser correction was applied. Homogeneity of variance was assessed using Levene's test, and p values associated with post-hoc tests were Bonferroni corrected.

To investigate the categorical HADS depression and anxiety clinical significance data (significant, not significant), the Fisher Exact test was used as data violated the assumptions of a chi-square test. Correlations were performed comparing change scores between baseline and follow-up for pain data (intensity, distress, interference) and mood measures (HADS Depression, HADS Anxiety, PHQ-2, Depression NRS). Since this data violated assumptions of normality, a Spearman's Rho correlation was conducted.

3. Results

3.1 Demographics (table 2) and Reported Alcohol Use (table 3)

There were 58 participants in total: 24 ketamine patients (17 female, 7 male) and 34 lidocaine patients (27 female, 7 male). There were no statistically significant group differences in gender ($\chi 2(1) = 0.565$, $p = 0.328$) or age ($t(56) = 1.032$, $p = 0.307$). The sample was predominantly female (ketamine=70% female, lidocaine=79% female). However, when compared with the population of patients receiving treatment at the study site over the course of the study (72% female) there were no differences in the number of males and females in the two populations ($\chi 2(2) = 0.817$, $p = 0.665$).

The highest level of educational attainment by ketamine and lidocaine participants respectively were: GCSEs or equivalent (9/14), A-Levels or equivalent (4/3), Undergraduate degree or equivalent (5/11), Post-graduate degree or equivalent

(4/4). There were no statistically significant group differences in educational attainment ($\chi 2$ (3) = 1.686, p = 0.640).

Participants in both treatment groups reported low levels of alcohol use. AUDIT total scores in the ketamine treatment group did not differ significantly from the lidocaine treatment group (*U=259.500, z=-1.34, p=0.179).* The majority of participants' scores fell in the low-risk range for the AUDIT total score (33 lidocaine, 20 Ketamine). The remaining participants scored in the 'increasing risk' range (2 lidocaine, 1 ketamine). No patients scored in the higher risk or possible dependence categories. The frequency of alcohol use in the ketamine treatment group did not differ significantly from the lidocaine treatment group (*U=256.500, z=-1.43, p=0.154).* Typical units of alcohol used in the ketamine treatment group did not differ significantly from the lidocaine treatment group (*U=312.500, z=-0.38, p=0.702).* The frequency of drinking more than six units of alcohol in the past year in the ketamine treatment group did not differ significantly from the lidocaine treatment group (*U=258.500, z=-1.54, p=0.124).*

Table 2 Summary of Group Demographics and AUDIT scores

		Ketamine		Lidocaine	
Age		**N**	**Mean (sd)**	**N**	**Mean (sd)**
	[1]Study Population	24	51.75 (13.19)	34	48.03 (13.76)
	[2]Full Population	74	55.77 (12.18)	188	50.20 (14.14)
Gender (Female)		**N (%)**		**N (%)**	
	Study Population	18 (70.8%)		27 (79.4%)	
	Full Population	46 (62.2%)		137 (72.9)	
AUDIT Total Score		**N**	**Mean (sd)**	**N**	**Mean (sd)**
	Study Population	22	2.09 (3.13)	30	2.47 (2.24)
Treatment Dose mg		**N**	**Mean (sd)**	**N**	**Mean (sd)**
	Study Population	24	20.52 (12.59)	34	195.80 (61.68)

[1]Study Population: All participants who participated in the full study, [2] Full Population: all patients attending the study site for infusions between February and May 2018. The study population data is included in the full population statistics.

Table 3 Summary of participants' alcohol use as AUDIT response frequencies

		Never	Monthly or Less	2-4 times p/m	2-3 times p/w	4+ times p/w
How often do you have a drink containing alcohol?	Ketamine	11	5	3	-	3
	Lidocaine	8	10	4	6	2
		0-2	**3-4**	**5-6**	**7-9**	**10+**
How many units of alcohol do you drink on a typical day when you are drinking?	Ketamine	15	5	-	1	1
	Lidocaine	18	11	1	-	-
		Never	**Less Than Monthly**	**Monthly**	**Weekly**	**Daily or Almost Daily**
How often have you had 6 or more units* in the last year?	Ketamine	17	2	1	-	1
	Lidocaine	15	13	1	1	-
		Low Risk	**Increasing Risk**	**Higher Risk**	**Possible Dependency**	
AUDIT Total Score	Ketamine	33	1	-	-	-
	Lidocaine	20	2	-	-	-

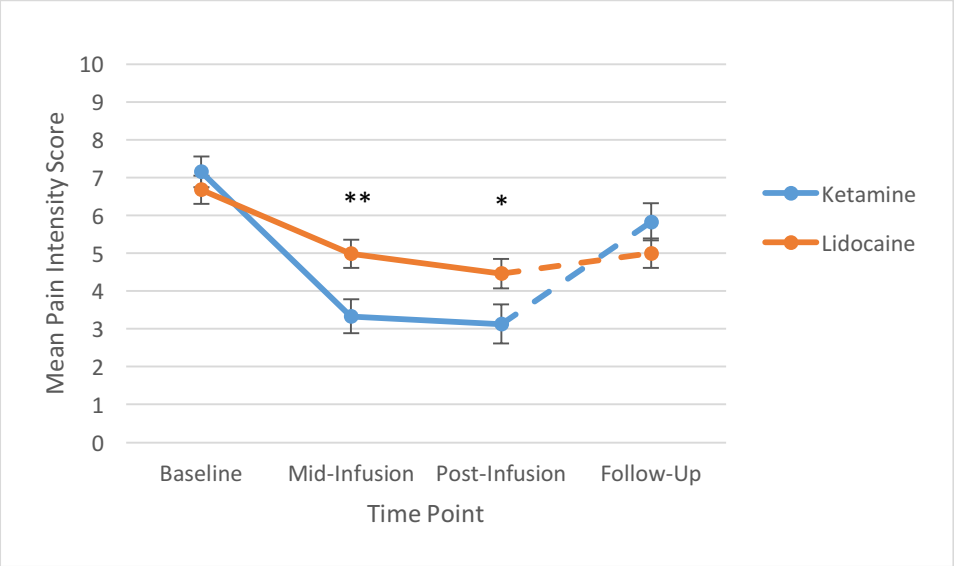
3.2 Pain – Acute Effects

3.2.1 Pain Intensity (Figure 1)

A 2X3 mixed ANOVA, comparing baseline, mid-infusion and post-infusion scores, showed a significant interaction between drug group and time ($F(1.89, 100)$ =

9.14, p<0.001) and a main effect of time (F(1.89, 100) = 64.57, p<0.001). No significant main effect of drug group was found (F(1, 50) = 3.02, p=0.088). Post hoc tests showed that the ketamine group scored significantly lower on pain intensity scores than the lidocaine group at mid-infusion (p=0.005, d= 0.82) and at the post-infusion time points (p=0.030, d= 0.63). Significant reductions in pain intensity scores were found between baseline and mid-infusion for the ketamine (p<0.001, d=1.81) and lidocaine (p<0.001, d=0.79) groups, as well between baseline and post-infusion for the ketamine (p<0.001, d=1.81) and lidocaine (p<0.001, d=1.03) groups.

Figure 1 Group means for pain intensity scores of ketamine and lidocaine patients at each study time point. Bars represent standard errors.



Bonferroni corrected post hoc tests comparing between group differences at acute time points (baseline, mid-infusion, post-infusion). *= p <0.05, **= p< 0.01, ***= p < 0.001

3.2.2 Pain Distress (table 4)

A 2X3 mixed ANOVA, showed no significant interaction between drug group and time (F(2, 100) = 1.42, p=0.248), but a significant a main effect of time (F(2, 100) = 62.36, p<0.001) which reflected a reduction in pain distress scores from baseline to mid-infusion to post-infusion. No significant main effect of drug group was found (F(1, 50) = 0.40, p=0.529).

Table 4 Group means (sd) for pain NRS data.

		Ketamine	Lidocaine
Pain Distress	Baseline	6.09 (2.89)	5.97 (2.51)
	Mid-Infusion	2.41 (2.58)	3.45 (2.56)
	Post-Infusion	2.17 (2.10)	2.31 (2.16)
	Follow-Up	4.83 (2.99)	4.00 (2.95)
Pain Interference	Baseline	7.35 (2.48)	6.13 (3.17)
	Follow-Up	7.21 (2.69)	5.45 (3.09)

3.3 Pain - Baseline and One-week follow-up

3.3.1 Pain Intensity (figure 1)

A 2X2 mixed ANOVA, looking at baseline and one-week follow-up scores, showed no significant interaction between drug group and time ($F(1, 53) = 0.62$, $p<0.433$) but a significant main effect of time ($F(1, 53) = 20.27$, $p<0.001$) reflecting a reduction in pain intensity scores from baseline to the one-week follow-up. No significant main effect of drug group was found ($F(1, 53) = 1.59$, $p=0.213$).

3.3.2 Pain Distress (table 4)

A 2X2 mixed ANOVA showed no significant interaction between drug group and time ($F(1, 53) = 1.46$, p=0.232). A significant main effect of time ($F(1, 53) = 71.62$, $p<0.001$) showed a reduction in pain distress scores from baseline to the one-week follow-up. No significant main effect of drug group was found ($F(1, 53) = 0.25$, $p=0.617$).

3.3.3 Pain Interference (table 4)

A 2X2 mixed ANOVA showed no significant interaction between drug group and time ($F(1, 52) = 0.74$, $p=0.394$). A significant main effect of time ($F(1, 52) = 12.14$, $p<0.001$) showed a reduction in pain interference scores from baseline to the

one-week follow-up. No significant main effect of drug group was found ($F(1, 52) = 0.21$, $p=0.649$).

3.4 Mood

3.4.1 PHQ-2 (table 5)

A 2X2 mixed ANOVA, looking at baseline and 1-week follow-up scores, showed no significant interaction between drug group and time ($F(1, 51) = 2.01$, $p=0.162$). A significant main effect of time ($F(1, 51) = 5.85$, $p=0.019$) showed a reduction in PHQ-2 depression scores from baseline to the one-week follow-up. No significant main effect of drug group was found ($F(1, 51) = 0.09$, $p=0.765$).

3.4.2 HADS Depression (table 5)

A 2X2 mixed ANOVA, looking at baseline and 1-week follow-up scores, showed no significant interaction between time and drug group ($F(1, 50) = 0.01$, $p=0.953$). No significant main effect of time ($F(1, 50) = 1.87$, $p=0.178$) or drug group ($F(1, 50) = 0.001$, $p=0.971$) was found.

3.4.3 HADS Anxiety (table 5)

A 2X2 mixed ANOVA, looking at baseline and 1-week follow-up scores, showed no significant interaction between time and drug group ($F(1, 51) = 2.87$, $p=0.096$). A significant main effect of time ($F(1, 51) = 53.58$, $p=0.005$) showed a reduction in HADS anxiety scores from baseline to one-week follow-up. No significant main effect of drug group was found ($F(1, 51) = 0.16$, $p=0.689$

Table 5 Group means (sd) for depression and anxiety measures.

		Ketamine	**Lidocaine**
PHQ-2	Baseline	3.05 (2.14)	3.19 (2.26)

	Follow-up	2.82 (2.46)	2.32 (2.02)
HADS Anxiety	Baseline	9.59 (5.54)	9.29 (4.29)
	Follow-up	7.32 (5.15)	8.68 (5.28)
HADS Depression	Baseline	9.41 (5.06)	9.33 (4.18)
	Follow-up	8.68 (4.98)	8.67 (4.83)

3.4.4 HADS Clinical Significance Data (table 6)

Fisher Exact tests were conducted on the population of patients who scored in the clinically significant range for HADS depression at baseline. The tests revealed that there were no significant differences in numbers of ketamine and lidocaine patients scoring in the clinically significant range and non-clinically significant range at the 1-week follow up (p=0.159).

Fisher Exact tests were also conducted on the patients who scored in the clinically significant range for HADS anxiety at baseline. The tests showed that there were no significant differences in the distribution of clinically significant and non-clinically significant scoring patients at the 1-week follow up (p=0.697).

Table 6 Group frequencies at one-week follow-up for clinical significance data

		Ketamine	**Lidocaine**
Anxiety	Normal	3	2
	Borderline	2	3
	Clinically Significant	6	9
Depression	Normal	0	2
	Borderline	1	4
	Clinically Significant	8	6

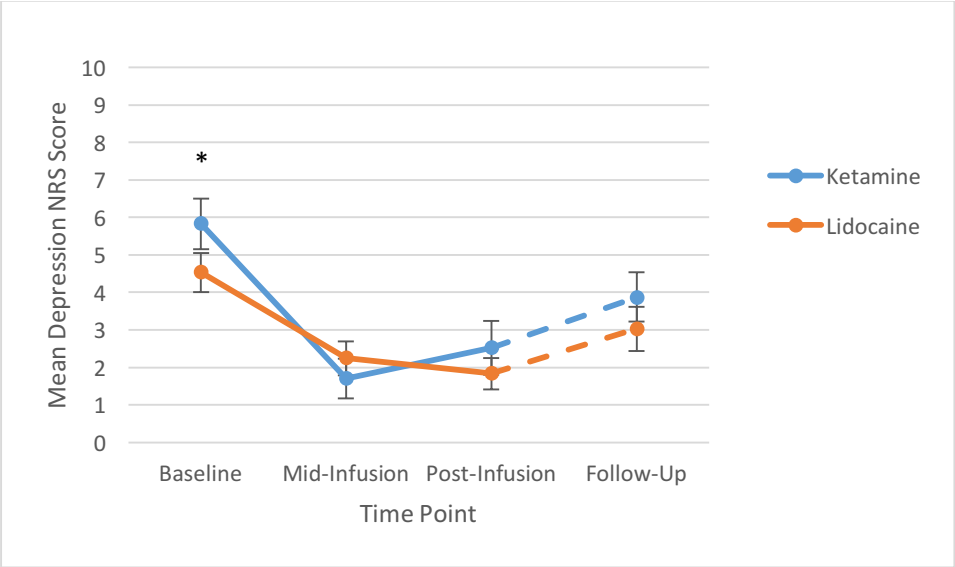
3.4.5 Depression NRS (figure 2)

Acute: A 2X3 mixed ANOVA, looking at baseline, mid-infusion, post-infusion scores, showed a significant interaction between drug group and time (F(2, 98) = 4.01, p=0.021) and a main effect of time (F(2, 98) = 47.58, p<0.001). No significant main effect of drug group was found (F(1, 49) = 0.89, p=0.351). To

explore the interaction, Bonferroni corrected post-hoc tests were used and revealed that the ketamine group had significantly higher depression ratings at baseline than the lidocaine group (p=0.041, d= 0.60). Significant reductions in depression scores were found between baseline and mid-infusion for the ketamine (p<0.001, d=1.39) and lidocaine (p<0.001, d=0.81) groups, as well between baseline and post-infusion for the ketamine (p<0.001, d=0.98) and lidocaine (p<0.001, d=0.96) groups.

Baseline and One-week follow-up: A 2X2 mixed ANOVA, looking at baseline and 1-week follow-up scores, showed that there was a no significant interaction between drug group and time (F(1, 52) = 0.44, p=0.512) and a significant effect of time (F(1, 52) = 21.16, p<0.001) reflecting a reduction in depression NRS scores from baseline to the one-week follow-up. No significant main effect of drug group was found (F(1, 52) = 1.90, p=0.174).

Figure 2 Group Means for depression NRS scores of ketamine and lidocaine patients at each study time point. Bars represent standard errors.



Bonferroni corrected post hoc tests comparing between group differences at acute time points (baseline, mid-infusion, post-infusion). *= p <0.05, **= p< 0.01, ***= p < 0.001

3.5 Drug Effects (table 7)

Table 7 Group means (sd) for the drug effects NRS and post-hoc significance data comparing between-group differences at each study time point (baseline, mid-infusion, post-infusion)

		Ketamine	Lidocaine	Significance
Dizziness	Baseline	3.67 (3.10)	3.18 (3.36)	
	Mid-Infusion	**5.87 (3.11)**	**2.36 (3.17)**	**b****
	Post-Infusion	3.04 (2.35)	2.13 (2.47)	
Drowsiness	Baseline	4.29 (3.14)	3.65 (3.30)	
	Mid-Infusion	**6.52 (3.06)**	**4.55 (3.24)**	**b***
	Post-Infusion	3.61 (2.71)	3.87 (3.37)	
Depression	Baseline	**5.83 (3.32)**	**4.53 (3.01)**	**a***
	Mid-Infusion	1.71 (2.56)	2.24 (2.59)	
	Post-Infusion	2.52 (3.41)	1.83 (2.35)	
	Follow-up	3.88 (3.26)	3.03 (3.22)	
Nausea	Baseline	2.67 (2.63)	1.88 (2.98)	
	Mid-Infusion	1.61 (2.04)	1.64 (2.87)	
	Post-Infusion	0.96 (1.36)	1.97 (2.95)	
Visual Distortions	Baseline	3.13 (3.49)	2.09 (2.95)	
	Mid-Infusion	**3.23 (2.69)**	**1.58 (2.57)**	**b***
	Post-Infusion	1.7 (2.06)	1.1 (1.69)	

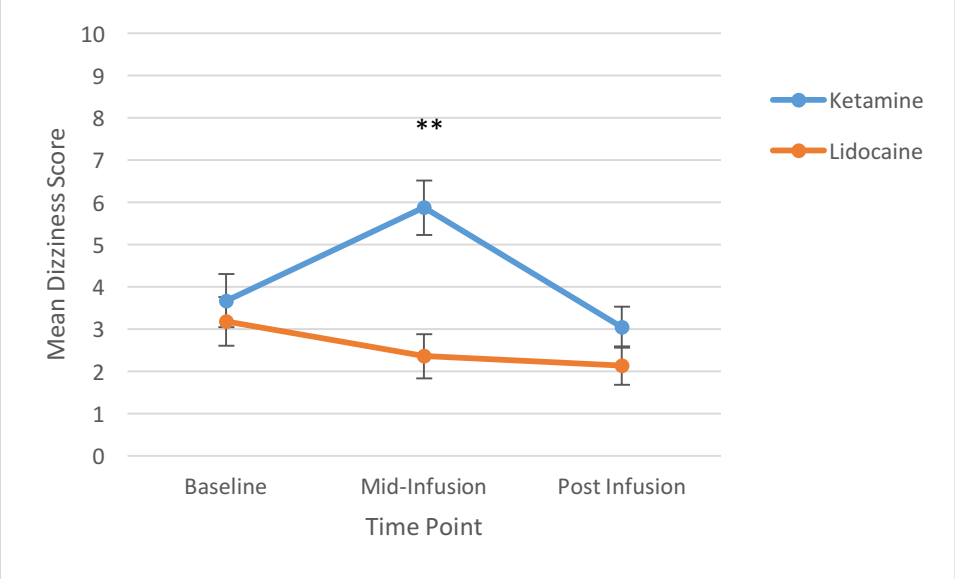
Out of Body Feeling	Baseline	1.58 (2.93)	1.24 (2.56)	
	Mid-Infusion	1.78 (2.94)	0.76 (1.94)	
	Post-Infusion	1.09 (2.13)	0.97 (2.21)	
Mental Confusion	Baseline	2.58 (3.23)	2.12 (3.10)	
	Mid-Infusion	3.13 (3.24)	1.18 (2.29)	
	Post-Infusion	1.91 (2.39)	0.9 (1.58)	
Feel Drug Effect	Mid-Infusion	**6.96 (3.08)**	**3.70 (2.91)**	**b*** **
	Post-Infusion	3.74 (1.98)	2.83 (2.96)	
High	Mid-Infusion	**6.13 (3.01)**	**1.3 (2.01)**	**b*** **
	Post-Infusion	**2.48 (1.73)**	**1.2 (2.11)**	**c*** **
Dislike Drug Effect	Mid-Infusion	1.74 (2.32)	0.58 (1.25)	
	Post-Infusion	1.78 (2.63)	0.83 (2.23)	
Liking Drug	Mid-Infusion	4.78 (2.97)	2.94 (3.29)	
	Post-Infusion	4.39 (3.13)	2.97 (3.19)	
Wanting More Drug	Mid-Infusion	2.65 (3.37)	2.00 (3.22)	
	Post-Infusion	2.00 (3.05)	2.14 (3.27)	

Bonferroni corrected post hoc tests comparing between group differences at acute time points (baseline, mid-infusion, post-infusion). *= p <0.05, **= p< 0.01, ***= p < 0.001
a = baseline b =mid-infusion c= post-infusion

3.5.1 Dizziness (figure 3)

A 2X3 mixed ANOVA, showed a significant interaction between drug group and time ($F(2, 100) = 5.30$, $p=0.006$) and a main effect of time ($F(2, 100) = 6.38$, $p=0.002$). No significant main effect of drug group was found ($F(1, 50) = 0.01$, $p=0.947$). Bonferroni corrected post-hoc tests revealed that the ketamine group felt significantly dizzier than the lidocaine group at mid-infusion ($p= 0.005$, $d= 0.82$). In addition, the ketamine group showed a significant increase in ratings of dizziness from baseline to mid-infusion ($p= 0.005$, $d= 0.71$).

Figure 3 Group means for dizziness scores of ketamine and lidocaine patients at each study time point. Bars represent standard errors.

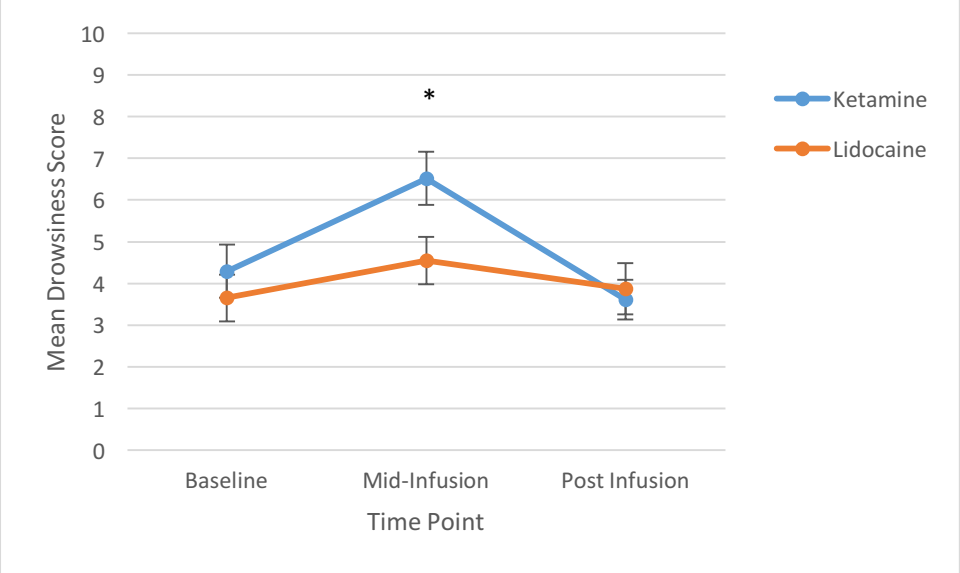


Bonferroni corrected post hoc tests comparing between group differences at acute time points (baseline, mid-infusion, post-infusion). *= p <0.05, **= p< 0.01, ***= p < 0.001

3.5.2 Drowsiness (figure 4)

A 2X3 mixed ANOVA showed that there was a trend towards a significant interaction between drug group and time ($F(2, 98) = 2.81$, $p=0.065$) and a significant main effect of time ($F(2, 98) = 9.11$, $p<0.001$). No significant main effect of drug group was found ($F(1, 49) = 1.94$, $p=0.170$). To explore the trend towards an interaction Bonferroni corrected post-hoc tests were carried out. Tests revealed that the ketamine group felt significantly drowsier than the lidocaine group at mid-infusion ($p=0.03$, $d=0.64$) and that the ketamine group showed a significant increase in ratings of drowsiness from baseline to mid-infusion ($p=0.045$, $d=0.84$).

Figure 4 Group means for drowsiness scores of ketamine and lidocaine patients at each study time point. Bars represent standard errors.

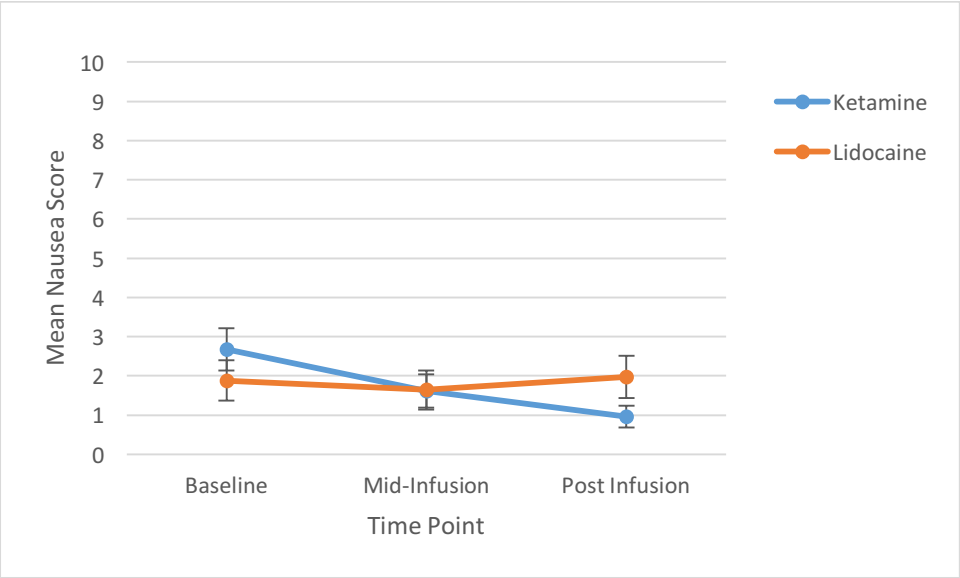


Bonferroni corrected post hoc tests comparing between group differences at acute time points (baseline, mid-infusion, post-infusion). *= p <0.05, **= p< 0.01, ***= p < 0.001

3.5.4 Nausea (figure 5)

A 2X3 mixed ANOVA showed a significant interaction between drug group and time ($F(2, 98) = 4.60$, $p=0.012$ and a significant main effect of time ($F(2, 98) = 3.24$, $p=0.40$). No significant main effect of drug group was found ($F(1, 49) = 0.01$, $p=0.952$). Bonferroni corrected post-hoc tests revealed that the ketamine group had a significant reduction in ratings of nausea from baseline to post-infusion ($p=0.005$, $d=0.72$).

Figure 5 Group means for nausea scores of ketamine and lidocaine patients at each study time point. Bars represent standard errors.

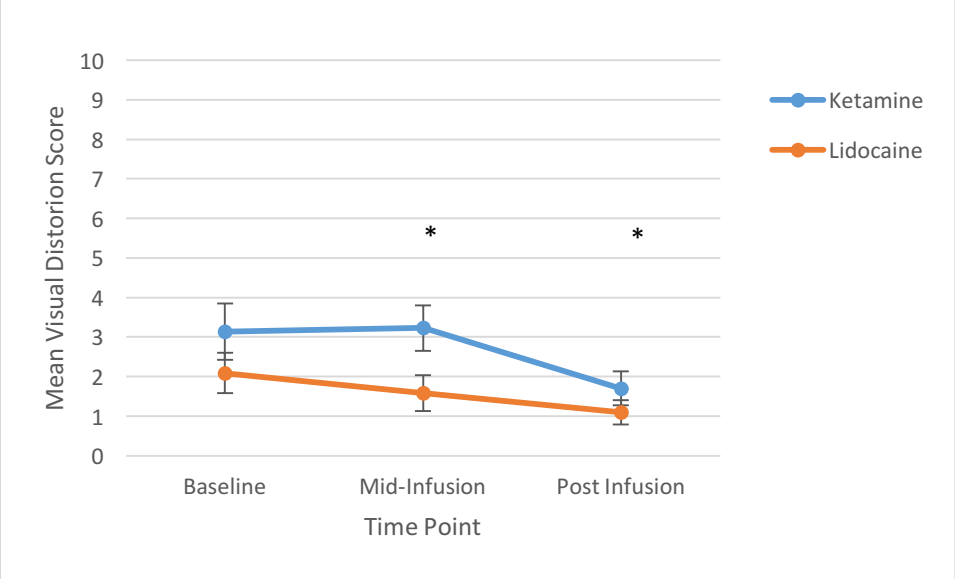


Bonferroni corrected post hoc tests comparing between group differences at acute time points (baseline, mid-infusion, post-infusion). *= p <0.05, **= p< 0.01, ***= p < 0.001

3.5.6 Visual Distortion (figure 6)

A 2X3 mixed ANOVA, showed a significant interaction between drug group and time ($F(2, 98) = 5.94$, $p=0.004$) and a significant main effect of time ($F(2, 98) = 11.37$, $p<0.001$). No significant main effect of drug group was found ($F(1, 49) = 1.22$, $p=0.275$). Bonferroni corrected post-hoc tests revealed that the ketamine group experienced significantly more visual distortions at the mid-infusion time point ($p=0.025$, $d=0.66$) and significantly more visual distortions at the post-infusion time point ($p=0.040$, $d=0.60$) than the lidocaine group.

Figure 6 Group means for visual distortion scores of ketamine and lidocaine patients at each study time point. Bars represent standard errors.



Bonferroni corrected post hoc tests comparing between group differences at acute time points (baseline, mid-infusion, post-infusion). *= p <0.05, **= p< 0.01, ***= p < 0.001

3.5.6 Out of Body Experience

A 2X3 mixed ANOVA showed no significant interaction between drug group and time ($F(2, 98) = 0.71$, $p=0.470$ and no significant main effect of time ($F(2, 98) = 0.76$, $p=0.470$) or drug group ($F(1, 49) = 1.56$, $p=0.218$).

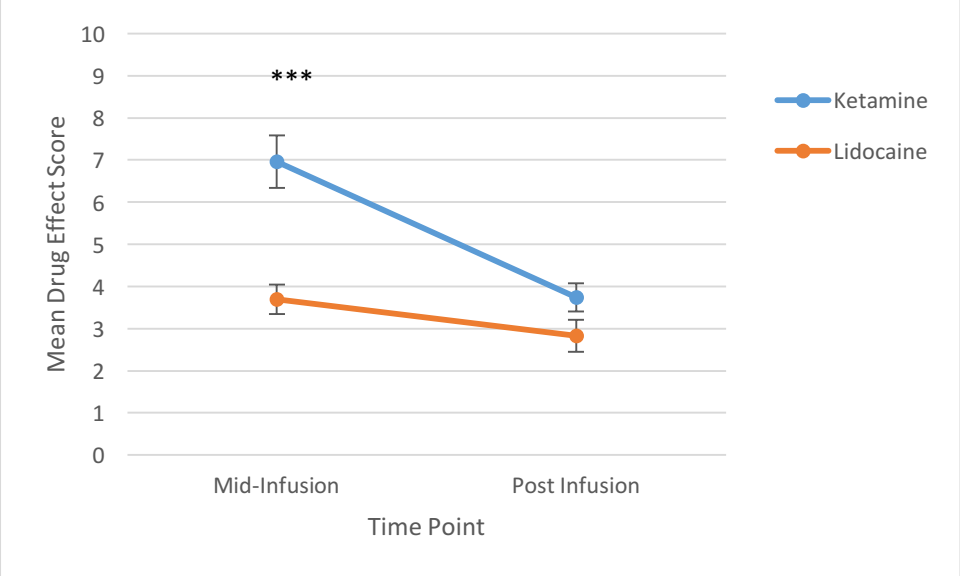
3.5.7 Mental Confusion

A 2X3 mixed ANOVA showed no significant interaction between drug group and time ($F(1.74, 3.67) = 1.64$, $p=0.203$). There was a significant main effect of time ($F(1.74, 3.67) = 3.86$, $p=0.030$) and drug group ($F(1, 49) = 5.73$, $p=0.021$). The main effect of time reflected a slight decrease in mean mental confusion scores post-infusion. The main effect of drug group reflected higher ratings of mental confusion in the ketamine group.

3.5.8 Feeling an effect of the drug (figure 7)

A 2X2 mixed ANOVA, looking at mid-infusion and post-infusion scores, showed a significant interaction between drug group and time ($F(1, 49) = 8.65$, $p=0.005$). There was a significant main effect of time ($F(1, 49) = 29.06$, $p<0.001$) and drug group ($F(1, 49) = 13.84$, $p=0.001$). Bonferroni corrected post-hoc tests showed that the ketamine group experienced a significantly greater feeling of a drug effect at the mid-infusion time point ($p<0.001$, $d= 1.29$) than the lidocaine group. Significant reductions in feeling a drug effect from mid-infusion to post-infusion were found for both the ketamine ($p<0.001$, $d=1.24$) and lidocaine ($p<0.001$, $d=0.30$) groups.

Figure 7 Group means for feeling a drug effect scores of ketamine and lidocaine patients at each study time point. Bars represent standard errors.



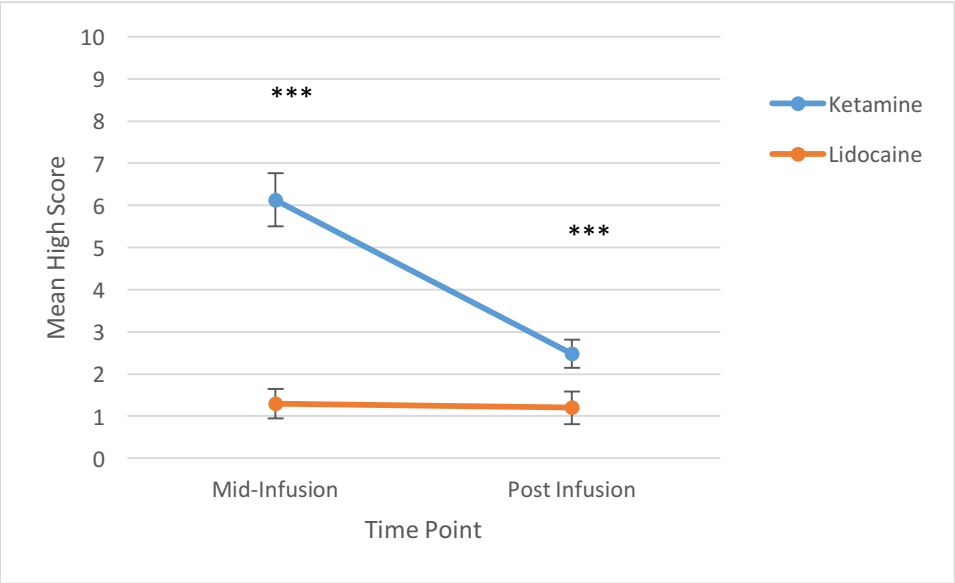
Bonferroni corrected post hoc tests comparing between group differences at acute time points (baseline, mid-infusion, post-infusion). *= p <0.05, **= p< 0.01, ***= p < 0.001

3.5.9 Feeling High (figure 8)

A 2X2 mixed ANOVA showed a significant interaction between drug group and time ($F(1, 49) = 20.95$, $p<0.001$). A significant main effect of time ($F(1, 49) = 37.06$, $p<0.001$) and drug group ($F(1, 49) = 35.64$, $p<0.001$) was found. Bonferroni corrected post-hoc tests revealed that the ketamine group experienced a significantly

greater feeling of being high than the lidocaine group, at the mid-infusion time point (p<0.001, d=1.82) and the post-infusion time point (p=0.001, d= 0.97). The ketamine group also showed a significant reduction in feeling high from mid-infusion to post-infusion (p<0.001, d=1.25).

Figure 8 Group means for feeling high drug effect scores of ketamine and lidocaine patients at each study time point. Bars represent standard errors.



Bonferroni corrected post hoc tests comparing between group differences at acute time points (baseline, mid-infusion, post-infusion). *= p <0.05, **= p< 0.01, ***= p < 0.001

3.5.10 Disliking the Drug Effects

A 2X2 mixed ANOVA, showed no significant interaction between drug group and time (F(1, 49) = 0.91, p=0.345). no significant main effect of time (F(1, 49) = 0.07, p=0.795) or drug group (F(1, 49) = 3.45, p=0.069) were found.

3.5.11 Subjective Ratings of Liking the Drug

A 2X2 mixed ANOVA showed that there was no significant interaction between drug group and time (F,(1.69, 71.28) = 0.84 p=0.418). There was no significant main effect of time (F(1.69, 71.28) = 0.28, p=0.435) but a significant main effect of drug group was found (F(1, 48) = 5.59, p=0.023) reflecting higher ratings of liking the drug effect in the ketamine group.

3.5.12 Wanting More of the Drug

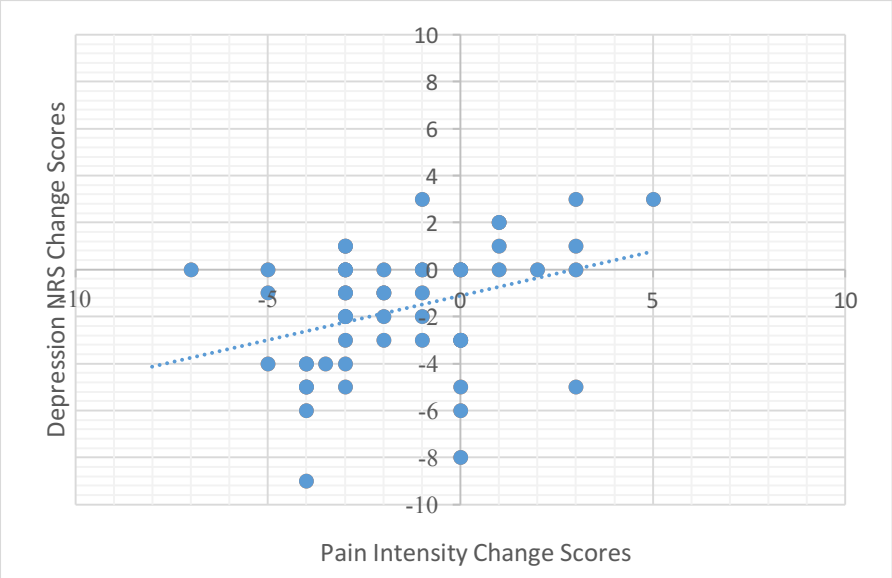
A 2X2 mixed ANOVA showed that there was no significant interaction between drug group and time ($F(1, 48) = 2.26$, $p=0.140$) and no significant main effect of time ($F(1, 48) = 1.48$, $p=0.229$) or drug group ($F(1, 48) = 0.53$, $p=0.088$) was found

3.6 Correlations - Pain and Depression Measures

3.6.1 Lidocaine group (Figure 9)

No significant correlations were found between change scores (baseline and 1-week follow-up) in pain intensity or pain interference and change scores in mood measures (HADS, PHQ-2, depression NRS). A significant correlation was found between pain distress and depression NRS change scores (r_s =0.400, p=0.043).

Figure 9 Lidocaine group: Correlation between Pain Intensity and Depression NRS Change Scores, (n=31)



3.6.2 Ketamine group (Figure 10)

A significant correlation was found between pain intensity change scores and HADS anxiety change scores (r_s =0.447, p=0.037) and pain interference and HADS anxiety change scores (r_s =0.467, p=0.029). A significant correlation was also found

between pain intensity change scores and the depression NRS change scores (r_s =0.509, p=0.016).

Figure 10a. Ketamine group: Correlation between Pain Intensity and HADS Anxiety Change Scores, (n=24)

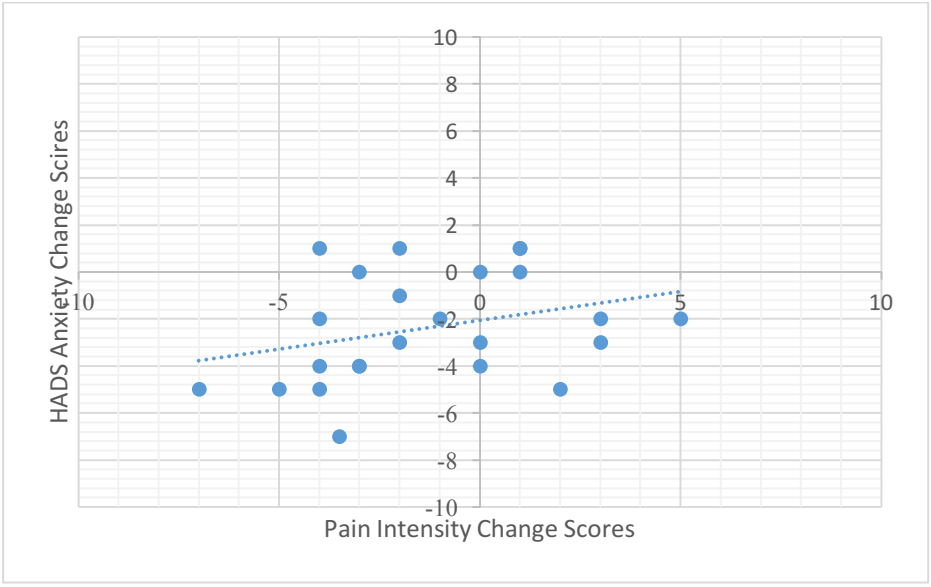


Figure 10b. Ketamine group: Correlation between Pain Interference and HADS Anxiety Change Scores, (n=24)

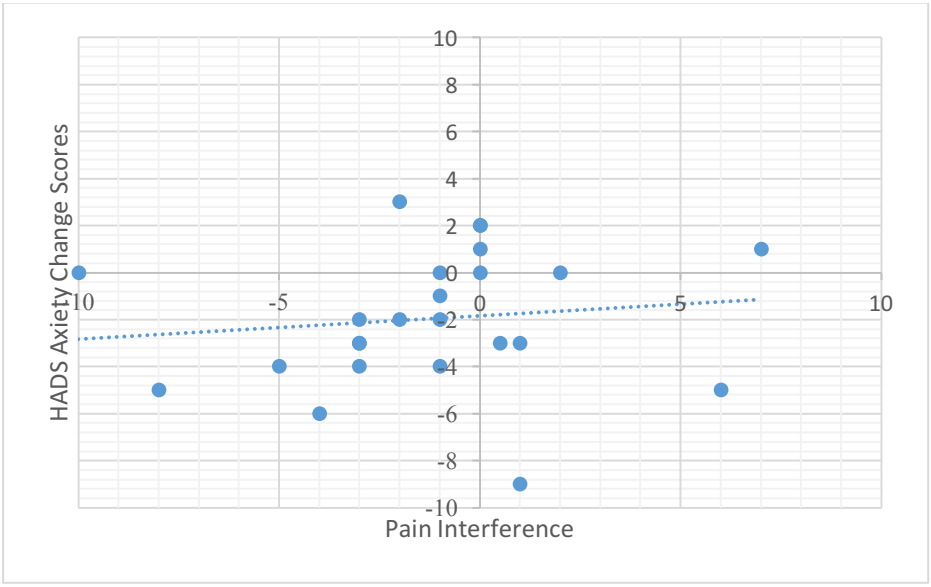
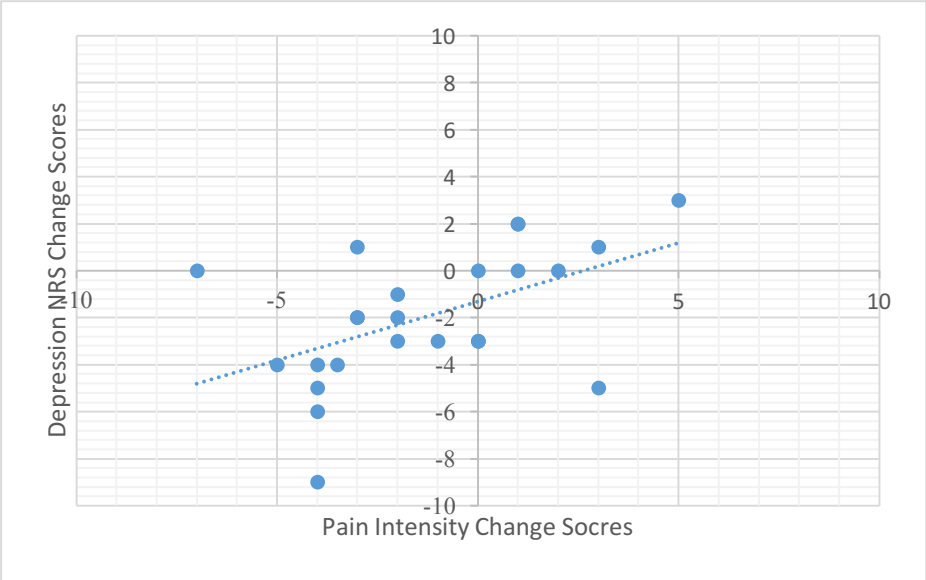


Figure 10c. Ketamine group: Correlation between Pain Intensity and Depression NRS Change Scores, (n=24)



4. Discussion

This study compared the effects of ketamine and lidocaine, in chronic pain patients on pain, mood and subjective drug effects. Both ketamine and lidocaine produced significant reductions in ratings of pain intensity and distress at the acute phase (baseline, mid-infusion and post-infusion). At the one-week follow-up, all three pain ratings (intensity, distress and interference) were significantly reduced relative to baseline. No group differences were seen at the follow-up. However, ketamine reduced pain intensity at the acute phase of treatment (mid-infusion and post-infusion) more than lidocaine.

Data from the mood measures presented a mixed picture. PHQ-2 and depression NRS data showed a significant reduction in scores at the one-week follow-up for both drug groups. However, HADS depression data did not show any significant changes, for either drug group, at any time-point. HADS anxiety scores were reduced from baseline to one-week follow-up in both drug groups. Depression

NRS ratings were acutely reduced in both ketamine and lidocaine (baseline, mid-infusion, post-infusion) but were higher in the ketamine group at baseline.

Regarding subjective drug effects, during the infusion, the ketamine group felt significantly more 'high', felt a greater sensation of a drug effect, liked the drug effect more, and felt more mentally confused than the lidocaine group. Additionally, the ketamine group experienced higher levels of visual distortions, dizziness, and drowsiness than the lidocaine group. This is in line with the known psychedelic and sedative effects of ketamine (Aan Het Rot et al., 2012, Blier et al., 2012).

4.1 Pain

Both drugs significantly reduced participants pain on all three indices measured (intensity, distress, interference). Ketamine produced a greater reduction in pain intensity, during the infusion, than lidocaine. However, at the one-week follow-up, no group differences were found indicating a similar impact in reducing participants pain between the two treatments at this time point. Indeed, a large number of studies have shown that ketamine is associated with significant pain relief during infusions (Hocking & Cousins, 2003; Nourozi et al. 2010; Finch et al., 2009). Given the design of our study, we were unable to investigate how long these effects were sustained for after the one-week follow-up. However, it appeared that the greater level of pain relief, reported at mid-infusion and post-infusion time-points, in the ketamine group was not sustained at the one-week follow-up. A meta-analysis by Niesters et al., (2013) suggested that to induce sustained analgesia, in patients with complex regional pain syndrome, a high frequency of infusions is needed (e.g. several infusions over 4-14 days). In the current study, patients were given infusions of ketamine for between 30 minutes to one hour in frequencies of every two-to-three

months. As such, further study will be needed to establish standards for routine treatment regimes.

Reductions in pain intensity reported at the one-week follow-up, for both drugs, was modest (ketamine mean pain intensity change score = -1.31; lidocaine mean pain intensity change score = -1.67). Thus, for both drugs, the pain relief benefits were small at the one-week time-point. However, during the one-week follow-up phone call seven ketamine participants and nine lidocaine participants stated that while they had not yet fully experienced the benefit of their infusion, based on previous experience with these treatments, they expected to experience a continued reduction in pain over the next one-to-two weeks. Thus, the study's one-week follow-up period may have been too short to assess the full benefits that the participants expected to gain from the treatment.

4.2 Depression

The results from this study show a mixed picture with regards to the effects of ketamine treatment on mood. Improvements in scores of depressed mood were found across both drug groups when looking at PHQ-2 and depression NRS data. However, this effect was not found when looking at the HADS depression data. Additionally, correlation analyses indicated that, for both ketamine and lidocaine patients, reductions in pain intensity scores were associated with reductions in depression NRS. Interestingly these correlations were not present for either the PHQ-2 scores or the HADS depression scores.

The lack of consistency in findings on measures of depression in the current study may further highlight the challenges of assessing mood in this population. Both the PHQ-2 and depression NRS ask broad questions regarding depressed mood.

However, the HADS depression scale was developed with the purpose of being used in a physical health setting. Indeed, a major methodological challenge in studying depression, in chronic pain populations, is measure choice. The HADS was chosen as the most suitable measure, and the PHQ-2 and depression NRS was chosen to provide generalizability of results to studies investigating the antidepressant and reinforcing properties of ketamine. One possible explanation for the discrepancy in the results may be that the PHQ-2 and Depression NRS lack specificity when used with this population. That is, given the small number of items, which broadly ask about depressed mood, alongside the presence of chronic pain, increases or reductions in scores may be inflated. Thus, results from the PHQ-2 and Depression NRS may also be measuring changes that are linked with changes in pain presentation. As such, scores from these measures should be interpreted with caution.

Given that ketamine has potent anti-depressant properties in depressed individuals, we aimed to explore ketamine's effects on mood in chronic pain patients. Secondary analysis, looking specifically at the group of participants who scored in the clinically significant range for depression on the HADS, indicated no significant differences between either drug group at the one-week follow-up. Interestingly, group frequencies showed that six out of the 12 lidocaine participants who scored in the clinically significant range at baseline, either fell in the borderline range (N=4) or normal range (N=2) at one-week follow-up. Conversely, out of the nine ketamine patients who scored in the clinically significant range only one moved to the borderline range at the one-week follow-up. Thus, a tentative interpretation of this may be that the ketamine group had less of a response, with regards to improvement in mood, than the lidocaine group, and statistical analyses lacked the power to confirm this. One explanation for this may be that the frequency and

duration of ketamine treatment received at the study site were not high enough to show an impact on participant's mood.

Research has shown that in the treatment of refractory depression, with ketamine, infusions three times a week over the course of 14-days have a median time of relapse of 18-days among the group of participants who responded to the treatment (Murrough et al., 2013). Thus, ketamine treatment for pain, depression or both co-morbidly may require maintenance dosing to maintain a response to the drug. However, given the lack of standardized protocol in treating pain and/or mood disorders with ketamine, further study will be necessary to establish treatment regimes.

Overall, these findings do not indicate that ketamine has specific antidepressant effects in a chronic pain setting. Tentative interpretation of results indicates that improvements in mood were observed in both ketamine and lidocaine groups. Thus, general improvements in quality of life (i.e. greater participation in social activities), as a result of pain relief, may have led to the improvements in depressed mood.

Additionally, the majority of participants in our study did not meet the criteria at baseline for clinically significant depression (HADS depression scores) so are very different from those with treatment-resistant depression who respond to the antidepressant effects of ketamine. Thus, one would not expect to see an effect in those who do not present as depressed at baseline.

4.3 Anxiety

There was a significant decrease in HADS anxiety scores from baseline to one-week follow-up for both drug groups. Correlation analyses indicated an

association between a reduction in both pain intensity and interference scores (baseline and one-week follow-up) with a reduction in HADS anxiety scores for the ketamine group. Indeed, several clinical studies have suggested that ketamine may have significant anxiolytic effects (Salvador et al., 2009; Zarate et al., 2006; Taylor et al., 2018). Thus, very tentatively, a possible direction for future research may be to explore the effects of ketamine on anxiety in the chronic pain population.

4.4 Subjective Drug Effects

Analysis indicated that the ketamine and lidocaine groups showed different ratings on some of the subjective drug effects NRS. The ketamine group felt significantly drowsier and dizzier than the lidocaine group at mid-infusion and had higher overall ratings of mental confusion. All measures returned to baseline levels at the post-infusion time-point indicating the short-lived nature of these side effects.

With regard to perceptual symptoms, the ketamine group experienced significantly stronger visual distortions at the mid-infusion time-point than the lidocaine group. This is in line with the expected side effect profile of ketamine (Aan Het Rot et al., 2012, Blier et al., 2012). However, mid-infusion means (ketamine M=3.23, SD= 2.69) indicate that these effects were mild which may reflect the relatively low doses administered at the study site.

The ketamine group experienced a much stronger ‘drug effect’ and felt more ‘high’ than the lidocaine group. In addition to this, the ketamine group on average liked the effects of the treatment more than the lidocaine group. Thus, given the acute reinforcing effects of ketamine in humans and animals, these effects were expected. Studies with healthy volunteers have also shown that ketamine increases subjective ratings of feeling ‘high’ (Krystal et al., 1999) and that these relate to its

abuse potential. However, in this study, participants average ratings of 'wanting more drug' were low at both mid-infusion and post-infusion. These findings may suggest that the ketamine treatment group are unlikely to seek the drug outside of the pain clinic for its reinforcing effects. Thus, the treatment offered at the study site may have a low abuse potential and chronic pain patients may react differently to healthy volunteers administered ketamine in a controlled study (cf. Morgan et al., 2004).

4.5 Methodological Considerations

Firstly, recruitment proved to be more challenging than expected. In particular, the population of patients being treated with the drug ketamine was smaller than initially anticipated. In addition to this, a high drop out rate was experienced throughout the study due to patients reporting that they were in too much pain to participate. Thus, we were unable to recruit the target number of 40 participants per group. As a result, the statistical analyses may have been underpowered therefore increasing the chance of Type II error.

The fact that a high proportion of the data violated assumptions of normality should be noted. Transformation of data did not better approximate normality. Where possible non-parametric tests were carried out. However, due to there being no non-parametric equivalent of a mixed ANOVA it was decided that researchers would carry out mixed ANOVAs in conjunction with secondary Mann-Whitney U tests as a means of checking the effects observed in the ANOVAs. Thus, the increased risk of Type 1 error associated with the large number of statistical analyses undertaken needs to be considered as a limitation.

The one-week follow-up phone call was not conducted in the same environment as the acute phase of the study. In addition to this, all questions were asked verbally by researchers at the one-week follow-up, whereas during the acute phase of testing participants were able to read the questions as they were being asked. This may have affected how participants responded to the self-rating measures at this time-point.

Perhaps the greatest methodological challenge in this study was measuring mood in the context of chronic pain. The HADS was chosen as the most practical measure for use in this population given its development for specific use in a physical health setting. However, given the HADS unstable factor structure (Coyne and van Sonderen 2012; Cosco et al. 2012) it remains problematic for use in research. Further to this, we used two further measures of mood (PHQ-2; depression NRS). These measures were chosen because of their past use in studies of the antidepressant and reinforcing effects of ketamine and their brevity. Having measures that could be completed quickly was important so the research would have minimal impact on the clinical team at the study site. However, given the lack of consistency in findings between the mood measures, these results need to be interpreted with caution. Indeed, further studies to validate the use of these measures, in this population is warranted. Further to this, these findings highlight the complexity and challenges of making accurate diagnoses of depression in this population.

Finally, the population of patients accessed at the study site varied considerably regarding age range, diagnoses, current medications and day-to-day functioning. Thus, there were many external factors which may have influenced the results which were difficult to control for.

4.6 Directions for Future Research

Future research should aim to conduct a similar study with a more comprehensive follow-up regime. This would allow researchers to gain a greater understanding of how long the effects of the treatment last. Future research should continue to look at the possibility of the treatment of co-morbid mood disorder and chronic pain. However, the mood measurement paradigm should be expanded to include a more comprehensive study of this area. Indeed, the development of new measures which are suitable for the diagnosis of depression in the chronic pain population is essential. Currently, there is a dearth of research in this area, and it is important to continue to explore treatment options for this group of patients. In particular, to carry out studies with larger sample sizes and more power.

4.7 Clinical Implications

The present study has several clinical implications. Firstly, subjective effects showed that the ketamine group felt significantly more intense drug effects, feeling more high and liking the effects of the drug more than those who were treated with lidocaine. Given the abuse potential of ketamine, this needs to be taken into consideration when treating people with ketamine. However, both the ketamine and lidocaine groups scored on average very low on the NRS ‘wanting more of the drug' indicating that the population being studied was unlikely to seek the drug for use outside of the clinic.

Secondly, the results of the study tentatively add to the evidence base for the efficacy of the drug ketamine in treating chronic pain. However, it is clear that

further comprehensive follow-up of the impact of the treatment is needed. In particular, how long effects are sustained for and how the dosing regime effects this.

Finally, the impact of ketamine treatment on mood in this population remains unclear. Thus, it is important that this is evaluated in clinical practice. Use of depression measures should be treated with caution, and the need for research to develop new measures is warranted.

4.8 Summary

In summary, the findings described here provide an exploratory analysis of the use of ketamine in the treatment of chronic pain. The findings tentatively suggest ketamine treatment reduced symptoms of chronic pain. Additionally, the study adds to the evidence base in describing ketamine's symptom profile and highlights how the patients in the study population responded to the drug. In particular, feeling high and liking the drug effects. Thus, providing important information for clinicians who are considering prescribing the drug. Finally, concerning ketamine's potential effects on mood in this population, the current study has highlighted the need for further research. In particular, for this research to include rigorous follow-up processes and careful choice of measures to evaluate treatment impact.

References

Aan Het Rot, M., Zarate, C. A., Charney, D. S., & Mathew, S. J. (2012). Ketamine for depression: where do we go from here?. *Biological Psychiatry*, *72*, 537-547.

Abdallah, C. G., Averill, L. A., & Krystal, J. H. (2015). Ketamine as a promising prototype for a new generation of rapid-acting antidepressants. *Annals of the New York Academy of Sciences*, *1344*, 66-77.

Azari, P., Lindsay, D. R., Briones, D., Clarke, C., Buchheit, T., & Pyati, S. (2012). Efficacy and Safety of Ketamine in Patients with Complex Regional Pain Syndrome. *CNS Drugs*, *26*, 215-228.

Banks, S., & Kerns, R. (1996). Explaining high rates of depression in chronic pain: A diathesis-stress framework. *Psychological Bulletin, 119*, 95–110.

Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., & Krystal, J. H. (2000). Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry*, *47*, 351-354.

Bjelland, I., Dahl, A.A., Haug, T.T., Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale an updated literature review. *Journal of Psychosomatic Research, 52,* 69-77.

Blier, P., Zigman, D., & Blier, J. (2012). On the safety and benefits of repeated intravenous injections of ketamine for depression. *Biological Psychiatry*, *72*, 11-12.

Blumer, D., & Heilbronn, M. (1982). Chronic pain as a variant of depressive disease: The pain-prone disorder. *The Journal of Nervous and Mental Disease, 170*, 381–406.

Bobo, W. V., Vande Voort, J. L., Croarkin, P. E., Leung, J. G., Tye, S. J., & Frye, M. A. (2016). Ketamine for treatment-resistant unipolar and bipolar major depression: critical review and implications for clinical practice. *Depression and Anxiety*, *33*, 698-710.

Bolton, J. E., & Wilkinson, R. C. (1998). Responsiveness of pain scales: a comparison of three pain intensity measures in chiropractic patients. *Journal of Manipulative and Physiological Therapeutics*, *21*, 1-7.

Bone, M., Critchley, P., & Buggy, D. J. (2002). Gabapentin in postamputation phantom limb pain: a randomized, double-blind, placebo-controlled, cross-over study. *Regional Anesthesia and Pain Medicine*, *27*, 481-486.

Breivik, E. K., Björnsson, G. A., & Skovlund, E. (2000). A comparison of pain rating scales by sampling from clinical trial data. *The Clinical Journal of Pain*, *16*, 22-28.

Caddy, C., Giaroli, G., White, T. P., Shergill, S. S., & Tracy, D. K. (2014). Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a

systematic review and meta-analysis of efficacy. *Therapeutic Advances in Psychopharmacology*, *4*, 75-99.

Chanques, G., Viel, E., Constantin, J. M., Jung, B., de Lattre, S., Carr, J., ... & Jaber, S. (2010). The measurement of pain in intensive care unit: comparison of 5 self-report intensity scales. *Pain*, *151*, 711-721.

Clements, J. A., Nimmo, W. S., & Grant, I. S. (1982). Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. *Journal of Pharmaceutical Sciences*, *71*, 539-542.

Corrsen G, Reves JG, Stanley TH (1988): Dissociative anesthesia: In: Corrsen G, Reves JG, Stanley TH, editors. *Intravenous Anesthesia and Analgesia.* Philadelphia: Lea and Febiger, 99–173

Cosco, T. D., Doyle, F., Ward, M., & McGee, H. (2012). Latent structure of the Hospital Anxiety and Depression scale: A 10-year systematic review. *Journal of Psychosomatic Research, 72*, 180–184.

Coyle, C. M., & Laws, K. R. (2015). The use of ketamine as an antidepressant: a systematic review and meta-analysis. *Human Psychopharmacology: Clinical and Experimental*, *30*, 152-163.

Coyne, J., & van Sonderen, E. (2012). No further research needed: Abandoning the

Hospital Anxiety and Depression Scale (HADS). *Journal of Psychosomatic Research, 72,* 173–174.

Dworkin, R. H., O'connor, A. B., Audette, J., Baron, R., Gourlay, G. K., Haanpää, M. L.,& Mackey, S. C. (2010, March). Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. In *Mayo Clinic Proceedings* (Vol. 85, No. 3, pp. S3-S14). Elsevier.

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39,* 175-191

Fayaz, A., Croft, P., Langford, R. M., Donaldson, L. J., & Jones, G. T. (2016). Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ open*, *6*, e010364.

Field, A. (2013). *Discovering statistics using IBM SPSS statistics*. Sage

Finch PM, Knudsen L, Drummond PD. (2009). Reduction of allodynia in patients with complex regional pain syndrome: a double-blind placebo-controlled trial of topical ketamine. *Pain, 146*, 18-25

Finnerup, N. B., Otto, M., McQuay, H. J., Jensen, T. S., & Sindrup, S. H. (2005).

Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain*, *118*, 289-305.

Fond, G., Loundou, A., Rabu, C., Macgregor, A., Lançon, C., Brittner, M., ... & Roger, M. (2014). Ketamine administration in depressive disorders: a systematic review and meta-analysis. *Psychopharmacology*, *231*(, 3663-3676.

Harrison, Y. E., Jenkins, J. A., Rocha, B. A., Lytle, D. A., Jung, M. E., & Oglesby, M. W. (1998). Discriminative stimulus effects of diazepam, ketamine and their mixture: ethanol substitution patterns. *Behavioural pharmacology*, *9*, 31-40.

Hocking, G., & Cousins, M. J. (2003). Ketamine in chronic pain management: an evidence-based review. *Anesthesia & Analgesia*, *97*, 1730-1739.

Jensen, M. P., Karoly, P., & Braver, S. (1986). The measurement of clinical pain intensity: A comparison of six methods. *Pain, 27,* 117–126.

Jensen, M. P., Karoly, P., O'Riordan, E. F., Bland, F., & Burns, R. S. (1989). The subjective experience of acute pain: An assessment of the utility of 10 indices. *The Clinical Journal of Pain, 5,* 153–159.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., & Wang, P. S. (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *Jama*, *289*, 3095-3105.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2003). The Patient Health Questionnaire-2: validity of a two-item depression screener. *Medical care*, *41*, 1284-1292.

Krystal, J. H., D'Souza, D. C., Karper, L. P., Bennett, A., Abi-Dargham, A., Abi-Saab, D., ... & Charney, D. S. (1999). Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. *Psychopharmacology*, *145*, 193-204.

Krystal, J. H., Petrakis, I. L., Limoncelli, D., Nappi, S. K., Trevisan, L., Pittman, B., & D'souza, D. C. (2011). Characterization of the interactive effects of glycine and D-cycloserine in men: further evidence for enhanced NMDA receptor function associated with human alcohol dependence. *Neuropsychopharmacology*, *36*, 701.

Krystal J. H., Petrakis I. L.,Webb E., CooneyN. L.,Karper L. P.,Namanworth S. (1998). Dose-related ethanol-like effects of the NMDA antagonist, ketamine, in recently detoxified alcoholics. *Archives of General Psychiatry, 55, 354–60*.

Lahti, A. C., Warfel, D., Michaelidis, T., Weiler, M. A., Frey, K., & Tamminga, C. A. (2001). Long-term outcome of patients who receive ketamine during research. *Biological Psychiatry*, *49*, 869-875.

Lanning, C.F., Harmel, M.H., 1975. *Ketamine anaesthesia*. Annual Review of Medicine. 26, 137–141.

McGirr, A., Berlim, M. T., Bond, D. J., Fleck, M. P., Yatham, L. N., & Lam, R. W. (2015). A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. *Psychological Medicine*, *45*, 693-704.

Mion, G., & Villevieille, T. (2013). Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). *CNS Neuroscience & Therapeutics*, *19*, 370-380.

Moore, K. (2004). A commitment to clubbing. *Peace Review*, *16*(4), 459-465.

Morgan, C. J., Mofeez, A., Brandner, B., Bromley, L., & Curran, H. V. (2004). Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose–response study. *Psychopharmacology*, *172*, 298-308.

Morley, S., Williams, A. C., & Black, S. (2002). A confirmatory factor analysis of the Beck Depression Inventory in chronic pain. *Pain, 99*, 289–298.

Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Green, C. E., Perez, A. M., ... & Charney, D. S. (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *American Journal of Psychiatry*, *170*, 1134-1142.

Murrough, J. W., Perez, A. M., Pillemer, S., Stern, J., Parides, M. K., aan het Rot, M., ... & Iosifescu, D. V. (2013). Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biological Psychiatry, 74,* 250-256.

Newport, D. J., Carpenter, L. L., McDonald, W. M., Potash, J. B., Tohen, M., Nemeroff, C. B., & APA Council of Research Task Force on Novel Biomarkers and Treatments. (2015). Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *American Journal of Psychiatry*, *172*, 950-966.

Niesters, M., Martini, C., & Dahan, A. (2014). Ketamine for chronic pain: risks and benefits. *British journal of clinical pharmacology*, *77*(2), 357-367.

Niesters, M., Martini, C., & Dahan, A. (2014). Ketamine for chronic pain: risks and benefits. *British Journal of Clinical Pharmacology, 77,* 357-367.

Nourozi, A., Talebi, H., Fateh, S., Mohammadzadeh, A., Eghtesadi-Araghi, P., Ahmadi, Z., ... & Mohebbi, A. (2010). Effect of adding ketamine to pethidine on postoperative pain in patients undergoing major abdominal operations: a double blind randomized controlled trial. *Pakistan journal of biological sciences*, *13*, 1214-1218.

Pincus, T., & Williams, A. (1999). Models and measurements of depression in chronic pain. *Journal of Psychosomatic Research, 47,* 211–219.

Reich, D. L., & Silvay, G. (1989). Ketamine: an update on the first twenty-five years of clinical experience. *Canadian Journal of Anaesthesia*, *36*, 186-197.

Romeo, B., Choucha, W., Fossati, P., & Rotge, J. Y. (2015). Meta-analysis of short- and mid-term efficacy of ketamine in unipolar and bipolar depression. *Psychiatry Research*, *230*, 682-688.

Schwartzman, R. J., Grothusen, J., Kiefer, T. R., & Rohr, P. (2001). Neuropathic central pain: epidemiology, etiology, and treatment options. *Archives of Neurology*, *58*, 1547-1550.

Shelton, K. L. (2004). Substitution profiles of N-methyl-D-aspartate antagonists in ethanol-discriminating inbred mice. *Alcohol*, *34*, 165-175.

Sigtermans, M. J., van Hilten, J. J., Bauer, M. C., Arbous, M. S., Marinus, J., Sarton, E. Y., & Dahan, A. (2009). Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain*,*145*, 304-311.

Tracey, I., & Mantyh, P. (2007). The cerebral signature for pain perception and its modulation. *Neuron, 55,* 377–391.

Treede, R. D., Jensen, T. S., Campbell, J. N., Cruccu, G., Dostrovsky, J. O., Griffin, J. W., ... & Serra, J. (2008). Neuropathic pain redefinition and a grading system for clinical and research purposes. *Neurology*, *70*, 1630-1635.

Turk, D. C., & Salovey, P. (1984). Chronic pain as a variant of depressive disease: A critical reappraisal. *Journal of Nervous and Mental Disease, 172*, 398–404.

Valentine, G. W., Mason, G. F., Gomez, R., Fasula, M., Watzl, J., Pittman, B., ... & Sanacora, G. (2011). The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [1H]-MRS. *Psychiatry Research: Neuroimaging*, *191*, 122-127.

White, P. F. (1982). Ketamine-its pharmacology and therapeutic uses. *Anesthesiology*, *56*, 119-136.

Zarate, C. A., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., ... & Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of general psychiatry*, *63*, 856-864.

Part 3: Critical Appraisal

Overview

The following critique will provide the reader with a reflection on the process of completing my DClinPsy research project. Conducting the major research project has been a challenging but ultimately rewarding experience. Over the course of the project, I have grown as a researcher, enhanced my critical thinking skills, and have found my clinical practice has significantly benefited from engaging in this process. Thus, highlighting the unique benefits and qualities that clinical training offers to those who are fortunate enough to embark on the journey. In the following review, I hope to allow the reader to gain a sense of my experiences and reflections alongside what I have gained from the experience. I will start by discussing the process of choosing a research topic. I then will provide reflections on the broader aspects of conducting the research. I then conclude with some reflections on working with individuals who live with chronic pain.

Choosing a Research Topic

Upon embarking on my training, I can remember speaking with a fellow trainee, soon after starting the course, and them telling me what research project they hoped to carry out and whom they were planning to contact to supervise it. I remember being surprised that someone had seemingly already planned out their research path but also excited to keep my options open and begin to build an image of what I would be interested in researching.

During my first year placement, I worked with several people who had been managing chronic pain for a significant number of years. I researched this area and became interested in the psychological therapies which are used to help those living with pain. I was particularly interested in the interaction between pain and mood

disorders and how closely the two were linked. I was intrigued by the wide variety of theories that attempt to explain the co-occurrence of pain and depression and the need to integrate psychological ways of conceptualising the two concepts with evidence from the field of neuroscience. Further, evidence showing how the presence of depressed mood was associated with poorer outcomes in pain management highlighted the importance of providing appropriate care to this population.

During the DclinPsy psychopharmacology teaching, I began to develop an interest in recreational substances and the fertile grounds for research that seemed to be developing around this topic. I became interested in the work of UCL's Clinical Psychopharmacology unit (CPU) and in particular the recent research which had been occurring with regards to the drug ketamine. The rapid-acting anti-depressant qualities that were being demonstrated in research intrigued me, as did the research looking into the use of MDMA and ketamine in the treatment of post-traumatic stress disorder. In response to this, I began to develop an interest in the use of these medications alongside psychotherapy to improve outcomes.

Thus, when it came to the time that we would start thinking about research projects the combination of investigating the drug ketamine within a chronic pain population appealed to me. I was interested in the previous literature which has indicated ketamine's ability to produce analgesia in patients experiencing chronic neuropathic pain, and the possible mechanisms that may underlie this. Furthermore, I had not had an opportunity to work in an adult health setting during my training. Thus, I felt that I would gain invaluable clinical and research experience through the opportunity to work within this setting.

During the development phase of the research, I had the opportunity to work with researchers from the CPU, a consultant anaesthesiologist from the study site and

a fellow trainee. This proved to be an interesting and invaluable experience. Initially, the range of perspectives allowed broad discussions about the research topic and possible areas of interest. By drawing on the expertise of my supervisors this then was able to become more focused and take shape as a research project. This period of formulating the research question and developing what we would explore was a period of the project that I particularly enjoyed. This gave me a sense of what it was like to be part of a research team conducting work in clinical settings.

NHS Ethics and the JRO

One area of particular difficulty that our project encountered was navigating the NHS ethics and UCL Joint Research Office (JRO) procedures. Indeed, this was a substantial piece of work which was further complicated by inconsistent responses from the JRO in the initial stages of our study. Unfortunately, our JRO caseworker was changed several times, and it was difficult getting a response from the JRO with regards to work that we had handed in for approval. We were told that our caseworker had left their role, or that our new caseworker was on leave. At times this was particularly frustrating. However, we found that the best method of managing our difficulties was to systematically contact the various workers we had been in contact with at the JRO to ensure that our project was being assessed. Unfortunately, as a result of these setbacks, it meant that we were unable to gain ethical approval until December 2017. On reflection, this provided me with a valuable experience into how important the administration in the early stages of a study is to the success of the research as a whole. In particular, the knock-on effect that difficulties of this nature can have on a research project. For our project, this meant a much shorter time frame for piloting the study and collecting data.

Recruitment and Sample

During the initial planning phase of the project, we put much thought into the recruitment process. This involved meeting with consultant anaesthetists, nurses and other members of staff at the study site. We anticipated that recruiting almost 80 participants into the study may be a challenge. However, it was deemed that this would be possible as we would be testing participants during their routine treatment.

Several issues were identified early on in the recruitment process. Firstly, there were not as many ketamine patients being booked into to receive this treatment as had initially been estimated. Thus, there were far fewer ketamine patients being treated on a weekly basis than lidocaine patients. In addition to this, many of the ketamine patients that were contacted did not meet the inclusion criteria. As the study moved forward, the task of getting enough participants became quite daunting.

A further complication with regards to recruitment was the high drop out rate that we experienced in our study. Although participants were often enthusiastic about the study in the preliminary phone call, on testing days many potential participants dropped out due to being to too much pain. Indeed, frequently on testing days we could have up to six people booked in for testing but due to drop-outs only test one person. Although wholly understandable, as a researcher this could be quite disheartening particularly as we approached the end of our agreed testing period.

However, when I reflect on my interactions with those who participated in this study, I am most struck by the openness, curiosity and wiliness to be a part of the project. The majority of participants I met showed a genuine curiosity in the research. There was also a wish to contribute and be part of the process of adding to the evidence base for treatments that, from conversations with many participants,

appeared to have had a real positive impact on their life. Indeed, I heard many anecdotes from participants about their journey to receiving treatment at the study site. Many participants reflected how grateful they were to be under the care of the study site. A common theme that emerged from discussions with participants was how the study site represented a 'last chance' to find a treatment that would help manage their pain.

Working at the Study Site and Coordinating with the Clinical Team

Conducting the study in a working NHS service provided a valuable opportunity to experience how researchers can carry out work while being embedded in a clinical environment. One of the highest priorities for myself as a researcher was to try and have as little of an impact on the study sites day-to-day functioning as possible. Thus, being prepared with a clear schedule for each testing day was essential. Particularly, communicating this clearly with the clinical team to manage the testing schedule in conjunction with the team's priorities for treating patients. Furthermore, we found that it was particularly important to coordinate with the nursing team and nursing assistants. Building strong working relationships with these team members was undoubtedly instrumental to the success of our work at the study site. Indeed, it was essential for us as a research team to let the staff group know about our appreciation, and this was most often shown with edible gifts.

Throughout the study, it was a pleasure to work with the team at the study site. I was grateful for the unequivocal support that the project received from all the staff members I came into contact with. Furthermore, the staff team showed a genuine interest in our study, the scientific justification for what we were doing, and a wider interest in our training and backgrounds as trainees. Many useful discussions

were had with staff members which allowed me to gain a deeper understanding of the work that the team was carrying out. However, in the planning phases of the research, these discussions allowed us to make critical adjustments to the design of our study so that the research had as little impact on the day-to-day functioning of the study site as possible.

Analysis

Moving from the testing phase to analysing and writing-up the data was an interesting shift. I had enjoyed the day-to-day of interacting with participants and staff members during the study. Once data collection had finished there was a very abrupt change in priorities. The beginning of the analysis involved focusing on minute statistical details. Many of the variables that we had planned to enter into our analysis were not normally distributed. Thus, I had to spend a significant amount of time applying transformations and exploratory analysis to the data. An added complication was that we had planned to conduct a mixed between-within subject's ANOVA, a statistical analysis that has no non-parametric equivalent. Thus, careful consultation of statistical manuals, internet forums and supervisors was utilized to make an informed decision on the best course of action. It was decided, based on the work of Field (2013), that carrying out the ANOVAs was still the most robust means of testing our data. This was based on several factors. Firstly, in samples of 40 or more with no outliers the sampling distribution is usually normal. Secondly, where possible it is preferable to carry out a robust analysis such as an F-test. Thirdly, there is no non-parametric equivalent of a mixed ANOVA. I found this a particularly challenging period of the project as there was always a feeling that more could be done, more could be read or understood to provide the best outcome for the project.

Limitations when Assessing Mood in the Chronic Pain Population

One of the greatest challenges in designing the study was deciding how we would measure mood in the chronic pain population. In particular, the tension between using measures which had been used in the previous researching looking into the antidepressant or reinforcing properties of ketamine and those that are used to measure mood in a chronic pain population. The Beck Depression Inventory (BDI) has been utilized in many studies investigating the antidepressant and reinforcing properties of ketamine. Thus, when considering comparability to these studies, it presents as a favourable measure. However, many depression measures, such as the BDI, include items which measure the prevalence of somatic and vegetative symptoms, such as sleep difficulties and health worries. Thus, these measures have been found to lack validity in a chronic pain population. Thus, we decided to utilize the Hospital Anxiety and Depression Scale (HADS) as it was the only scale that had been developed to be used in the context of medical problems. Thus, omitted somatic and vegetative items from the measure. In addition to this, we decided to employ the PHQ-2 and simple NRS that asked participants how depressed they were feeling at that moment in time. The decision to include these measures was two-fold. Firstly, because they had been used in the previous literature investigating the effects of ketamine on mood and reinforcing effects. Secondly, neither of these measures included any somatic items. In hindsight the use of these measures was problematic. In particular, the lack of specificity and broad questions employed by the measures. This was shown in the results of this study where both the PHQ-2 and Depression NRS scores were significantly reduced from baseline to one-week follow-up. However, this was not replicated with the HADS data.

Participants Reported Experiences of Chronic Pain

Living with chronic pain can be an all-encompassing experience which has significant and possibly debilitating consequences on people's lives. Treatment is often complicated by there being an unclear cause for the pain, high frequencies of poor response to treatment and psychological factors which also need to be taken into account. Indeed, patients route to diagnoses can be challenging with the lack of physiological evidence often leading to a misattribution of psychological factors, and feelings of hopelessness as patients are not responding to treatment. Further to this, patients can also undergo significant investigations and invasive treatments which further exacerbate their pain.

Over the course of the research project, I was struck by the stories that patients told me about their journey to being diagnosed. Many patients spoke of the hopelessness they felt before receiving a diagnosis, and the many professionals that they consulted before receiving treatment at the study site. In addition to this, there was often a strong sense of loss that patients had with regards to their personal life, professional life and their sense of who they were.

I can remember being struck by how prominent the feeling of difference was in participant's sense of self. Stories were often segmented into how patient's lives were before pain and then their current life. Or indeed, their past selves and present selves. I can remember one patient speaking of her previous career as a successful musician, she spoke of leading a full life characterized by exercise, travel and performance. However, since living with chronic pain she felt that the parts of herself, which used to enjoy these aspects of her life, had disappeared. She told me that she had retreated from her social network as she felt ashamed that she was no

longer able to be her former self. This led to her loosing touch with many close friends.

I was also struck by the emotional impact that listening to participant's stories had on me. Some participants were experiencing significant amounts of emotional distress, and many participants had also endured a range of challenging life events which were related to their pain. I was often left feeling hopeless about their difficulties as though I could do nothing to help them or their situation. Indeed, this was likely a communication of how the participants felt themselves. However, it also made me reflect on the position of the supporting family members and the lack of agency that may sometimes be felt when unable to help a loved one. I was able to reflect on this experience with my fellow research colleagues and team members at the study site.

During this research project, I was unfortunate enough to be in a significant accident which left me with injuries that will likely cause me some pain for years to come. Thus, I had the experience of contemplating how my life may involve managing some degree of pain whilst working with participants who were already managing life with chronic pain. This allowed me to reflect on how much one can take health and wellness for granted but also how quickly things can change for individuals.

Conclusion

In conclusion, the research project has provided a challenging and fulfilling experience from which I have learned a great deal. Although there were a number of limitations of the empirical paper which could be improved there were also strengths in the studies design and execution. The experience I gained working with both the

staff team and patients at the study site highlighted how crucial the ongoing work at the study site is. Meeting participants highlighted how complex one's experience of chronic pain is. In particular, how chronic pain can affect relationships, sense of self and well being. I was struck by the kind and sensitive nature of all the members of staff working with this patient group. In particular, the intuitive and open way of meeting patients needs. However, I was also left with a sense of the emotional demand that working within this patient group may have on the clinician.

Appendix 1: Details Regarding Each Individual's Contribution to the Joint Research Project

This thesis forms part of a joint research project with fellow DClinPsy trainee Catherine Trotman (Trotman, 2018).

Recruitment and testing were undertaken jointly by Catherine and myself. We each tested approximately half of the participants. Post-doc Dr Will Lawn conducted two testing sessions when myself and Catherine were unable to conduct testing.

Catherine investigated the effect of sub-anaesthetic doses of ketamine on cognitive functioning and so her paper includes an analysis of data from several tests of cognitive functioning (Serial Sevens, Story Recall Sub-Test of Rivermead Behavioural Memory Test and a task of Verbal Fluency). These tasks were completed by all participants but are not discussed within the current project.

The current project focused on on the effect of sub-anaesthetic doses of ketamine on pain, mood and subjective drug effects. Data was collected at three time points during patient treatment (baseline, mid-infusion and post-infusion). The current paper also collected data during a one-week follow-up phone call. This was not part of the protocol for Catherine Trotman's project.

Data was scored and entered into a database by myself and Catherine Trotman. Both empirical papers include the analysis of sample demographics and pain numerical rating scales. The current paper includes the analysis of one-week follow up data, as well as scores on measures of anxiety, depression, and subjective drug effects.

Appendix 2: NHS Ethics Approval from South Central Berkshire NHS Research Ethics Committee

Health Research Authority
South Central - Berkshire Research Ethics Committee
Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 020 7104 8057

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

06 December 2017

Prof Valerie Curran
UCL
Gower Street
London
WC1E 6BT

Dear Prof Curran,

Study title:	**Comparing the Effects of Ketamine and Lidocaine on Cognition, Pain and Mood**
REC reference:	**17/SC/0567**
Protocol number:	**N/A**
IRAS project ID:	**214864**

Thank you for your letter of 1st December 2017 responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

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

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with

before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance Proof]	1	04 October 2017
IRAS Application Form [IRAS_Form_25102017]		25 October 2017
IRAS Application Form XML file [IRAS_Form_25102017]		25 October 2017
IRAS Checklist XML [Checklist_01122017]		01 December 2017
Letter from sponsor [HRA cover letter]	1	04 October 2017
Non-validated questionnaire [Depression VAI]	1	22 April 2017
Other [Hayling Sentence Completion Task]	1	13 October 2017
Other [Spot the Word Test]	1	13 October 2017
Other [Trail Making Task]	1	13 October 2017
Other [Prose Recall Task]	1	13 October 2017
Other [Cognitive Measure N-Back]	1	13 October 2017
Other [Study Insurance Certificate]	2	14 November 2017
Other [REC Response Email]	1	20 November 2017
Participant consent form [Consent Form]	3	12 November 2017
Participant information sheet (PIS) [Participant Info]	4	12 November 2017
Research protocol or project proposal [Protocol]	1	21 June 2017
Summary CV for Chief Investigator (CI) [CI CV]	1	05 October 2017
Summary CV for student [CT CV]		04 October 2017
Summary CV for student [MK CV]		04 October 2017
Summary CV for supervisor (student research) [CV]	1	05 October 2017
Validated questionnaire [BDI]		
Validated questionnaire [PHQ-9]		
Validated questionnaire [Pain]		
Validated questionnaire [Drug Effects Questionnaire]		

Statement of compliance

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

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our RES Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/SC/0567	**Please quote this number on all correspondence**

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

Yours sincerely

Mr David Carpenter
Chair

Email: nrescommittee.southcentral-berkshire@nhs.net

Enclosures: *"After ethical review – guidance for researchers" [SL-AR2]*

Copy to: *Ms Nikkayla Dixon*

Mr Joe Mirza, UCLH NHS Foundation Trust

Appendix 3. Consent Form

IRAS ID: 214864 Version 3 (12/11/17)

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Comparing the Effects of Ketamine and Lidocaine on Cognition, Pain and Mood

Name of Researcher: Matt Knox and Catherine Trotman

Please initial box

1. I confirm that I have read the information sheet 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 or legal rights being affected. ☐
3. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐
4. I agree to a follow up phone call one week after taking part in the study ☐
5. If during the course of the research, suicidal thoughts or depression are discussed this information will be passed on to your consultant to inform your care. ☐
6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix 4. Participant Information Sheet

Comparing the Effects of Ketamine and Lidocaine on Cognition, Pain and Mood

Participant Information Sheet

(Version 4: 12/11/17) IRAS ID: 214864

We would like to invite you to take part in our research study which is a student research project that will contribute to a clinical psychology doctorate. Before you decide, we would like you to understand why the research is taking place and what it would involve for you. Please take the time to read the following information carefully, and discuss it with family, friends and your GP if you wish.

Part 1 tell you about the purpose of this study and what will happen if you take part.

Part 2 gives you more detailed information about the conduct of the study, please keep the information in case you wish to refer to it later.

This study has been reviewed by Dr Amanda C de C Williams and is sponsored by UCL as part of the Doctorate in Clinical Psychology. The ethics application has been reviewed by the South Central Berkshire Research Committee.

Part 1

What is the purpose of the study?

The purpose of this study is to investigate the psychological effects of ketamine in people with chronic pain. In particular, we are interested in how ketamine effects thinking, pain and mood. We will compare the effects of ketamine with the effects of the control condition lidocaine. Previous studies have shown both medications to be effective treatments for the management of chronic pain and we hope to add to this body of evidence by investigating their broader psychological effects.

Why have I been invited?

You are being invited because you are currently being treated for chronic pain with an infusion of either ketamine or lidocaine.

Do I have to take part?

No. It is entirely up to you to decide whether or not to take part in the study. If you do agree to take part, we will then ask you to sign a consent form. However, you are free to withdraw at any time, without giving a reason.

What are the possible benefits of taking part?

Taking part in the study will not benefit you directly, but everyone who decides to participate will contribute to scientific knowledge about chronic pain. Your participation will also contribute to the continual development of best clinical practice for the treatment of chronic pain.

Expenses and payments
No expenses or payments can be issued to participants of the study who will be receiving their normal clinical care.

What will happen if I take part and what will I have to do?
A researcher will meet with you before your infusion, go through what is involved, answer questions, and make sure you are able to take part in the study.

The study involves complete some questionnaires at three different points on the day of your infusion (before, during and after). These will ask you to rate your pain, your mood, and your response to the effects of your medication.

You should not need to stay any longer than you would do for your treatment as usual.
As part of the follow-up process you will also be asked to participate in a brief follow up phone call with you 1 week after your treatment. The researcher will ask you some questions about how things have been since your infusion and you will be asked to complete the same questionnaires as you did before. This should take around 15 minutes.

In total you will be involved in the study for around 2 weeks and we will require an extra 15 minutes in addition to the time needed for you to complete your treatment as usual.

What are the possible disadvantages or risks of taking part?
The study includes a questionnaire about your mental health. You might like to talk to someone about any issues it raises. Researches would be able to discuss this with you and make appropriate recommendations. You may also find some of the questionnaires tedious. However, we endeavour to make participation in the research as engaging as possible.

What if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information about these processes are given in Part 2.

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

Part 2 – Further Details

What will happen if I don't want to carry on with the study?
You are free to withdraw from the study at any time on the day that you participate simply by telling the researcher or a member of your clinical team that you wish to do so. Your further treatment would not be affected in any way by withdrawing from the study. Once your data has been entered into the study database, it will be anonymised and thus it would not be possible to identify your specific data.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. You can contact them by ringing on the numbers given below. If you remain unhappy and wish to complain formally you can do this by contacting the Patient Advice and Liaison service at the University College London Hospital. You can contact them by ringing 020 3

Will my taking part in the study be kept confidential?
All information which is collected about you during the course of the research will be kept confidential. If you take part in the study you will be assigned a code number that will be used to identify you on all computerised and written data. Your name, and any other identifying information, will not be attached to the information obtained from the study. All personal data will be kept securely in locked filing cabinet with access available only to members of the research team. Electronic anonymised data will be kept in password protected files and will be stored securely. Data will be kept for no more than 20 years and will then be destroyed.

What will happen to the results of the research study?
The results of this study will be reported in scientific journals and are likely to be published after the whole study finishes in 2018. You can obtain a copy of the published results by contacting us at address on the bottom of this sheet after the study has finished. You will not be identified in any report or publication resulting from this study.

Further Information
If during the course of the trial you have questions about the nature of the research, your rights as a patient, or you believe you have sustained a research related injury, or you are concerned about any aspects of the study, please contact:

Thank you for taking the time to read this information sheet

Contacts

Primary Researchers: Professor Valerie Curran (v.curran@ucl.ac.uk), Catherine Trotman (catherine.trotman.15@ucl.ac.uk), Dr Sunjeev Kamboj (Sunjeev.kamboj@ucl.ac.uk), Matthew Knox (ucjumkn@ucl.ac.uk): Address: UCL, Gower Street, London, WC1E 6BT

Consultant Anaesthesiologists: Dr Dimitry Kruglov, Dr Roman Cregg: Address: University College Hospital, 235 Euston Road, London, NW1 2BU

Patient Advice and Liaison Service

PALS can be accessed by visiting the office at either UCH Monday to Friday, or the NHNN Wednesday to Friday 9am – 4pm or by telephone (020 3447 3042)

Appendix 5. Hospital Anxiety and Depression Scale (HADS)and Patient Health Questionnaire-2 (PHQ-2)

Removed Due to Copyright

Appendix 6. Pain Numerical Rating Scales

HOW ARE YOU FEELING?

Instructions: **On each scale, please circle the number that best describes how you feel RIGHT NOW.**

Pain intensity

No pain	0	1	2	3	4	5	6	7	8	9	10	Extremely intense pain

Pain distress

Not distressing	0	1	2	3	4	5	6	7	8	9	10	Extremely distressing

Pain interference

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Interferes with everything

Appendix 7. Subjective Drug Effects Numerical Rating Scales

HOW ARE YOU FEELING?

Instructions: **Like we did before, on each scale, please circle the number that best describes how you feel RIGHT NOW**

Dizziness

Not at all	0	1	2	3	4	5	6	7	8	9	10	Extremely

Feel a drug effect

Not At All	0	1	2	3	4	5	6	7	8	9	10	Extremely

Drowsiness

Not at all	0	1	2	3	4	5	6	7	8	9	10	Extremely

"High"

Not At All	0	1	2	3	4	5	6	7	8	9	10	Extremely

Nausea

Not at all	0	1	2	3	4	5	6	7	8	9	10	Extremely

Dislike the effects of the drug

Not At All	0	1	2	3	4	5	6	7	8	9	10	Extremely

Visual distortion

Not at all	0	1	2	3	4	5	6	7	8	9	10	Extremely

Like the effects of the drug

Not At All	0	1	2	3	4	5	6	7	8	9	10	Extremely

Out of body experiences

Not at all	0	1	2	3	4	5	6	7	8	9	10	Extremely

Want more of the drug

Not At All	0	1	2	3	4	5	6	7	8	9	10	Extremely

Mental confusion

Not at all	0	1	2	3	4	5	6	7	8	9	10	Extremely

Depressed

Not at all depressed	0	1	2	3	4	5	6	7	8	9	10	Extremely depressed

Appendix 8. The Alcohol Use Disorders Identification Test (AUDIT) and the Highest Level of Educational Attainment

Removed Due to Copyright

Appendix 9. Secondary Analysis, Mann-Whitney U Test Results

1. **Pain**

Acute Effects

Pain Intensity

Exploratory analysis of the pain intensity change score data was conducted using Mann–Whitney U tests. Results showed that the ketamine group had a significantly larger reduction in pain intensity from the lidocaine group from baseline to mid-infusion *U=178.000, z=-3.56, p<0.001, r=0.47*. This difference was also significant when comparing the change scores from baseline to post-infusion *U=215.000, z=-2.3516, p=0.019, r=0.32*.

Baseline and one-week follow-up

Pain Intensity

Exploratory non-parametric analysis, using Mann–Whitney U tests, of the base line and one-week-follow-up pain intensity change score data showed no significant differences between the ketamine group and the lidocaine *U=402.000, z=0.515, p=0.607, r=0.07.*

Pain Interference

Exploratory analysis, using Mann–Whitney U tests, of the baseline and one-week-follow-up pain interference change score data showed no significant differences between the ketamine group and the lidocaine *U=413.000, z=0.929, p=0.353, r=0.01.*

2. **Drug Effects**

Dizziness

Exploratory Mann-Whitney U analysis of change scores showed that the lidocaine treatment group showed a significantly higher increase in subjective feelings of dizziness, than the ketamine group, when comparing baseline and mid-infusion scores *U=578.000, z=3.364, p<0.001, r=0.45*

Drowsiness

Exploratory Mann-Whitney U tests showed that the ketamine group almost met significance for having greater reduction in drowsiness when comparing baseline scores and post-infusion scores *U=240.000, z=-1.902, p=0.057.*

Depression NRS

Acute: Exploratory analysis, using Mann–Whitney U tests of change score data showed that the ketamine group had a significantly larger reduction in self reported depression than the lidocaine group from baseline to mid infusion *U=249.500, z=-2.19, p=0.029, r=0.29*. No other change scores were significant.

Baseline and one-week follow-up: No significant differences were found between the ketamine and lidocaine groups when comparing pre-infusion data and the data collected at the one-week follow-up when using Mann-Whitney U tests.

Nausea

Exploratory Mann-Whitney U tests revealed that participants in the ketamine group were found to have a significantly greater reduction in feelings of nausea when

comparing baseline and post-infusion scores *U=217.500, z=-2.482, p=0.013, r=-0.34.*

Visual Distortion

Exploratory Mann-Whitney U tests revealed that the ketamine group showed a significantly greater reduction in visual distortions when comparing the baseline and post infusion scores *U=252.500, z=-1.9629, p=0.050, r=-0.26.*

Feeling a Drug effect

Exploratory Mann-Whitney U tests revealed that the ketamine group showed a significantly greater reduction in feeling a drug effect, than the lidocaine group, when comparing results from the mid-infusion and post-infusion time points *U=168.000, z=-2.898, p=0.004, r=-0.40.*

Feeling High

Exploratory Mann-Whitney U tests revealed that ketamine patients also showed a significantly greater reduction in self-reported feelings of being high on the treatment, when comparing mid-infusion and post-infusion data *U=149.000, z=-3.534, p<0.001, r=-0.49*.