The Cognitive Effects of Sub-Anesthetic Ketamine and Lidocaine in individuals with a diagnosis of Chronic Pain

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D.Clin.Psy Thesis (Volume 1), [2020]

University College London

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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: Georgia Halls

Date: 11/6/20

Overview

This thesis explores the cognitive effects of ketamine in both individuals with chronic pain and treatment-resistant depression. Part one presents a literature review that investigates the cognitive effects of ketamine in individuals with a diagnosis of treatment-resistant depression. The results suggested that when changes in depression symptomology were controlled for, both acute and repeated ketamine infusions were not significantly associated with cognitive performance.

Part two presents an empirical paper exploring the cognitive and analgesic effects of sub-anaesthetic ketamine and lidocaine on individuals with a diagnosis of chronic pain. It also investigates the associations between changes in mood, pain and cognitive functioning. Acute ketamine produced greater acute pain relief than lidocaine and impaired working and episodic memory more than lidocaine. Decreased pain was strongly correlated with improved mood in both treatment groups. The analgesic effects of ketamine are in-keeping with previous research on the topic. Previous research on the cognitive effects of ketamine also found cognitive impairment in different groups of people, but the research on individuals with chronic pain is limited.

Part three is a critical appraisal of the research. It describes the process and experience of conducting the research, particularly with those who have chronic pain. This was a joint project with a fellow DclinPsy student, Joe Kibble (Kibble, 2020). See Appendix 2.3 for a breakdown of the contributions of each student.

Impact Statement

There are two major sections to this thesis. The first being a systematic review that investigated the cognitive effects of ketamine when used with individuals with a diagnosis of treatment-resistant depression. The second being a research paper on the cognitive and analgesic effects of sub-anaesthetic IV ketamine and lidocaine on individuals who have a diagnosis of chronic pain.

The literature review suggested that when changes in depression symptomology were controlled for, both acute and repeated ketamine infusions were not significantly associated with cognitive performance. This information contributes to the controversial discussion surrounding the safety of ketamine when used to treat psychiatric conditions, and deepens the knowledge of the acute cognitive side effects associated with ketamine use. It also furthers the understanding of the tightly knit relationship between cognitive functioning and mood.

The findings of the study indicated that both ketamine and lidocaine provide acute pain-relief for individuals with chronic pain, whilst ketamine provided a greater degree of pain relief. This information, once disseminated to the clinic, could impact on staff views of the treatment options they offer. Moreover, ketamine and lidocaine as treatment options for chronic pain are not widely available. Further research needs to be done into the efficacy of this as a treatment option in order to work towards it becoming more accessible.

The more that is understood about ketamine when used medically can also contribute to our knowledge about when ketamine is used recreationally or therapeutically. A deeper understanding of the cognitive impairments that ketamine is associated with could inform drug and alcohol service interventions or the more recent psychedelic-assisted psychotherapy interventions.

However, as the study results suggest that ketamine is linked to cognitive impairments, it is important this is further understood and considered when offering this as a treatment option. If clear links are made, then patients need to be aware of this effects so that they can make a fully-informed decision.

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Acknowledgements

I would like to thank my friends and family for being so supportive, understanding and caring. In particular, my D.Clin.Psy cohort, who are now my close friends, were incredibly encouraging, helpful and knowledgeable. Their intelligence and compassion continually amazed me.

I'm very appreciative of my partner Ross, who was unrelentingly supportive, flexible and kind. I'm also eternally grateful for my dog Monty, who was my main source of therapy, distraction and cuddles. He made sure I finished work on time and kept the all-important work-life balance.

Thank you to my supervisors Prof H. Valerie Curran and Dr Sunjeev Kamboj. Their guidance and expertise have been invaluable.

Thank you to Consultant Anaesthesiologist Dr Dmitry Kruglov and all the staff at the Pain Management Centre. Your friendliness, humour and knowledge made data collection significantly easier and more enjoyable. The clinic are very lucky to have such an amazing team of individuals.

Finally, I'd like to thank those who participated in the study. Their willingness to participate in the study even when in significant pain was inspiring and an amazing reminder of the resilience and strength of people.

Part 1: Literature Review

A Systematic Review of the Cognitive Effects of Ketamine with patients diagnosed with Treatment-Resistant Depression

1.1 Abstract

Background and Aim: Since ketamine was first trialed as an anti-depressant in 2000, it has been growing in popularity due to its fast-onset anti-depressant effects. The cognitive effects of ketamine when self-administered recreationally or administered acutely to healthy participants have been examined in many studies (Morgan & Curran, 2006). However, it is unclear how ketamine may impact cognitively on people with treatment-resistant depression, as mood and cognitive functioning are closely linked. The aim of this paper is to review current understanding of the cognitive effects of ketamine when used to treat individuals with treatment-resistant depression.

Method: A systematic review of PsycINFO, Embase and OVID MEDLINE was conducted to find studies that utilised cognitive assessments during ketamine infusions in patients with treatment-resistant depression. Seventeen articles were identified and met the inclusion criteria for the review. There were three types of articles included that explored the cognitive effects of ketamine. Firstly those that used sub-anaesthetic ketamine infusions, secondly those used sub-anaesthetic ketamine infusions plus an anaesthetic agent, and thirdly those that used anaesthetic ketamine infusions. Included studies were quality assessed using the Cochrane Risk of Bias 2 and Risk of Bias in Non-Randomised Studies – of Interventions.

Results: Of the 17 articles included, 10 found that when changes in depression symptomology were controlled for, both acute and repeated ketamine infusions were not significantly associated with cognitive performance. Three of the papers found that baseline cognitive functioning could predict individual's improvements in mood following ketamine administration. Methodological variations meant a wide range of cognitive domains were explored, using various

ketamine dosages and assessment intervals. There was considerable variability in the quality of the research.

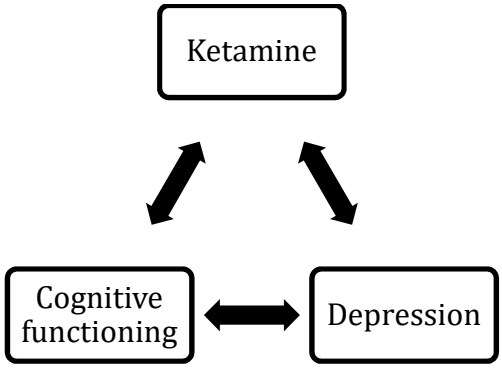
Conclusions: Methodological heterogeneity rendered findings inconclusive as to whether ketamine affects cognitive functioning within a treatment-resistant depression population. The relationship between ketamine's impact on mood and subsequent cognitive changes are important to assess. Further high quality research needs to be done to fully document the cognitive side-effects of ketamine infusions so that patients and their doctors can make fully informed decisions.

2.0 Introduction

This review will begin by providing a short summary as to what ketamine is, before delving into the triad relationship between ketamine and depression, depression and cognitive functioning, and finally cognitive functioning and ketamine (see Figure 1).

Figure 1

A visual depiction of the inter-relationships between ketamine, cognitive functioning and depression



2.1 Uses of Ketamine

Ketamine is a high-affinity, non-competitive N-methyl-D-Aspartate (NMDA) glutamate receptor antagonist that was first synthesised in 1962, and added to the WHO Essential Medicines List as an intravenous anaesthetic in 1985. Ketamine is the most widely used anaesthetic in veterinary medicine, especially equine medicine. This has led to it becoming known within the general population as the “horse tranquiliser”. Ketamine also has very important analgesic and anaesthetic properties in human medicine.

2.1.1 Medical Uses

Ketamine has been used medically for 58 years and is an indispensable drug in many areas including remote medical locations, such as disaster situations, conflict zones and rural areas in the developing world, where running water, electricity and resuscitation equipment are scarce. This is because part of its unique safety profile as an anaesthetic is that it does not depress breathing or lower blood pressure, therefore, it is considered a lower risk anaesthetic in certain situations.

Ketamine is commonly used today in specialist anaesthesia and analgesia, such as paediatrics. In particular, it is seen as an ideal agent within emergency paediatrics (Holloway et al., 2000; McGlone et al., 1998) as it has a rapid onset, maintains spontaneous respiration, causes a lack of response to painful stimulus, has rapid recovery, and minimal side effects (Doyle, 2002).

Alongside its anaesthetic effects, ketamine also has a potent analgesic effect, both acutely and chronically. It is believed to prevent "wind-up" which is where neurones in the spinal cord become sensitised to painful stimuli (Sunder et al., 2008). Anaesthetic dosages (>0.5mg/kg) of ketamine have been shown to significantly reduce levels of pain in individuals with complex regional pain syndrome for periods of up to six months (Keifer et al, 2008). A single IV infusion of ketamine has been shown to relieve on-going pain in patients with peripheral nervous system disease-related pain (Backonja et al., 1994). Nikolajsen et al. (1996) examined the impact of ketamine compared to a placebo on stump and phantom limb pain to find that ketamine increased pressure pain thresholds and reduced the previously mentioned "wind-up like" pain.

Ketamine is used predominantly as an anaesthetic and analgesic, but it is also being investigated as a treatment option for alcohol misuse (McAndrew et al., 2017), as well as more recently, for Alzheimer's disease (Lozupone et al., 2018).

2.1.2 Non-Medical Uses of Ketamine

When used medically, ketamine is predominantly used in liquid form, and administered via infusions, sub-cutaneous injections or intramuscularly. However, when used recreationally, it is primarily in a powder form, which is usually snorted. Recreationally, ketamine is rarely taken as a tablet orally, as this way ketamine is metabolised differently, which produces a more sedative and less psychedelic experience. At lower doses, ketamine produces hallucinations, mild dissociations and distortion of time and space. In low doses, its euphoric and dissociative effects are sometimes referred to as "k-land," whilst at larger doses, ketamine can produce what is commonly known as the "k-hole", where the individual feels as if they have detached from reality. There are long-term health conditions associated with chronic use of recreational ketamine, including ulcerative cystitis (a lower urinary tract irritation) (Shahani et al., 2007), kidney dysfunction (Chu et al., 2008) and intense abdominal pain (Muetzelfeldt et al., 2008).

2.2 Ketamine as a treatment for Treatment Resistant Depression

In more recent years, ketamine has been investigated as a treatment option for Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD). MDD is the experience of a distinct alteration in mood that represents a change from previous functioning, and must include either depressed mood or loss of interest/pleasure (The *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed.; *DSM–5*; American Psychiatric Association, 2013). Anti-depressants are commonly prescribed as part of the treatment package for TRD, however, not all individuals respond to the course of prescribed anti-depressants, with some research finding that 50-60% of individuals are non-responsive (Fava, 2003). When there is an inadequate response to a variety of different anti-depressants, which are of

adequate doses and duration, it is considered TRD (Su et al., 2017). However, a consistent definition of TRD in terms of how many anti-depressants and psychological treatments must be tried and failed before it is considered TRD has not yet been widely agreed upon.

Due to TRD being a common clinical presentation, researchers have been looking to find alternative treatments. As previously mentioned, ketamine works as an antagonist at the NMDA glutamate receptor, whereas most approved anti-depressant medications primarily target the brain monoamine systems (Matthew et al., 2008). The first placebo-controlled, double-blinded trial of ketamine on MDD found a significant improvement in depressive symptoms within 72 hours (Berman et al., 2000), whereas other anti-depressant medications can take 4-6 weeks. This rapid anti-depressant effect of ketamine has been replicated in many studies, with reviews finding that a single low-dose ketamine infusion exerted a rapid and sustained anti-depressant effect on samples of TRD patients (Corriger & Pickering, 2019; Seranfini et al., 2014; Xu et al., 2016).

2.3 The Cognitive Performance Effects of Depression

For the purpose of this paper, when cognitive functioning or performance is referenced, it is referencing the way in which the brain acquires, processes, stores and retrieves information (Lawlor, 2002). The neurocognitive domains include execution function (e.g., planning, decision making, working memory, inhibition etc.), language, learning and memory, social cognition, complex attention and perceptual-motor function (The *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed.; *DSM–5*; American Psychiatric Association, 2013). However, it must be kept in mind that these neurocognitive domains are not rigidly separate, they

can overlap, and the completion of cognitive tests frequently requires the activation of multiple domains.

2.3.1 Acute Effects

Depression can impact on a wide range of cognitive functions and is reported to have an unspecific impairment profile, rather than only certain domains being affected (Majer et al., 2004; Reppermund et al., 2009). For example, it has been found to moderately impair a range of cognitive domains such a visual-motor sequencing, executive function, memory and attention (Paradiso et al., 1997; Reppermund et al., 2009). It has been theorised that as there is no relationship between level of depression and level of impairment, cognitive deficits are not merely a by-product of mood disturbances, but there is a core cognitive impairment that exists independently of mood difficulties and can be seen as a trait marker of acute depression (Reppermund et al., 2009). One narrative review of the literature reported that multiple studies found that these cognitive impairments exist independently of differences in age, depression severity, depression subtype or motivation (Austin et al., 2001).

2.3.2 Chronic Effects & Recovery/Remission of Depression

Cognitive impairment is often associated with depression, but the literature is not in agreement as to whether these impairments are state and/or trait characteristics. When examining the chronic cognitive effect of depression, Halvorsen et al. (2011) assessed the verbal learning (California Verbal Learning Test) at baseline and again nine years later of 112 clinically depressed (CDs), previously depressed (PDs), and never depressed (NDs) participants. At follow-up, irrespective of which group individuals were in, there was a significant decline in recall measures over time. CDs, PDs and NDs showed the same pattern of verbal

memory performance over time. Their results suggest that individuals with mild to moderate unipolar depression may not be significantly affected by verbal memory impairments in the long-term.

However, when individuals with either first episode of MDD or recurrent depression were cognitively assessed (using tests such as digit span, story recall, cancellation, divided attention task, searching tasks etc.) on admission and one-week prior to discharge to an in-patient unit, there was no significant changes in memory, attention and executive function scores, with up to 57% still scoring as cognitively impaired (defined as one standard deviation below the mean score of the normative samples according to age and gender) (Reppermund et al., 2009). Whilst Majer et al. (2004) also found that on discharge, individuals with acute major depression or bipolar disorder still had cognitive functioning within the abnormal range, but less distinct. This suggests that perhaps either cognitive impairments are not significantly related to depression symptomology but a trait marker, or cognitive functioning takes longer to return to premorbid functioning after experiencing acute depression.

It has been reported that even when patients with remitted MDD are assessed, they are still impaired compared to controls. This has been demonstrated on tasks of rapid visual information processing, psychomotor performance, spatial working memory, verbal memory and verbal fluency (Neu et al., 2005; Weiland-Fielder et al., 2004). In one study, once residual depressive symptoms were controlled for, significant deficits in sustained attention still remained (Weiland-Fielder et al., 2004). Whilst Hammar et al., (2003) found that individuals with MDD had an impaired performance for effortful, but not automatic, visual search performance. This impairment remained six months later, despite significant improvements in their

depression scores. This continues to suggest that cognitive impairments are not significantly related to depression symptomology but a trait marker.

2.4 Electroconvulsive Therapy and TRD

Electroconvulsive therapy (ECT) is used to treat some psychiatric illnesses, such as depressive illnesses, prolonged mania and catatonia (NICE, 2014). It is common to receive a general anaesthetic during ECT as this beneficially impacts on medical aspects of the seizure (Boylan et al., 2000; Galvez et al., 2015a) as well as cognitive side effects (Ingram et al., 2007). Ketamine has been used as an alternative anaesthetic within ECT for decades, but more recently it is being used alongside ECT specifically due to its previously mentioned rapid anti-depressant effect (Seranfini et al., 2014).

2.4.1 The Cognitive Effects of ECT

ECT can be seen as a controversial treatment, partially due to its cognitive effects. For example, it has been found to negatively impact on an individual's memory, especially declarative memory which affects the ability to learn new information (Rami-Gonzalez et al., 2001). Furthermore, ECT patients have been found to have significant impairments in visual and visuospatial memory during the ECT, and at one week follow-up (Falconer et al., 2010). They also found that most impairments were gone one month after the ECT, except for spatial recognition which still remained significantly impaired. This memory impairment after ECT could be due to indiscriminate activation or saturation of glutamate receptors, therefore disrupting the hippocampal plasticity involved in memory (Anderson et al., 2017). Ketamine can stimulate glutamate release and increases glutamate functioning, therefore it may counteract some of the disruptive effects of ECT on hippocampal function.

2.5 Cognitive Effects of Ketamine

2.5.1 Acute Effects

The majority of studies investigating ketamine's application in the medical and psychiatric field do not assess the cognitive side-effects, and if they do, they are commonly assessed in the short-term, such as during the infusion or immediately post-infusion (Short et al., 2018). In healthy participants, ketamine has been shown to acutely impair working memory (Honey et al., 2003). Morgan et al. (2004) also found that acute doses of ketamine (0.4mg/kg and 0.8mg/kg) were associated with dose-related impairments in episodic memory (Prose Recall subtest of the Rivermead Behavioural Memory Battery, Source Memory task), semantic memory (Speed of Comprehension test), and response inhibition (Hayling task) immediately after infusion. Studies have also found that visual perception, planning skills (Honey et al., 2003) and verbal fluency (Fu et al., 2005) are acutely effected by ketamine.

Despite there being several systematic reviews on the topic, conclusions have been varied. For example, one systematic review of the use of ketamine for depression reported various short-term negative cognitive side-effects, assessed through cognitive tasks, such as memory, poor concentration, confusion and cognitive impairment (Short et al., 2018). Whilst another proposed a neuroprotective cognitive effect of ketamine for individuals diagnosed with MDD, TRD or bipolar disorder, specifically related to improvements in visual, simple and complex memory (Lee et al., 2016).

On top of this, it must be kept in mind that there is substantial evidence of the impact of mood on cognitive functioning (Gotlib & Joormann, 2010) and therefore the separation between ketamine's effects on cognitive functioning, compared to ketamine's effect on mood which then in turn affects cognitive functioning, is not simple to distinguish.

2.5.2 Chronic Effects

Long-term cognitive deficits associated with ketamine use have been inconsistently reported. Frequent ketamine use has been associated with impairments in visual recognition, spatial working memory and executive functioning, although only visual recognition and spatial working memory negatively correlated with changes in ketamine use (Morgan et al., 2009; Stewart et al., 2001). Whilst in other studies, executive dysfunction was not found in frequent ketamine users (Liang et al., 2013; Morgan et al., 2004b), but verbal and visual memory impairments were, which persisted in ex-users, which was defined as those who had been abstinent for more than 30 days (Liang et al., 2013). Although, on a longer-term scale, these memory impairments were not found in a group of ex-ketamine users after one year, suggesting that the results could be reversible (Morgan et al., 2010). One theory is that these inconsistencies may be due to chronic ketamine users also taking other drugs which may also cause cognitive impairment (Liang et al., 2013; Morgan et al., 2010).

2.6 Rationale

There have been various systematic reviews looking at the general side effects of ketamine (Morgan & Curran, 2006; Short et al., 2018), and the role of ketamine in treatment-resistant depression (Serafinni et al., 2014); however, we are unaware of any that purely focus on the cognitive effects of ketamine infusions, whether this is used alone or alongside ECT in people with a diagnosis of TRD. A systematic review was chosen, rather than a meta-analysis, as on exploration it became apparent that the studies were not sufficiently similar in terms of design, outcome measures, dosages and assessment intervals, in which case the Cochrane manual suggests a systematic review.

Therefore, in this review I address the question:

1. What are the effects of intravenous ketamine infusions on cognitive functioning in people with a diagnosis of treatment-resistant depression?

3.0 Method

3.1 Eligibility Criteria

This review included studies published up until September 2019 that met the following inclusion criteria: (1) Humans aged 18 to 80 years old; (2) To have a diagnosis of bipolar or unipolar depression, specifically treatment-resistant depression (3) To be given intravenous ketamine either sub-anaesthetically as a stand-alone intervention, sub-anaesthetically alongside an another anaesthetic drug prior to ECT or as a full-anaesthetic prior to ECT (4) The article reported cognitive outcome measures (5) The study was published in a peer-review journal (6) The study was reported in English. Studies meeting these criteria were subjected to formal quality and relevance assessment.

3.2 Search Strategy

To identify studies meeting the inclusion criteria, PsycINFO, OVID Embase and OVID MEDLINE were searched for entries containing the following terms (or synonyms): (1) ketamine (2) treatment-resistant depression and (3) cognitive (see appendix 1.1)

3.3 Risk of bias Assessment for Individual Studies

For the non-randomised controlled trials (non-RCT), quality was assessed using the 0Cochrane Risk of Bias in Non-Randomised Studies – of Interventions

(ROBINS-I) and for randomised controlled trials (RCT), the Cochrane Risk of Bias 2 (RoB 2) was used. Studies were evaluated according to their risk of bias.

For both the RoB 2 and ROBINS-I, the classifications they look at are (1) deviations from the intended interventions, (2) missing outcome data, (3) measurement of the outcome, and the (4) selection of the reported result. Whilst RoB 2 additionally looks at the randomisation process, and the ROBINS-I additionally examines (5) confounding variables, (6) selection of participants and (7) the classification of interventions.

Each study was rated using set questions (see appendix 1.2) to assist in rating each of the classifications previously mentioned in the above paragraph (one to four for RoB 2 and one to seven for ROBINS-I), and from that an overall risk of bias category was reported (See table 1) with comments as to why that category was given.

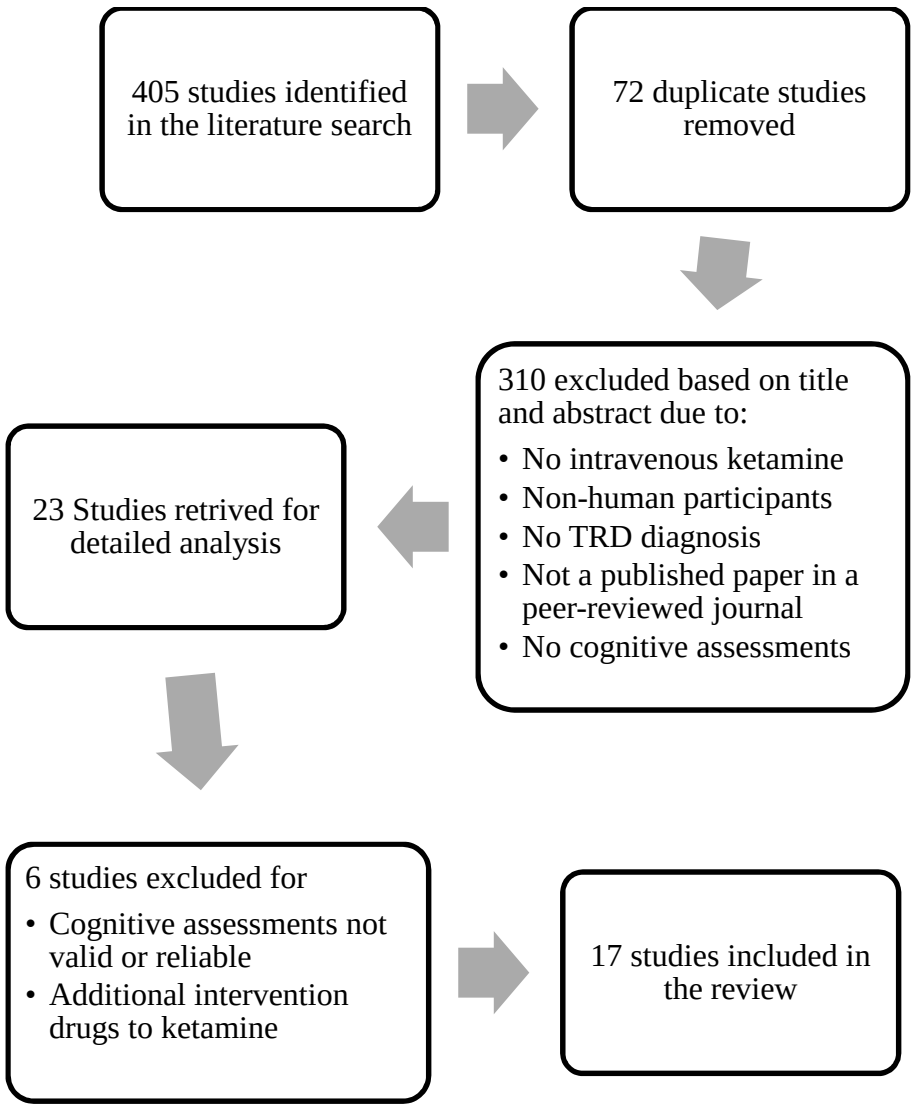
The ROBINS-I has five different levels of risk that can be allocated to each assessment area, these levels are (1) low risk, (2) moderate risk, (3) serious risk, (4) critical risk or (5) no information. The RoB 2 has three different levels of risk that can be allocated to each assessment area, these levels are: (1) low risk, (2) some concerns about risk or (3) high risk of bias. The overall "score" is the highest rate they receive. For example, if a study receives all 'low risk' ratings for each classification, then their overall score would be "low", however, if the majority receive low risk classifications ratings but also one 'high', then their overall score would be "high". Between raters, there was a 76% agreement. We resolved discrepancies through discussion.

4.0 Results

4.1 Study Selection Process

Figure 2

A flowchart of the study selection process



4.2 Characteristics and Demographics of Included Studies

4.2.1 Sub-anaesthetic Ketamine Infusion Alone

There were seven studies (two RCTs and five non-RCTs) that met inclusion criteria and used sub-anaesthetic ketamine infusions (see table 1). These ranged in dosages from 0.2mg/kg to 0.5mg/kg and administered between one and six repeated infusions during the study. For the two RCTs included, one used an active control of midazolam (n=43; Murrough et al., 2015) and one had a placebo control (n=71; Chen et al., 2018). The five non-RCTs had no control group (Diamond et al., 2014; Murrough et al., 2014; Shiroma et al., 2014, Zheng et al., 2019; Zhou et al., 2018).

4.2.2 Sub-anaesthetic Ketamine Infusion + Anaesthetic Agent

Five RCT studies explored the cognitive effects of sub-anaesthetic doses of ketamine (<0.5mg/kg) when combined with another anaesthetic agent (see table 1). The latter included propofol (Anderson et al., 2017; Chen et al., 2017; Zhang et al., 2018; Zhong et al., 2016), or thiopentone (Loo et al., 2012). The number of sessions ranged from four to ten infusions. Zhong et al. (2016) compared the effects of 0.5mg/kg ketamine combined with propanol against both 0.8mg/kg ketamine alone and 0.8mg/kg propofol alone. Three of the studies used saline solution as a placebo control (Anderson et al., 2017; Chen et al., 2017; Loo et al., 2012) and the remaining study, Zhang et al. (2018), also used propofol as an active control, similar to Zhong et al. (2016).

4.2.3 Anaesthetic Ketamine Infusion

Six studies (five RCTs and one non-RCT) compared anaesthetic doses of ketamine (>0.8mg/kg-2mg/kg) to an active control, consisting of thiopentone (Yoosefi et al., 2014), propofol (Fernie et al., 2017; Zhong et al., 2016), methohexital

(Rasmussen et al., 2015; Ray-Griffith et al., 2017) or etomidate (McDaniel et al., 2006) (see table 1). The number of infusions varied from an average of five sessions to an average of eight for one study. Zhong et al.'s (2016) study is repeated in both sections 3.2.2 and 3.2.3 due to having one condition of sub-anaesthetic ketamine infusion plus anaesthetic agent as well as an anaesthetic ketamine infusion only condition.

Table 1

Participant characteristics in Included Studies

Author/ Year/ Country	Study Design	N (ketamine)	Male (%)	Age Mean (range)	Dosage (mg/kg) (no. infusions)	Cognitive Domains Tested	1st or 2nd Aim	Cognitive Tests	ECT	Results
Sub-Anaesthetic Ketamine Infusions Alone										
Chen, M., et al. (2018) China	PCR DB BS	71 (24, 23)	52%	47 (21-65)	0.5 or 0.2 (1)	ATT RC WM	1	WMGNG	No	Sig. relationship between changes in depressive symptoms and performance on go/no-go task. No sig. group effect, no time effect, and no group×time interaction effect for cognitive function among baseline, Day 3, and Day 14 among the three groups. Performance on the go/nogo task improved sig. compared with baseline in the ketamine group.
Diamond et al. (2014) UK	OLS NC NB BS	28 (28)	57%	47	0.5 (3 or 6)	M	1	AMI-SF, AFT, SRT, ECT-MQ	No	Not powered sufficiently to detect differences in autobiographical memory.
Murrough, J. W., et al. (2014) USA	SA OLS NC NB WS	25 (25)	60%	49 (21-70)	0.5 (1)	ATT PS VerL VisL WM	1	MCCB (TMT, WMS, HVLT, L-NS, DS, BVMT, CF, CPT-IP)	No	Sig. effect of ketamine on delayed recall at 40 minutes, but not learning or category fluency. Lower levels of baseline processing speed and older age sig. associated with increased antidepressant response to ketamine.

Murrough, J. W., et al. (2015) USA	ACR DBBS	62 (47)	45.2 %	46 (21-80)	0.5 (1)	PBS PS VerL VisL WM	1	MCCB (CF, TMT, WMS, HVLT, L-NS, DS, BACS, MA)	No	When controlling for change in depression, both groups cognitive performance improved from baseline (processing speed, verbal learning, and visual learning). No sig. change to working memory or reasoning scores. No sig. effect of ketamine on cognitive performance. No sig. effect of antidepressant response on cognitive performance. Poor processing speed at baseline was associated with improved antidepressant response to ketamine.
Shiroma, P. R., et al. (2014) USA	OLS NC NB WS	15 (15)	100%	52 (23-69)	0.5 (6)	ATT PS SS M WM	1	CogState battery	No	Antidepressant response to infusions was greater among depressed subjects with lower attention at baseline, greater verbal memory and younger age of onset of depression. Significant improvement in cognitive performance (visual memory, simple working memory, complex working memory) over time after 6 infusions compared to baseline. These changes are non-sig. when change in depression accounted for. No sig difference in other cognitive domains
Zheng, W., et al. (2019) China	OLS NC NB WS	64 (64)	39.1 %	33.3 (NI)	0.5 (6)	PS M WM	1	MCCB (CF, TMT, SC, WMS, HVLT-R, BVMT-R)	No	Sig. improvements found in verbal learning at day 13, and speed of processing at day 13 and day 26, even

										when changes in depression were controlled for. Verbal learning and speed of processing were partially mediated by changes in depression score (Sobel test), suggesting that there although there was sig. improvement, this can be partly accounted for by changes in depression. No sig. association of depression change score with baseline scores of neurocognitive performance (verbal and visual learning, working memory, and speed of processing).
Zhou, Y., et al. (2018) China	SA OLS NC NB WS	84 (84)	47.6 %	34.8 (18-65)	0.5 (6)	PS M WM	1	MCCB (CF, TMT, WMS, HVLT-R, BVMT-R)	No	Compared to baseline, there were sig. improvements found in verbal learning at day 13, and speed of processing at day 13 and day 26 (depression were controlled for). Sig. indirect effects (Sobel test) between time and improvement in speed of processing and verbal learning, which were both significantly mediated by changes in depression scores. Individuals with better visual learning at baseline and without psychiatric comorbidity were more likely to obtain an antidepressant response to ketamine.
Sub-Anaesthetic Ketamine Infusions + Anaesthetic Agent										

Anderson, I. M., et al. (2017) UK	PCR Mc DB PG	79 (40)	37%	54 (>18)	0.5 (>4)	L M	1	HVLT-DR	Yes	No sig. difference between groups on the HVLT-R-DR test at any time point. Sig. advantage for the placebo group at mid-ECT for forward digit span and the end of treatment HVLT-R recognition discrimination.
Chen, Q. et al. (2017) China	PCR DB BS	127 (63)	35%	39 (18-65)	0.3 (M=7-10)	GCF M	1	WMS, MMSE	Yes	Sig. reduction in memory for the control group compared to the ketamine group. Ketamine sig. weakened the ECT-induced learning and memory impairment.
Loo, C. K., et al. (2012) Australia	PCR DB PG	51 (26)	35%	43 (NI*)	0.5 (M=9.5)	L M	1	CFT, HVLT, COWAT, SDMT, WJCO, AMI-SF	Yes	No sig. effect of ketamine on cognitive performance compared to control.
Zhang, M., et al. (2018). China	A R DB BS	77 (43)	47%	30 (NI*)	0.5 (6)	ATT PBS PS SC L WM	2	MCCB (CF, TMT, SC, CPT-IP, WMS, HVLT-R, BVMT-R, MA, MSCEITTM)	Yes	No sig. difference was found on the MCCB between the control and ketamine group. Sig time-effect for Reasoning and Problem Solving and Social Cognition but no sig group-by-time interaction effects.
Zhong, X., et al. (2016) China	A R DB BS	90 (30, 30)	40%	30 (15-67)	0.8 or 0.5 (8)	EF L M	2	WF, DSy, DS, WCST, TH, TMT, VRT	Yes	Decline in executive functioning for both groups, but sig. more severe decline in control group than ketamine group. No sig. differences in other cognitive domains.

Fernie, G. et al. (2017). UK	A R DB PG	40 (20)	45%	50 (18-75)	<2 (M= 7.88)	SRM	2	CANTAB-SRM	Yes	No sig. effect of ketamine on cognitive performance compared to control.
McDaniel, W. (2006) USA	A NR NB BS	10 (5)	NI*	46 (28-70)	1 (6)	M	1	MMSE (Short term memory item only)	Yes	After 6th treatment, ketamine group could remember sig. less items on the recall test compared to the control.
Rasmussen et al . (2014) USA	A R DB BS	38 (21)	37%	48 (NI*)	>1 (6)	GCF	2	MMSE	Yes	No sig. effect of ketamine on cognitive performance compared to control.
Ray-Griffith, S. et al. (2017) USA	A R DB BS	16 (8)	18.8 %	40.9 (NI*)	1 (M=4.9)	GCF	2	MMSE	Yes	No sig. effect of ketamine on cognitive performance compared to control.
Yoosefi, A., et al. (2014) Iran	A R DB PG	29 (15)	52%	44 (20-50)	1-2 (6)	GCF	2	MMSE	Yes	Sig. improvement in cognitive function for ketamine between baseline and last assessment, compared to control.
Zhong, X., et al. (2016) China	A R DB BS	90 (30, 30)	40%	30 (15-67)	0.8 or 0.5 (8)	EF L M	2	WF, DSy, DS, WCST, TH, TMT, VRT	Yes	Decline in executive functioning for both groups, but sig. more severe decline in control group than ketamine group. No sig. differences in other cognitive domains.

Note. WMGNG = Working memory task and go-no-go, MCCB=Matric Consensus Cognitive Battery, CF= Category Fluency, TMT= Trail Making Test, SC= Symbol Coding, WMS=Weschler Memory Scale, HVLT(-R) = Hopkins Verbal Learning Test (Revised), HVLT-DR=Hopkins Verbal Learning Test Delayed Recall, BVMT-R=Brief Visuospatial Memory Test-Revised, L-NS=Letter-number sequencing, DS=Digit Span, AMI-SF= Autobiographical Memory Interview - Short Form, AFT= Autobiographical Fluency Task, SRT=Story Recall test, ECT-MQ=ECT Memory Questionnaire, MMSE=Mini-Mental State Examination, MA=Mazes, CFT=Complex Figure Test, COWAT= Controlled Oral Word Association Test, SDMT= Symbol Digit Modalities Test, WJCO= Woodcock Johnson Cross-Out Test, WF=Word Fluency test, DSy=Digit Symbol test, WCST=Wisconsin Card Sorting Test, TH=Tower of Hanoi, VRT=Visual Regeneration test, CPT-IP=Continuous Performance Test – identical Pairs versions, BACS=Brief Assessment of Cognition in Schizophrenia, CANTAB-SRM= Cambridge Neuropsychological Test Automated Battery-Spatial Recognition Memory, MSCEITTM=Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions.

Note. Primary Aim = 1, Secondary Aim = 2

Note. ATT= Attention, EF = Executive Functioning, GCF= Global Cognitive Functioning, L= Learning, M= Memory, PBS = Problem Solving, PS = Processing Speed, RC = Response Control, SC= Social Cognition, SRM = Spatial Recognition Memory, SS = Set Shifting, VerL = Verbal Learning, VisL = Visual Learning, WM = Working Memory

4.2.4 Aims of Included Studies

For 11 of the studies included, assessing the cognitive effects of ketamine was a primary aim whilst for six studies it was a secondary aim (see table 2)

4.2.5 Assessment Intervals

Between the studies there was variability in the time interval between drug treatment and cognitive testing (see table 3). For the first post-infusion testing (i.e., assessment interval) following treatment, this time range varied from immediately to one week. For the last follow-up, this time frame ranged from one week to 26 weeks. Many studies had multiple testing points, but only reported the difference between baseline and last testing. However, due to difficulty in retaining participants for follow-ups, some studies did not analyse the longer-term follow-ups that they had intended.

Table 3

Assessment Intervals of Included Studies

Sub-anaesthetic Ketamine Infusion Alone	
Chen, M., et al. (2018)	Baseline 3 days post 14 days post.
Diamond et al. (2014)	Baseline 4-7 days after final infusion 12 weeks 26 weeks
Murrough, J. W., et al. (2014)	Baseline, Immediately after infusion
Murrough, J. W., et al. (2015)	Baseline, 7 days post infusion
Shiroma, P. R., et al. (2014)	Baseline 1 week 2 week

	3 week 4 week
Zheng, W., et al. (2019)	Baseline 24hr after 6th infusion 2 weeks follow-up
Zhou, Y., et al. (2018)	Baseline 24hr after 6th infusion 2 weeks follow-up
Sub-anaesthetic Ketamine Infusion + Anaesthetic Agent	
Anderson, I. M., et al. (2017)	Baseline Within 5 days after 4(+-1) treatments Within 12 days of last treatment 1 month post 4 month post
Chen, Q. et al. (2017)	Baseline 24hr post.
Loo, C. K., et al. (2012)	Baseline 24hr after 6th treatment 1-3 days after last treatment
Zhang, M., et al. (2018).	Baseline After 6th session 1-4 weeks after last treatment
Zhong, X., et al. (2016)	Baseline 48-72hr after last treatment.
Anaesthetic Ketamine Infusion	
Fernie, G. et al. (2017).	Baseline 24-48hr after 4th treatment 24-48hr after last treatment 1 month after
McDaniel, W. (2006)	Baseline >48 hours after 6th treatment
Rasmussen et al . (2014)	Baseline 48hr after 2 sessions 48hr after 4 sessions

	48hr after last session
Ray-Griffith, S. et al. (2017)	Baseline 24-48 hours after each treatment Day 7, 21, 60, 90 after last treatment
Yoosefi, A., et al. (2014)	Baseline 48hrs after 1st 3-7 days after final/6th 1 month post.
Zhong, X., et al. (2016)	Baseline 48-72hr after last treatment.

4.2.6 Heterogeneity of Inclusion Criteria

A source of variability amongst the studies was the inclusion or exclusion of those with bipolar disorder. For those who controlled for the diagnosis in their analysis, none found that this significantly impacted on results (e.g. Murrough et al., 2015). Interestingly, Zheng et al. (2019) and Zhou et al. (2018) had very similar studies in terms of location, cognitive tests and results (significant findings); however, Zhou et al. (2018) included those with bipolar disorder, whilst Zheng et al. (2019) excluded them. Both studies concluded a significant effect of ketamine on cognitive functioning, regardless of diagnostic exclusion criteria.

Another variability with inclusion criteria was medication or how it was controlled for. Two of the studies recorded and reported levels of additional anti-depressant medication (Chen et al., 2017; Rasmussen et al., 2014). Other studies did not report exact numbers, but did allow continuation of other anti-depressant medication as long as it remained stable throughout the duration of the study (Anderson et al., 2017; Chen et al., 2018; Diamond et al., 2014; Fernie et al., 2017; Loo et al., 2012; Ray-Griffiths et al., 2017; Shiroma et al., 2014), with two studies specifying a four week medication stability period prior to enrolment (Zheng et al.,

2019; Zhou et al., 2018). Two studies did not mention their protocol for additional medication management (McDaniel et al., 2006; Yoosefi et al., 2014). Four studies specified that no additional anti-depressant medication was to be prescribed during the study (Zhang et al., 2018; Zhong et al., 2016), with two specifying a "wash-out" period of one to four weeks (Murrough et al., 2014; Murrough et al., 2015). Of the seven studies that found significant effects of ketamine on cognition, three allowed a continuation of anti-depressant medication (Chen et al., 2017, Zheng et al., 2019, Zhou et al., 2018), two were unclear on medication management (McDaniel et al., 2006; Yoosefi et al., 2014) and two had no additional anti-depressant medication during the trial (Murrough et al., 2014, Zhong et al., 2016).

4.2.8 Cognitive Assessments

17 studies were included in this review (see Table 1), 10 of which examined the cognitive effects of ketamine alongside ECT. The included studies had a large variability in the number of cognitive tests used, ranging between one small sub-section of a small test to nine individual cognitive assessments, with only a few of them having overlapping instruments. Therefore a wide variety of cognitive domains were examined, with memory, learning and global cognitive functioning being the most common.

The most commonly used cognitive test was the HVLT (seven studies), or a variety of it, which assesses verbal learning. Five of those studies who used this measure found that using ketamine did not significantly impact on cognitive functioning immediately to five days after treatment (Murrough et al., 2015; Murrough et al. 2014; Loo et al., 2012; Anderson et al., 2017; Zhang et al., 2018). However, two studies found that those who were treated with ketamine had an improvement in their verbal learning (Zhou et al., 2018; Zheng et al., 2019); one

study did not have a control group and therefore could not control for practice effects (Zhou et al., 2018), whilst the other had a control group and therefore could control for any changes in verbal learning due to practice effects.

From the included studies, few had overlapping instruments. There were five studies that used the MMSE, three of those found that those who were administered ketamine had significantly less cognitive impairment than those who were not, regardless of the dosage variation between the studies (0.3mg/kg to 2mg/kg) or time variation of the follow-up assessments (24 hours to seven days) (McDaniel et al., 2006; Chen et al., 2017; Yoosefi et al., 2014). Two studies found no significant differences in global cognitive functioning (Rasmussen et al., 2014; Ray-Griffith et al., 2017).

Eight of the 17 studies used extensive neuropsychological test batteries, consisting of more than six assessments. Half of those studies found no difference in cognitive functioning for those being administered ketamine compared to a placebo (Loo et al., 2012), active control (Murrough et al., 2015; Zhang et al., 2018) or no control (Shiroma et al., 2014). The other half found a range of differences in cognitive functioning, including processing speed, verbal learning, delayed recall and executive functioning (Murrough et al., 2014; Zheng et al., 2019; Zhong et al., 2016; Zhou et al., 2018).

4.3 Risk of bias Assessment Results

4.3.1 Individual Studies

There were several studies where there was found to be a serious or high risk of bias. Although Rasmussen et al. (2014) used a randomised approach and only three of their 38 participants dropped out due to intervention (8%) which consequently reduced their risk of bias for some categories, they had additional

issues. These included missing data due to patients not receiving study treatments or the wrong study anaesthetic being used as well as reporting that the assessment measures they used were not as sensitive as in-depth neuropsychological testing. However, the primary aim of their study concerned the anti-depressant effects of ketamine, and they looked at the cognitive side effects as a secondary aim, which could explain the limited outcome measures. With this assessment tool, as previously mentioned, even if a study scores a low level of risk of bias in the majority of areas and only one rating of high concerns, the overall score is not an average but rather their highest rating.

Zhong et al.'s (2016) wider variety of cognitive outcome measures decreased its risk of bias, but it unfortunately did not report on any deviations from intended treatment, missing data or pre-registered protocol. This made it difficult to assess the risk of bias in other areas, thus putting it at an overall high risk of bias. However, this could be due to several research studies with a similar protocol being conducted at a similar time, in a similar location, and therefore they were registered under that protocol but did not report it (e.g., Zheng et al., 2019; Zhou et al., 2018). This could also apply to Zhang et al. (2018) who similarly did not report a pre-registered protocol.

Yoosefi et al. (2014) was also recorded as being at high risk of bias, and acknowledges that their strict exclusion criteria reduced the sample size, thus reducing the validity of the study. They also note that the Mini-Mental State Examination (MMSE), which is their cognitive function tool, is not a specific scale to evaluate cognitive function impairment, and reduces the validity of the study further. However, as the cognitive effects were their secondary aim for the study, this

could therefore perhaps explain the limited assessment. There was also no reporting of missing data.

Zhou et al. (2018) was another study that was deemed to be at high risk of bias. They reported that three participants withdrew consent (3%) and 13 participants (13%) discontinued with the treatment due to concern about side effects or dissatisfaction with the therapeutic efficacy. Following on from this, an additional 12% withdrew and did not complete the last follow-up. Due these numbers, follow-ups could not be gathered and this could have produced sample selection bias. In addition to this, there was also no blinding or control group, which thus increased its risk of bias. Once again, the risk of bias tool used scores papers so that they are overall rated by their worst score, and therefore although there were areas which this paper had a lower risk of bias, that is not reflected in the overall score given.

It is common in open label studies to not blind participants, but this has affected the risk of bias score for Shiroma et al. (2014). This aspect alone is not necessarily an issue, however, her sample was only of males with an extensive exclusion criteria, which does reduce the validity of the sample and increase the risk of bias.

McDaniel et al. (2006) were specifically looking at cognitive functioning and had an exceptionally small cognitive assessment compared to the other included studies. Whilst other studies above reported that their chosen test, the full MMSE, was not sufficient to detect cognitive impairment, this study only used one small sub-test within that test. Although they reported that the test is so simple and reproducible that it was not a limitation, it did not consider how the simplicity may create a ceiling effect. Therefore, compared to other studies and the length of assessment they

completed, this aspect of the study significantly impacted on their risk of bias score and reliability.

Table 2

Risk of Bias Assessments

Author/Year	Overall Risk of Bias	Comments
ROBINS-I for Non-RCTs		
Diamond, P. et al. (2014)	Moderate	No blinding. Drop-outs kept in data analysis. No pre-registered protocol.
McDaniel, W. et al. (2006).	Serious	No blinding. 3 participants deviated from intended intervention.
Murrough, J. W., et al. (2014).	Moderate	No blinding. No information on missing data. Extensive exclusion criteria.
Shiroma, P. R., et al. (2014)	Serious	No blinding. No pre-registered analysis plan. Extensive exclusion criteria.
Zheng, W., et al. (2019)	Moderate	No blinding. High drop-out rate. Not blind. Extensive exclusion criteria.
Zhou, Y., et al. (2018).	Serious	No blinding. High deviation from intended intervention. Change to analysis plan.
RoB 2 for RCTs		
Anderson, I. M., et al. (2017).	Some concerns	Adherence to time frame limited. Deviation from data analysis plan post-hoc.
Chen, M. et al. (2018)	Some concerns	No information on baseline comparisons between groups.

Chen, Q., (2017).	Some concerns	Significant differences between groups at baseline that had to be accounted for in analysis.
Fernie, G., et al., (2017).	Low risk.	None.
Loo, C. K., et al. (2012).	Some concerns	Adherence to treatment dictated by psychiatrist. Change in analysis plan due to lack of follow-up data.
Murrough, J., et al. (2015).	Low risk	None.
Rasmussen, K. et al. (2014)	High risk	Deviations from intended intervention due to allocation. Missing data due to patients not receiving treatment or the wrong drug given. Inappropriate measures.
Ray-Griffith, S. et al. (2017)	Some concerns	Deviation from data analysis plan post-hoc. Inappropriate measures.
Yoosefi, A., et al. (2014).	High risk	No information on missing data. Inappropriate measures. No pre-registered protocol. Strict exclusion criteria.
Zhang, M., et al. (2018).	Some concerns	Significant differences between groups at baseline not controlled for.
Zhong, X., et al., (2016).	High risk	No information on deviations from treatment. No information on extent of missing data.

4.3.2 Risk of Bias Across Studies

Six studies were rated as high risk, or significant concerns of bias; four of these studies found significant cognitive effects of ketamine, which accounts for over half (57%) of all the included studies which found significant effects.

The main themes that arose which increased studies risk of bias were the lack of blinding amongst the non-RCTs, a lack of reporting if there was a pre-registered protocol, no information on missing data, extensive exclusion criteria and cognitive measures that lack in sensitivity to cognitive impairment.

4.4 Key Findings

4.4.1 Sub-anaesthetic Ketamine Infusion Alone

4.4.1.1 Significant Results

When investigating the cognitive effects of sub-anaesthetic ketamine infusions, Chen et al. (2018) found no group main effect, no time main effect and no group x time interaction for cognitive function amongst the three groups (placebo, 0.2mg/kg ketamine, 0.5mg/kg ketamine). However, within the 0.5mg/kg group they found that, once they adjusted for age, sex and education, there was a positive association between depressive symptoms from baseline to 14 days post-infusion and change in omission in the go/no-go task (i.e., not responding to the ‘go’ stimuli), as well as a negative association between the same depressive symptoms and the change of correct responses in the go/no-go task. This indicates that for individuals who received a single dose of 0.5mg/kg ketamine infusion, there is an association between improvement in depressive scores and improvement in inhibitory control, which is a subdomain of executive functioning.

Murrough et al. (2014) investigated the acute effects (40 minutes post-infusion) of 0.5mg/kg ketamine on verbal learning and executive functioning using a subset of the Matric Consensus Cognitive Battery (MCCB). They found that in terms of cognition, the acute effects of low-dose of ketamine can cause selective impairments in the delayed recall component of the HVLT, but not the HVLT learning and category fluency tests.

Shiroma et al. (2014) investigated the changes between baseline cognitive functioning and at weekly intervals for five weeks after six 0.5mg/kg ketamine infusions. They found that over time, individuals had significant improvements in their cognitive performance, including visual memory (one card learning task), simple working memory (one back test), complex working memory (two back task).

4.4.1.2 Non-Significant Results

Murrough et al. (2015) examined the cognitive effects of a single dose of 0.5kg/mg ketamine seven days after infusion using a subset of the MCCB (see table 1.). They found that although there was no difference between ketamine and the active control, there was a significant improvement in participant's performance from baseline on the cognitive domains of processing speed, verbal learning and visual learning across both treatment conditions for both groups, but no change in the domains of working memory or reasoning. There was no effect of ketamine on cognitive performance and no effect of antidepressant response on cognitive performance. Diamond et al. (2014) similarly reported that up to six 0.5mg/kg ketamine infusions can be given without significantly impacting on cognitive performance, whilst individuals continued their pre-study prescribed antidepressants. This is perhaps suggestive that ketamine neither improves nor compromises cognitive performance.

Zheng et al. (2019) also used a subset of the MCCB to investigate cognitive changes following six sessions of 0.5mg/kg ketamine infusions. They examined the changes between baseline, one day post-infusion (day 13) and two weeks post-infusion (day 26). They found significant improvements from baseline functioning at day 13 and day 26 in regards to verbal learning (η^2=0.43) and speed of processing (η^2=0.59). These effect sizes indicate that there is a strong relationship between ketamine intake and cognitive changes, and that those who were infused with ketamine experienced significant cognitive improvements. These were still significant when changes in depression symptoms were controlled for as a covariate, but when the Sobel test was used to look at the significance of depression as a mediator, it found that improvements in verbal learning and speed of processing were mediated significantly by changes in depression symptoms. This suggests that ketamine has both a direct and indirect effect on cognitive performance.

Similar to Zheng et al. (2019), Zhou et al. (2018) also used a subset of the MCCB to investigate cognitive changes between baseline, one day post-infusion (day 13) and 14 days post-infusion (day 26), using the same dosage and number of sessions. They found that compared to baseline, there were significant improvements at day 13 and day 26 to speed of processing (d=.581) and verbal learning (d=.456). These medium effect sizes suggests that the positive relationship between the variables is stronger for the speed of processing, but still of a medium strength for the verbal learning variable. No other aspects of cognitive performance showed significant change compared to baseline after six ketamine infusions. However, when changes in depressive symptoms were controlled for as a mediator using the Sobel test, the results were no longer significant. This is a reflection of the difficulty to disentangle the direct cognitive effects of ketamine and indirect effects, i.e., the

changes in cognition following changes in depressive symptoms following ketamine infusions.

4.4.1.3 Predictive Factors

Murrough et al. (2014) also investigated whether cognitive functioning or age could be a predictor of an individual's antidepressant response to ketamine. They found that lower levels of baseline processing speed (i.e. Category Fluency, Trails A, Brief Assessment of Cognition in Schizophrenia Digit Symbol) and older age in TRD are associated with an increased antidepressant response (i.e. reduced MADRS scores) 24 hours after one infusion of 0.5mg/kg of ketamine (β=-0.39 for age and β=0.42 for speed of processing). This result investigating baseline processing speed was replicated in their Murrough et al. (2015) paper.

Interestingly, Shiroma et al. (2014) also found that poor performance on attention tests (i.e., Identification Task) at baseline, and a younger age at onset of major depressive episode were significant predictors of a greater change in severity of depressive symptoms over six infusions, as measured by changes in MADRS scores. They also found that better performance on the verbal memory test was predictive of greater improvement from depression through repeated ketamine infusions (0.5mg/kg).

Zhou et al. (2018) found that a better performance in visual learning at baseline and individuals without psychiatric comorbidity were significant more likely to experience an antidepressant response to ketamine (β=-0.150 for visual learning).

In terms of predictive factors, Zheng et al. (2019) was the only paper included within the sub-anaesthetic ketamine infusion category that found no significant association of change in depression score with baselines scores of neurocognitive performance.

4.4.2 Sub-anaesthetic Ketamine Infusion + Anaesthetic Agent

4.4.2.1 Significant Results

Anderson et al. (2017) reported no significant difference in scores on the HVLT-R-DR between those receiving sub-anaesthetic ketamine (0.5mg/kg) alongside the propofol anaesthetic and the placebo group (η^2=-0.13). Although they did find a significant advantage for the placebo group at the end of treatment for HVLT-R recognition discrimination (η^2=-0.01), the effect size is very small and suggests a weak relationship between the group variable and improvement in the HVLT-R recognition discrimination variable.

On the other hand, Chen et al. (2017) found that both the ketamine (0.3mg/kg) and control group had a reduction in score for memory, as assessed by the WMS, but the reduction in scores in the control group was significantly greater than that of the study group. Interestingly, Zhong et al. (2016) looked at three groups, one was only ketamine (0.8mg/kg), one was using ketamine (0.5mg/kg) as an adjunctive to an anaesthetic and the third was using propofol as the control anaesthetic. They found that individuals who were in the ketamine-only group (0.8mg/kg) scored significantly better than those in the ketamine plus anaesthetic group and the control group. This is suggestive of a neuroprotective element to ketamine, specifically in larger doses (0.8mg/kg).

4.4.2.2 Non-Significant Results

Chen et al. (2017) also reported that 24 hours after the full course of ECT, there were reductions in both groups for short-term memory and immediate-memory scores, but these changes were not significant between groups. Similarly, Loo et al. (2012) also found within-groups changes in cognitive performance following a

course of ECT (mean=9.5 sessions), but no difference between those receiving ketamine (0.5mg/kg) as an adjunct to their anaesthetic and those receiving the placebo. However, they do acknowledge that their study was powered to detect large effects only. Zhang et al. (2018) also found no significant between-groups cognitive effects on any of the sub-tests of the MCCB, for those receiving either only propofol or ketamine (0.5mg/kg) as an adjunctive to propofol. However, similar to above, they found a significant time effect for the tests which assessed reasoning and problem solving and social cognition domains. This is perhaps suggestive that ketamine does not have a neuroprotective element to it.

4.4.3 Anaesthetic Ketamine Infusion

4.4.3.1 Significant Results

Zhong et al. (2016) found that after eight ECT treatments, individuals in the propofol (control) group had a greater degree of impairment within their executive functioning domain and visual attention, as measured by the WCST, trail making test and tower of hanoi, than those in the ketamine groups. However, there were no significant difference in cognitive impairment as measured by the word fluency test, the digit symbol test, the digit span test or the visual regeneration test. Yoosefi et al. (2014) used a smaller cognitive assessment, specifically the MMSE, and found a significant difference between the ketamine group (1-2mg/kg) and control group. They found that those receiving ketamine had a significant improvement in cognitive function between baseline and last assessment compared to the control group. This is suggestive of a neuro-enhancing element to ketamine.

However, McDaniel et al. (2006) found that those receiving ketamine (1mg/kg) remembered significantly less items on a recall test, compared to the control, which suggests that ketamine negatively impacts on word retention.

4.4.3.2 Non-Significant Results

Fernie et al. (2017) found no main effects of drug (η^2=0.03), age, gender or time (η^2=0.02) when examining the effects on short-term memory (CANTAB-SRM) of ketamine (<2mg/kg) compared to a control group. Similarly, Rasmussen et al. (2014) and Ray-Griffith et al. (2017) found the same results when assessing using the MMSE, even with a different dosage (>1mg/kg and 1mg/kg respectively) and different number of ECT sessions (six sessions and an average of 4.9 sessions respectively). This is suggestive that ketamine does not affect cognitive performance.

5.0 Discussion

This discussion will firstly summarise the findings, including the assessment of study quality, before moving onto discussing the limitations of the included studies, the limitations of the review process, and finally the implications of the findings and conclusion.

5.1 Summary

This review aimed to explore the cognitive effects of intravenous ketamine on individuals with a diagnosis of treatment-resistant depression. Ten of the 17 included studies found non-significant results, suggesting that ketamine infusions do not positively or negatively impact on cognitive functioning when administered to individuals with a diagnosis of TRD.

The vast range of cognitive tests, testing environments, study quality and dosages emphasise the methodological variances within the field. Despite this, this review was able to bring to light firstly that specific baseline cognitive deficits may predict improvement of depressive symptoms in adults when administered ketamine (Murrough et al., 2014; Murrough et al., 2015; Shiroma et al., 2014). Secondly, many studies have found that ketamine does not directly affect cognitive functioning of individuals with TRD. Thirdly, for those studies that did find significant results, it raised the questions as to whether changes in cognitive functioning are direct effects, or indirect effects largely determined by changes in depression symptoms. However, further testing needs to be done using in-depth neuropsychological measures, a larger sample size and longer follow-ups in order to further explore and understand this field.

5.2. Assessment of Study Quality

The studies included ranged in their quality and had a variety of limitations. The risk of bias of the studies, as measured by the ROBINS-I and RoB 2, was low to severe. One common theme was that many studies did not report the specific details relating to recruitment and for those who did, several of the studies were completed with participants who were at specialist research centres or inpatient facilities. For example, four of the 17 studies included were completed in the same research centre location, therefore reducing the generalisability of the results. Three of those studies (Zhou et al., 2018; Zheng et al., 2019; Zhong et al., 2016) found that the administration of ketamine had significant cognitive effects, whilst Zhang et al. (2018) found no significant findings. One limitation is that Zhou et al. (2018) and Zheng et al. (2019) both recruited in a similar period from the same location and found similar results, however, they had different sample sizes and exclusion criteria.

In terms of potential confounding variables within the included studies, although it appeared to be commonplace in these selected studies to not request clients to stop all other medications, it was not clear if all studies controlled for medication in their analysis, especially opioids. This would be important as ketamine has been found to reverse an individual's tolerance to opioids (Hoffmann et al., 2003) and therefore could influence an individual's response to the drug. Another potential confound that was not always controlled for was baseline cognitive functioning, which could as some studies found, be predictive of an individual's response to ketamine (Murrough et al., 2014; Murrough et al., 2015; Shiroma et al., 2014).

Both ketamine and ECT are not always well-tolerated, so it is common to have drop-outs, which can affect studies validity if not controlled for. These studies were no different in that some had difficulties with recruitment and drop out, but it becomes an issue when this is not clearly reported or controlled for. Moreover, many of the studies had a small sample to begin with, so once there were inevitable drop-outs during or after treatment, the sample was too small with too little power to draw meaningful statistical conclusions (Ray-Griffith et al. 2017), especially for the longer-term data (Loo et al., 2012).

For the two studies identified with the least risk of bias, the results found no significant change to cognitive functioning when individuals were administered ketamine compared to another anaesthetic agent, such as midazolam (Murrough et al., 2015) or propofol (Fernie et al., 2017).

5.3 Limitations of Included Studies

5.3.1 Sample size and Power Issues

Many of the studies had a small sample size, or were only powered to detect a large effect. Therefore, it is possible that ketamine could have direct cognitive effects, but this would only be detected with a larger sample size. Two studies acknowledge they were underpowered to detect any changes, although one reports no significant cognitive effects found (Ray-Griffith et al., 2017) whilst the other found significantly less impairment of short-term memory for those receiving ketamine (McDaniel et al., 2006). However, McDaniel et al. (2006) used only a subsection of an already small test, to which Ray-Griffith et al. (2017) used the whole test. Anderson et al. (2017) had similar issues with power, originally using three different cognitive assessments but having to not analyse the results of two of the assessments, due to poor recruitment, and therefore issues with power.

5.3.2 Assessment Intervals

Ketamine has an initial half-life of 16 minutes and a terminal half-life of three hours (Khan et al., 2014). There was only one study that assessed individuals whilst the ketamine was still active in their system, i.e., immediately after their infusion (Murrough et al., 2014). As many of the studies were primarily exploring the anti-depressant effects of ketamine, this could explain why the majority allowed 24 hours between infusion and testing to ensure that what they are reporting was an anti-depressant effect and not the acute psychoactive phenomena that individuals can experience on emergence from anaesthesia (Hansen et al., 1988).

Assessing at various time points can always lead to drop-outs in research, and it can therefore affect whether studies have enough participants in order to analyse their follow-up data as planned. For example, Loo et al. (2012) were not able to

formally analyse their test scores at one-week and one-month follow up due to the small number of participants at these points. Zhang et al., (2018) follow-up period had the largest range (1-4 weeks), and it brings into question whether it could have impacted on results.

5.4 Limitations of Review Process

Although the risk of bias assessment of the included studies was completed by two researchers, the search process itself and decisions of inclusion/exclusion were completed by one researcher, thus increasing the chance of bias.

The relatively small number of available studies that examine the cognitive effects of ketamine is a limitation within this review, especially as the included studies are methodologically diverse, such as dosage, heterogeneity of participant characteristics and outcome measures. This discussion will now explore the aforementioned differences in methodology.

5.4.1 Dosage Differences

Nine of the 17 studies used 0.5mg/kg, which is the standard sub-anaesthetic dosage for ketamine, with anything above 0.8mg/kg producing a full anaesthetic state (see table 2). For the included studies that found significant results, one study used a dose of 0.3mg/kg (Chen et al., 2017), four studies used a dose of 0.5mg/kg (Murrough et al., 2014; Zheng et al., 2019; Zhou et al., 2018; Zhong et al., 2016), one study used a dose of 0.8mg/kg (Zhong et al., 2016), one study used a dose of 1mg/kg (McDaniel et al., 2006), and one study used a dose ranging between 1mg/kg to 2mg/kg (Yoosefi et al., 2014).

Dosage is important to consider as Zhong et al. (2016) found that 0.8mg/kg ketamine effected cognitive functioning significantly differently to the 0.5mg/kg

dosage. Loo et al. (2012) suggests that ketamine may have neuroprotective effects at doses others than 0.5mg/kg due to complex dose-response relationships, as well as other effects of ketamine, such as psychomimetric effects, have been found to be dose-dependent (Bowdle et al., 1998).

5.4.2 Heterogeneity of Participant Characteristics

5.4.2.1 Bipolar Disorder Exclusion

One of the variabilities between studies was those who included excluded those with a lifetime history of bipolar disorder, for example Zheng et al. (2019), Shiroma et al. (2014), Murrough et al., (2014) chose to exclude. Moreover, for those who did include individuals with bipolar disorder, they reported controlling for the diagnosis in the analyses (Zhou et al., 2018; Zhang et al., 2018) and several had to drop out due to changes in symptomology following the ketamine infusion. For example, Loo et al. (2012) found that two of the nine bipolar participants changed in symptomology whilst receiving ketamine; one became hypomanic and the other developed rapid cycling mania symptoms. Diamond et al. (2014) also had two of their six bipolar participants drop out due to significant changes in mood. Whilst on the other hand, Zhang et al. (2018) found no major adverse effect that were severe enough to require discontinuation of treatment.

5.4.2.2 Medication Exclusion

As previously mentioned, another inconsistency with exclusion criteria was medication or how it was controlled for. If we consider that cognitive functioning and mood are related, then differences in mood regulating medication could potentially impact on the results. For example, as previously mentioned, ketamine has been found to reverse an individual's tolerance to opioids (Hoffmann et al.,

2003) and therefore could influence an individual's response to their medication, which would then potentially impact on their cognitive functioning.

Chen et al (2018) acknowledged that their results could be from a combinatory or a regulatory effect of ketamine with the medications that people were already using. However, they are clear they are looking at the add-on effect of ketamine, which provides a more naturalistic study and is more ethically appropriate for such severely depressed patients. Within the included studies, there was not a clear pattern between the outcome of the studies and whether they did or did not control additional medication use.

A meta-analysis by Rosenblat et al. (2016) of randomised placebo-controlled trials evaluating the cognitive effects of seven different anti-depressants found that they had a significant positive effect on psychomotor speed and delayed recall. The effects on executive function did not reach statistical significance. However, once one of the anti-depressants (vortioxetine) was removed from analysis, only improvement on delayed recall was significant. When they compared the results of eight active-control randomised trials of selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, tricyclic anti-depressants and norepinephrine and dopamine reuptake inhibitors, no statistically significant difference in cognitive effects was found. This suggests that anti-depressant medication can significantly impact on cognitive function compared to placebos, but there is not one anti-depressant that has a significantly larger or smaller impact.

5.4.3 Measures of Cognitive Function

The variety of cognitive assessments used in the included studies means there were more areas that were tested, but this makes it more difficult to directly compare the results of the studies for the purpose of finding consistent themes. Although

previous studies looking at the effects of ketamine have found that it predominantly affects memory and learning in healthy participants (Honey et al., 2003), when depression is included into the mix, it must be held in mind that depression can affect a wide variety of cognitive functions (Paradiso et al.,1997; Reppermund et al., 2009), and therefore it could be challenging to pin-point one area of cognitive functioning to assess.

Several of the studies used multiple tests that were sensitive to small levels of change and therefore appropriate for examining possible changes within a pre and post-drug trial. The MMSE was used in five of the studies included, which is widely used as a screening measure for dementia and mild cognitive impairment (Arevalo-Rodriguez et al., 2015). However, it is questionable as to whether this is an appropriate measure in this instance due to its simplicity, low sensitivity to change and floor and ceiling effects (Philipps et al., 2014); especially as one study (McDaniel et al., 2006) only used one small subsection from within this already small assessment. Other studies used an extensive battery of neuropsychological tests which granted a greater insight into ketamine's effect on various cognitive domains, rather than the generic "global cognitive functioning".

The decision as to what, or how many, cognitive assessments a study would use could relate to whether a study examined the cognitive effects as part of their primary or secondary hypothesis (see table 2). For example, of the five tests that utilised the MMSE, which is fast to administer (5-10 minutes), four of those had cognitive effects as a secondary aim. One study (Chen et al., 2017) also acknowledged that they used a specific memory test which had not been adapted to the population they were testing, therefore reducing the validity of the findings.

5.5 Implications

Due to ketamine recently becoming more popular as an anti-depressant treatment option, it is important to fully understand all of the potential side-effects, including the cognitive ones. However, due to the relationship between mood, cognition and ketamine, this can be difficult to pull apart.

If we contextualise the results in terms of existing knowledge, a key question is raised. If we consider the theory that the cognitive impairments associated with depression are more trait-like than state-like (Reppermund et al., 2009), this could imply that studies which found no significant cognitive effects of ketamine (59% of the studies) was due to ketamine being unable to alleviate the cognitive trait-like symptoms of depression and only impact on the mood symptoms for those with TRD. This would be further supported by research finding that when mood symptoms have been alleviated and are in remission, there are still cognitive impairments (Neu et al., 2005; Weiland-Fielder et al., 2004).

This theory could also account for the handful of studies that initially found significant changes in cognitive functioning after receiving ketamine, but when they controlled for depressive symptoms, the results were no longer significant (Chen et al., 2018; Shiroma et al., 2014; Zheng et al., 2019; Zhou et al., 2018). These results could be demonstrating that ketamine can impact on an individual's mood, which then in-turn improves their cognitive functioning to a minor extent, but the ketamine infusion is unable to remove the core-trait of cognitive impairment that is associated with depression. Perhaps these results are suggesting that there is a ceiling effect on how much changes in mood symptomology, caused by drug or remission, can impact on an individual's cognitive functioning when they have the core-trait of cognitive impairment from depression.

Some studies found that baseline cognitive functioning could predict antidepressant response to ketamine (Murrough et al., 2014; Murrough et al., 2015; Shiroma et al., 2014), in particular, poorer cognitive performance was indicative of a greater antidepressant response to ketamine. Perhaps these results could suggest a flooring effect of using ketamine to treat depression, such that individuals need to have more severe cognitive impairment in order to fully benefit from the antidepressant effects of it. This would also be in-keeping with Majer et al. (2004), who found that non-responders to anti-depressant medication had significantly more impaired baseline cognitive functioning in some domains.

As previously mentioned, to our knowledge there have been no systematic reviews looking purely at the cognitive effects of ketamine for individuals with a diagnosis of treatment-resistant depression. However, reviews which have broadly looked at the side-effects of ketamine, and include a small subsection on cognitive effects, reported that due to such diverse tests, they were unable to synthesise the data (Zheng et al., 2019). This paper adds to the body of evidence that the field is in need of more good quality research that uses consistent and valid neuropsychological measures.

5.6 Conclusion

The findings from this systematic review are not consistent enough to draw strict conclusions. We cannot be clear whether the use of ketamine on individuals with treatment-resistant depression has definite cognitive implications, however, the possibility raised that baseline cognitive functioning could be predictive of an individual's antidepressant response to ketamine should be further investigated. If prior to treating an individual with ketamine there is a way of establishing whether the treatment will work for that person, it is important to further understand this.

Perhaps ketamine does have a minor direct effect on cognitive performance, or perhaps it can indirectly effect it through its antidepressant response, as several studies found their results to no longer be significant once they controlled for depression. However, there is not enough evidence to conclude whether these theories could be true.

However, if we focus more on the studies which found that ketamine did not significantly impact on cognitive performance, and if we consider the theory that cognitive impairment is a trait of depression, rather than related to severity of depression, then perhaps ketamine is only able to affect an individual's mood but not impact on the trait-like aspect of cognitive functioning. Another interpretation could be that cognitive functioning within TRD has a flooring effect, such that it is too impaired by the depression to be further significantly reduced. This kind of exploring would require studies with large power, which many of the studies included here did not have, and therefore were not able to pick up on small changes, if there were any to be found.

The findings here have a number of clinical implications. Predominantly that we cannot be overly sure what cognitive effects individuals with TRD may experience when being treated with ketamine. It is important that further research is done so that we can fully inform patients of all the possible side effects, including cognitive, to ensure informed consent to treatment.

In conclusion, the variability in research within the field of cognitive effects of ketamine is too broad to draw any definite conclusions, such as whether there are no effects, in-direct effects or direct effects. However, it is important to keep in mind the findings that there are predictors of an individual's antidepressant response and consider how this could be utilised moving forward.

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Part 2: Empirical Paper

The Cognitive Effects of Sub-Anesthetic Ketamine and Lidocaine in individuals with a diagnosis of Chronic Pain

2.1 Abstract

Aims: To explore the analgesic and cognitive effects of sub-anaesthetic IV ketamine and lidocaine on individuals with a chronic pain diagnosis. The association between pain, mood and cognitive performance were also evaluated.

Method: This non-randomised, between subjects, active control study measured participant pain and cognitive performance before and at the mid-point of drug administration. Pain was assessed using visual analogue scales of pain intensity, distress and interference. Cognition was assessed using the Story Recall subtest of the Rivermead Behavioural Memory Test, a serial sevens subtraction task and a verbal fluency task.

Results: Baseline comparisons between the lidocaine group (n=56) and ketamine group (n=43) showed significant differences for age. Data was analysed using repeated-measures ANCOVAs and Pearson correlations. Both ketamine and lidocaine reduced pain on all three scales, with ketamine reducing pain significantly more than lidocaine. Ketamine, but not lidocaine, impaired individual's phonetic fluency, working memory, concentration and episodic memory. There was no association between changes in cognitive functioning and changes in mood or pain. Decreased pain was strongly correlated with improved mood in both treatment groups.

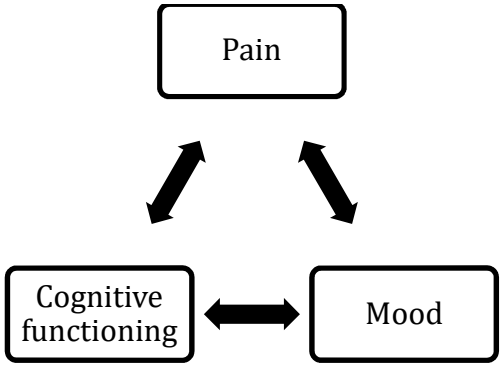
Conclusion: Sub-anaesthetic IV ketamine for the treatment of chronic pain produced more short-term pain relief than lidocaine. Ketamine impaired cognitive functioning. There was an improvement in cognitive functioning scores for those on lidocaine, which is theorised to be due to practice effects. Future research should investigate the longer term analgesic properties of ketamine in individuals with chronic pain, along with the acute and chronic impairments to cognitive functioning.

2.2 Introduction

This introduction will first give a brief overview of ketamine and lidocaine, before exploring how each of the drugs interacts with pain, cognitive functioning and mood (see Figure 1). It will finish by briefly exploring how additional opioid medications interact with ketamine and lidocaine.

Figure 1

A visual example of the relationship between pain, cognitive functioning and mood.



2.2.1 Study Aims

The primary aim is to explore the cognitive and analgesic effects of sub-anaesthetic ketamine and lidocaine on individuals who have a diagnosis of chronic pain. The secondary aim will be to investigate how these drugs interact within the triad (see figure 1), and if there is a relationship between additional opioid medication and the cognitive effects of the drug.

2.2.2 Ketamine

Ketamine is a high-affinity, non-competitive N-methyl-D-Aspartate (NMDA) glutamate receptor antagonist that was first synthesised in 1962, and added to the WHO Essential Medicines List as an intravenous anaesthetic in 1985. Ketamine has important uses in human medicine, but is also the most widely used anaesthetic in

veterinary medicine, especially equine medicine. This has led to it being commonly referred to as a “horse tranquiliser” in the general population.

2.2.2.1 Medical Uses

Glutamate is the major excitatory neurotransmitter in the brain and has three main receptors, one of which is the N-methyl-aspartate (NMDA) receptor. This receptor in particular is vital in learning and memory due to its role in synaptic plasticity. Ketamine, which as previously mentioned, is a non-competitive antagonist of this NMDA receptor, is used widely medically for anaesthesia and analgesia (WHO, 2016).

Ketamine has been used medically for approximately 58 years due to its unique safety profile, which includes not depressing breathing or lowering blood pressure. Therefore, it is considered an indispensable drug in remote locations, such as rural areas in the developing world, disaster situations and conflict zones.

Ketamine is used commonly as an anaesthetic and analgesic within emergency paediatrics (Holloway et al., 2000; McGlone et al., 1998) due to its rapid onset, maintenance of spontaneous respiration, causation of a lack of response to painful stimulus, rapid recovery, and minimal side effects (Doyle, 2002). However, more recently, ketamine is also being investigated as a treatment option for alcohol misuse (McAndrew et al., 2017) and Alzheimer’s disease (Lozupone et al., 2018).

2.2.2.2 Non-medical Uses

When used recreationally at lower doses, ketamine is commonly insufflated (snorted) and produces hallucinations, mild dissociations and distortion of time and space. “K-land” is when individuals experience the euphoric and dissociative effects of ketamine, whilst the “K-hole” is where the individual feels they have detached from reality.

There are long-term health conditions associated with chronic use of recreational ketamine, including ulcerative cystitis (a lower urinary tract irritation) (Shahani et al., 2007), kidney dysfunction (Chu et al., 2008) and intense abdominal pain (Muetzelfeldt et al., 2008). Another consequence of recreational use of ketamine is cognitive impairment, which is associated with daily administration of grams of street ketamine (Morgan & Curran, 2006). Although when researching recreational usages of ketamine, it must be kept in mind that individuals in some cases may be taking additional drugs alongside ketamine, and furthermore, the purity or quality of the ketamine may be different to medicinal ketamine.

2.2.2.3 Side Effects

Ketamine is a very important and widely used drug, but it does not come without side effects. These can include bronchodilation and stimulation of the sympathetic nervous system and cardiovascular system (Sinner & Graf, 2008). This is experienced by individuals as an increased heart rate, respiratory rate and agitation. When used with individuals with a diagnosis of neuropathic pain, side effects can be experienced as dizziness, sedation, loss of appetite, nausea, and vomiting (Cvrček, 2008). Higher doses of ketamine can cause tachyarrhythmias, hallucinations, flashbacks and erratic behavior (Kosharskyy et al., 2013).

2.2.3 Lidocaine

Lidocaine is another widely-used non-opioid drug with anaesthesia applications. It is also known as lignocaine. It works by blocking the initiation and transmission of nerve impulses where it is applied (WHO, 1989). When used intravenously for chronic pain management, it blocks the sodium channels in the neuronal cell membrane. These channels are believed to play a role in maintenance of both neuropathic and inflammatory pain.

2.2.3.1 Side Effects

The possible side effects of lidocaine include seizures, drowsiness, confusion, headache, nausea, vomiting, numbness and tingling, dizziness, metallic taste, tremor, dry mouth, insomnia, cardiac arrhythmias and hemodynamic (blood flow) instability (Kosharskyy et al., 2013).

2.2.4 Pain

Pain has been described as "a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components" (Williams & Craig, 2016).

2.2.4.1 Ketamine and Pain

It is theorised that hyperactivity of the NMDA receptor could play a role in chronic pain, specifically neuropathic pain (Woolf & Thompson, 1991). Ketamine has a potent analgesic effect, both acutely and chronically, and is believed to increase pain thresholds and to prevent "wind-up" pain (Nikolajsen et al.,1996), which is where neurones in the spinal cord become sensitised to painful stimuli (Sunder et al., 2008). Anaesthetic dosages (>0.5mg/kg) of ketamine have been shown to significantly reduce levels of pain in individuals with complex regional pain syndrome for up to six months (Keifer et al, 2008). A single IV infusion of ketamine has been shown to relieve on-going pain in patients with peripheral nervous system disease-related pain (Backonja et al., 1994).

However, the degree of pain reduction varies between individuals (Visser & Schug, 2006), dosages and medical conditions (Cohen et al., 2018). Therefore, there is a question as to whether there are other factors mediating the effects of ketamine on chronic pain.

2.2.4.2 Lidocaine and Pain

Intravenous lidocaine has analgesic effects and is regularly used for patients with chronic pain, although the duration of the relief is variable (Souza & Kraychete, 2014). The variability in pain relief could be for various reasons, such as pain etiology (Galer et al., 1993). For example, patients with peripheral nervous system (PNS) injury reported significantly more pain relief following lidocaine than those with central nervous system (CNS) injury or with pain of an unknown etiology (Galer et al., 1993).

When exploring post-operative pain in patients who had undergone laparoscopic cholecystectomy, a meta-analysis of randomised control trials concluded that intravenous use of lidocaine is able to reduce acute postoperative pain (Gang et al., 2018). However, one study that looked at post-operative pain following hip surgery found no difference in pain scores or morphine consumption at 24 or 48 hours with perioperative lidocaine infusions, compared to a placebo (Martin et al., 2008). This difference in outcome, according to Dunn et al. (2017), is because hip surgery has a limited degree of inflammation and suggests that a lidocaine infusion for hip surgery may not improve outcomes, whilst for something like spine surgery, lidocaine infusions have been found to have both short-term and long-term analgesic benefits to patients (Farag et al., 2013).

2.2.5 Cognitive Functioning

For the purpose of this paper, the term ‘cognitive functioning’ refers to the brain’s acquisition, processing, storage, and retrieval of information (Lawlor, 2002).

2.2.5.1 Ketamine and Cognitive Functioning

There is substantial research demonstrating that ketamine impacts cognitive functioning (Morgan & Curran, 2011), but this impact varies depending on dosage, frequency and population (Visser & Schug, 2006).

Healthy participants were given acute heat pain, which was then treated with a single dose of ketamine. When a neurocognitive battery of tests was administered, they found that those who had been administered ketamine experienced cognitive impairment, specifically their memory, reaction times and attention (Olofsen et al., 2012). Moreover, Honey et al. (2003) also found that a higher dose (plasma concentration of 50 or 100 ng/ml) of ketamine acutely impaired working memory in healthy participants, specifically their verbal working memory.

Morrison et al. (2018) examined the effects of a singular dose of intranasally administered esketamine (84mg) on 24 participants. They found that it was associated with significant acute cognitive performance impairment (measured using the CogState battery) 40 minutes post-dose, which returned to placebo-comparable levels two hours later.

There can be long-term cognitive impairments for frequent recreational ketamine users, such as working, episodic and semantic memory (Visser & Schug, 2006), as well as short and long-term memory (Morgan & Curran, 2011). In fMRI studies, repeat ketamine exposure in recreational users has been linked to decreases in brain volume in the frontal cortex, striatum and cerebellum (Chesters, 2019), with the frontal cortex being strongly linked to executive functioning.

For those using ketamine medicinally, a study which looked at individuals with complex regional pain syndrome found that those who used ketamine long-term, which was defined as twice a month for at least six months, performed significantly worse on tasks tapping into attention, psychomotor coordination and

memory compared to those who never received ketamine, received it infrequently (less than twice a month) or received it acutely (less than six months) (Kim et al., 2016).

2.2.5.2 Lidocaine and Cognitive Functioning

Studies have investigated whether lidocaine can impact on post-operative cognitive dysfunction. For example, one study has suggested that lidocaine may have an acute neuroprotective element when infused during surgery, as evaluated by scores pre-infusion and nine days after the infusion using a battery of nine neuropsychological tests, such as Digit Span and WMS (Wang et al., 2002).

However, when Kinger et al. (2019) also used a standard neurocognitive battery of tests (e.g., Weschler Memory Scale, Hopkins Verbal Learning Test, Digit Span) to look at longer term cognitive changes (six weeks after cardiac surgery), they found no significant differences between those who received a lidocaine infusion following the anaesthetic dosage and those who received the placebo (saline solution). For individuals undergoing elective cataract surgery, individuals who received lidocaine, compared to those receiving bupivacine as the anaesthetic, did not perform significantly worse on cognitive tests (paired associate learning test and verbal fluency) (Fathy et al., 2019). Furthermore, Mitchell et al. (2009) concluded that lidocaine does not have neuroprotective effects following cardiac operations, and they believe that a previous study (Mitchell et al., 1999) that found significant effects may represent a Type I error.

2.2.6 Ketamine and Depression

For around 20 years, research has explored the use of ketamine in treatment resistant depression (TRD) and major depressive disorder (MDD) (WHO, 2016). Ketamine works as an antagonist at the NMDA glutamate receptor, whereas most

approved anti-depressant medications primarily target the brain monoamine systems (Matthew et al., 2008). Unlike monoaminergic antidepressants, ketamine has a rapid antidepressant effect, within hours following intravenous treatment (Carlson et al., 2006). The first placebo-controlled, double-blinded trial of ketamine on MDD found a significant improvement in depressive symptoms within 72 hours (Berman et al., 2000), whereas other anti-depressant medications can take up to six weeks. This rapid anti-depressant effect of ketamine has been replicated in many studies, with reviews finding that a single low-dose ketamine infusion exerted a rapid and sustained anti-depressant effect on samples of TRD patients (Corriger & Pickering, 2019; Xu et al., 2016).

2.2.7 Interacting Factors

2.2.7.1 Pain & Mood Interaction

When individuals are given ketamine infusions for their pain, the degree of analgesic effect varies between individuals (Visser & Schug, 2006). Therefore, there is a question as to whether there are additional factors influencing the analgesic effects of ketamine.

Chronic pain produces psychological distress, which in turn can lead to mood disorders such as depression. Depression and depressive-like symptoms are frequently reported by people who have a diagnosis of chronic pain (Banks & Kerns, 1996). Biologically speaking, chronic pain and major depression overlap in the areas of genetic, structural, functional, neuroendocrine and neurotransmitter functionality (Narasimhan & Campbell, 2010). Therefore, it is important to consider their interaction when treating either pain or mood.

2.2.7.2 Cognitive Functioning & Mood Interaction

There is strong evidence demonstrating the impact of ketamine treatment on improving depressive symptoms (Carlson et al., 2006). However, it has also been shown that when used to treat suicidality and treatment resistant depression, individuals also experienced improvements in various aspects of their memory (Lee et al, 2016). Thus demonstrating an important interaction between ketamine, mood and cognitive functioning.

Chen et al. (2018) found that a single ketamine infusion (0.5mg/kg) did not impair the cognitive functioning of individuals with treatment-resistant depression, and two weeks following infusion, they had an improvement in sustained attention and response inhibition, measured using the go/no-go task. They also found that there was a positive association between depressive symptoms and change in omission in the go/no-go task, as well as a negative association between depressive symptoms and correct responses in the go/no-go task.

2.2.7.3 Interaction of Cognitive Functioning & Pain

Hedges et al. (2019) explored the interaction between chronic pain and cognitive functioning. They found that those with chronic pain appeared to have poorer cognitive functioning than healthy controls, particularly in the areas of attention, processing speed and executive functioning. Moreover, the duration and intensity of the reported chronic pain was correlated with cognitive function, finding that those with higher pain levels performed poorer on cognitive functioning tasks.

2.2.7.4 Interaction of Additional Medication

If we consider that pain, mood and cognitive functioning are related, then mood regulating or pain relieving medication could impact on cognitive functioning.

Opioids can impair cognitive functioning in healthy volunteers, but perhaps due to tolerance, those who use them habitually (e.g., for chronic pain) are much less likely to have impaired cognitive processes (Zacny, 1995). However, as ketamine has been found to reverse an individual's tolerance to opioids (Hoffmann et al., 2003), it could therefore could influence an individual's response to their regular medication, which would then potentially impact on their cognitive functioning.

Research has shown that through using other medications at the same time, the effects of ketamine could be prolonged (Caddy et al., 2015). However, it is unknown how this changes when using sub- anaesthetic doses for chronic pain.

2.2.8 Rationale and Research Questions

2.2.8.1 Rationale for this study

This study will build on an existing evidence base exploring the impact of sub-anaesthetic ketamine on pain and cognitive functioning compared to lidocaine. There have been various studies exploring the impact of ketamine on cognitive functioning in healthy participants, but fewer in clinical participants, including those with a diagnosis of chronic pain. According to Zhang and Ho (2016), due to the recent controversy about the commonly believed adverse effects of ketamine on cognition, it is an area that needs to be further researched. Moreover, we know that the analgesic impact of the ketamine and lidocaine treatment can vary between participants, so this study will explore the association between three interacting variables as previously mentioned (cognitive functioning, mood and opioid medication).

2.2.8.1 Research aims

This project has multiple aims, the primary aim is:

1. To explore the cognitive effects of sub-anaesthetic IV ketamine and lidocaine on participants with a diagnosis of chronic pain. The independent variable is the drug (lidocaine or ketamine) and the dependent variables are the cognitive tests (story recall, verbal fluency and serial sevens).

The secondary aims of the project are:

1. Explore the analgesics effects of ketamine and lidocaine with participants who have a diagnosis of chronic pain. The independent variable is the drug (lidocaine or ketamine) and the dependent variables are the subjective pain tests (distress, interference and intensity).
2. Explore the relationship between participant's additional opioid medication and acute cognitive change. The independent variable is the opioid usage (yes or no) and the dependent variables are the cognitive tests (story recall, verbal fluency and serial sevens).
3. Explore any correlational relationships between cognitive functioning, mood and pain.

2.3 Method

2.3.1 Setting

The research was completed in a clinic which is nationally recognised for its excellence for people with chronic pain. Their clients travel from both local and national areas to access their renowned services. The centre has a multidisciplinary team, as it approaches pain treatments from both a medical and psychosocial angle. The clinic not only provides ketamine and lidocaine treatments for pain, but other specialist treatments such as psychological support, peripheral and central nerve

blocks, radio frequency lesioning and spinal implants, access to Transcutaneous Electrical Nerve Stimulation (TENS) machines and acupuncture.

Within this clinic, if the clinical team recommend drug infusions for pain management, the first drug they would prescribe is lidocaine. However, if patients have a minimal response to the lidocaine treatment, a history of heart disease or a high risk for cardiac complications, they are prescribed ketamine instead.

2.3.2 Inclusion Criteria

All of the participants in this study were receiving either ketamine or lidocaine infusions at this clinic as part of their routine medical care for chronic pain. The inclusion criteria for this study were:

- Be willing and able to provide informed consent
- Be receiving either ketamine or lidocaine IV infusions for moderate or severe pain
- Aged between 18 and 70 years
- Be sufficiently fluent in English to validly complete neuropsychological testing
- Have normal or corrected to normal vision and hearing
- Have no record of serious head injury or learning difficulties
- Participants were not eligible for infusions by the clinic if they had been diagnosed with a severe psychiatric illness, were pregnant or breastfeeding.

2.3.3 Sample size

A power calculation was conducted in order to establish required sample size. The power was put as 80%, the significance level as 5%, and two independent

groups. The proposed statistical analyses was an ANOVA. The previous thesis written on this study by C. Trotman reported multiple effect sizes for the interaction between cognitive task, drug and time period as there were various cognitive tasks and not an overall effect size. Therefore, the smallest effect size was used to allow for an over-estimation of sample needed rather than an under-estimation.

The effect size used was for the interaction between the verbal fluency cognitive task result, drug and time period (Cohen's d=0.18). From this, it was suggested that a maximum of 119 participants would be needed in order to gain enough statistical power for all cognitive tasks. At the end of recruitment in February 2019, there were complete data sets from a total of 99 participants. As such, the current study is underpowered to detect differences on tasks showing smaller effects.

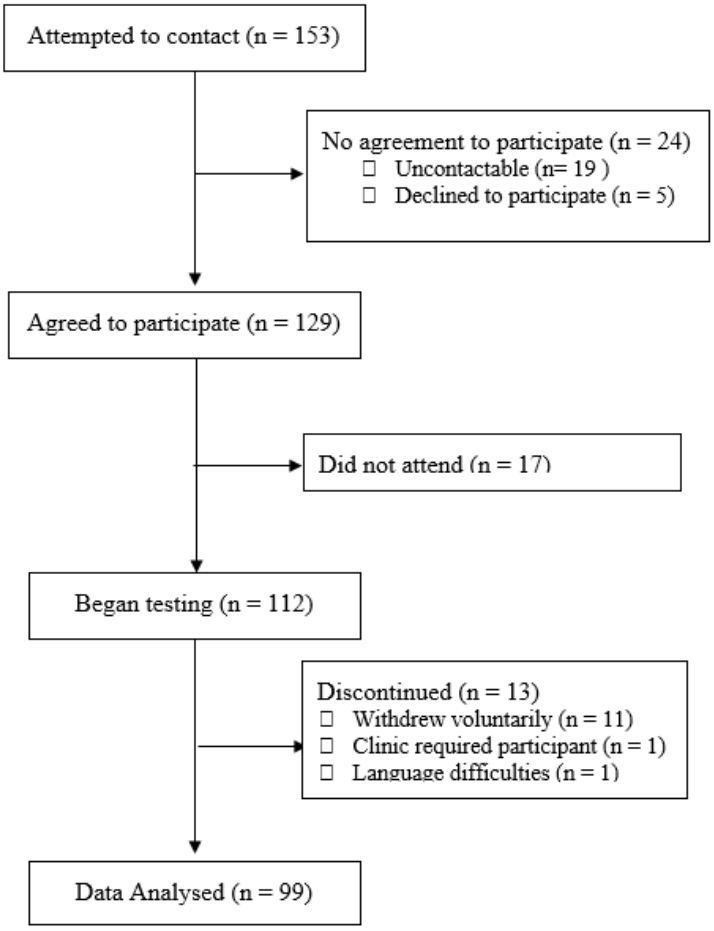
This research was started in 2017 by previous UCL clinical psychology doctoral trainees (C. Trotman and M. Knox) . That data was collected from February 2018 to May 2018, whilst the current data was collected from April 2019 to February 2020. On completion on the recruitment period, we amalgamated the data for a total of 56 lidocaine participants and 43 ketamine participants. The number discrepancy between the groups was due to less availability of eligible participants, as ketamine was the less common drug treatment compared to lidocaine, and clinic cancellations due to staff shortages.

2.3.4 Recruitment Response Rate

Attempts were made, either via phone or face-to-face, to contact all patients identified by the staff who were due to receive a ketamine or lidocaine infusion. See figure 2 for response rate flowchart.

Figure 2

Participation flowchart



2.3.5 Demographics

Participants provided demographic information, such as gender, age, ethnicity and education.

2.3.6 Ethics

Ethical approval for this research project was granted by the South Central - Berkshire Research Ethics Committee, Integrated Research Application System Number 214864, (see appendix 2.1). Participants were given information about the

study at least 24 hours prior to participating (appendix 2.1). They were all required to give informed consent prior to taking part (appendix 2.1). Participants were informed that their participation was voluntary, it did not affect their routine treatment and that they could withdraw at any point, with no implications for their on-going care at the clinic. It was important that there were no changes made to participant's routine medical care.

2.3.7 Procedure

The direct care team at the site identified possible study participants, which were then contacted by researchers to determine eligibility. If they wished to participate, an information sheet was emailed to them. Their medical team were informed of their wish to participate at their next infusion. When they attended their appointment, they were given the opportunity to ask further questions and asked if they would like to continue with the research. If they agreed, their consent and demographic details were collected, and then testing began.

Ketamine infusions lasted 30-60 min, however one participant received a two-hour ketamine infusion. Most lidocaine infusions lasted between one and three hours. Treatment doses were 0.15-0.6mg/kg for ketamine participants and 2-3mg/kg for lidocaine participants. The naturalistic method of this study meant that the dosage and length of infusion varied from participant to participant. The individual's medical team decided on dosage and length of infusion based on the client's needs and previous responses to treatment.

As previously stated, within this clinic, the first line of treatment for infusion patients is lidocaine, but patients' medical team may decide to switch them to

ketamine if analgesic response to lidocaine is inadequate. As such, 70% of the ketamine participants had previously received and failed to adequately respond to lidocaine (see table 3) The clinic's policy was to offer an infusion treatment to a patient maximum of every three months, regardless of drug.

2.3.7.1 Pre-infusion

Depending on how busy the clinic staff were on the day, the pre-infusion baseline was collected before or just after physiological instruments to monitor vital signs (heart rate, systolic/diastolic blood pressure, respiratory rate and oxygen saturation) were attached and participants cannulated. This flexibility ensured that the research did not interfere with usual patient care. See Table 1 for order of questionnaires.

2.3.7.2 Mid-infusion

Infusion mid-point was determined for each participant based on anticipated infusion duration provided by clinic staff. See Table 1 for the order of questionnaires and tests at mid-infusion.

Table 1.

Procedure for questionnaires and cognitive tests

Prior to Infusion (Time 1)	Mid Infusion (Time 2)
Visual Analog Scale	Visual Analog Scale
- Pain Intensity	- Pain Intensity
- Pain Distress	- Pain Distress

- Pain Interference - Depression	- Pain Interference - Depression
Story 1 - Immediate Recall	Story 2 - Immediate Recall
Verbal Fluency	Verbal Fluency
Serial Sevens	Serial Sevens
	Story 1 - Delayed Recall
	Story 2 - Delayed Recall

Note. The latter cognitive tasks were counterbalanced across participants. Once completed, the nurses would begin the infusion and the start time was noted.

2.3.7.3 Post infusion

Immediately post-infusion, participants were debriefed by researchers and given the opportunity to ask questions. Participants stayed in the clinic and were monitored until cleared to leave by the clinical team.

2.3.8 Design

This study used a non-randomised, independent groups design to compare patients receiving ketamine with those receiving lidocaine. Due to the drug being a part of participants' regular medical treatment, it was not possible to randomise or to blind participants. Furthermore, infusion length was significantly different for the two groups (30-60 minutes for ketamine and 2-3 hours for lidocaine), therefore the researchers were unable to be blinded.

2.3.9 Measures

Demographic details, including education and prescribed medication were collected alongside subjective measures of pain and cognitive tests (See table 1 and appendix 2.2). The original study chose these specific tasks through consultation with clinic staff and piloting.

- **Visual Analogue Scales (VAS).** Participants indicated their current state on four 0-10 VAS related to aspects of pain and depression as follows:
    - Pain Intensity (0 – no pain, to 10 – extremely intense pain)
    - Pain Distress (0 – no distress, to 10 – extremely distressing)
    - Pain Interference (0 – does not interfere, to 10 – interferes with everything).
    - Depression (0 – not depressed at all, to 10 – extremely depressed).
- **Story recall.** Immediate and delayed episodic memory was tested using two stories from the Story Recall subtest of the Rivermead Behavioural Memory Test (SR-78 RBMT – Wilson et al., 1985). The Story Recall subtest involves measures of delayed and immediate recall. In the immediate recall condition, the participant was asked to listen to a short passage of prose being read aloud, immediately after which they were asked to recall as much of the passage as they remembered. In the delayed recall condition, the participant was asked to recall as much as they could of the passage they heard earlier (see appendix 2.2).
- **Serial sevens.** This subtraction task is a test of working memory and concentration. Participants were given a three-digit number (303 or 304) and asked to sequentially subtract seven from that number as many times as they

could for 60 seconds. The number of correct subtractions were recorded along with errors made.

- **Verbal fluency.** The verbal fluency task measures semantic memory, verbal production and phonetic fluency, and is largely influenced by frontal lobe function. Participants were given a letter of the alphabet (H or L, which begin with a similar number of words in the Oxford minidictionary) and asked to list as many words as possible (excluding proper nouns) within 60 seconds that begin with that letter. Words were scored as either correct, repetitions or error if they used the incorrect letter or were proper nouns.

2.3.10 Statistical Analyses

All analyses were carried out with the Statistical Package for Social Sciences (SPSS Version 26). Descriptive statistics were used to summarise demographic variables (see table 1) and groups were compared at baseline using independent t-tests or chi-square tests.

Data was examined for the assumptions of parametric tests and where variables were not normally distributed, transformations were attempted. These were not retained as they did not improve the distribution of data. Histograms were created to explore the data, and no skewness or kurtosis was found. Furthermore, as the F-test in ANOVA is a robust measure (Field, 2018), meaning that it can tolerate violations of its assumption of normality, this test was used predominantly to explore the difference between ketamine and lidocaine on subjective pain (intensity, distress and interference) and cognitive functioning.

The method of data analysis addressed several independent questions and was conducted in a stepwise manner as follows:

1) Primary Analysis

    a. A Repeated Measures Analysis of Covariance (RM-ANCOVA) was conducted to explore the interactions between drug and time for subjective pain ratings and cognitive performance (prose recall, verbal fluency and serial sevens). Age was included as a covariate due to baseline group difference. This model was used due to its robust nature and ability to control for the covariate (age).

2) Secondary Analyses

    a. An independent samples t-test was applied separately to each drug group. This was chosen due to the data being normally distributed and therefore it was the most appropriate method to explore the changes in cognitive performance (prose recall, verbal fluency and serial sevens) between those on and not on prescribed opioids (independent variable).

    b. Correlational analyses was applied separately for each drug group to explore the relationship between changes in cognitive performance (prose recall, verbal fluency and serial sevens) with changes in subjective pain (intensity, distress and interference) and mood from baseline to midpoint. Pearson correlation analysis was applied as visual examination of histograms of the change scores suggested that they met the assumption of normal distribution.

2.3.11 Joint Work Declaration

This was a joint project with Joe Kibble. He investigated the relationship between the drugs, pain and mood using the same sample.

2.4 Results

2.4.1 Group Descriptives and Baseline Comparisons

Including the previously collected data, there were 99 individuals (72 female and 27 male). For the more recent data collection, we added an additional variable (psychotropic medication), therefore this variable will only be available for 41 of the participants (11 lidocaine and 19 ketamine).

There was a significant group difference in age, where those in the ketamine group were significantly older than those in the lidocaine group ($t(97)=-1.99$, $p=.049$). As the treatments being compared here are part of a stepped model of care, with individuals first being prescribed lidocaine, before moving onto ketamine if required, it is therefore unsurprisingly that the ages of the individuals in the ketamine group are significantly higher than those in the lidocaine group.

Table 2

Demographics and Results of Baseline Comparisons

	Ketamine (n = 43)	Lidocaine (n = 56)
Age, years	51.19 ± 11.70	45.93 ± 13.93
Gender, female	67%	77%
Education Years	13.59 ± 2.73	14.24 ± 2.61
Ethnicity, White British	53%	55%
Pain Relief - Opioids	8 (42%)	11 (50%)
Baseline Scores		

Story Recall 1	4.94 ± 3.20	4.88 ± 2.82
Verbal Fluency	10.88 ± 3.95	11.25 ± 4.73
Serial Sevens	7.57 ± 5.91	8.13 ± 7.44
Depression	5.40 ± 3.27	4.45 ± 3.00
Pain Intensity	6.79 ± 2.19	6.54 ± 2.24
Pain Distress	5.72 ± 3.01	5.52 ± 2.84
Pain Interference	6.97 ± 2.52	6.87 ± 2.85

* Significant baseline differences

As previously stated, within this clinic, the first line of treatment for infusion patients is lidocaine, but their medical team may decide to switch them to ketamine instead. Therefore, some participants had previously been infused with the other drug than what they were receiving the day of testing (see table 3).

Table 3.

Procedure Details

	Ketamine Group	Lidocaine Group
Mean dosage per kg	0.21 ± 0.91	2.61 ± 0.49
Mean length of infusion in minutes	45.58 ± 20.97	132.32 ± 36.08
Mean number of previous ketamine infusions	3.93 ± 4.92	0.07± 0.32
Mean number of previous lidocaine infusions	1.49 ± 1.65	9.45 ± 17.92

In all statistical tests used, Time 1 was defined as tasks completed prior to the

infusion, while Time 2 was defined as tasks completed at the mid-point of the infusion.

2.4.2 Pain

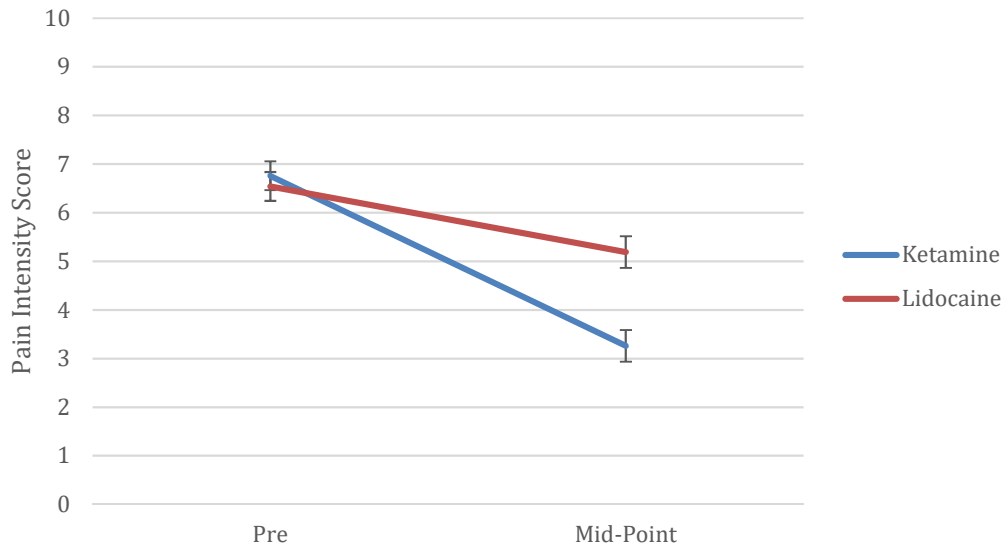
Acute changes in pain were analysed using Repeated Measures Analysis of Covariance (RM-ANCOVA). Age was included as a co-variate.

2.4.2.1 Pain Intensity

There was a significant interaction between drug and time for pain intensity ($F(1,95)=24.08$, $p<.001$, $\eta^2=.202$) (see figure 3). Post hoc comparisons using the Bonferroni correction indicated that from baseline to mid-point, pain intensity for the ketamine group reduced significantly more than the lidocaine group (Mean difference at time 2=-1.96, SE=0.50, p<.001, 95% CI [0.96-2.91).

Figure 3

Measure of pain intensity before and at mid-point of drug administration

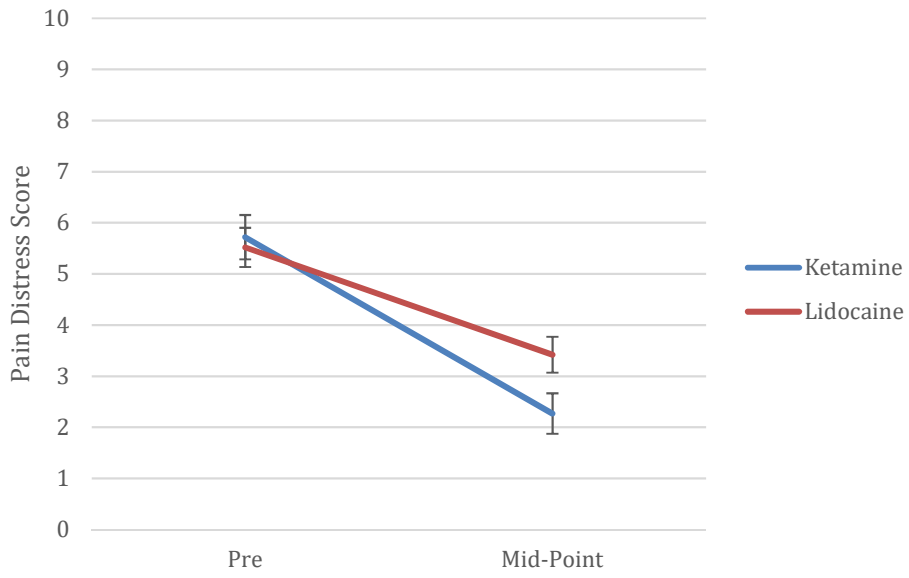


2.4.2.2 Pain Distress

There was a significant interaction between drug and time for pain distress ($F(1,95)=6.07$, $p=.016$, $\eta^2=.060$). Post hoc comparisons using the Bonferroni correction indicated that from baseline to mid-point, pain distress for the ketamine group changed significantly more than the lidocaine group (Mean difference at time 2=-1.16, SE=0.53, p=.010, 95% CI [0.10-2.22) (see figure 4).

Figure 4

Measure of pain distress before and at mid-point of drug administration

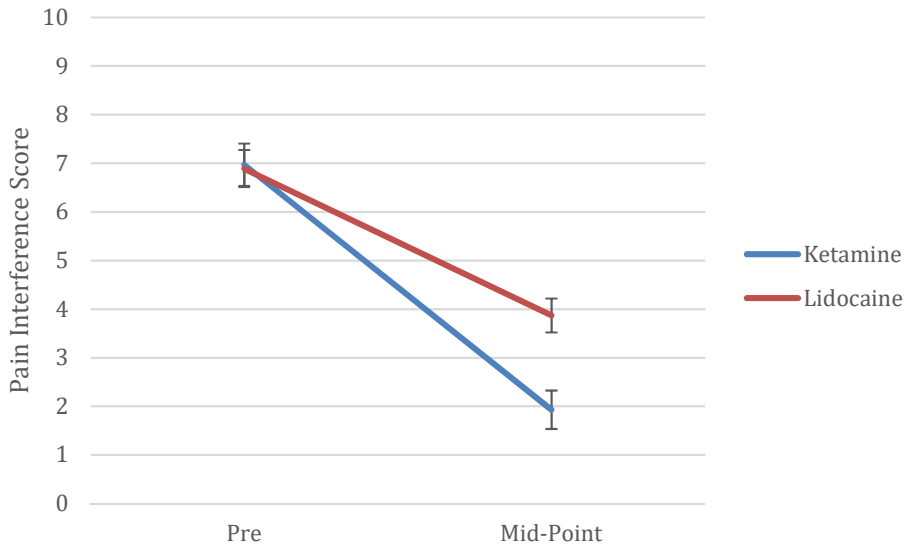


2.4.2.3 Pain Interference

There was a significant interaction between drug and time for pain interference ($F(1,94)=8.42$, $p=.005$, $\eta^2=.082$). Post hoc comparisons using the Bonferroni correction indicated that from baseline to mid-point, pain interference for the ketamine group changed significantly more than the lidocaine group (Mean difference at time 2=-1.94, SE=0.59, p=.001, 95% CI [0.79-3.10]) (see figure 5).

Figure 5

Measure of pain interference before and at mid-point of drug administration



2.4.3 Cognition

Changes in scores on cognitive tasks were analysed using RM-ANCOVAs with age as a co-variate.

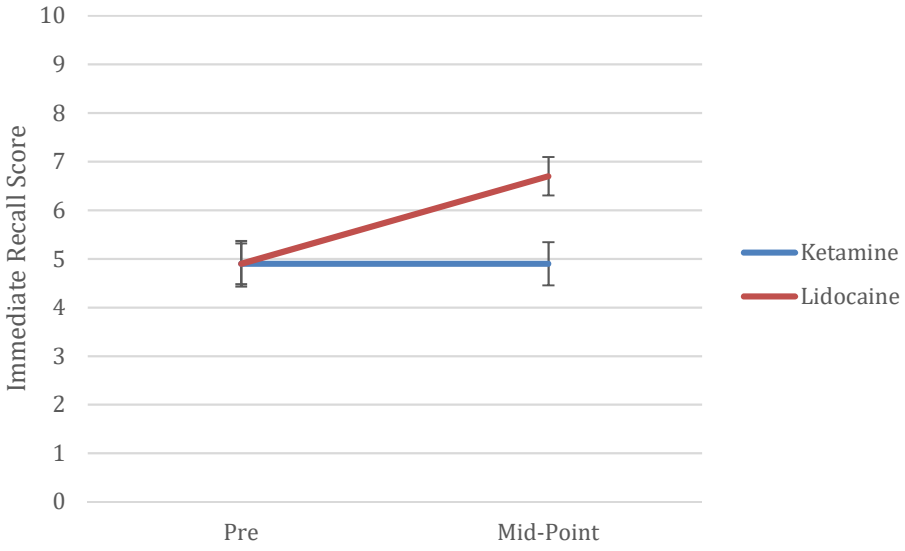
2.4.3.1 Story Recall

2.4.3.1.1 Immediate Story Recall

There was a significant interaction between drug and time for immediate story recall ($F(1,94)=8.85$, $p=.004$, $\eta^2=.0.86$). Post hoc comparisons using the Bonferroni correction indicated that from baseline to mid-point, immediate story recall scores for the lidocaine condition increased significantly more than the ketamine condition (Mean difference at time 2=-1.75, SE=0.60, p=.005, 95% CI [0.59-2.91]) (see figure 6).

Figure 6

Immediate Recall Score Before and at Mid-Point of Drug Administration

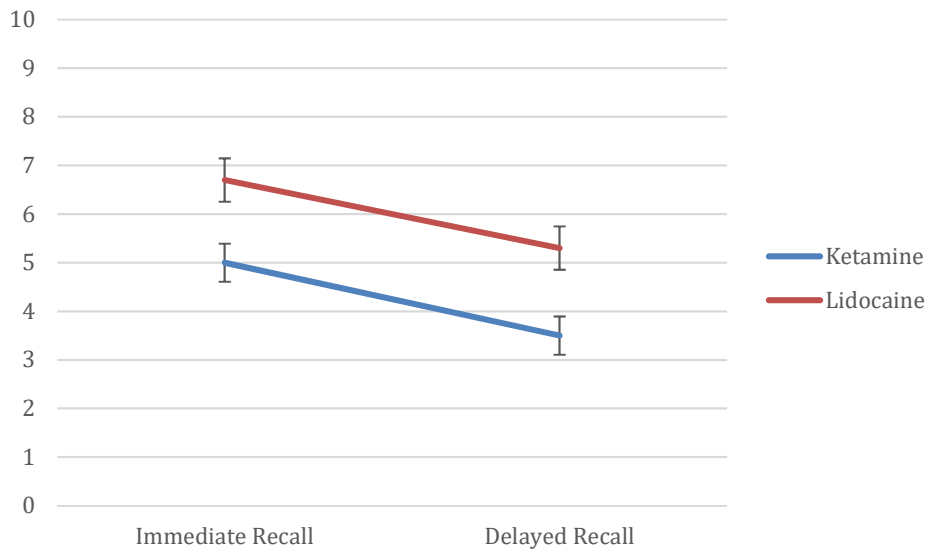


2.4.3.1.2 Mid-Infusion Prose Recall (Immediate and Delayed Recall)

There was no significant interaction between drug and time for mid-infusion prose recall ($F(1,93)=0.003$, $p=.958$, $\eta^2=.000$). There was no main effect of time ($F(1,93)=0.063$, $p=.803$), suggesting that there were no significant differences in mid-infusion task scores from time 1 to time 2. There was a significant main effect of drug ($F(1,93)=9.05$, $p=.003$). Post hoc comparisons using the Bonferroni correction indicated that those in the ketamine condition scored significantly less in both tasks than those in the lidocaine condition (Mean difference at time 2=-1.77, SE=0.57, $p=.003$, 95% CI [0.64-2.91]) (see figure 7).

Figure 7

Immediate and Delayed Recall Score at Mid-Point of Drug Administration

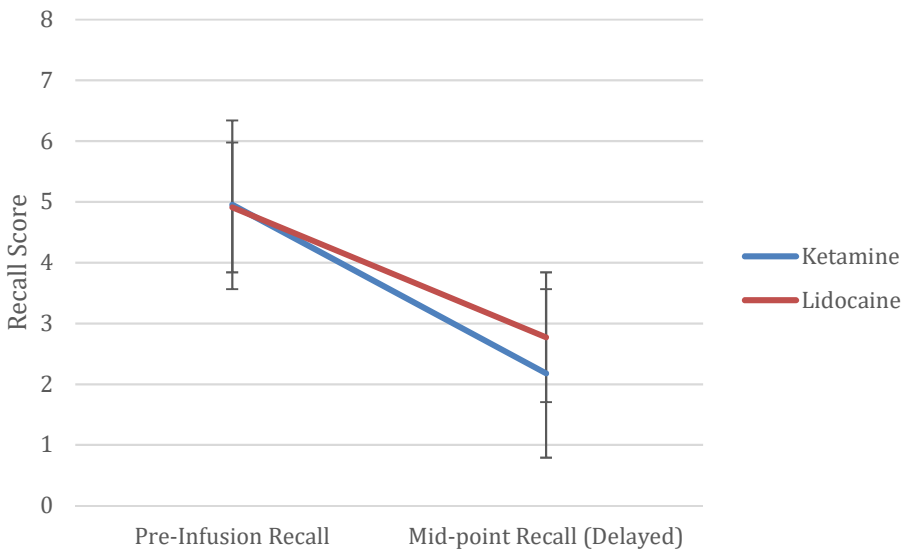


2.4.3.1.3 Prose Recall

There was no significant interaction between drug and time for immediate recall scores at time 1 (pre-infusion) and delayed recall scores at time 2 (mid-infusion) ($F(1,94)=2.54$, $p=.114$, $\eta^2=.026$). There was no significant main effect of drug ($F(1,94)=1.42$, $p=.707$). There was a significant main effect of time ($F(1,94)=8.04$, $p=.006$) (see figure 8).

Figure 8

Recall Score Before and at Mid-Point of Drug Administration



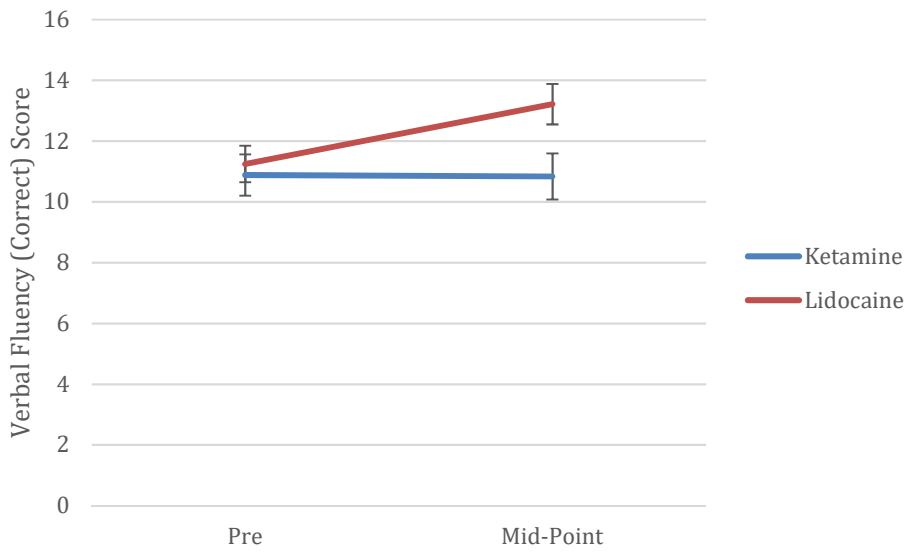
2.4.3.2 Verbal Fluency

There was a significant interaction between drug and time for verbal fluency correct scores ($F(1,95)=4.82$, $p=.031$, $\eta^2=.048$). Post hoc comparisons using the Bonferroni correction indicated that from baseline to mid-point, verbal fluency for the lidocaine condition increased significantly more than the ketamine condition (Mean difference at time 2=-2.38, SE=1.00, p=.036, 95% CI [0.39-4.37]) (see figure 9).

There was no significant interaction or main effects on verbal fluency errors ($F(1,92)=0.47$, $p=.494$, $\eta^2=.005$) or repetitions ($F(1,92)=0.57$ $p=.451$, $\eta^2=.004$).

Figure 9.

Verbal Fluency (correct) Score Before and at Mid-Point of Drug Administration

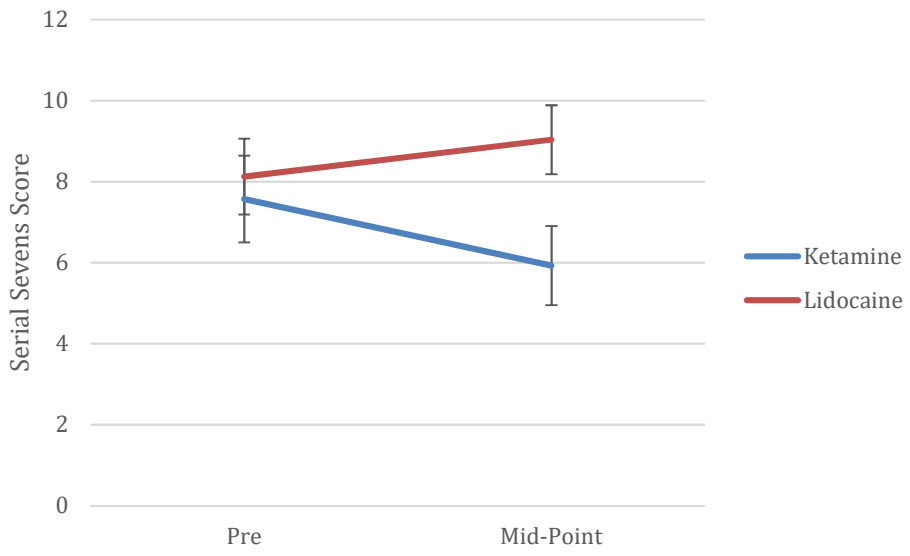


2.4.3.3 Serial Sevens

There was a significant interaction between drug and time for serial sevens ($F(1,94)=8.64$, $p=.004$, $\eta^2=.084$). Post hoc comparisons using the Bonferroni correction indicated that from baseline to mid-point, serial sevens for the ketamine group changed significantly more than the lidocaine group (Mean difference at time 2=-3.11, SE=1.30, p=.043, 95% CI [0.54-5.68]) (see figure 10).

Figure 10

Serial Sevens Score Before and at Mid-Point of Drug Administration



2.4.4 Secondary Analysis – Additional Medication

2.4.4.1 Ketamine Group

There was no significant difference in change from baseline to mid-point scores between those who were on prescription opioids and those who were not for immediate recall (t(17)=1.66, p=.115, d=0.67, 95% CI [-5.12-1.32]), verbal fluency (t(17)=-0.93, p=.366, d=0.53, 95% CI [-2.70-3.24]) or serial sevens (t(16)=1.18, p=.256, d=0.63, 95% CI [-3.87-2.42]).

2.4.4.2 Lidocaine Group

There was no significant difference in change from baseline to mid-point scores between those who were on prescription opioids and those who were not for immediate recall (t(19)=-1.23 p=.232, d=0.76, 95% CI [-4.48-0.53]), verbal fluency (t(20)=-0.19, p=.850, d=0.08, 95% CI [-4.66-0.72]) or serial sevens (t(20)=-0.48 p=.635, d=0.21, 95% CI [-1.24-4.36]).

2.4.5 Secondary Analysis – Correlations

Table 4 shows the Pearson correlation coefficient for the changes in scores on the pain measures, depression measure and cognitive tasks from baseline to follow-up. This is separated by drug group.

2.4.5.1 Ketamine Group

There was a significant correlation between changes in scores on the immediate recall task and serial sevens task. Furthermore, there were significant correlations between changes in VAS depression and all of the pain subscales (intensity, distress and interference).

2.4.5.2 Lidocaine Group

There was a significant correlation between changes in scores on the verbal fluency task and serial sevens task. Furthermore, there were significant correlations between changes in VAS depression and all of the pain subscales (intensity, distress and interference).

Table 4

Pearson's correlations between changes in cognitive performance, depression and pain scores

Ketamine								
Scale	N	1	2	3	4	5	6	7
1. Immediate Story Recall	43	–						
2. Verbal Fluency	43	.078	–					
3. Serial Sevens	42	.382*	.123	–				
4. Depression VAS	42	-.183	-.084	-.023	–			
5. Pain Intensity	43	.028	.072	.070	.418**	–		
6. Pain Distress	43	-.067	.121	.036	.482**	.731**	–	
7. Pain Interference	42	-.211	.142	.242	.440**	.526**	.593**	–

Lidocaine								
Scale	N	1	2	3	4	5	6	7
1. Immediate Story Recall	54	–						
2. Verbal Fluency	54	-.144	–					

3. Serial Sevens	54	-.144	.283*	–				
4. Depression VAS	54	.063	.011	.047	–			
5. Pain Intensity	54	.010	.020	-.013	.400**	–		
6. Pain Distress	54	-.065	.013	.004	.537**	.507**	–	
7. Pain Interference	54	-.005	-.066	-.100	.368**	.403**	.662**	–

Correlation is significant at the 0.05 level *

Correlation is significant at the 0.01 level**

2.5 Discussion

2.5.1 Summary

This paper describes a naturalistic study exploring the effects of acute sub-anaesthetic IV ketamine and lidocaine treatment on pain and cognitive functioning in individuals with a diagnosis of chronic pain. The associations between changes in pain, mood and cognitive performance were also explored.

2.5.2 Pain

As expected, both ketamine and lidocaine significantly reduced participants' reported pain from baseline to mid-infusion on all three measures (intensity, distress and interference). Those in the ketamine condition reported a significantly greater reduction in pain than those in the lidocaine condition. Due to the design of the study, we were unable to ascertain how long this pain relief lasted, and what variables, such as social interaction during infusion or activity post-infusion, impacted on the rate at which the pain returned.

These results are in-keeping with previous research that found that ketamine significantly reduced levels of pain in individuals with complex regional pain syndrome (Keifer et al, 2008) and that a single IV infusion of ketamine can relieve on-going pain in patients with peripheral nervous system disease-related pain (Backonja et al., 1994).

2.5.3 Cognitive Functioning

2.5.3.1 Episodic Memory

Individuals who received the lidocaine infusion improved their immediate prose recall scores from pre-infusion to mid-infusion, which could tentatively be explained by practice effects in this group. Those who received ketamine showed no change in their immediate recall scores so this group did not benefit from practice effects. This explanation fits with experimental studies which have used randomised, placebo-controlled designs and shown that ketamine blocks practice effects (for review see Morgan & Curran, 2006). Pain reduction is not an explanation as there was no correlation between change in pain and change in cognitive functioning.

When examining the drug impact on delayed recall, it was dependent on whether encoding took place whilst on the drug or prior to the infusion. When encoding into episodic memory took place pre-drug, there was a main effect of time suggesting that both conditions remembered significantly less at delayed recall than at the immediate recall, but ketamine did not impair significantly more than lidocaine.

However, when encoding took place mid-infusion, there was a main effect of drug, which is suggestive that those in the ketamine condition remembered on average significantly less on both tasks than lidocaine. This is suggestive that those in the lidocaine condition have improvements in their encoding of episodic memory during infusion, which in turn improves their retrieval at mid-infusion. These improvements could be due the cognitive improvements associated with a reduction in pain, or practice effects, but those in the ketamine condition appeared to be unable to access these benefits.

These findings are consistent with previous research that found acute ketamine is associated with memory impairment (Honey et al., 2003; Morgan & Curran, 2006; Olofsen et al., 2012). However, this study specifically found that ketamine impacts on individuals' ability to benefit from practice effects. Therefore, on the surface there appears to be limited change to episodic memory, however, once compared to another drug, in this case lidocaine, there appears to be a practice-blocking effect on how l individuals can perform cognitively once ketamine is in acutely their system.

2.5.3.2 Working Memory and Concentration

Individuals in the ketamine condition were significantly impaired on a task of working memory and concentration (serial sevens task) compared to the lidocaine condition following drug administration. Those in the lidocaine condition had a small increase in scores, which could potentially be explained by practice effects, whilst the ketamine group experienced a small decrease in scores. This suggests that the ketamine impacted the participants in a way that meant they were unable to access the benefit of practice effects like the lidocaine group were able to.

Ketamine has been found to not impair simple maintenance of information in the working memory (Morgan & Curran, 2006), but the serial sevens task requires not only maintenance of information, but manipulation of that same information (i.e. working memory). This more advanced cognitive ability has been shown to be impaired by ketamine (Honey et al., 2013; Morgan & Curran, 2006).

2.5.3.3 Semantic Memory, Verbal Production and Phonetic Fluency

Individuals in the ketamine condition did not improve their scores over time on a task of semantic memory, verbal production and phonetic fluency (verbal fluency task)

such as the lidocaine group did. The improvement in the lidocaine group could again be due to practice effects.

Interestingly, there were no significant changes in errors or repetitions from baseline to midpoint for either drug condition. This is suggestive that ketamine's impact does not stretch to memory issues concerning what words the individual has already said or what the rules are (e.g., no proper nouns). It could also be interpreted that the ketamine did not impact on individuals' response inhibition, as if they were unable to think of a correct answer, they would stay quiet rather than say any word and make an error or repetition.

Nagels et al. (2011) reported that within healthy subjects, ketamine significantly impacted on lexical and semantic verbal fluency, compared to a placebo, but not phonetic fluency. This is in-keeping with our results. Chan et al. (2013) found that ketamine users, compared to healthy controls, had significantly impaired verbal fluency, however, that is within a group of frequent recreational users, rather than frequent users for medicinal purposes.

2.5.4 Pain, Cognitive Functioning and Mood

There was no significant relationship between changes in cognitive functioning and changes in pain or depression scores. These results are different to those of Chen et al. (2018) who found associations between depressive symptoms and scores on the go/no-go task. However, that task specifically assess the inhibitory control aspect of cognitive functioning, which this study did not assess.

However, there were significant correlations between changes in all pain measures and depression for both drugs, suggesting that the greater the reduction in pain, the greater the improvement in mood for both drugs.

For those in the ketamine condition, changes in scores on the serial sevens task were significantly related to changes in the immediate story recall task. This could be because both of these tasks require elements of working memory and concentration. However, this same significant relationship was not found in the lidocaine condition, suggesting that lidocaine does not impact on working memory and concentration in the same way that ketamine does.

2.5.5 Additional Medication

Analysis indicated that there were no significant differences in cognitive performance at mid-point for those in either the ketamine or lidocaine condition who use additional opioid medication. However, the data on additional medication was only collected for approximately half of the participants, and therefore the power would have been considerably lower for this variable, thus a high risk of a Type II error.

Research has found that those who use opioids frequently, such as for chronic pain, are much less likely to experience cognitive impairment (Zacny, 1995), which would be in-keeping with the results from this study. However, other research found that within palliative care, instant release morphine, when taken on top of a slow release opioid, produced transient anterograde and retrograde memory impairments (Kamboj et al., 2015). Ketamine has been found to reverse tolerance to opioid medications (Hoffmann et al., 2003), therefore, with a bigger sample it would be interesting to

explore whether there is a difference in pain and cognitive functioning response to ketamine between those taking opioids and those not taking opioids.

2.5.6 Limitations

As this was a naturalistic study where participants' drug, dosage and infusion length were decided by their medical team as part of their on-going care, it was not possible to control these areas, nor blind participants, researchers or staff to the drug group.

Sensitisation, which is an increase in an effect of a drug with repeated use (such as for use in chronic pain), research has found that with rats, administration of ketamine within a novel environment increased the sensitisation compared to in a "home environment", but the sensitisation did not occur in social isolation, but did within pairs (Trujillo & Heller, 2020). Many patients chose to sleep or quietly rest during their infusions, which reduced noise, but others chose to actively engage with other patients or their family/friend escort. A limitation of the current study is that the level of social engagement prior to and during the experimental session could not be controlled. This could suggest that those who are less familiar with the clinic environment experience an increased effect of the drug compared to those who are familiar. Furthermore, this research suggests that those who interacted with another person during the infusion would experience an increase in the effect of the drug compared to those who chose to sleep or quietly rest.

We were unable to control how many, previous infusions of either ketamine or lidocaine individuals had received. However, the clinic protocol was for infusions to be a minimum of three months apart. This time lapse ensured that the previous drug would

be out of the individuals system (Khan et al., 2014) before their infusion for which they were tested on, and therefore have a minimal to no chance of impacting on their performance.

The previously mentioned difference in infusion lengths also impact on the time elapsed between cognitive tasks. Ketamine infusions were 30-60 minutes long, therefore they repeated the cognitive tasks 15-30 minutes after baseline. Whereas lidocaine infusions were two to three hours long, therefore they repeated the tasks 60-90 minutes after baseline. Moreover, this was only if there were no medical or staffing complications that delayed the start of the infusion, such as difficulties cannulating or awaiting a doctor to sign a prescription or consent form. Therefore, due to recency effects, it could be argued that those receiving ketamine had an advantage, but the results show that individuals in the ketamine condition scored lower than those in the lidocaine condition.

In hindsight, it may have been beneficial to conduct a delayed recall task at baseline in order to use this as a control for changes in delayed recall. For this study, the first delayed recall task was conducted 15-30 mins after the immediate recall (ketamine condition) or 60-90 minutes (lidocaine condition), whilst the second delayed recall was only 5-10 minutes after the initial immediate recall, with other cognitive tasks in-between that acted as distractors. Therefore, there is a greater chance of recency effects improving the scores of the second, more recent, delayed recall. This was controlled for the in analysis by looking at each delayed recall score independently to the other.

The clinic is nationally recognised for its excellence for people with chronic pain, and therefore their clients' pain has a varied etiology. Our participants had experienced different intensity, chronicity and location of pain. This in turn also meant

they were on varying medications, with some participants reporting that they prefer a more natural or holistic way of managing their pain, with others on a variety of medication. The study recorded those who were on opioids to explore if this played a role on the impact on cognitive functioning. However, there would be too many confounding factors to control for, such as interaction with other medication, tolerance of medications, type of opioid, how recently they had taken other medication and dosage. Other studies, such as Chen et al. (2018), also allowed their participants to continue prescribed medication, as they felt it would be unrealistic and unethical to request they stop all medication when they have complex medical and psychiatric conditions.

2.5.7 Implications

Chronic pain is a debilitating condition which can dramatically impact on individuals' lives. The research here demonstrates that both lidocaine and ketamine sub-anaesthetic infusions are able to significantly reduce pain intensity, distress and interference for individuals with a varied etiology of their chronic pain. However, as ketamine has been shown to reduce pain significantly more, and in a shorter time frame (30-60 minutes compared to 2—3 hours), it is curious as to how this may impact on opinions of the drug in the clinic, especially as it is only considered once lidocaine does not work, or is not medically appropriate. However, it is unclear how long this reduction in pain lasts, and whether it lasts for more or less time than the effects of the ketamine.

Although the results of the study tentatively add to the evidence base for the efficacy of acute sub-anaesthetic ketamine infusions in treating chronic pain, further understanding of the longer-term effects on cognitive performance need to be explored.

For example, we need a greater understanding if there is a slow cognitive decline over several years for individuals who are receiving ketamine infusions consistently every three months, or individuals need to be fully informed if their episodic memory is compromised in the short-term.

Finally, the implications of the cognitive effects of ketamine need to be considered in clinical practice, for example, a greater emphasis on not providing or discussing important information with patients once the infusion has begun, or providing this in written format so that they may read over it again in their own time.

2.5.8 Directions for Future Research

Future research should aim to conduct a similar study, but with a more comprehensive battery of neuropsychological tests, taking into account that participants are in pain, and a more comprehensive follow-up. It would be interesting to understand how long the cognitive impairments found continue for, and if there are other specific areas of cognitive functioning that are impacted. However, this needs to be balanced against acceptability of research protocols, which can be taxing for participants and can interfere with their treatment.

Future studies, if possible, should be blinded and explore individuals' subjective expectations of when the drug will make a difference. Although this was a quantitative study, the researchers found that multiple participants gave very specific verbal expectations of when the drug would make a difference, with some stating the effect is immediate, whilst others believed the drug took 2-3 days to make a difference to their pain. It would be interesting for future qualitative and quantitative studies to explore this. Furthermore, this could also potentially explore how an individual's perception of

the strength or impact of ketamine (a well-known recreational drug) compared to lidocaine (a less well-known medical drug) and how this may impact on their subjective pain experience.

Another interesting research direction would be exploring whether clinic environment, participation in the study, or social interaction during the infusion impacts on individuals changes in pain, mood and cognitive performance. Trujillo and Heller (2020) found that within rats, there was an increase in the effect of ketamine when administered in a novel environment or within social pairs. This could be suggestive that "regulars" at the clinic may benefit less from the ketamine infusion over time, and that those who sleep or do not socialise during the infusion may benefit less than those who remain socially active throughout, such as by talking with other patients, staff or their escort.

2.5.8 Conclusions

In summary, an exploratory analysis of the use of sub-anaesthetic ketamine in the treatment of chronic pain suggest that acute ketamine infusions produced more short-term pain relief than lidocaine.

Working memory and concentration (serial sevens task) was impaired by ketamine, as well as phonetic fluency (verbal fluency task). For episodic memory, encoding, processing and retrieval were impaired by ketamine, dependent on whether encoding took place on the drug or off of the drug.

Future research should investigate the longer term analgesic properties of ketamine in a chronic pain population, along with the impairments to cognitive

functioning, both acute and chronic. This would be beneficial information for clinicians who are considering prescribing the drug for their chronic pain patients.

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Part 3: A Critical Appraisal

3.1 Overview

This critical appraisal offers personal reflections on the experience of conducting the systematic review and empirical study. It draws on a reflective journal that I kept over the research period and incorporates existing literature where possible. Firstly, it will reflect on my experiences of picking a research project and joining a pre-established study. Secondly, it will discuss my experiences of the difference between working clinically in neuropsychology compared to when conducting research in neuropsychology. Finally, the report considers the experience of writing up research and conducting statistical analysis when you have limited experience in that area.

3.2 Choosing a Research Topic

At the time of choosing research topics, one of my areas of key interest was the link between gut health and mental health. Although I was interested in this very niche area, I knew very little about it, and had very limited research experience. There was the opportunity to do a study along these lines, but the topic and research methods were very vague and therefore for me, slightly intimidating. I remember at the time feeling like the doctoral course was already challenging enough and I felt I would be shooting myself in the foot. From this, I decided it would be more sensible to choose a topic I was interested in but one that had a clearer structure and direction.

The literature on clinical psychology trainees speaks to individuals being "perfectionists" (Richardson et al., 2018), which I feel I can relate to, and perhaps my avoidance of my passion project actually had underlying tones of a sense of not being able to do it perfectly, and therefore I avoided it all together. However, it could also be argued that my decision came from a place of self-compassion; an awareness that I was

already being challenged and to not take on too much. It has been found that with psychology doctoral trainees, self-compassion is linked with lower levels of depression and burn-out (Richardson et al., 2018), which is perhaps why I feel although I've had my fair share of ups, downs and exhaustion, I've managed the majority of difficulties in my stride.

3.3 Joining a Study

One of the differences with the ketamine study that I completed compared to the other options was that it was already an established study, meaning that previous clinical psychology doctorate trainees had started this study as their project, and they were looking for new trainees to continue and expand on this study.

There are pros and cons to joining an established study. Firstly, I count myself very lucky to not have to have gone through the pain of UCL and NHS ethics. Watching the stress, exhaustion and pain of my cohort applying for ethics made me very grateful for the hard work of the previous trainees. The study had ethical approval for five years already, and therefore unless we wanted to make major changes, which we didn't, we would not need to apply for alterations. Secondly, my experience prior to the doctorate is predominantly with clinical work and I feel research is not something that comes naturally to me, although this could once again be a reflection of the perfectionism traits associated with clinical psychology trainees (Richardson et al., 2018). Therefore, at the time I assumed that a pre-established study would be better suited to my ability level.

However, there are also cons to joining a study. Firstly, it can be challenging to understand why things were designed in a certain way when you were not present at the study planning meetings and discussions, and perhaps in some cases, you feel you would

have preferred to do things slightly differently. Secondly, you have to ensure you copy the previous trainees' methods of data collection and storage to ensure reliability across researchers. This was challenging at times as the previous trainees had left UCL, and therefore communication took a while.

Going into the study, I was aware that I was already building on an established dataset, had approximately nine months for data collection, and therefore felt less pressured with the recruitment process. However, the logistics of data collection made it hard to assess more than one participant a day, and we had limited days in the clinic. For example, we could not assess two participants near to each other in the clinic, as they would overhear each other and then possibly be primed for the cognitive assessments; thus we were limited to one participant per ward per time slot (AM or PM). Therefore, the pressure quickly built, knowing that one participant could require you to be in the clinic for up to five hours.

3.4 Joint Working

Prior to the study, myself and my study-partner Joe did not really know each other and it could be considered a risk taking on a long-term study with someone you do not know. However, I think going into the study I underestimated the benefits of having a study-partner. I feel we worked well together and it was really beneficial having him as additional support and somebody to bounce ideas off of.

I was conscious to ensure that Joe and I were splitting the work evenly, but also playing to our strengths and availability. To begin with, Joe was very quick at booking in clients, whilst I spent more time scoring the questionnaires and managing the data

entry. I believe by the end of data collection, we had both assessed roughly the same amount of participants.

Another benefit to joint working was discussing our experiences of assessing individuals in research, compared to our usual therapeutic settings, and their reports of what it was like to participate in research. At times I almost felt uncomfortable asking about depression, for fear of starting a conversation that I wasn't in a position to then provide containment for. When conducting the research, there were a few participants who commented that I was one of the first people to ask about their depression in years, or told me detailed accounts of their battles with mental health, and I almost felt responsible then for their treatment, which was not my role. Although I passed this information onto their clinical team, it was hard to shake off the feeling of wanting to do more.

Research suggests that therapists significantly overestimate the negative effects and underestimate the benefits of individuals participating in research (Marshall et al., 2001). In the same research, participants commented that questionnaires during treatment were 'slightly to moderately' helpful in promoting self-realisation. This I find particularly interesting, as I do wonder how asking individuals to actively track how the drug is affecting their pain, mood and cognitive functioning, impacts on their experience. For example, is it disappointing when it feels like the drug has not changed things and then that impacts on future ratings, or is there a moment of realisation that treatment has reduced their pain which in previous infusions may have not been noticed.

My study-partner and I discussed that many participants were keen to participate and a delight to work with. On reflection, I went into this study thinking that it would be hard to recruit, whereas once participants were identified, the majority of them wanted to

participate, with several commenting that they wanted to contribute to science, they enjoyed it, or it distracted them from their pain. According to Zullino et al. (2003), participants mainly agree to participate in studies in order to help science progress and to allow future patients to benefit from improved diagnosis and treatment. In fact, many participants requested us to send them the results as soon as possible.

3.5 Neuropsychology in Research compared to Clinical Practice

One of the main reasons I was interested in the ketamine and cognitive functioning study is due to my interest in neuropsychology. However, my adult neuropsychology placement in my second year threw up lots of questions about my research. I quickly learnt that clinical neuropsychology in practice and its assessments are different to the world of neuropsychology research.

Firstly, as I learnt quickly completing my literature review, the term “cognitive functioning” is used far more broadly in research than in clinical work. For example, within clinical work, for somebody to make conclusions on an individual’s “cognitive functioning”, then multiple time-consuming tests would have been conducted, along with references to pre-morbid functioning and multiple hypotheses for those results. However, in research, I was surprised to find that some research uses the MMSE, which is mainly a screening tool, to make conclusions on participants “cognitive functioning”.

After my literature search, I felt that reduced cognitive testing (compared to clinical settings) was commonplace in research for a variety of reasons, such as time constraints. It initially felt uncomfortable for me to state that my study looked at cognitive functioning, when I knew I meant only three small areas of it, which was a very small amount within clinical neuropsychology work. However, working with

individuals with chronic pain is complicated as you have to navigate their pain, distress and the nursing care they are receiving at the same time.

A methodological issue I struggled with, which relates to joining a study where you did not participate in the design process, was picking the cognitive tests and their order. I did not know the literature on the pre-established cognitive effects of ketamine well-enough to understand why certain tests had been picked. Moreover, from my clinical experience, I felt there would have been other tests I would have liked to include to get a deeper understanding of their cognitive functioning. For example, I felt lots of people reported their dislike for the serial sevens tasks, as they weren't confident with maths, and I know there are other working memory assessments that take the pressure off of mathematical skills, such as digit span, which can also give insight into effort levels. However, I'm aware that there was a lot of careful thought and effort in choosing the final tests, and also there had to be a balance in how much we assessed these individuals, as we were also collecting mood data for Joe's part of the study.

The final methodological issue I grappled with was assessing immediate memory and delayed memory, but labelling it as "memory". For me in the way that I've been taught clinically, these are two areas that contribute to an individual's memory rather than form the entity of. However, in research, I have found it is common-place to be more broad with terminology.

3.6 Statistical Analysis and Research Writing

As I previously mentioned, I feel I have limited experience in research, but the course were clear from the outset that as this is doctoral level work, there is a greater expectation of your independence when it comes to these projects. To begin with,

reading around the subject was difficult as I truly didn't understand some of the papers I was reading. Thankfully, I discovered some helpful podcasts that were able to explain the basics to me, so that when I did read the more advanced papers, I could better understand them.

Both statistical analysis and report writing felt like a steep curve to me as it is not something we regularly practice. My style of writing has always been more casual, which fits well when writing therapeutic reports, but not when writing research. My supervisors gave me lots of constructive feedback which I tried to carry through any report I was writing. However, with constant constructive feedback and a perfectionist mindset, it was challenging to not let this "get me down" and feel I'm not intelligent enough for this work. On reflection, this was a test of my high standards for academics and perfectionism.

Reflecting back now, I know significantly more about ketamine and its effect on cognitive functioning than ever before, and yet I am nowhere near to being an expert on the topic. The brain and its reaction to drugs is a complex phenomenon that seems to change between individuals and conditions. I originally thought that identification of which aspects of cognitive functioning are effected by ketamine would be fairly straight-forward, as long as you were looking in the right place. I assumed this due to my clinical work, where patients cognitive functioning is normally based on injury or impairment to one specific area of the brain. However, it dawned on me that within my experiences of clinical neuropsychology, their cognitive functioning does not change on a minute-by-minute basis depending on how much drug is in the system. Their consistent cognitive impairment makes it easier for them to identify exactly what they find easy and difficult, and then we would test that. Whereas with ketamine, it appears the impairment can be so

acute, it can be hard for individuals to pinpoint what it is that they find tricky with the drug in their system compared to when it is not in their system.

3.7 Conclusion

To conclude, I didn't apply for the doctorate for the research opportunity, my main love is clinical work. However, the experience has taught me a lot and I am glad I got the opportunity. Firstly, I now know a lot more about ketamine, chronic pain and research into cognitive functioning. Secondly, no matter how hard I found it, I still completed a doctoral level thesis which reminds me of my intelligence, diligence and transferable skills. What I have learnt about cognitive functioning, and the difference between research and the clinical world, have furthered my passion for the area, and if given the opportunity, I would like to contribute to the world of research again.

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Appendices

Appendices Part 1: Systematic Review

Appendix 1.1: Search strategy used for PsychINFO database

Table 1

Search strategy used for PsychINFO database

Database: PsycINFO <1806 to September Week 2 2019>
Search Strategy:
1 Ketamine/ (1925)
2 Neuropsychological Tests/ or Executive Function/ or Cognition/ (41437)
3 Attention/ (36822)
4 Learning/ or "Memory and Learning Tests"/ (62796)
5 language.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (229546)
6 Memory, Long-Term/ or Memory Consolidation/ or Memory, Short-Term/ or Wechsler Memory Scale/ or "Memory and Learning Tests"/ or Spatial Memory/ or Memory/ or Memory, Episodic/ (70163)
7 cogniti*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (575034)
8 major depressive disorder.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (19951)

9 bipolar disorder.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (39346)
10 treatment resistant depression.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (2889)
11 8 or 9 or 10 (58650)
12 exp Cognitive Ability/ or exp Cognition/ or exp Cognitive Processes/ (770021)
13 brain function.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (8669)
14 mental function.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (772)
15 2 or 3 or 4 or 5 or 6 or 7 or 12 or 13 or 14 (1249119)
16 1 and 11 and 15 (69)
17 limit 16 to (human and english language and abstracts) (57)

Appendix 1.2: Tools Used to Assess Studies

Tool 1: Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I)

Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355; i4919; doi: 10.1136/bmj.i4919.

Figure 1

A summary table from the ROBINS-I assessment tool

Table 1. Bias domains included in the ROBINS-I tool

Domain	Related terms	Explanation	
Pre-intervention			
Bias due to confounding	Selection bias *as it is sometimes used in relation to clinical trials* (and currently in widespread use within Cochrane); Allocation bias; Case-mix bias; Channelling bias.	Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline. ROBINS-I can also address time-varying confounding, which occurs when individuals switch between the interventions being compared and when post-baseline prognostic factors affect the intervention received after baseline.	Pre-intervention or at-intervention domains for which risk of bias assessment is mainly distinct from assessments of randomized trials
Bias in selection of participants into the study	Selection bias *as it is usually used in relation to observational studies and sometimes used in relation to clinical trials*; Inception bias; Lead-time bias; Immortal time bias. Note that this bias specifically excludes lack of external validity, which is viewed as a failure to generalize or transport an unbiased (internally valid) effect estimate to populations other than the one from which the study population arose.	When exclusion of some eligible participants, or the initial follow up time of some participants, or some outcome events, is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical. This form of selection bias is distinct from confounding. A specific example is bias due to the inclusion of prevalent users, rather than new users, of an intervention.	
At intervention			
Bias in classification of interventions	Misclassification bias; Information bias; Recall bias; Measurement bias; Observer bias.	Bias introduced by either differential or non-differential misclassification of intervention status. Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null. Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias.	

Post-intervention			Post-intervention domains for which there is substantial overlap with assessments of randomized trials
Bias due to deviations from intended interventions	Performance bias; Time-varying confounding	Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s). Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention).	
Bias due to missing data	Attrition bias; Selection bias *as it is sometimes used in relation to observational studies*	Bias that arises when later follow-up is missing for individuals initially included and followed (e.g. differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders.	
Bias in measurement of outcomes	Detection bias; Recall bias; Information bias; Misclassification bias; Observer bias; Measurement bias	Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects.	
Bias in selection of the reported result	Outcome reporting bias; Analysis reporting bias	Selective reporting of results in a way that depends on the findings.	

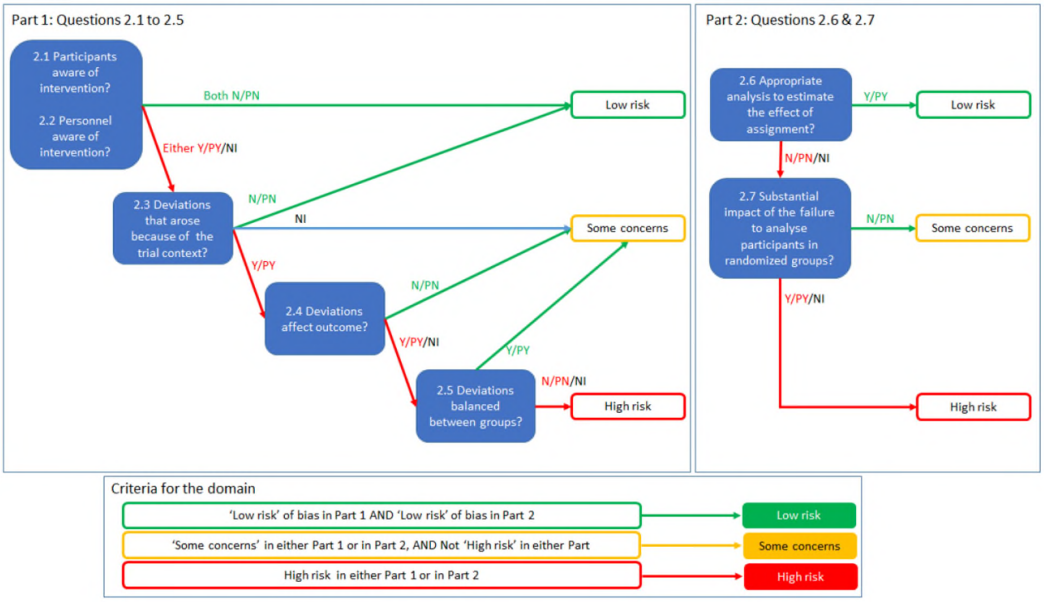
Tool 2: Risk of Bias in Randomised Trails (ROB-2)

Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.

Figure 2

An example from the ROB-2 assessment tool

Figure 2. Algorithm for suggested judgement of risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*).



Appendices Part 2: Empirical Paper

Appendix 2.1: Confirmation of Ethical Approval, Information Sheet and Consent Form

NHS
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

[redacted]

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

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 3447 3042.

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 Anaesthesiologist's: 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)

IRAS ID: 214864 Version 4 (25/1/19)

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: Georgia Halls and Joe Kibble

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 2.2: Participant Research Pack

Participant ID			

BASELINE TASKS

HOW ARE YOU FEELING?

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

Pain intensity

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

Pain distress

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

Pain interference

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

Depressed

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

Participant ID			

IMMEDIATE STORY RECALL, STORY 1 [1 of 1]

Next I am going to play you a short passage.
Listen carefully, and when it has finished, tell me back as much as you can remember.
Ready?

[Play story 1]

Now tell me back as much as the story as you can

Three hundred men / walked out / of a car factory / on Clydeside / this morning / following an announcement / of large - scale redundancies. / Mr David / Mitchell, / a company director / told reporters / that the factory / had suffered losses / because of high interest rates / low productivity / and foreign competition. / Union officials / have agreed to begin / negotiations / with management / tomorrow.

Participant ID			

 **[60 seconds]** **VERBAL FLUENCY**

In a minute I'm going to give you a letter of the alphabet and I'd like you to say as many words you can think of that begin with that letter in 60 seconds.

For example, if I said 'F' you could say friend, face, funny, flat and so on.

Please do not say people's names or places. OK?

The letter is H

Immediately start timing & write down all responses.

Score – number correct and errors (repetitions; proper nouns).

Participant ID			

 **[60 seconds]** **SERIAL SEVENS**

Next I'm going to say a number and I want you to repeat that number and then subtract 7 from it, and then take another 7 from that number and so on.

So if I said 207, you would say 207, 200, 193, 186 and so on for 60 seconds.
OK?

The number is 304

Immediately start timing & write down all responses.

4

Participant ID			

INFUSION TIME STARTED: _____

MID INFUSION TASKS

HOW ARE YOU FEELING?

Instructions: **Like we did before, 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

Depressed

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

Participant ID			

IMMEDIATE STORY RECALL, STORY 2 [1 of 1]

Next I am going to play you a short passage. Listen carefully, and when it has finished, tell me back as much as you can remember. Ready?

[Play story 2]

Now tell me back as much as the story as you can

A wide stretch / of the River Trent / in Nottinghamshire / was closed / by police / at the weekend / when divers / discovered / an old bomb / from an RAF Lancaster / which had crashed / in 1943. / All the surrounding farms / and villages / were evacuated / whilst military experts / detonated / the bomb. / The blast / could be heard/ over five miles away.

Participant ID			

 **[60 seconds]** **VERBAL FLUENCY**

In a minute I'm going to give you a letter of the alphabet and I'd like you to say as many words you can think of that begin with that letter in 60 seconds.

For example, if I said 'F' you could say friend, face, funny, flat and so on.

Please do not say people's names or places. OK?

The letter is L

Immediately start timing & write down all responses.

Score – number correct and errors (repetitions; proper nouns).

Participant ID			

 **[60 seconds]** **SERIAL SEVENS**

Next I'm going to say a number and I want you to repeat that number and then subtract 7 from it, and then take another 7 from that number and so on.

So if I said 207, you would say 207, 200, 193, 186 and so on for 60 seconds.
OK?

The number is 303

Immediately start timing & write down all responses.

Participant ID			

DELAYED STORY RECALL, STORY 1 & STORY 2 [1 of 1]

Do you remember the two stories you heard earlier? Tell me as much of them as you can.

Three hundred men / walked out / of a car factory / on Clydeside / this morning / following an announcement / of large - scale redundancies. / Mr David / Mitchell, / a company director / told reporters / that the factory / had suffered losses / because of high interest rates / low productivity / and foreign competition. / Union officials / have agreed to begin / negotiations / with management / tomorrow.

A wide stretch / of the River Trent / in Nottinghamshire / was closed / by police / at the weekend / when divers / discovered / an old bomb / from an RAF Lancaster / which had crashed / in 1943. / All the surrounding farms / and villages / were evacuated / whilst military experts / detonated / the bomb. / The blast / could be heard/ over five miles away.

Scoring Guidelines for Story Recall Task

Table 2.2.1.

Scoring Guidelines for Story 1

	Exact Phrase	Alternate	Score (1)
1.	Three hundred men	Three hundred people	1.0
		Three hundred workers	0.5
		X-hundred men	0.5
		Three hundred employees	0.5
		Lots of people	0.0
2.	walked out	Went out	0.5
		Left	0.5
3.	of a car factory	A car plant	1.0
4.	on Clydeside	Clydesdale	0.5
5.	this morning	This a.m.	1.0
		Today	0.5
6.	following an announcement		
7.	of large scale redundancies.	Because of redundancies	0.5
		Job losses	0.5
		Lost their jobs	0.5
		Laid off	0.5
		Going to be sacked	0.5
8.	Mr David	Davies	0.0
9.	Mitchell		
10.	a company director,	Director of the company	1.0
		A/the managing director	0.5
		A/the director	0.5
		A spokesman	0.0
11.	told reporters	Talked to reporters	0.5
		Spoke to the press	0.5
12.	that the factory		
13.	had suffered losses	Losses due to	0.5
		Had been recording losses	0.5
14.	because of high interest	Interest rates were higher	1.0
	rates,	Due to high interest rates	1.0
		Because of high interest	1.0
		Because of the interest rates	0.5
15.	low productivity	Productivity	0.5
16.	and foreign competition.	Competition from abroad	1.0
		Competition overseas	1.0
17.	Union officials	The unions	1.0
		Union people	1.0
		Union representatives	1.0
		A union	0.5
18.	have agreed to begin		

19.	Negotiations	In talks with	0.5
		To talk	0.5
20.	with management		
21.	tomorrow		

Table 2.D.2

Scoring Guidelines for Story 2

	Exact Phrase	Alternate	Score (1)
1.	A wide stretch	A long stretch	0.5
		A large stretch	0.5
		A stretch of	0.5
		A large part of	0.5
		A section of	0.5
2.	of the River Trent	A river	0.5
3.	in Nottinghamshire	In Nottingham	0.5
4.	was closed	Was cordoned off	1.0
		Was sealed off	1.0
		Was shut/ shut it	1.0
		Shut down	0.5
		Was evacuated	0.5
5.	by police		
6.	at the weekend	This weekend	1.0
		Over the weekend	1.0
7.	when divers		
8.	Discovered	Found	1.0
9.	an old bomb		
10.	from an R.A.F. Lancaster		
11.	which had crashed	That had dropped	0.5
12.	in 1943.		
13.	All the surrounding farms	The nearby farms	1.0
		All other areas	0.5
		The surrounding area	0.5
14.	and villages		
15.	were evacuated	Sealed off	0.0
		Had to be moved away	1.0
		Was closed	0.5
16.	whilst military experts	The army	0.5
		Bomb disposal unit	0.5
		RAF bomb squad	0.5
		Bomb experts	0.5
		Whilst they	0.0
17.	Detonated	Exploded	1.0
18.	the bomb		

19.	The blast	The detonation	1.0
		The explosion	1.0
		The bomb	0.5
20.	could be heard		
21.	over five miles away	Five miles away	0.5

Appendix 2.3: Statement of Joint Working

This was a joint project carried out by two UCL Doctorate in Clinical Psychology trainees. The partner project evaluates the effect of ketamine on mood. Proposals for each project were completed independently. Collection of data was completed by the two trainees. The analysis and report writing of the literature review, empirical paper and critical review were completed by myself alone.