Exploring the Effects of Acute Sub-Anaesthetic Ketamine on Cognitive Function

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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:

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Date:

Overview

Part 1 of this thesis is a qualitative narrative systematic literature review which examines how the administration of acute sub-anaesthetic ketamine affects cognitive function in non-healthy patients in medical and psychiatric settings. Ten studies were included in the review, and study quality, the effect of ketamine on cognition, and ketamine's effect on the medical and psychiatric problems identified is discussed.

Part 2 describes a study of chronic pain patients receiving either acute sub-anaesthetic intravenous ketamine or lidocaine. It measures participant pain and cognitive performance before and after drug administration, and explores the relationships between pain, cognition and the drugs administered. 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. All work was completed jointly by the two researchers.

Finally, Part 3 of this thesis, the Critical Appraisal, discusses the process of completing this piece of research.

Impact Statement

This thesis consisted of two major parts: a systematic literature review examining how the administration of acute sub-anaesthetic ketamine affects cognitive function in non-healthy patients in medical and psychiatric settings, and a non-randomised between-subjects study of the effects of sub-anaesthetic IV infusions of ketamine compared to the effects of IV infusions of lidocaine on the cognitive functioning in participants receiving the drugs for chronic pain.

The literature review indicated that while ketamine appears to provide useful relief for persons suffering with treatment resistant depression, and may provide some relief in post-surgical patients, there is not enough research on the cognitive effects of acute non-anaesthetic ketamine. Literature on the chronic and recreational use of ketamine is prevalent, but it is important that further study be carried out on the cognitive ramifications of acute sub-anaesthetic ketamine administered to medical and psychiatric patients.

Though chronic neuropathic pain is a costly burden at the individual, social and economic levels, and can lead to absenteeism, reduced productivity and long-term incapacity, there is still no readily available pharmacological treatment that works for all patients. Indeed, though research on the pain relieving properties of NMDA receptor antagonists has been ongoing for almost three decades, little is known about the cognitive effects of acute sub-anaesthetic doses of ketamine in patients with chronic neuropathic pain.

The findings of this study indicated that acute ketamine worked to significantly reduce pain, and indeed provided significantly more short-term more pain relief than lidocaine. Due to this, further research should focus on the longer term pain relieving properties of the drug, and on comparisons of ketamine's efficacy to other common

analgesics, so that medical personnel can be more confident in the use of ketamine for the relief of chronic pain.

However, as ketamine impaired working memory, and as episodic memory for information learned under the influence of the drug was also impaired by ketamine administration, further research on the cognitive consequences of long term and repeated ketamine administration in persons with chronic pain is needed.

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Part 1: Literature Review

Exploring the Cognitive Effects of Acute Sub-Anaesthetic Ketamine in Patients with Medical or Psychiatric Disorders

1.1 Abstract

Aims: This qualitative narrative systematic literature review aimed to examine how the administration of acute sub-anaesthetic ketamine affects cognitive function in non-healthy patients in medical and psychiatric settings.

Methods: Database searching in EMBASE, PsycINFO and MEDLINE followed by application of inclusion criteria identified 10 studies which were analysed and used in this review. Study quality was assessed using an amended version of the Checklist for Measuring Study Quality in Randomised Controlled Trials and Non-randomised Trials by Downs and Black (1998).

Results: Six studies looked at ketamine use in psychiatric settings, while four took place in a medical setting. Studies were described and overall quality of the studies was assessed in terms of their quality of reporting and external and internal validity. The effect of ketamine on the cognitive functioning of participants was reported, and finally the effect of ketamine on the various medical and psychiatric problems was reported.

Conclusions: Studies reviewed differed in their overall quality and their reported effects of ketamine on cognition, as well as the effects of ketamine on medical and psychiatric problems. These differences are discussed, as are limitations of the current review.

1.2 Introduction

Ketamine is a non-competitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, developed as a replacement human anaesthetic for phencyclidine (PCP). Because it does not impair spontaneous respiration or block the airways and works to produce both amnesia and analgesia when used for anaesthetic purposes, it has been a part of the World Health Organisation's (WHO) Essential Medicines List since 1985 (WHO, 2016). As this is the method in which it is most bioavailable, ketamine is most often administered intravenously, however it can be administered by intramuscular, intrarectal, intranasal or oral routes (Mion &Villevielle, 2013). The WHO Expert Committee on Drug Dependence indicates that though ketamine is used recreationally worldwide and chronic recreational use can cause adverse side effects, the medical usefulness of the drug is such that it should not be controlled under international drug control conventions (WHO, 2016).

1.21 The Use of Ketamine in Medical & Psychiatric Settings

Along with its use as an anaesthetic, ketamine has been employed to treat a range of medical and psychiatric problems. Ketamine appears to be effective in treating both chronic and acute pain. Anaesthetic dosages of ketamine resulted in significant levels of pain reduction and increased physical functioning in complex regional pain syndrome (CRPS) patients for periods of up to 6 months (Keifer et al, 2008). Additionally, sub-anaesthetic doses of IV ketamine appear to provide short term relief of chronic neuropathic pain, to reduce the need for opioid analgesics, and to effectively control post-operative pain (Bell, 2009; Nourouzi et al, 2010; Subramaniam, Subramaniam & Steinbrook, 2004; Visser & Schug, 2006). Ketamine has also been used for the treatment of opioid-tolerant cancer pain, with mixed results (Bell, Eccleston & Kalso, 2017).

Research indicates that drugs which modulate the NMDA receptor may aid in treating depression (Matthews, Henter & Zarate, 2012). Several research trials have found that sub-anaesthetic doses of ketamine produce a time limited antidepressant effect in patients with refractory or treatment resistant major depression, and in patients with refractory or treatment resistant bipolar depression (Abdallah, Averill & Krystal, 2015; Berman et al, 2000; Fond et al, 2014; Lara, Bisol & Munari, 2013). A review by Abdallah et al (2015), also suggests that ketamine may be useful in treating trauma-related disorders, and recent research indicates that sub-anaesthetic doses of intravenous ketamine may be effective in ameliorating the symptoms of post-traumatic stress disorder (Albott et al, 2017).

Interestingly, ketamine may be a more effective treatment for depression in patients with a family history of alcoholism (Luckenbaugh et al, 2012), and indeed, research from as long as two decades ago indicates that there may be a reduction in relapse rates in alcoholics who receive a combination of ketamine and "psychotherapy" (Krupitsky & Grinenko, 1997). There may also be an effect of ketamine on relapse rates and intensity of cravings in recovering heroin addicts (Krupitsky et al, 2002).

1.22 Cognition

Cognition can be broadly defined as the way in which the brain acquires, processes, stores and retrieves information (Lawlor, 2002). Cognitive functions include psychomotor speed, the executive functions (such as attention, inhibition, planning, switching, searching, use of strategy and flexible thinking) and the various types of memory: episodic memory, semantic memory, working memory, procedural memory and the perceptual representation system (Kalechstein, De La Garza, Mahoney, Fantegrossi & Newton, 2007; Tulving & Donaldson, 1972; Rasmussen, 2005; Schacter,

1990). It is important to note that the cognitive domains discussed are not rigidly separate categories, and there is no neurocognitive task that can test only one domain.

1.23 Ketamine & Cognition: Healthy Participants

Ketamine research has largely focused on the cognitive effects of recreational ketamine, or on the cognitive effects of ketamine as a general anaesthetic. Frequent, long-term recreational ketamine users appear to experience cognitive disruptions, especially related to their episodic and semantic memory, but also related to spatial working memory and visual recognition (Morgan & Curran, 2006; Morgan, Muetzelfeldt & Curran, 2010; Morgan & Curran, 2011; Visser & Schug, 2006). Persons who experience these impairments in cognition may not see a return to pre-drug functioning (Morgan & Curran, 2006). When used as a general anaesthetic, ketamine does not appear to impair cognitive function, and may indeed attenuate post-operative cognitive dysfunction (Deiner & Silverstein, 2009; Hudetz et al, 2009; Koffler et al, 2016; Lee et al, 2015). However, there is less research exploring the effect of acute sub-anaesthetic ketamine on cognitive functioning.

Healthy participants administered low and high doses of acute sub-anaesthetic intravenous ketamine (target plasma levels of 50ng/ml and 100ng/ml) or placebo (saline) found disruptions in the manipulation of information in working memory, but no significant differences in visual perception, spatial working memory, or the ability to carry out a planning task (Honey et al, 2003). Acute sub-anaesthetic ketamine administered to healthy volunteers had little effect on the results of verbal fluency tasks as compared to a placebo (Fu el at, 2005). However, the latter study reported neuroimaging evidence indicating that for more demanding tasks, ketamine-administered participants had increased activity in the anterior cingulate, prefrontal, and striatal regions (Fu et al, 2005).

In healthy volunteers, a dose of acute sub-anaesthetic IV ketamine (0.4 or 0.8 mg/kg) as compared to a saline placebo appears to impair response inhibition (Morgan, Mofeez, Brandner, Bromley & Curran, 2004b). This study found that acute ketamine impaired episodic memory for information learnt under the influence of the drug but did not impair information learnt before ketamine was administered and did impair semantic memory. Further research has also indicated that an acute dose (0.4 or 0.8 mg/kg) of ketamine produces a dose-dependent impairment in episodic and working memory in healthy participants (Morgan, Mofeez, Brandner, Bromley & Curran, 2004a). Ketamine also acted to slow semantic processing and impair recognition memory and procedural learning (Morgan et al, 2004a).

A review of the cognitive effects of acute ketamine found that the processing of semantic memory may be impaired (Morgan & Curran, 2006). Episodic memory appears to be impaired for information learned on ketamine, but not for the recall of information learned before drug administration (Morgan & Curran, 2006). As this review also indicated that ketamine may impair the encoding aspect of procedural learning, it can be suggested that ketamine may impair the encoding of information into memory (Morgan & Curran, 2006). The authors of this 2006 review found that while it was unclear if sustained attention was impaired by ketamine, tasks assessing simple attention and selective attention appeared largely unimpaired by the drug. Additionally, ketamine appeared to have little impact on other tasks of executive function once deficits in memory were controlled for (Morgan & Curran, 2006). Finally, the maintenance of information in working memory appears to be unaffected by ketamine administration, however impairments are seen in the manipulation of information in working memory (Morgan & Curran, 2006).

More recent research appears to agree with findings from Morgan and Curran's 2006 review. A study of healthy participants receiving a dose of sub-anaesthetic ketamine or placebo found that as the difficulty of a visual working memory task increased, the performance of participants administered ketamine decreased significantly compared to those receiving placebo (Koychev, Deakin, El-Deredy, & Haenschel, 2017). Healthy participants who experienced induced heat pain and were then administered an acute dose of ketamine, demonstrated significantly impaired cognition in the domains of memory, psychomotor speed, complex attention, and the executive function of cognitive flexibility as compared to their placebo counterparts (Olofsen et al, 2012). There was a smaller, but still significant, impairing effect of ketamine on reaction time (Olofsen et al, 2012). Finally, a study of healthy participants administered three increasing doses of ketamine found that ketamine produced dose dependant effects on tasks of complex reaction time, visuospatial working memory and spatial planning, but no effect on simple reaction time (Hayley et al, 2017). This study also reported a post-drug return to baseline performance in all domains (Hayley et al, 2017).

1.24 Ketamine & Cognition: Medical and Psychiatric Patients

There is less research on the cognitive effects of acute ketamine for medical or psychiatric problems. A study of complex regional pain syndrome patients found that participants who had long-term frequent ketamine infusions (at least twice a month for six months) performed significantly worse on measures of attention, working memory, semantic memory, and psychomotor coordination than those who never or infrequently received ketamine (Kim, Cho & Lee, 2016).

A review of sub-anaesthetic ketamine for suicidality in treatment resistant depression (TRD) indicated that acute administration of the drug may lead to

improvements in visual memory, simple working memory, and complex working memory (Lee et al, 2016). It is important to note however, that these cognitive changes are reported alongside a simultaneous reduction in depression. Persons with depression often experience impaired cognition, especially in the domains of attention, reaction time and memory (Gotlib & Joormann, 2010), and it is possible that a decrease in depression may have led to an increase in cognitive functioning. This review also indicated that participants with low pre-ketamine attention and processing speed may be more likely to see a mood response to ketamine (Lee et al, 2016).

1.25 Aims of the Current Review

The acute effects of ketamine outlined stem largely from research on healthy participants in a laboratory setting. Indeed, a 2015 review of ketamine for depression in bipolar disorder found no double-blind, randomised, placebo-controlled trials in patient groups which assessed cognitive function (McCloud et al, 2015). There is therefore a need for a comprehensive review of the acute effects of ketamine in non-healthy participants. This systematic literature review aims to examine how the medical and psychiatric use of acute sub-anaesthetic ketamine affects cognitive function in studies with more robust external validity. That is, in studies which recruit participants representative of the population the intervention is aimed at – patients, not healthy controls. It also aims to explore other reported effects of acute sub-anaesthetic ketamine used in various medical and psychiatric disorders.

1.3 Method

1.31 Search Strategy

As literature related to ketamine and neuropsychological functioning can be found in medical, psychological and psychiatric resources, a systematic literature search was carried out using three electronic databases: EMBASE, MEDLINE, and PsycINFO.

The thesaurus function on the EMBASE and PsycINFO databases, and the "tree" function on the MEDLINE database were used to find broader terms and words related to the search terms memory, brain function, cognition, mental function and neuropsychology. The search terms were collated, and duplicates and unsuitable terms were removed (See: Appendix 1.A: Creation of Search Terms). This search process was designed to be wide and inclusive, so that relevant studies would not be lost.

In each of the databases explored, searches of terms related to neuropsychological functioning were combined with the results of a search for ketamine using the Boolean operators "AND" or "OR". These searches were then limited to studies that were written in English, that used human adult participants, and to those that used a clinical trial methodology (See: Appendix 1.B: Search Process).

After duplicates were removed, the abstracts of these studies were screened according to inclusion criteria. Initially, each study was required to contain a control group, and each group needed to include at least 12 participants. However, this resulted in only five eligible studies. As a result of this, studies were screened to meet the following criteria:

1. Ketamine was used with a medical or psychiatric population
2. Ketamine was administered at sub-anaesthetic doses
3. Objective neuropsychological tasks were used to measure cognitive function
4. Studies were published in an English language peer-reviewed journal

Studies that appeared to meet these criteria were selected for further, full text review to ensure relevance (See: Figure 1.1: Selection of Included Studies). This full search process retrieved all articles that met inclusion criteria for this review. Data from these articles, including author and source information, study design, medical or psychiatric context of the study, domains of cognition assessed, and dosages of

ketamine and active control or placebo used, was extracted to create a table of article characteristics (See Table 1.1: Characteristics of Included Studies).

This literature review uses a qualitative narrative approach, as the studies identified differ widely in their administrative route of ketamine, the doses of ketamine used, the medical and psychiatric problems they address, and the control or active control drugs that they use. Because of this, a quantitative analysis of this small number of studies would not be meaningful.

1.32 Assessment of Study Quality

Study quality was assessed using an amended version of the Checklist for Measuring Study Quality in Randomised Controlled Trials and Non-randomised Trials by Downs and Black (1998) **(See Appendix 1.C: Tool Used to Assess Study Quality)**. This is a 26-item scale that assesses studies by the overall study quality as well as external validity, and internal validity – bias and confounding. This tool was used as it is one of the few measures for assessing study quality that can be applied to controlled, non-controlled, randomised and non-randomised studies. It has been tested and meets acceptable criteria for face, content and criterion validity. It also meets acceptable standards for internal consistency, test-retest reliability, and inter-rater reliability (Downs & Black, 1998).

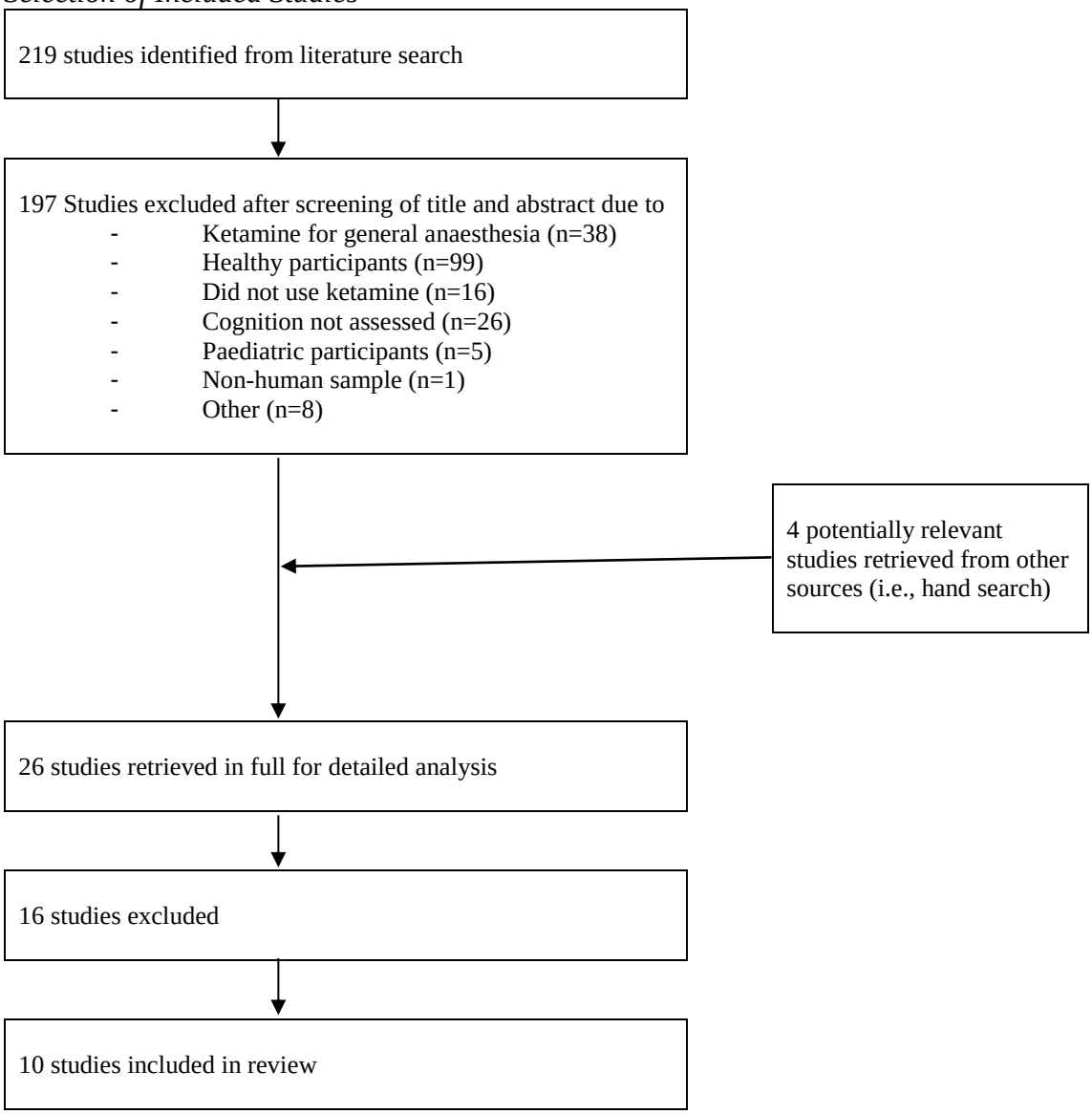
1.4 Results

As outlined in Figure 1.1, database searching in EMBASE, PsycINFO and MEDLINE identified 4,468 relevant items. Refining the search to include only clinical trials in English, with adult human participants identified 283 items, 219 with duplicates removed. 197 studies were excluded after title and abstract screening if they examined ketamine as a general anaesthetic, used healthy participants, did not use ketamine or assess cognitive function, or used paediatric or non-human participants.

A further four potentially relevant studies were retrieved from a hand search of reference lists, giving a total of 26 studies retrieved in full for detailed analysis. 16 of these studies were excluded as they did not measure cognition or utilised subjective measures of cognition, used healthy participants, did not use a trial methodology or were reported as conference abstracts. The 10 studies which remained were analysed and used in this review.

Figure 1.1

Selection of Included Studies



1.41 Description of Studies

10 studies meeting the amended inclusion criteria and published between January 1996 and March 2018 were identified. The studies were undertaken in various countries – six in the USA, two in Australia, one in Israel and one in France. (See Table 1.1: Characteristics of Included Studies).

Methodology. Six studies used an active control and had a randomised, double-blinded, between-subjects methodology (Reeves, Lindholm, Myles, Fletcher & Hunt, 2001; Zohar et al, 2002; Aubrun et al, 2008; Murrough et al, 2015; Grunebaum et al, 2017; Gálvez et al, 2018). Three studies were placebo controlled quasi-randomised and double-blinded, and of these, two used a within-subjects design (Malhotra et al, 1997; Murman et al, 1997), and one used a between-subjects design (LaPorte, Lahti, Koffel, & Tamminga, 1996). One study used a within-subjects open label design and had no control or blinding (Shiroma et al, 2014).

Study Context. Of the 10 studies included, four examined ketamine's effect on cognitive function in a medical context, and six in a psychiatric context. One study used medical ketamine in participants with Huntington's disease (Murman et al, 1997), while three used ketamine for the relief of acute post-surgical pain (Reeves et al, 2001; Zohar et al, 2002; Aubrun et al, 2008). In studies of psychiatric conditions, ketamine was used in participants with treatment resistant depression (TRD) in three studies (Shiroma et al, 2014; Murrough et al, 2015; Galvez et al, 2018), and participants with bipolar depression in one study (Grunebaum et al, 2017). Participants in two studies were diagnosed with schizophrenia (LaPorte et al, 1996; Malhotra et al, 1997). These studies did not use ketamine as treatment, but instead were exploring the ways in which ketamine affects people with a diagnosis of schizophrenia.

Table 1.1

Characteristics of Included Studies

1a. Participants with a medical diagnosis

Author/ Year/ Country/ Source	Study Design	Context	Ketamine	Comparator	Patient Characteristics	Cognitive Assessment	Results
1997 **Murman et al** USA Neurology, 49, 153-161	Placebo controlled Quasi-randomised (to placebo/ ketamine on first day) Double blinded Within-subjects	Medical: Huntington's Disease	IV ketamine Escalating doses: 0.10, 0.40 & 0.60 mg/kg/hr	IV placebo	Huntington's Disease & Mild Cognitive Impairment N=10 4 male/ 6 female Age (yrs) = ranged from 28-67 (average=48.4)	*Cognitive Testing Procedure:* All repeated 20 min post dose change *Domains tested:* Verbal memory – immediate & delayed Visual memory – immediate & delayed Verbal fluency Attention (reaction time and digit span) Psychomotor agility	At the 0.4 dose of ketamine immediate verbal memory, delayed visual memory & verbal fluency was impaired At the 0.6 dose immediate visual memory, psychomotor agility and one measure of attention (reaction time) was impaired Delayed verbal memory and attention (digit span) was not affected by ketamine in any dose
2001 **Reeves et al** Australia Anesthesia & Analgesia 93(1), 116–20	Active control Randomised Double-Blinded Between-subjects	Medical: Pain	IV ketamine & morphine (patient controlled) ketamine 1 mg/ml +	IV morphine (patient controlled) morphine 1 mg/mL	Post abdominal surgery N=71 Morphine & Ketamine: N=36	*Cognitive Testing Procedure:* Baseline (pre-op) & at 48h post-op *Domains tested*	Psychomotor agility with switching significantly impaired in morphine & ketamine group (P=0.037)

			morphine 1 mg/ml		20 male/ 16 female Age (yrs) = 54± 13 Morphine only: N=35 16 male/ 19 female Age (yrs) = 47 ± 14	Attention/ psychomotor agility (trails A) Switching/ psychomotor agility (Trails B)	
2002 **Zohar et al** Israel Journal of Clinical Anaesthesia 14(7), 505–511, 2002	Active control Randomised Double blinded Between-subjects	Medical: Pain	Wound infiltration of bupivacaine & ketamine (patient controlled) 0.125% bupivacaine & ketamine (1 mg/mL) Ceiling of 9ml/hour Rescue morphine if needed	Wound infiltration of bupivacaine (patient controlled) 0.125% bupivacaine Ceiling of 9ml/hour Rescue morphine if needed	Post C-Section N=50 All female Bupivacaine & ketamine: N=25 Age (yrs) =33 ± 6 (20-45) Bupivacaine alone: N=25 Age (yrs) = 32 ± 6 (21-43)	*Cognitive Testing Procedure:* Baseline (pre-op), immediately post-op, at 2 hour-intervals while in recovery & at 24h post-op *Domains tested:* Digit Substitution Test & Mini-mental test *[find further info on test domains]*	No s.d.in cognitive functioning No s.d. in: Analgesia Use of drug Morphine consumed Pain satisfaction
2008 **Aubrun et al** France European Journal of Anaesthesiology, 25(2), 97–105	Active control Randomised Double blind Between-subjects	Medical: Pain	IV ketamine & morphine (patient controlled) Morphine 1mg/mg & ketamine 0.5mg/ml	IV morphine (patient controlled) Morphine 1mg/ml	Patients having abdominal gynaecological surgery N=90 All female Ketamine: N=45	*Cognitive Testing Procedure:* Baseline (pre-op); Immediately post-op; Day 1 - a.m.; Day 2 - a.m.; Day 2 - p.m. *Domains tested:* Orientation	No s.d. in cognitive functioning between ketamine and placebo No s.d. between pre- & post-op cognitive functioning No s.d. in:

					Age (yrs) =50 ± 10 Morphine: N=45 Age (yrs) =49 ± 12	Registration Recall Attention Verbal fluency Memory (and processing speed? DSST/Coding) Working memory	Pain relief Additional morphine Adverse effects Mood

1b. Participants with a psychiatric diagnosis

Author/ Year/ Country/ Source	**Study Design**	**Context**	**Ketamine**	**Comparator(s)**	**Patient Characteristics**	**Cognitive Assessment**	**Results**
1996 **LaPorte et al** USA Journal of Psychiatric Research, 30(5), 321-330	Placebo controlled Quasi-randomised [treatment counterbalanced] Double blinded Between-subjects	Psychiatric: Schizophrenia	Injection of ketamine 0.5 mg/kg	Injection of placebo	Right-handed people with a diagnosis of schizophrenia N=7 5 male/ 2 female Age (yrs) = 27.3; ranged from 22-36	*Cognitive Testing Procedure:* Pre-injection and 30-45min post-injection *Domains Tested* Control tasks used to rule-out generalized impairment: Verbal fluency Visuospatial Pre & Post drug: Learning Immediate & delayed verbal memory Visual memory	No significant drug vs placebo differences in cognition Learning score lower following ketamine administration (non-significant)

1997 **Malhotra et al** USA Neuropsycho-pharmacology, 17(3), 141-150	Placebo controlled Within-subjects & between- subjects (people with a diagnosis of schizophrenia & healthy participants) Double blinded	Psychiatric: Schizophrenia	IV ketamine Bolus of 0.12 mg/kg of ketamine followed by 1hr infusion of 0.65 mg/kg of ketamine (total dose of 0.77 mg/kg/hr)	IV placebo Saline infusion of 1 hour	*Diagnosis of Schizophrenia:* N=13 10 male/ 3 female Age (yrs) = 31.3 ± 2.8 *Healthy:* N=16 12 males/ 4 females Age (yrs) = 27.8 ± 1.9	*Cognitive Testing Procedure:* Baseline at 30min pre-infusion Testing at 10min, 55min, 90min and 120min post-infusion *Domains tested:* Attention Verbal memory-recall Verbal memory-recognition	Ketamine impaired recall & recognition memory in healthy participants and those with a diagnosis of schizophrenia. Participants with a diagnosis of schizophrenia were significantly more impaired in recall than healthy participants Attention was not significantly impaired by ketamine in either group.
2014 **Shiroma et al** USA International Journal of Neuropsycho-pharmacology, 17(11), 1805–1813	Open label study No control No blinding Within-subjects	Psychiatric: treatment resistant depression	IV ketamine 0.5 mg/kg ketamine HCl over 40 min per session 6 sessions in two weeks (Mon; Wed; Fri; Mon; Wed Fri)	N/A	TRD participants N=15 (28-69) All male Age (yrs) = mean 52; no range given	*Cognitive Testing Procedure:* Pre-infusion baseline and after completion of all 6 infusions at each follow-up (week 3, 4, 5 & 6) *Domains tested:* Attention Working memory – simple & complex Visual memory Verbal memory Processing speed Set shifting (switching)	Significant improvement in simple & complex working memory and visual memory. These changes are n.s. when change in depression accounted for. No s.d. in other cognitive domains

2015 **Murrough et al** USA Neuropsycho-pharmacology, 40(5), 1084–1090	Active control Randomised (2 ketamine: 1 midazolam) Double-blind Between-subjects	Psychiatric: Treatment resistant depression	IV ketamine Ketamine 0.50 mg/kg over 40 min	IV midazolam Midazolam 0.045 mg/kg over 40 min	Total N=62 28male/ 34 female Age (yrs) = 46.1 ± 12.2 Ketamine: N=43 Age (yrs) =47.1 ± 12.6 19 male/ 24 female Midazolam: N=19 Age (yrs) =43.8 ±11.0 9 male/ 10 female	*Cognitive Testing Procedure:* Within 1 week pre-infusion & 7 days post infusion *Domains tested:* Category fluency Processing speed Working memory Verbal learning Visual learning Reasoning/ problem solving	Significant improvement in processing speed and verbal & visual learning in ketamine and midazolam groups (when controlling for change in depression) No sig. effect of ketamine on cognition No sig. effect of anti-depressant response on cognition
2017 **Grunebaum et al** USA Bipolar Disorders, 19(3), 176–183.	Active control Randomised Double blind Between-subjects	Psychiatric: bipolar depression	IV ketamine racemic ketamine HCl 0.5 mg/kg 100 mL of normal saline over 40 minutes	IV midazolam midazolam 0.02 mg/kg in 100 mL of normal saline over 40 minutes	Ketamine: N=7 Age (yrs)= 39 ± 10.2 4 male/ 3 female Midazolam: N=9 Age (yrs) = 43 ± 13.9 2 male/ 7 female	*Cognitive Testing Procedure:* At baseline & Participants performed a neurocognitive battery at baseline and day 1 testing *Domains tested:* Reaction time Processing speed Attention Memory Working memory	Improved reaction time, attention and memory in both groups Verbal fluency declined in ketamine vs midazolam groups NB: correlations of cognition to improvements in depression severity

						Pattern separation Verbal fluency Impulsiveness	
2018 **Gálvez et al** Australia Journal of Psychopharma-cology, 32(4), 397–407	Active control Randomised Double blind Between-subjects	Psychiatric: Treatment resistant depression	Intranasal ketamine ten sprays of 100 mg of ketamine (ketamine HCl 200 mg/2 mL, Ketalar®) 3/week for 2 weeks, then weekly for 2 weeks	Intranasal midazolam ten sprays of 4.5 mg midazolam (midazolam HCl, Hypnovel® 5 mg/mL, diluted with 0.9% saline) 3/week for 2 weeks, then weekly for 2 weeks	Ketamine: N=3 1 male/ 2 female Age (yrs) = ranged from 52-64 Midazolam: N=2 2 male Age (yrs) = ranged from 41-59	*Cognitive Testing Procedure:* Baseline & 48–72 hr after treatment course *Domains tested:* Verbal memory Visual memory Working memory Set-shifting Reaction time	1 ketamine participant sig. impaired in reaction time 1 midazolam participant sig. impaired in working memory

Sample sizes. The total number of participants included in this review was 371. The smallest sample size was 5 (Galvez et al, 2018) and the largest was 90 (Aubrun et al, 2008).

Treatment. Doses of ketamine ranged from 0.10mg/kg (Murman et al, 1997) to 0.77mg/kg (Malhotra et al, 1997). The time-period of treatment and number of treatments also varied. Seven studies gave one acute dose of ketamine (LaPorte et al, 1996; Malhotra et al, 1997; Reeves et al, 2001; Zohar et al, 2002; Aubrun et al, 2008; Murrough et al, 2015; Grunebaum et al, 2017), one administered serial escalating doses during the testing day (Murman et al, 1997), one administered six doses of ketamine over two weeks (Shiroma et al, 2014) and one administered eight doses over four weeks (Galvez et al, 2018).

Ketamine was administered by various routes. Seven studies administered ketamine via intravenous infusion (Malhotra et al, 1997; Murman et al, 1997; Reeves et al, 2001; Aubrun et al, 2008; Shiroma et al, 2014; Murrough et al, 2015; Grunebaum et al, 2017), one study used a subcutaneous injection (1996, LaPorte), and one study utilised an intranasal spray (Galvez et al, 2018). Finally, Zohar et al (2002) utilised wound infiltration of the surgical site to deliver treatment, a process by which analgesia is delivered directly to the wound via a catheter embedded in the skin.

Of the six studies which used an active control, three used midazolam (Murrough et al, 2015; Grunebaum et al, 2017; Galvez et al, 2018), two used morphine (Reeves et al, 2001; Aubrun et al, 2008), and one used bupivacaine (Zohar et al, 2002). Route of administration of placebo or active control was the same as ketamine in all studies.

Cognition. All studies assessed pre-treatment cognitive function. Four studies re-assessed cognition between 20 and 120 minutes post-administration (LaPorte et al, 1996; Murman et al, 1997; Malhotra et al, 1997; Grunebaum et al, 2017). Of the

remaining six studies, two re-assessed cognitive function both post- treatment and at 24 hours post treatment (Zohar et al, 2002; Aubrun et al, 2008). Two assessed cognition between 48 and 72 minutes post treatment (Reeves et al, 2001; Galvez et al, 2018), one study had a seven-day cognitive follow up (Murrough et al, 2015), and the final study assessed cognitive functioning post-treatment weekly for four weeks (Shiroma et al, 2014).

Domains of cognition varied, as did neuropsychological tests used. Participant memory was assessed in eight of the 10 studies, attention in six, psychomotor agility in four, and processing speed in three studies. Fluency was assessed by four studies, higher executive function tasks such as reasoning, pattern separation, and switching was assessed by five studies, and one study assessed participant impulsiveness.

1.42 Assessment of Study Quality

Quality was assessed using an amended version of the Checklist for Measuring Study Quality in Randomised Controlled Trials and Non-randomised Trials (See: Table 1.2: Assessment of Study Quality). Studies were evaluated according to the quality of their reporting, their external validity, and their internal validity. For more detailed information see Appendix 1.D: Detailed Critical Appraisal of Included Studies.

Reporting. To determine the quality of reporting, the clarity and transparency of the studies were examined. All studies clearly described their hypotheses, main outcomes, characteristics of participants, intervention of interest and principal confounders. Two studies did not report simple outcome data (Shiroma et al, 2014; Grunebaum et al, 2017), and four studies did not systematically measure and report adverse effects (LaPorte, 1996; Murman et al, 1997; Shiroma et al, 2014; Murrough et al, 2015). All but one study described characteristics of participants lost to follow up

(Galvez et al, 2018), and all but two also reported actual probability values (Zohar, 2002; Galvez et al, 2018).

Table 1.2

Critical Appraisal of Studies by Quality of Reporting, External Validity, Bias and Confounding

Study (Maximum score)	Reporting (11)	External Validity (3)	Internal Validity – Bias (7)	Internal Validity – Confounding (6)
1996, LaPorte et al	10	0	7	3
1997, Mahotra et al	11	0	7	4
1997, Murman et al	10	1	7	6
2001, Reeves et al	11	2	5	4
2002, Zohar et al	10	2	4	4
2008, Aubrun et al	11	1	6	6
2014, Shiroma et al	9	0	5	2
2015, Murrough et al	10	0	7	3
2017, Grunebaum et al	10	0	6	5
2018, Galvez et al	9	0	7	3

External validity. The external validity of most included studies was poor, and so it is difficult to generalise their results to other situations or people. No studies reported how many potential participants were approached, or whether the distribution of confounding factors in participants was similar to the distribution of those factors in the study's sample or in the source population. In addition, of the 10 studies included, only four were completed at locations which would normally treat patients with the diagnosed problems (Murman et al, 1997; Reeves et al, 2001; Zohar, 2002; Aubrun et al, 2008). Further damaging external validity, only 2 studies ensured that participants were representative of the source population, by approaching all appropriate potential participants in a particular service during a prescribed time frame (Reeves et al, 2001; Zohar, 2002).

Bias. Eight studies were double blinded, and two reported no form of blinding (Reeves et al, 2001; Shiroma et al, 2014). It did not appear that any study results were based on ad-hoc analysis. It was not possible to identify any statistical adjustments

made for differing follow-up times between participants in one study (Zohar, 2002), however for all others the follow up was the same or analysis was adjusted for differing follow-up times. Compliance with treatment appeared reliable for all studies as there was no mention of non-compliance, and statistical testing appeared appropriate for all but two studies for which the reviewer was unable to determine appropriateness (Zohar, 2002; Aubrun et al, 2008). Finally, while it was not possible to determine the validity and reliability of outcome measures used in two studies (Zohar, 2002; Grunebaum et al, 2017), outcome measures were clearly described in the remaining eight.

Confounding. There appeared to be a high risk of selection bias in several studies. It was not possible to determine if cases and controls were recruited from the same population in three studies (Murrough et al, 2015; Grunebaum et al, 2017; Galvez et al, 2018), and not possible to determine if cases and controls were recruited over the same time period for seven (LaPorte et al, 1996; Malhotra et al, 1997; Reeves et al, 2001; Zohar, 2002; Shiroma et al, 2014; Murrough et al, 2015; Galvez et al, 2018). Three studies did not randomise participants to interventions. One study used a within-subjects design (Shiroma et al, 2014), one did not report their method of randomisation (Murrough et al, 2015), and one used alternate allocation to treatment (LaPorte et al, 1996). Four of ten studies either did not adjust analysis for confounding factors or did not report doing this (LaPorte et al, 1996; Zohar, 2002; Shiroma et al, 2014; Galvez et al, 2018). However, all studies reported taking missing data or participant discontinuation into account during the analysis.

1.43 The Effect of Ketamine on Cognitive Function

The neuropsychological tasks used, and the effect of ketamine on cognitive function for each of the review articles is outlined in Table 1.3 (Details of Neuropsychological Tasks Used in Included Studies).

Table 1.3.

Details of Neuropsychological Tasks Used in Included Studies

1a. Patients with a medical diagnosis

Study Details	Neuropsychological Task	Task Procedure	Domain Reported	Results
1997 **Murman et al** Medical – Huntington's Disease	Buschke Selective Reminding Test	Participants learn a list of 12 related words that are presented in six trials, during which subjects are selectively reminded of forgotten words. Immediate recall is measured initially, and delayed recall measured 30 minutes later.	Memory, Verbal – Immediate & Delayed	At the 0.4 dose of ketamine immediate verbal memory, delayed visual memory & verbal fluency was impaired
Two within-subjects groups: 1. IV ketamine: Escalating doses: 0.10, 0.40 & 0.60 mg/kg/hr 2. IV placebo	Washington Square Picture Memory Test	Immediate and delayed recognition of pictures of common objects	Memory, Visual – Immediate & Delayed	At the 0.6 dose immediate visual memory, psychomotor agility and one measure of attention (reaction time) was impaired
	Letter Fluency	Participants given one minute to generate words in response to a stimulus letter. Alternate consonants of comparable difficulty used with each drug administration	Verbal Fluency, Semantic Memory & Executive Cognitive Skills	
Test Procedure: All tests repeated 20 min post dose change	Digit Span Forward	Pairs of lists of numbers are read aloud, each pair of lists is one digit longer than the previous pair. Participants repeat the lists of numbers.	Attention	Delayed verbal memory and attention (digit span) was not affected by ketamine in any dose
(NB: measures of attention and motor agility used to monitor for sedative/ anaesthetic effects of ketamine or the development of fatigue)	Reaction Time, Simple	Time in milliseconds required to respond verbally to a visual cue	Attention	
	Finger Tapping	The average number of finger taps performed in 30 seconds during three trials with each hand.	Motor Agility	
2001 **Reeves et al** Medical – Post-Surgical Pain	Trail Making Test A & B	Participants asked to connect circles as quickly as possible: A: participants connect circles with numbers in them in increasing order	Attention & Perception	Psychomotor agility with switching significantly impaired in morphine & ketamine group (P=0.037)

Two between-subjects groups: 1. IV ketamine & morphine (patient controlled). Ketamine 1 mg/ml + morphine 1 mg/ml 2. IV morphine (patient controlled). Morphine 1 mg/ml Test Procedure: Baseline (pre-op) & at 48h post-op		B: circles connect both numbers and letters in increasing order		
2002 **Zohar et al** Medical – Post-Surgical Pain Two between-subjects groups: 1. Wound instillation of bupivacaine & ketamine (patient controlled). 0.125% bupivacaine & ketamine (1 mg/mL) 2. Wound instillation of bupivacaine (patient controlled). 0.125% bupivacaine. Ceiling of 9ml/hour. Rescue morphine if needed Testing Procedure: Baseline (pre-op), immediately post-op, at 2 hour-intervals while in recovery & at 24h post-op	Digit Symbol Substitution Test (DSST) Mini-Mental State Examination (MMSE)	Participants are given a matrix with matching digits and symbols. They are then given a page of digits and are asked to write the corresponding symbols below. Orientation: What is the (year, season, date, day, month)? & Where are we (state, country, town, hospital, floor)? Registration: Number of trials to learn a list of 3 objects Attention: Serial sevens/ spell "world" backwards Recall: of word list previously presented Language: 6 tasks of ability to follow instructions	Memory Orientation Registration Recall Attention Language Fluency	No s.d.in cognitive functioning No s.d. in: Analgesia Use of drug Morphine consumed Pain satisfaction

2008 **Aubrun et al** Medical – Post-Surgical Pain Two between-subjects groups: 1. IV ketamine & morphine (patient controlled) - Morphine 1mg/mg & ketamine 0.5mg/ml 2. IV morphine (patient controlled) - Morphine 1mg/ml Testing Procedure: Baseline (pre-op); Immediately post-op; Day 1 - a.m.; Day 2 - a.m.; Day 2 - p.m.	Mini-Mental State Examination (MMSE) Digit Symbol Substitution Test (DSST) Digit Span (WAIS) – Forward & Backwards	Orientation: What is the (year, season, date, day, month)? & Where are we (state, country, town, hospital, floor)? Registration: Number of trials to learn a list of 3 objects Attention: Serial sevens/ spell "world" backwards Recall: of word list previously presented Language: 6 tasks of ability to follow instructions Participants are given a matrix with matching digits and symbols. They are then given a page of digits and are asked to write the corresponding symbols below. Pairs of lists of numbers are read aloud, each pair of lists is one digit longer than the previous pair. Participants repeat the list of numbers either in the same order or in the reverse order	Orientation Registration Recall Attention Language Fluency Memory Working Memory	No s.d. in cognitive functioning between ketamine & placebo No s.d. between pre- & post-op cognitive functioning No s.d. in: Pain relief Additional morphine Adverse effects Mood

1b. Patients with a psychiatric diagnosis

Study Details	**Neuropsychological Task**	**Task Procedure**	**Domain Reported**	**Results**
1996 **LaPorte et al** Psychiatric: Schizophrenia Two between-subjects groups: 1. Injection of ketamine - 0.5 mg/kg 2. Injection of placebo Testing Procedure:	Letter Fluency – Controlled Oral Word Association Test (Control Task 1) Category Fluency – Controlled Oral Word Association Test (Control Task 2) Line Bisection (Control Task 3) Serial Digit Learning	Participants are given one minute to generate words in response to each of three stimulus letters Participants given one minute to generate words in response to one of three stimulus categories (e.g. animals) Participants asked to bisect 20 offset lines of varying lengths Participants learn a supraspan digit sequence (normal span + 2 digits) over 12 trials.	Verbal Fluency Verbal Fluency Visuoperceptual Attention (Sustained) Learning	No significant drug vs placebo differences in cognition Learning score lower following ketamine administration (non-significant)

Pre-injection & 30-45min post-injection [Authors note: "control tasks were administered at baseline and 30-45 min post-injection… to rule-out generalized impairment"]	Logical Memory (Wechsler Memory Scale-Revised; Wechsler, 1987) Figural Reproduction (Wechsler Memory Scale-Revised; Wechsler, 1987)	Recall a short story immediately after it is read & and to repeat it again after 30-40 min A figure is presented for 10 seconds after which the participant is asked to immediately reproduce it	Memory, Episodic Immediate & Delayed Memory, Visual	
1997 **Malhotra et al** Psychiatric: Schizophrenia Two within-subjects groups: 1. IV ketamine - Bolus of 0.12 mg/kg of ketamine followed by 1hr infusion of 0.65 mg/kg of ketamine (total dose of 0.77 mg/kg/hr) 2. IV placebo - Saline infusion of 1 hour Testing Procedure: Baseline at 30min pre-infusion; Repeated at 10min, 55min, 90min and 120min post-infusion	Word List Part 1 Word List Part 2 Word List Part 3	Participants read a list of 12 categorically related words. 6 words were read once, 6 were repeated. Participants were asked to say repeat when a word was repeated. Participants asked to recall the 12 previously presented words after a 2-minute delay. Participants were read a list of 12 distractor items and 12 previously presented words and asked to identify if each word was new or previously presented.	Attention & Working Memory Memory, Verbal – Free Recall Memory, Verbal – Recognition	Ketamine impaired recall & recognition memory in healthy participants and those with a diagnosis of schizophrenia. Participants with a diagnosis of schizophrenia were significantly more impaired in recall than healthy participants Attention was not significantly impaired by ketamine in either group.
2014 **Shiroma et al** Psychiatric: Treatment Resistant Depression One group: 1. IV ketamine - 0.5 mg/kg ketamine HCl over 40 min per session. 6 sessions in two	Identification Task N-Back Task (1-Back; 2-Back) Groton Maze Learning Test Continuous Paired Associate Learning Task One Card Learning Task	Identify if the card presented is red Identify if a card presented is the same as the card before Identify if a card presented is the same as the one two cards before Find the hidden pathway in a 10x10 grid of tiles Find the correct location of an object Identify if card has been seen before in a task	Attention Working Memory Working Memory - Spatial Memory, Visual Memory, Visual	Significant improvement in simple & complex working memory and visual memory. These changes are n.s. when change in depression accounted for

weeks (Mon; Wed; Fri; Mon; Wed Fri) Testing Procedure: Pre-infusion baseline and after completion of all 6 infusions at each follow-up (week 3, 4, 5 & 6)	Groton Maze Learning Test – Delayed Recall	Remember the hidden pathway learned previously in a 10x10 grid of tiles	Memory, Visual	No s.d. in other cognitive domains
	International Shopping List Task – Immediate Recall	Remember items read from a shopping list	Memory, Verbal – Immediate	
	International Shopping List Task – Delayed Recall	Remember items from a previously read shopping list	Memory, Verbal – Delayed	
	Groton Maze Change Test	Chase a target in a 10x10 grid of tiles	Processing Speed	
	Detection Task	Identify once a card is flipped over and face up	Processing Speed	
	Set-Shifting Task	Identify whether a card is the target stimulus dimension (a colour or a number)	Set Shifting (Executive Function)	
2015 **Murrough et al** Psychiatric: Treatment Resistant Depression Two between-subjects groups: 1. IV ketamine - Ketamine 0.50 mg/kg over 40 min 2. IV midazolam - Midazolam 0.045 mg/kg over 40 min Testing Procedure: Within one week pre-infusion & at 7 days post infusion	Matrics Consensus Cognitive Battery:			Significant improvement in processing speed and verbal & visual learning in ketamine and midazolam groups (when controlling for change in depression No sig. effect of ketamine on cognition No sig. effect of anti-depressant response on cognition
	Trail Making Test A	Participants connect circles with numbers in them in increasing order as quickly as possible	Processing Speed	
	Digit Symbol Substitution Test (DSST) (Brief Assessment of Cognition In Schizophrenia)	Participants are given a matrix with matching digits and symbols. They are then given a page of digits and are asked to write the corresponding symbols below.	Processing Speed	
	Category Fluency Task	Participants given one minute to generate words in response to a stimulus category	Processing Speed	
	Spatial Span (Wechsler Memory Scale)	Duplicate a pattern after it has been demonstrated	Working Memory	
	Letter-Number Sequencing	Participant is read a list of numbers and letters and must recall the numbers in ascending order and the letters in alphabetical order	Working Memory	
	Hopkins Verbal Learning Test (HVLT) – Learning and Delay Conditions	Participants are read a 12-item list and asked to repeat it. There are 3 trials of this. After a delay, participants must to recall the words. They are then read a list of 24 words and asked to say if they were on the original list	Verbal Learning	
	Brief Visual Memory Test (BVMT) – Learning Conditions	Participants are shown 6 geometric designs for 10 seconds and asked to reproduce them. This is repeated 3 times. After a 30-minute delay,	Visual Learning	

		participants are asked to reproduce the 6 figures again.		
	Mazes – Neuropsychological Assessment Battery	Timed paper and pencil mazes of increasing difficulty	Reasoning/Problem Solving	
2017 **Grunebaum et al** Psychiatric: Bipolar Depression	Reaction Time, Simple (Computerised)	Participants are shown a black screen with a square outlined in white. Participants are asked to press a key each time a red X is presented in the box. The X is presented after a randomised delay of 50-250ms. (Sackiem et al, 2001)	Reaction Time	Improved reaction time, attention and memory in both groups Reaction time improved more in midazolam group than ketamine
Two between-subjects groups: 1. IV ketamine – racemic ketamine HCl 0.5 mg/kg 100 mL of normal saline over 40 minutes 2. IV midazolam - midazolam 0.02 mg/kg in 100 mL of normal saline over 40 minutes	Reaction Time, Choice (Computerised)	Participants are shown a black screen with four squares outlined in white laid out in a windowpane pattern. A red X appears in one box and participants are asked to hit the key corresponding to the box with the X in it. A new layout of boxes is presented every 50ms. (Sackiem et al, 2001)	Reaction Time	Verbal fluency declined in ketamine vs midazolam groups on day 1 Ketamine: Poor baseline memory encoding correlated with improvement in HDRS-17 and SSI.
	Digit Symbol Substitution Test (DSST) (WAIS III)	Participants are given a matrix with matching digits and symbols. They are then given a page of digits and are asked to write the corresponding symbols below.	Processing Speed	
Testing Procedure: At baseline & after testing	Trail Making Test A & B	Participants asked to connect circles as quickly as possible: A: participants connect circles with numbers in them in increasing order B: connect circles with both numbers and letters in increasing order	Processing Speed	Ketamine: Increased memory (SRT) at day 1 correlated with reduction in HDRS-17 and reduction in SSI. Midazolam: Poor baseline memory correlated with reduction in HDRS-17 & SSI at day 1.
	Continuous Performance Test, Identical Pairs Version (Computerised)	Participants are shown a series of 4-digit numbers and asked to indicate when the same 4-digit number is shown twice in a row (Sackiem et al, 2001)	Attention	

	Stroop (Computerised)	A stimulus is presented, and participants are asked to identify the name of or colour of the stimulus. Stimuli are colour names presented in that colour, X's presented in different colours, and colour names presented in incongruous colours (Sackiem et al, 2001)	Attention	Midazolam: Increased day 1 memory encoding related to reduction in HDRS-17 and SSI
	Buschke Selective Reminding Test	Participants are given a list of 12 words and immediately asked to recall them over 6 trials. They are reminded only of words they did not recall during the previous trial. They are asked to free recall the entire list after 30 minutes (Sackiem et al, 2001).	Memory	
	Benton Visual Retention Test, Administration D	Participants are exposed to 10 designs for 10 seconds each. They are asked to reproduce the design after a 15 second delay (Sackiem et al, 2001)	Memory	
	A Not B Reasoning (Computerised)	Participants shown a statement that describes the relationship between two letters. They are shown an arrangement of the two letters below the statement. They are asked to indicate if the statement is correct or not using yes/no keys (Sackiem et al, 2001)	Working Memory	
	N-Back Task (Computerised)	Identify if a letter presented is the same as the one before (1-back), the one two letters before (2-back) or the one three letters before (3-back) (Sackiem et al, 2001)	Working Memory	
	Letter Fluency – Controlled Oral Word Association Tests	Participants are given one minute to generate words in response to a stimulus letter (Keilp et al, 2005)	Language Fluency	
	Category Fluency – Controlled Oral Word Association Tests (Animals)	Participants given one minute to generate words in response to a stimulus category (Keilp et al, 2005)	Language Fluency	
	Go-No Go (Computerised)	Participants are shown a letter X on one of 6 locations on the computer screen. They are simultaneously played a high or low tone.	Impulsiveness	

		They are instructed to hit a response key when the X appears in the top half of the screen and is accompanied by a low tone (Keilp et al, 2005).		
	Time Production (Computerised)	A beep is sounded, and participants are given a time interval – they are asked to press a key when they think that interval of time has passed (Keilp et al, 2005).	Impulsiveness	
2018 **Gálvez et al** Psychiatric: Treatment Resistant Depression Two between-subjects groups: 1. Intranasal ketamine - ten sprays of 100 mg of ketamine (ketamine HCl 200 mg/2 mL, Ketalar®). 3/week for 2 weeks, weekly for 2 weeks 2. Intranasal midazolam - ten sprays of 4.5 mg midazolam (midazolam HCl, Hypnovel® 5 mg/mL, diluted with 0.9% saline). 3/week for 2 weeks, then weekly for 2 weeks Testing Procedure: Baseline & at 48–72 hr after treatment course	Identification Task Detection Task N-Back Task (2-Back Task) International Shopping List Task One Card Learning Task Set-Shifting Task	Identify if the card presented is red Identify once a card is flipped over and face up Identify if a card presented is the same as the one two cards before (complex working memory) Remember items from a previously read shopping list Identify if card has been seen before in a task Identify whether a card is the target stimulus dimension (a colour or a number)	Reaction Time Reaction Time Working Memory Memory, Verbal – Immediate & Delayed Memory, Visual Set-Shifting (Executive Function)	1 ketamine participant sig. impaired in reaction time 1 midazolam participant sig. impaired in working memory

In medical use. Four studies explored the effects of ketamine on cognitive functioning in a medical context.

Pain. One study of acute post-operative pain (Reeves et al, 2001) found no significant psychomotor agility differences for participants receiving IV ketamine and morphine versus those receiving IV morphine alone. However, they did find that a task of psychomotor agility with switching was significantly impaired in the morphine and ketamine group.

There were no differences in pre-and post-operative cognitive functioning between participants given IV ketamine plus morphine and those given IV morphine alone, and no significant differences in cognitive functioning between the two groups (Aubrun et al, 2008). However, this study reported that the Digit Symbol Substitution Task (DSST) was a measure of memory, and while this study used the same dose of morphine as the previous, it administered a lower dose of ketamine.

Finally, participants receiving ketamine plus bupivacaine or bupivacaine alone via wound infiltration found no significant differences in domains of attention and switching, or in the domains of orientation, attention, memory and language functioning (Zohar, 2002).

Huntington's disease. Participants with Huntington's disease (Murman et al, 1997) given a moderate dose of ketamine found that immediate verbal memory, delayed visual memory, and performance in a verbal fluency task were impaired. At a high ketamine dose, immediate visual memory, psychomotor agility, and attention were impaired. Performance on tasks of delayed verbal memory and another task of attention was not affected by ketamine in any dose.

In psychiatric use. Six studies explored the effects of ketamine on cognitive functioning in a psychiatric context.

Schizophrenia. Two studies explored the cognitive ramification of ketamine in participants with schizophrenia. One study administered ketamine via IV infusion in people with a diagnosis of schizophrenia and healthy controls (Malhotra et al, 1997), while the other administered injections of ketamine in participants with a diagnosis of schizophrenia (LaPorte et al, 1996).

Participants with a diagnosis of schizophrenia injected with ketamine experienced no drug effect in domains of episodic verbal memory or visual memory, and there were no differences in retention of episodic memory between drug and placebo (LaPorte et al, 1996). Performance in tasks of letter and category fluency were not affected by ketamine, and there was no significant difference pre and post drug for either group of participants. Visuoperceptual performance was also not affected by ketamine, and again there was no significant difference pre and post drug for either group (LaPorte et al, 1996). Though non-significant, there was some evidence of learning impairment in the ketamine group (LaPorte et al, 1996).

Participants with a diagnosis of schizophrenia and healthy controls administered IV ketamine experienced no differences in attention among the four groups (people with a diagnosis of schizophrenia; healthy participants; ketamine; placebo) (Malhotra et al, 1997). There was impairment in recall and recognition memory in participants with a diagnosis of schizophrenia and healthy participants receiving ketamine, and a significant impairment in recall for participants with a diagnosis of schizophrenia as compared to healthy participants (Malhotra et al, 1997).

Depression. Four studies looked at the cognitive ramifications of ketamine in various types of depression.

Bipolar depression. Though participants with bipolar depression administered IV midazolam, or midazolam and ketamine exhibited higher than average intelligence,

baseline reaction time, baseline memory and baseline language fluency was below the population average for both groups (Grunebaum et al, 2017).

Attention increased in both groups after drug administration, as did reaction time and memory. Reaction time was more improved in the midazolam group than in the ketamine group. After drug administration, ketamine participants saw impairment in their language fluency performance; however the midazolam group did not. There were no significant group results in the domains of impulsiveness, working memory, or processing speed (Grunebaum et al, 2017).

TRD. Participants receiving six sessions of IV ketamine over two weeks experienced significant improvements in one task of visual memory and in measures of simple working memory and complex working memory (Shiroma et al, 2014). However, two tasks of visual memory, showed no significant changes. In addition, tasks which measured attention, spatial working memory, immediate and delayed verbal memory, processing speed and the executive function of set-shifting, did not show significant changes after drug administration (Shiroma et al, 2014).

Seven days after receiving an acute infusion of IV ketamine or IV midazolam, both groups of participants displayed improved cognitive function in the domain of processing speed (Murrough et al, 2015). There was significant improvement in visual and verbal memory, no change in working memory or problem solving, and there was no significant difference in the cognitive performance of either group post drug (Murrough et al, 2015).

Finally, a small five participant trial which administered intranasal ketamine or intranasal midazolam over five weeks found impairment in reaction time for one participant receiving ketamine, and impairment in working memory for one participant receiving midazolam (Galvez et al, 2018). This study did not report differences in the

executive function of set shifting, or in the domains of visual or verbal memory (Galvez et al, 2018).

1.44 Other Effects of Ketamine

In medical use.

Pain. Participants receiving patient-controlled IV morphine plus ketamine, or patient controlled IV morphine alone after major abdominal surgery saw no group differences in their pain intensity at rest or on movement, their assessment of analgesic efficacy, or their overall opioid consumption (Reeves et al, 2001). After a major gynaecological surgery, there were no group differences in pain relief, opioid consumption, adverse effects, or mood for participants receiving patient-controlled IV morphine plus ketamine, or patient controlled morphine alone (Aubrun et al, 2008). Finally, participants receiving patient-controlled wound infiltration of ketamine plus bupivacaine, or bupivacaine alone after caesarean section did not exhibit group differences in amount of drug self-administered, pain at rest or on movement, overall analgesic satisfaction or additional opioid consumption (Zohar et al, 2002).

Huntington's disease. Participants with Huntington's disease were given low, medium and high doses of ketamine, as well as a placebo infusion on a separate day (Murman et al, 1997). At the high ketamine dose, incidence of adverse effects, psychiatric symptoms and worsening eye movements were significantly increased (Murman et al, 1997).

In psychiatric use.

Schizophrenia. Participants with a diagnosis of schizophrenia injected with ketamine experienced an acute increase in psychotic symptoms within 20 minutes of ketamine administration as compared to those administered a placebo (LaPorte et al, 1996). Psychotic symptoms largely returned to baseline within 45 minutes post drug

administration (LaPorte et al, 1996). A study of people with a diagnosis of schizophrenia and healthy participants administered IV ketamine and IV placebo on two separate days found that ketamine increased psychotic symptoms in participants with a diagnosis of schizophrenia, but not in healthy controls (Malhotra et al, 1997). Ketamine administration did not lead to a change in anxiety or mood in either group (Malhotra et al, 1997).

***Depression*.** Participants with bipolar depression administered an IV infusion of ketamine had non-significantly lower suicidal thoughts compared to participants administered midazolam (Grunebaum et al, 2017). In the ketamine group, poor encoding of memory correlated with reduced suicidal thoughts (Grunebaum et al, 2017)

Participants receiving six infusions of IV ketamine over two weeks in an uncontrolled trial saw a statistically significant reduction in depression symptoms (Shiroma et al, 2014). Low baseline attention was a predictor of decrease in depression severity, and of the likelihood that participants' depression would respond to ketamine. Conversely, better performance in baseline verbal memory predicted a decrease in depression severity. Change in cognitive performance over the treatment period was accounted for by a reduction in depression severity, however, cognitive performance did not predict relapse over the four-week post-treatment follow-up period (Shiroma et al, 2014).

Participants with TRD receiving either IV ketamine or IV midazolam experienced similar antidepressant response regardless of drug administered (Murrough et al, 2015). As outlined in the cognitive effects section, processing speed, and visual and verbal learning improved in both groups, and this change remained significant when controlling for a reduction in depression. Participants whose depressive symptoms responded to ketamine administration had a slower baseline processing speed than those

who did not respond to ketamine. There was no association between cognitive performance and antidepressant response in midazolam participants (Murrough et al, 2015).

A study administering intranasal ketamine or midazolam over four weeks found that ketamine participants experienced more frequent dissociative symptoms and higher blood pressure than their midazolam counterparts (Galvez et al, 2018). This study also determined that variable absorption and tolerability are two drawbacks of using participant administered intranasal ketamine (Galvez et al, 2018).

1.5 Discussion

This review aimed to explore the cognitive effects of sub-anaesthetic ketamine used for psychiatric and medical problems. It also aimed to explore other effects of ketamine when used in these populations. This discussion will focus on the strengths and limitations of the studies selected, as well as on the effect of ketamine on cognition and on the various problems identified.

1.51 Strengths and Limitations of Studies

Assessment of Study Quality. This literature review aimed to look at studies which by virtue of their population of patients receiving treatment would be more externally valid than studies using healthy volunteers. However, the external validity of the studies, as measured by the Downs & Black (1998) checklist was low. This is because many studies did not report the ratio of participants to source population, did not report the number of participants who declined to participate, did not report the time frame during which recruitment was ongoing, or treated participants at specialist or inpatient research facilities.

As outlined in the results section, the quality of reporting in most of the selected studies was high. All studies ensured that participants were complaint with prescribed

interventions, were statistically appropriate, and none reported results based on ad-hoc analysis. In addition, all studies reported using intent to treat analysis, and most studies randomised participants to treatment condition and then concealed this from participants and staff. However, it was difficult to determine if active and control participants were recruited from the same population or over the same time period as this was largely unreported. Further, almost half of the studies did not adjust for potential confounds

Measures of Cognitive Function. Most studies used standardised, clearly described measures of cognition. Indeed, most neurocognitive tasks used were sensitive to small levels of change and therefore appropriate for measuring differences in pre and post drug functioning. However, two studies used the Mini-Mental State Examination to measure changes in cognitive function before, during and after administration of ketamine in participants post-surgery (Aubrun et al, 2008; Zohar et al, 2002). The Mini-Mental State Examination is a 0-30 item which measures orientation, registration, recall, attention and language fluency, and is widely used as a screening measure for identifying dementia and mild cognitive impairment (Arevalo-Rodriguez et al, 2015). The simplicity of the task, its floor and ceiling effects, and its low sensitivity to change (Philipps et al, 2014) means that this is not appropriate for measuring potentially small pre and post drug cognitive changes.

A major issue with the studies was related to reporting domains associated with neurocognitive tasks. Cognitive domains are not rigidly separate categories, and neurocognitive tasks are often a predictor of functioning in multiple domains. However, several studies used the same neurocognitive task but reported that the task measured different cognitive domains. Four studies used the Digit Symbol Substitution Test (DSST) as a measure of cognition. The DSST measures perceptual and processing speed, as well as memory and motor speed to a lower degree (Laux & Lane, 1985).

Performance in this task is also associated with learning, and with working memory (Jaeger & Zaragoza Domingo, 2016). While two of the four studies reported that the DSST is a measure of memory (Aubrun et al, 2008; Zohar et al, 2002), the other two reported that it is a measure of processing speed (Grunebaum et al, 2017; Murrough et al, 2015).

Three studies used the Trail-Making Task A and B. This task has been evaluated to be a measure of psychomotor speed (Trails A) and of executive function and psychomotor speed (Trails B) (Salthouse, 2011). One study reported that it is a task of psychomotor speed and switching (a task of executive function) and also that the task is a measure of attention and perception (Reeves et al, 2001). Another study reported Trails A as a measure of psychomotor speed (Murrough et al, 2015), and one reported that Trails A & B both measure psychomotor speed only (Grunebaum et al, 2017).

Tasks involving letter (phonemic) and category (semantic) fluency also showed variations in the reporting of their underlying domains. Research indicates that executive control and verbal ability (semantic memory) are predictors of performance on both fluency tasks (Shao, Janse, Visser & Meyer, 2014), and that phonological fluency appears to be more related to executive function, while semantic fluency appears to be more related to semantic memory (Crawford, Vennero & O'Carroll, 1998). In addition, more recent research indicates that the tasks are significantly more related to language than they are to executive functioning (Whiteside et al, 2016). However, the studies that used phonological fluency tasks reported that the same task measured verbal fluency (LaPorte et al, 1996), language fluency (Grunebaum et al, 2017) or a combination of verbal fluency, semantic memory and executive cognitive skills (Murman et al, 1997). The three semantic fluency tasks were reported as either

measures of verbal fluency (LaPorte et al, 1996), language fluency (Grunebaum et al, 2017) or processing speed (Murrough et al, 2015).

1.52 Ketamine's Effect on Cognitive Functioning

The 10 studies reviewed all looked at the cognitive effects of acute sub-anaesthetic ketamine used for medical and psychiatric patients. However, the amount of between study variations introduced a level of difficulty when comparing study results. As outlined in the results section, studies varied by dose and type of ketamine administered, route of drug administration, use of an active or placebo control, neurocognitive tasks used, population characteristics, test settings, and time between ketamine administration and neurocognitive testing. Because of these study variations, it is not possible to draw a single conclusion about the effect of sub-anaesthetic ketamine on domains of cognition. However, an outline of cognitive trends by study context can be discussed.

Previous research has indicated that in healthy participants, an acute dose of sub-anaesthetic ketamine has little impact on executive functioning and does not appear to impair simple reaction time or either simple attention or selective attention as compared to baseline performance or to placebo (Hayley et al, 2017; Morgan & Curran, 2006). It also appears to impair episodic memory of information learned under the influence of the drug but not information learned prior to administration, the manipulation but not the maintenance of information in working memory, and the processing of semantic memory (Honey et al, 2003; Koychev, Deakin, El-Deredy, & Haenschel, 2017, Morgan & Curran, 2006; Morgan et al, 2004b). More relevant to this review, pain patients receiving long term ketamine had impairments in attention, working memory, semantic memory, and psychomotor coordination (Kim, Cho & Lee, 2016). In depressed patients, ketamine may lead to improvements in visual memory and simple and complex working

memory by virtue of its anti-depressant properties and participants with low pre-ketamine attention and processing speed may be more likely to see a mood response to ketamine (Lee et al, 2016).

In medical use. A study focused on the effect of ketamine on pain as compared to an active control found impairment in a task of psychomotor agility with switching in the ketamine group (Reeves et al, 2001). It is important to note here, that psychomotor agility was measured in this study with the Trail Making task, which is often reported to measure several different cognitive domains. There was no difference in the domains of orientation, attention, psychomotor agility, working memory, language functioning, or the executive function of switching in this or either of the other studies of ketamine for pain (Zohar, 2002; Aubrun et al, 2008). However as outlined above the Mini Mental State Examination may not have been a sensitive enough instrument to pick up subtle differences in cognitive functioning.

Only one study explored the effects of ketamine in patients with Huntington's disease (Murman et al, 1997). This study found no cognitive impairment at a low dose of ketamine, impairments in immediate verbal memory, delayed visual memory and verbal fluency tasks at a moderate dose of ketamine, and impairments in immediate visual memory, psychomotor agility and attention at a high dose of ketamine. In addition, delayed verbal memory and one measure of attention was not affected by ketamine at any dose (Murman et al, 1997). While verbal fluency has not been found to be impaired by ketamine in healthy participants, a 2005 neuroimaging study by Fu et al did see disruption in more difficult fluency tasks.

In psychiatric use. A study of the effects of ketamine on participants with a diagnosis of schizophrenia found no difference in ketamine and placebo in the domain of visuoperceptual performance, or on tasks of letter and category fluency (LaPorte et

al, 2016). There was no impairment of visual memory, or of performance on or retention of episodic verbal memory, however, in line with previous research there was a trend towards learning impairment in ketamine participants (LaPorte et al, 2016). In addition, a study of the effects of ketamine and placebo on participants with a diagnosis of schizophrenia and healthy participants found no difference in attention between the groups but found that ketamine impaired recall and recognition memory in both participants with a diagnosis of schizophrenia and healthy participants (Malhotra et al, 1997). Participants with a diagnosis of schizophrenia were significantly more impaired than healthy participants (Malhotra et al, 1997).

A review of the cognitive ramifications of depression indicated that psychomotor speed, memory, attention and executive functioning are typically impaired in depressed patients (Lee, Hermens, Porter & Redoblado-Hodge, 2012). In line with this, a study of ketamine and bipolar depression found that participants receiving an acute infusion of IV midazolam or IV midazolam plus ketamine had lower baseline reaction time, memory and language fluency than the general population (Grunebaum et al, 2017). Attention, reaction time and memory improved post drug administration in both groups, however the midazolam group saw more improvement in reaction time. Language fluency was improved post drug in the ketamine group, but not the midazolam group. Finally, impulsiveness, working memory and processing speed was unchanged from baseline (Grunebaum et al, 2017). In the ketamine group, poor encoding of memory correlated with reduced suicidal thoughts (Grunebaum et al, 2017).

An uncontrolled study administering six infusions of ketamine over two weeks found improvements in a task of visual memory and in simple and complex working memory (Shiroma et al, 2014). Other tasks of visual memory, and tasks of attention, spatial working memory, immediate and delayed verbal memory, processing speed and

the executive function of set-shifting were unchanged (Shiroma et al, 2014). Low baseline attention was a predictor of decrease in depression severity, and of the likelihood that participants' depression would respond to ketamine, and better performance in baseline verbal memory was a predictor of decrease in depression severity. Change in cognitive performance over the treatment period was accounted for by a reduction in depression severity, however, cognitive performance did not predict relapse over the four-week post-treatment follow-up period (Shiroma et al, 2014).

A week after administration of IV ketamine or IV midazolam, processing speed and visual and verbal memory was improved in both groups (Murrough et al, 2015). There was no change in working memory or problem solving, and no difference in cognitive performance by drug (Murrough et al, 2015). As outlined in the cognitive effects section, processing speed, and visual and verbal learning improved in both groups, and this remained so when controlling for a reduction in depression. Participants whose depressive symptoms responded to ketamine administration had a slower baseline processing speed than those who did not respond to ketamine. There was no association between cognitive performance and antidepressant response in midazolam participants (Murrough et al, 2015).

Finally, reaction time for one ketamine participant and working memory for one midazolam participant was impaired in a small study using an intranasal route (Galvez et al, 2018). There was no difference in executive function or in visual or verbal memory (Galvez et al, 2018).

1.53 Other Effects of Ketamine

In medical use. This review indicated that ketamine does not appear to effect a reduction in opioid consumption or to provide an increased analgesic effect when added to commonly used analgesics in participants with acute post-surgical pain. However,

while previous research has argued ketamine is effective in treating post-surgical pain, most studies appear to indicate that ketamine is most effective in the treatment of chronic neuropathic pain conditions (Bell, 2009; Nourouzi et al, 2010; Subramaniam, Subramaniam & Steinbrook, 2004; Visser & Schug, 2006). In addition, it is possible that adding ketamine to another analgesic may have somewhat masked both its pain controlling and opioid reducing effects. Further studies comparing common analgesics to an administration of ketamine alone need to be conducted to fully evaluate its analgesic properties.

Huntington's is an incurable neurodegenerative disease which leads to changes in motor function, psychiatric function and cognitive ability (Dale & van Duijn, 2015). Researchers have theorised that the excitotoxin quinolinic acid may be a useful behavioural model of Huntington's as it creates similar lesions in the brain (Jiang, Büchele, Papazoglou, Döbrössy, Nikkhah, 2009). Ketamine anaesthesia appears to disrupt these lesions created by quinolinic acid when administered to rats (Jiang et al, 2009). This may begin to explain the results of this review, which indicated that participants with Huntington's disease administered sub-anaesthetic ketamine experienced increased eye movements and psychiatric symptoms, however there is little further research on Huntington's and ketamine.

In psychiatric use. This review found that participants with a diagnosis of schizophrenia administered sub-anaesthetic ketamine saw an increase in psychotic symptoms, and that healthy controls did not experience psychosis (LaPorte et al, 2016; Malhotra et al, 1997). In line with these results, researchers have used the glutamate increase caused by ketamine as a model for schizophrenia and found that healthy participants were unaffected by a dose at which participants with a diagnosis of schizophrenia experience increased psychosis (Etkin, 2016).

This review indicated that ketamine appears to be as effective in the short-term amelioration of treatment resistant depressive symptoms, bipolar depression, and suicidal ideation as more established anti-depressant drugs. This is in line with previous research indicating that ketamine's modulation of the NMDA receptor is useful in the treatment of previously intractable depression (Abdallah et al, 2015; Berman et al, 2000; Fond et al, 2014; Lara et al, 2013; Matthews et al, 2012).

1.54 Limitations and Conclusions

Despite the very different characteristics of the reviewed studies, results appeared to triangulate with previous literature. In medical patients, acute sub-anaesthetic ketamine appears to affect memory - memory for information presented under the influence of the drug is impaired, as is the manipulation of information in working memory. Ketamine does not appear to decrease opioid use, or decrease pain when added to commonly used analgesics, however it is important that future research focus on the impact of ketamine alone on acute pain and ketamine alone on chronic neuropathic pain.

In participants with depressive disorders, ketamine appears to improve memory, reaction time, and attention; however these effects are often accounted for by the antidepressant properties of the drug. In addition, poor baseline processing speed, memory and attention appear to be correlated to a decrease in depressive symptoms post-treatment. Ketamine appears to be as effective as active control when administered as an IV, however further research on the efficacy of intranasal ketamine is needed.

Limiting this review is the small number of available studies focusing on the cognitive effects of acute sub-anaesthetic ketamine in non-healthy participants. Further research on ketamine used for patients with medical and psychiatric problems is essential to truly understand the cognitive effects of the drug.

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Part 2: Empirical Paper

The Cognitive Effects of Acute Sub-Anaesthetic Ketamine and Lidocaine on Participants Experiencing Chronic Pain

2.1 Abstract

Aims: The study aimed to describe the relationships between cognitive functioning and acute pain relief in patients receiving acute sub-anaesthetic intravenous ketamine, and those receiving acute lidocaine as part of routine treatment for chronic pain.

Method: This non-randomised, between subjects, active control study measured participant pain and cognitive performance before and after drug administration. Pain was measured using visual analogue scales of pain intensity, distress and interference. Cognition was measured using the Story Recall subtest of the Rivermead Behavioural Memory Test, a serial sevens subtraction task and a verbal fluency task. Data was analysed using mixed ANOVAs, and as data appeared non-parametric, Mann-Whitney tests were used to confirm results. Secondary data analysis involved investigating correlations among pain and cognitive domains.

Results: 58 statistically similar participants completed the study: 34 received lidocaine and 24 received ketamine. Ketamine was significantly more effective than lidocaine in acutely reducing pain intensity and interference. Both groups had significantly improved verbal fluency post drug administration. As compared to lidocaine, ketamine significantly impaired post-drug serial seven performance and story recall performance for information learned under the influence of the drugs.

Conclusions: Ketamine was effective in reducing acute pain, and impaired working memory, and the recall of information learned under drug influence. Results are discussed in relation to previous literature, and study limitations are discussed.

2.2 Introduction

This study investigates the effects of acute sub-anaesthetic ketamine infusion on pain and cognitive functioning in participants with chronic neuropathic pain, using similar participants receiving acute lidocaine infusions as active control. This introduction describes the relationships between ketamine, pain and cognition according to published literature.

2.21 Ketamine

Ketamine is a non-competitive antagonist of the *N*-methyl-d-aspartate (NMDA) receptor, first synthesised in 1962 as a replacement human anaesthetic for phencyclidine (PCP). Because it does not impair spontaneous respiration or block the airways and works to produce both amnesia and analgesia when used for anaesthetic purposes, it has been a part of the World Health Organisation's (WHO) Essential Medicines List since 1985 (WHO, 2016). The WHO Expert Committee on Drug Dependence indicates that while ketamine is used recreationally worldwide, and that chronic recreational use can cause adverse side effects, the medical usefulness of the drug is such that it should not be controlled under international drug control conventions (WHO, 2016).

There has been increased research interest in the use of medical ketamine for treating pain. EMBASE database searches for "ketamine and pain" returned close to 3000 results from the period 1998-2008, but close to 5000 results from the period 2008 to 2018. However, as outlined in the previous literature review, searching for clinical trials which assess the cognitive effects of acute sub-anaesthetic ketamine in non-healthy participants returned only ten relevant studies. Only three pain studies were found, and all administered ketamine to post-surgical patients alongside another analgesic agent. As there is a dearth of information regarding the cognitive effects of ketamine in pain, more research is needed.

2.22 Pain

Pain is a complex phenomenon described by The International Association for the Study of Pain (IASP) as ‘‘an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage’’ (IASP, Task Force on Taxonomy, 1994). More recent discourse highlights the importance of cognitive and social aspects of pain, describing pain as “a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components” (Williams & Craig, 2016).

This study looks at participants experiencing chronic neuropathic pain. Neuropathic pain, as defined by the IASP, is that pain which is “initiated or caused by a primary lesion or dysfunction in the nervous system” and can refer to pain affecting the peripheral or central nervous system (IASP, Task Force on Taxonomy, 1994). Chronic pain is that which has been experienced for six months or more (IASP, Task Force on Taxonomy, 1994).

When evaluating the efficacy of interventions on pain, measurement of pain change alone is not sufficient - physical and emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition should also be considered (Turk et al, 2003). Indeed, NICE guidelines on the pharmacological management of neuropathic pain recommend that regular clinical reviews focus on monitoring pain reduction, daily activities and participation, patient mood, overall patient rating of improvements, adverse effects, and finally, quality of sleep (NICE, 2011).

Pain and ketamine. When used as an anaesthetic, ketamine also provides an analgesic effect (WHO, 2016). Indeed, anaesthetic doses of ketamine lead to pain

reduction and functional increase in participants with the chronic neuropathic illness complex regional pain syndrome (CRPS) (Keifer et al, 2008).

A 2004 review exploring sub-anaesthetic ketamine adjuvant to an opioid for pain relief found that administration of a bolus of, or IV infusion of ketamine decreased opioid requirements in about half of the clinical trials reviewed but did not lead to a significantly greater pain reduction than the opioid alone (Subramaniam, Subramaniam & Steinbrook, 2004). However, a 2017 review indicated that an acute dose of sub-anaesthetic ketamine does appear to lead to pain reduction as well as to a decrease in morphine consumption in participants with opioid-resistant cancer pain (Bell, Eccleston & Kalso, 2017).

Research on participants receiving patient controlled sub-anaesthetic ketamine for acute post-surgical pain indicated little benefit of adding the drug to other analgesics (Aubrun et al, 2008; Reeves et al, 2001; Zohar et al, 2002). However, ketamine appears to have analgesic properties for chronic neuropathic pain participants at a sub-anaesthetic dose, though degree of pain reduction varies between participants (Visser & Schug, 2006).

2.23 Cognitive Function

Cognition can be broadly defined as the way in which the brain acquires, processes, stores and retrieves information (Lawlor, 2002).

Cognitive function and ketamine. Concerns about the use of acute non-anaesthetic IV ketamine in treatment for chronic pain stem from research indicating that frequent recreational ketamine users show impairment in cognitive functioning. A review by Visser & Schug (2006) indicated that long term recreational ketamine users experience severe impairment of working, episodic and semantic memory. Additionally, a more recent review by Morgan and Curran (2011) indicated that frequent recreational

ketamine users have impairments in short and long-term memory, alongside disruption of visual recognition and impairments in spatial working memory.

A one-year longitudinal study of recreational ketamine users showed decreases in spatial working memory and in pattern recognition memory (Morgan, Muetzelfeldt, Curran, 2010). Finally, a study involving patients with complex regional pain syndrome found that participants who had ketamine infusions twice a month for six months performed significantly worse on measures of attention, working memory, psychomotor coordination, and semantic memory than those who never or infrequently received ketamine (Kim, Cho & Lee, 2016).

It is important to note that the controlled acute non-anaesthetic use of a drug can often have very different consequences than those associated with frequent recreational use. While there appear to be significant cognitive consequences related to long term recreational use of ketamine, there is less definitive evidence on the effect of acute sub-anaesthetic intravenous doses of ketamine.

In a 2006 review of ketamine and cognition, Morgan and Curran reported that episodic memory is impaired for information learned on ketamine, but not for recall of information learned before drug administration. The processing of semantic memory may be impaired, and as ketamine may also impair procedural learning, it can be suggested that ketamine may impair the encoding of information into memory (Morgan & Curran, 2006). It was unclear if sustained attention was impaired, simple attention and selective attention was largely unimpaired by the drug, and there was little impact on tasks of executive function once memory deficits were controlled for (Morgan & Curran, 2006). Finally, the maintenance of information in working memory appears to be unaffected by ketamine administration, however impairments are seen in the manipulation of information in working memory (Morgan & Curran, 2006).

A more recent study indicated that as the difficulty of a visual working memory task increased, performance of healthy participants who were administered sub-anaesthetic ketamine decreased compared to placebo (Koychev, Deakin, El-Deredy, & Haenschel, 2017). Healthy participants experiencing induced heat pain and administered an acute dose of ketamine (s-ketamine, 0.29mg/kg/hr), were impaired in memory, psychomotor speed, complex attention, and the executive function of cognitive flexibility, as well as in reaction time as compared to their placebo counterparts (Olofsen et al, 2012). Healthy participants given increasing doses of ketamine (8mg/hr; 12mg/hr; 20 mg/hr) experienced dose dependant effects in complex reaction time, visuospatial working memory and spatial planning, but not on simple reaction time (Hayley et al, 2017).

One study with participants receiving ketamine for medical and psychiatric problems found those with suicidality and treatment resistant depression (TRD) experienced improvements in visual memory, simple working memory, and complex working memory (Lee et al, 2016). However, these changes were reported alongside a simultaneous reduction in depression (Lee et al, 2016). Research exploring the cognitive effects of ketamine for post-surgical pain have found various cognitive effects. Reeves et al (2001) found that participants receiving IV ketamine were impaired in psychomotor agility when switching as compared to participants receiving IV morphine. Two studies showed working memory, attention and switching were not affected when participants received either IV ketamine or morphine (Aubrun et al, 2008; Zohar, 2002). Unfortunately, there is little research on the cognitive effects of ketamine on participants receiving acute sub anaesthetic ketamine for chronic pain.

Cognitive function and pain. According to a narrative review of chronic pain and cognition, persons living with chronic pain often experience a disruption of their

cognitive functioning, especially as regards attention, speed of processing information, and executive functioning (Baker, Georgiou-Karistianis, Gibson & Giummarra, 2016). These authors suggest that the effects of pain on cognition may occur due to several mechanisms. They posit that the capacity needed to process pain signals may disrupt other cognitive processes - that is, the inherent biological need to pay attention to pain signals results in poor attention to other stimuli. They also state that due to the plasticity of the human brain, patients experiencing chronic pain may over time have a reduction in the volume of their prefrontal cortex and a corresponding increase in amygdala function, leading to decreased cognitive control. The authors also note that persons experiencing chronic pain are more likely to be tired, to be taking medications which may disrupt cognitive functioning, and to have disturbances in mood, all of which influence cognitive functioning (Baker et al, 2016).

In their 2011 review of chronic pain and cognition, Moriarty and colleagues explore the specific cognitive consequences of chronic pain. They found that patient self-report measures and empirical studies indicate that attention appears to decrease with increasing pain, and that the speed at which persons experiencing chronic pain process information is slower than controls, especially in tasks which require psychomotor ability and perceptual learning ability. The review indicated that tasks of executive functioning, especially those which require attention switching or high levels of interference, are affected by chronic pain more so than more automatic and less complicated or complex tasks (Moriarty, McGuire & Finn, 2011). Finally, the reviewers indicated that while the capacity and recall of working, or explicit, memory, verbal memory and spatial memory is negatively affected by pain, there is little difference in implicit memory performance between chronic pain patients and controls. The reviewers do note however that the exact cognitive consequences of chronic pain are

difficult to discover, as chronic pain is frequently comorbid with stress, mood disorders and fatigue (Moriarty, McGuire & Finn, 2011)

2.24 Side Effects of Ketamine

In their review of ketamine for pain, Neisters, Martini and Dahan (2013) indicate that hallucinations, urological symptoms, somnolence, dizziness, memory deficits, and a feeling of being high appear to be common side-effects of recreational ketamine use. Due to this, the authors argue that ketamine should only be used for patients with severe and treatment resistant neuropathic pain until further studies are carried out (Neisters, Martini & Dahan, 2013). In addition, Visser and Schug (2006) indicate that acute sub-anaesthetic doses of IV ketamine can cause side effects such as sedation and dizziness. However, a study by Cvrcek (2008) indicated that while almost half of participants treated with acute sub-anaesthetic ketamine experienced dizziness after infusion, no participants experienced memory deterioration or hallucinations, and only one experienced nausea and vomiting.

2.25 Lidocaine

Lidocaine, also known as lignocaine, is widely used non-opioid anaesthetic drug which works in nerves by blocking sodium channels and interrupting transmission (Eipe, Gupta & Penning, 2016).

Lidocaine and pain. Acute intravenous lidocaine is regularly used in the management of neuropathic pain and may be an effective treatment for reducing severe chronic pain (Carroll, Gaeta & Mackey, 2007). A randomised double-blind study indicated that an infusion of lidocaine was beneficial for participants with diabetic neuropathy at one and eight days after infusion, and that the effect of the drug lasted up to 21 days for some participants (Kastrup, Petersen, Dejgård, Angelo, & Hilsted, 1987). A more recent review of the literature by Souza and Kraychete (2014) indicated that

intravenous lidocaine appears to have an analgesic effect in patients with chronic pain, but that the duration of this pain relief is variable.

Lidocaine and cognitive function. In animal models, injections of lidocaine do not appear to negatively affect social memory, and may indeed be neuroprotective (Mitchell & Merry, 2009; Noack, Murau & Englemann, 2015). Lidocaine appears to be neuro-protective when administered to participants undergoing cardiac surgery, and there is little evidence that the drug causes specific cognitive deficits (Mitchell & Merry, 2009).

Side effects of lidocaine. Side effects of lidocaine may include, sedation, sleepiness, a metallic taste, numbness of the tongue, light-headedness, relaxation, euphoria and feeling unreal or feeling intoxicated (Eipe et al, 2016; Kosharskyy, Almonte, Shaparin, Pappagallo & Smith, 2013). As concentrations of lidocaine reach a toxic level, visual disturbances, muscle twitching and seizures may develop, along with unconsciousness, coma, respiratory arrest and cardiovascular collapse (Eipe et al, 2016; Kosharskyy et al, 2013).

2.26 Rationale for Current Study

Cognitive function can be affected by pain, mood, and analgesic drugs. The relationship between the three factors appears to be as illustrated in Figure 2.1.

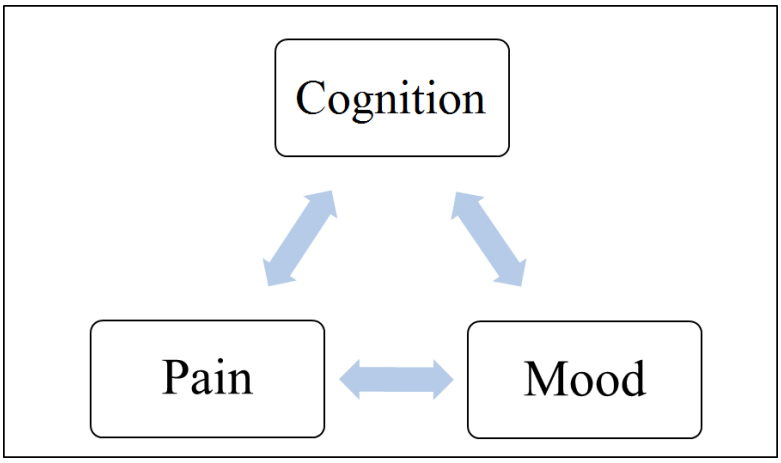

Figure 2.1: The relationship between cognition, pain and mood

The study aims to investigate the effects of ketamine on cognitive functioning and chronic pain, and to describe the relationships between cognitive functioning and acute pain relief in patients receiving acute sub-anaesthetic intravenous ketamine, and those receiving acute lidocaine as part of their routine treatment for chronic pain.

This was a joint project, and the partner project focuses on exploring the relationship between pain and mood.

2.3 Method

2.31 Ethics

Ethical approval for this study, Integrated Research Application System Number 214864, was granted by the South Central - Berkshire Research Ethics Committee (see Appendix 2.A). No modifications were made to participants' routine medical care, and all participants were required to give informed consent before taking part. Information about the study was provided to participants at least 24 hours before they were scheduled to participate (See Appendix 2.A and 2.B for information sheets and consent forms used). Participants were assured that involvement was voluntary, that they could withdraw from the study at any time, and that not participating in the study would not affect their treatment or care in any way. All participants provided informed consent.

2.32 Setting & Participants

The study site is a nationally recognised centre of excellence for people with chronic pain, which serves both the local and national population. The team is multidisciplinary, and pain is viewed through medical, psychological and social lenses. Along with infusions of ketamine and lidocaine, the service also provides other specialist interventions such as systemic drug treatment, intravenous drug infusions, peripheral and central nerve blocks, radio frequency lesioning and spinal implants, psychological support, access to TENS machines and acupuncture.

Lidocaine is typically used as the first line of treatment for infusion patients at the clinic. However, those patients with a history of heart disease or those who are deemed to be at high risk for cardiac complications will be prescribed ketamine. Patients without cardiac complications will be prescribed ketamine only if they show no or limited response to lidocaine.

Participants were patients receiving specialist pain management in the UK, and all participants were receiving either ketamine or lidocaine as part of their routine medical treatment for chronic pain. In order to be considered for inclusion in the study, potential participants were required to:

- Be receiving ketamine or lidocaine IV infusions for moderate or severe chronic neuropathic pain
- Be between the ages of 18 and 70
- Be native or fluent English speakers
- Have normal or corrected to normal vision
- Have normal or corrected to normal hearing
- Have no record of serious head injury
- Have no record of learning difficulties
- Be willing and able to provide informed consent

Potential participants were excluded if they had been diagnosed with a psychiatric illness, were pregnant or breastfeeding, or were unable to provide informed consent.

The researchers aimed to recruit 24 participants for each treatment condition; a total of 48 participants. As this study was exploratory in nature, intended sample size was determined by discussions of feasibility with a Consultant in Pain Medicine and Anaesthesia, and by a historical review of numbers of infusions occurring at the study site.

Attempts were made to contact all patients due to receive a ketamine or lidocaine infusion between the beginning of February 2018 and end May 2018. Participants were 58 adults between the ages of 20 and 70. 24 participants, seven male and 17 female were receiving ketamine, and 34 participants were receiving lidocaine, seven male and 27 female. Characteristics of participants are described in Table 2.2 in the results section

2.33 Research Design

This study used a non-randomised, between subjects, active control design. As the independent variable of drug (ketamine or the control lidocaine) was a part of participants' regular medical treatment, it was not possible to blind participants. In addition, as infusion length was significantly different between the two drug groups, with ketamine infusions lasting from 30 minutes to one hour, and lidocaine infusions lasting from one hour to two hours, it was not possible to blind researchers.

2.34 Measures

Along with demographic details, three measures of pain and three measures of cognition were included (See Appendix 2.C for pain and cognitive measures given to participants). The decision to use the specific tasks outlined below was made in consultation with clinic staff and through piloting.

Pain visual analogue scales. Participants indicated their current state on three 0-10 Visual Analogue Scales (VAS) related to aspects of pain 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).

Story recall. Immediate and delayed episodic memory was tested using two stories from the Story Recall subtest of the Rivermead Behavioural Memory Test (SR-

RBMT – Wilson, Cockburn & Baddeley, 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.D for an overview of the scoring guidelines used for the story recall tasks)

Serial sevens. The Serial Sevens Subtraction task is a task of working memory and attention. Participants were given a number and asked to subtract seven from that number. They were then asked to subtract seven from the resulting number and to continue subtracting seven over a period of 60 seconds.

Verbal fluency (H & L). The verbal fluency task measures the production of words beginning with the same letter within a timed period. Participants were given a letter of the alphabet and asked to produce as many words as possible (excluding proper nouns) starting with that letter in 60 seconds. Proper nouns, words did not start with the target letter or repetitions were scored as errors.

2.35 Procedure

The direct care team at the site identified possible study participants. Participants thus identified were contacted by researchers to determine eligibility. Upon arrival at their appointment, participants provided informed consent and their demographic details (gender, age and highest level of education).

Pre-infusion baseline. Participants first completed the three pain VAS, and then the cognitive tasks in the following order: story 1 of the SR-RBMT, immediate recall condition; a verbal fluency task; a serial sevens subtraction task. The latter tasks were counterbalanced across participants.

Infusion. Prior to infusion, physiological instruments to monitor vital signs (heart rate, systolic/diastolic blood pressure, respiratory rate and oxygen saturation) were attached and participants cannulated. Ketamine infusions lasted 30-60 min, however one participant received a two-hour ketamine infusion. Most lidocaine infusions lasted between one and two hours. Protocols for treatment dose were 0.5mg/kg for ketamine participants and 2 or 3mg/kg for lidocaine participants. Infusion start time was noted and intended length of infusion was reported to the researchers by the clinical staff.

Mid-infusion. Infusion mid-point was determined for each participant based on anticipated infusion duration, and at this time the three pain VAS were repeated. Participants then were asked to complete story 2 of the SR-RBMT, immediate recall condition, another verbal fluency task and a serial sevens task (again, these tasks were counterbalanced across participants). Finally, participants completed story 1 of the SR-RBMT, delayed recall condition, and story 2 of the SR-RBMT, delayed recall condition.

Post infusion. Immediately post-infusion, participants were debriefed by researchers and given the opportunity to ask questions. Participants stayed in the clinic post infusion and were monitored until cleared to leave by the clinical team. An overview of task timing during the study is given below in Table 2.1.

Table 2.1

Timing of task administration

Prior to Infusion (Time 1)	Infusion Begins	Mid Infusion (Time 2)
Visual Analog Sale	-	Visual Analog Sale
- Pain Intensity	-	- Pain Intensity
- Pain Distress	-	- Pain Distress
- Pain Interference	-	- Pain Interference
Story 1	-	Story 2
- Immediate Recall	-	- Immediate Recall
Verbal Fluency	-	Verbal Fluency
Serial Sevens	-	Serial Sevens
	-	Story 1
	-	- Delayed Recall
	-	Story 2
	-	- Delayed Recall

2.36 Statistical Analysis

Variables related to pain and cognitive functioning were evaluated for normality of distribution, using the Shapiro-Wilk Test, a preferable test of normality due to its power, (Ghasemi & Zahediasl, 2012; Mohd Razali & Yap, 2011). Missing variables were excluded pairwise (See Appendix 2.E for the results of the Shapiro-Wilk tests of normality for baseline and midpoint pain and cognition scores). In the Shapiro-Wilk test, a significant value indicates a deviation from normal, and according to results much of the data did not appear to be normally distributed. It is important to note that while statistical tests of normality are useful, they can be prone to error, so plots of the

data were visually examined for normality – that is, histograms were created which were then compared to a normal bell curve. Quartile-quartile plots of the data indicated that the data appeared to be linear, however histograms of the data showed the effects of skew and kurtosis.

There is no easily accessible non-parametric variation of a mixed ANOVA. According to Field (2018) however, the F-test in ANOVA is a robust measure – that is, it can tolerate violations of its assumption of normality. In addition, Field noted that in samples of 40 or more, the sampling distribution is usually normal, and recommended that where possible it is preferable to use a robust measure such as the F-test, especially if the data is linear but affected by skew or kurtosis (Field, 2018). Thus, in order to explore the interactions between drug and time, the main effects of drug, and main effects of time on the domains of pain and cognition, mixed ANOVAs were used.

Nonetheless, to confirm results of these parametric analyses, non-parametric Mann-Whitney tests were used to determine if change scores for pain and cognition were significantly different in the lidocaine and ketamine groups.

Secondary data analysis involved exploring the ways in which variables were associated. Correlations were run to determine if there was covariance in the ways in which the domains of pain and the domains of cognitive functioning changed over time. As tests of normality on change scores appeared to be non-parametric, and histograms of the data did not appear to follow the normal bell curve, the Spearman's rho correlation coefficient was used (See Appendix 2.F for Shapiro-Wilk tests of normality for pain and cognition change scores).

2.4 Results

2.41. Demographics

58 participants completed the study, 34 in the lidocaine group and 24 in the ketamine group. Demographic details collected included participant age, sex and highest educational level. Participants in each group were statistically similar, and the characteristics of the study sample are given in Table 2.2. Age and gender distributions for the total study population, including those of the population who were included in the study sample are given in Table 2.3.

Table 2.2.

Characteristics of study sample and results of the statistical differences between groups

Characteristic	Lidocaine	Ketamine	Statistical Tests
N	34	24	
Age:			t(56)=1.032, *p*=0.307
Mean ± SD	48.03±13.76	51.75±13.19	
(range)	(20-69)	(24-70)	
Sex:			$X^2(1)$ =0.565, *p*=0.328
Male	7 (20.6%)	7 (29.2%)	
Female	27 (79.4%)	17 (70.8%)	
Education level (years)*:	13.31	13.36	t(52)=0.011, *p*=0.991
Dose of drug (mg)	195.80 (61.68)	20.52 (12.59)	

*. Data missing for four participants, two lidocaine and two ketamine

Table 2.3.

Age and gender distributions for the total study population

		Ketamine		Lidocaine	
Age		N	Mean ± SD	N	Mean ± SD
	[1]Study Population	24	51.75± 3.19	34	48.03±13.76
	[2]Full Population	74	55.77±12.18	188	50.20±14.14
Gender (Female)		N (%)		N (%)	
	[1]Study Population	17 (70.8%)		27 (79.4%)	
	[2]Full Population	46 (62.2%)		137 (72.9)	

[1]Study Population: All participants who participated in the study

[2] Full Population: all patients attending the study site for infusions between February and May 2018, including the study population

In all statistical tests used, Time 1 was defined as tasks completed prior to infusion, while Time 2 was defined as tasks completed at the mid-point of the infusion.

2.42. Pain

Change in pain was analysed using mixed ANOVAs, the full results of which are reported in Table 2.4.

Results indicated a significant interaction between time and drug (see figure 2.2), no main effect of drug, and a main effect of time on pain intensity.

Table 2.4.

Results of mixed ANOVA exploring the effects of drug and time on pain

Pain Domain	Time 1 Means: Lidocaine (SD) Ketamine (SD)	Time 2 Means: Lidocaine (SD) Ketamine (SD)	ANOVA Conditions	F(1,55)	Sig. (*p*)
Pain Intensity	6.58 (2.09) 7.15 (1.98)	4.98 (2.10) 3.33 (2.22)	**Drug x time**	**15.74**	**.0001***
			Drug	1.22	.274
			Time	**93.11**	**.0001***
Pain Distress	5.82 (2.70) 5.96 (2.90)	3.32 (2.47) 2.31 (2.57)	Drug x time	2.78	.101
			Drug	.48	.490
			Time	**79.91**	**.0001***
Pain Interference	7.16 (2.90) 7.41 (2.52)	3.75 (3.40) 1.91 (2.27)	**Drug x time**	**4.97[a]**	**.030***
			Drug	1.57[a]	.213
			Time	**89.84[a]**	**.0001***

*. Indicates significance at the 0.05 level [a]. Indicates F(1,53)

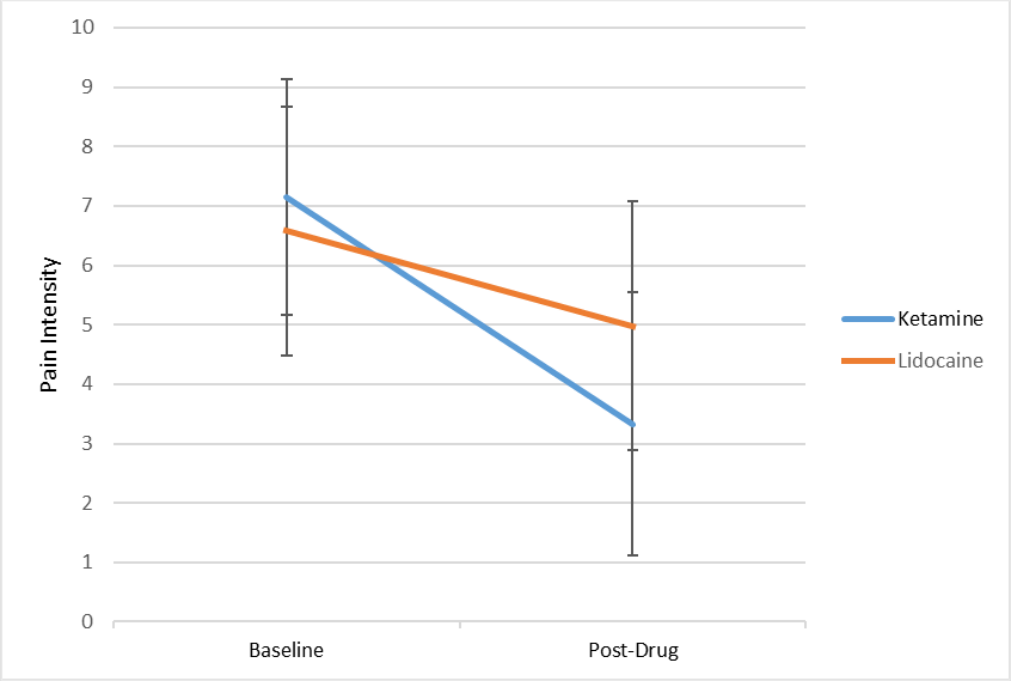

Figure 2.2: *Measure of Pain Intensity Before and After Drug Administration for Participants Administered Ketamine and Lidocaine*

There was no significant effect of time and drug on pain distress, and no main effect of drug. There was however a significant reduction in pain-related distress after drug administration. Pain interference showed an interaction between time and drug (See figure 2.3). There was no main effect of drug, but there was a significant effect of time

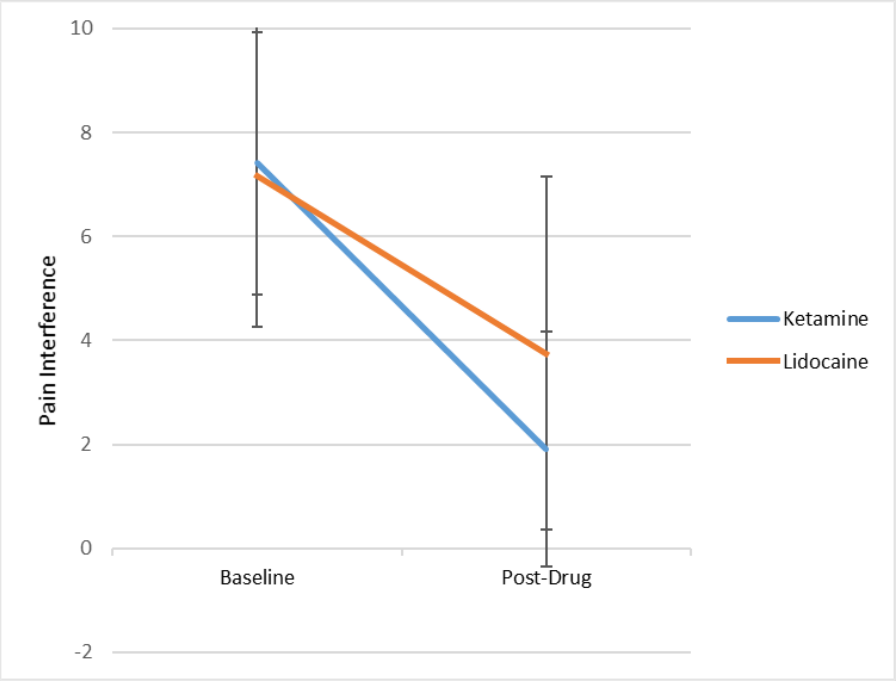

Figure 2.3: *Measure of Pain Interference Before and After Drug Administration for Participants Administered Ketamine and Lidocaine*

As the data appeared non-parametric, the more conservative Mann-Whitney tests were used to confirm findings. Change scores were computed in SPSS by taking the baseline value from the midpoint value for each variable. Results of these tests are shown in Table 2.5. Ketamine participants experienced a significantly larger decrease in pain intensity after drug administration than lidocaine patients. This group of participants also displayed a significantly larger decrease in pain interference as compared to their lidocaine counterparts. There was no significant difference found between the groups on the domain of pain distress, indicating that the significant ANOVA results for pain distress should be treated with caution.

Table 2.5.

Mann-Whitley tests on change scores of pain

	Median Ketamine (N)	Median Lidocaine (N)	U	Z	P	R
Pain Intensity	**0 (24)**	**1 (33)**	**614.00**	**3.56**	**0.001***	**0.47**
Pain Distress	0 (24)	1 (33)	502.50	1.74	0.082	0.23
Pain Interference	**1 (23)**	**2 (32)**	**488.50**	**2.07**	**0.038***	**0.27**

*. Indicates a significant difference at the 0.05 level

2.43. Cognition

Change in cognitive functioning was analysed using mixed ANOVAs, the full results of which are reported in Table 2.6.

Verbal fluency. There were significant main effects of drug and time on correct responses during the verbal fluency task, but no interaction between time and drug. The lidocaine group produced more correct responses than the ketamine group at both T1 and T2; the main effect of time reflected more correct responses overall at T2 than T1. There was no significant interaction between drug and time on the total number of errors made during the verbal fluency task, no main effect of drug, and no main effect of time.

Table 2.6.

Group means (SD) pre-drug (T1) and post-drug (T2) and results of mixed ANOVAs exploring the effects of drug and time on cognitive tasks

Cognitive Domain	Time 1 Means: Lidocaine (SD) Ketamine (SD)	Time 2 Means: Lidocaine (SD) Ketamine (SD)	ANOVA Conditions	F(1,55)	Sig. (p)
Verbal Fluency N Correct	11.24 (5.05) 10.67 (4.16)	13.76 (5.90) 11.25 (4.52)	Drug x Time	2.214	0.142
			Drug	**6.906**	**0.011***
			Time	**5.696**	**0.020***
Verbal Fluency Total Errors	0.55 (0.75) 1.04 (1.23)	0.64 (0.96) 0.79 (1.02)	Drug x Time	0.995	0.323
			Drug	2.611	0.112
			Time	0.217	0.643
Serial Sevens	8.12 (7.10) 8.42 (6.78)	8.61 (6.14) 5.79 (4.85)	**Drug x Time**	**9.830**	**0.003***
			Drug	0.600	0.442
			Time	**4.655**	**0.035***
Story 1 Recall	4.89 (2.62) 5.07 (3.18)	2.58 (2.13) 2.50 (2.75)	Time x Drug	0.296[a]	0.589
			Drug	0.007[a]	0.935
			Time	**101.961[a]**	**0.0001***
Story 2 Recall	6.50 (2.34) 5.22 (3.53)	4.98 (2.37) 3.46 (3.58)	Time x Drug	0.183[a]	0.671
			Drug	3.666[a]	0.061
			Time	**32.502[a]**	**0.0001***
Immediate Story Recall	4.88 (2.62) 5.04 (3.12)	6.50 (2.34) 5.06 (3.53)	**Drug x time**	**4.836**	**0.032***
			Drug	.885	0.351
			Time	**5.091**	**0.028***
Delayed Story Recall	2.58 (2.13) 2.50 (2.75)	4.98 (2.37) 3.46 (3.58)	**Drug x Time**	**5.368**	**0.024***
			Drug	1.496	0.227
			Time	**28.818**	**0.0001***

*. Indicates significance at the 0.05 level

[a]. Indicates F(1,53)

Serial Sevens. There was a significant interaction of drug and time and a significant main effect of time (see figure 2.4), but no main effect of drug.

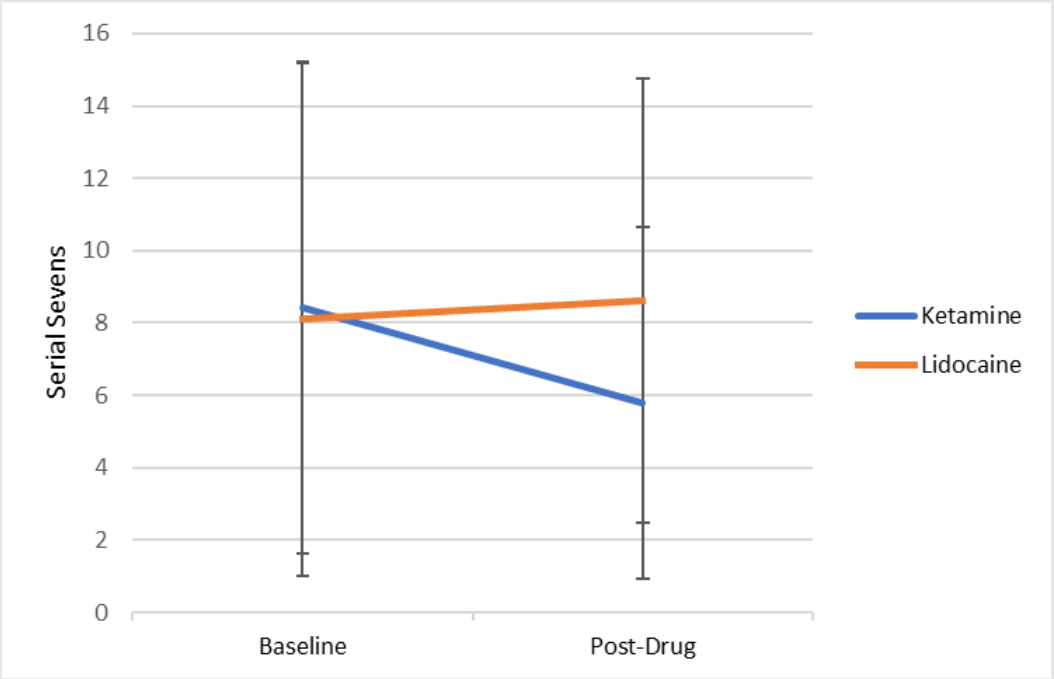

Figure 2.4: *Changes in Serial Sevens Performance Before and After Drug Administration for Participants Administered Ketamine and Lidocaine*

Story Recall. Results indicated a main effect of time on the recall of story 1, where both groups showed a significant decline in recall. However, there was no interaction of time and drug, and no main effect of drug. The ability to recall story 2 was significantly affected by time, but again there was no significant interaction between time and drug, and no significant main effect of drug.

For the immediate recall of a story pre-drug (T1) and post-drug (T2) there was a significant main effect of time, and a significant interaction between time and drug (see figure 2.5), but no significant main effect of drug. For the delayed recall of a story post drug administration, there was a significant interaction of time and drug (see figure 2.6), and a significant main effect of time, but no significant main effect of drug

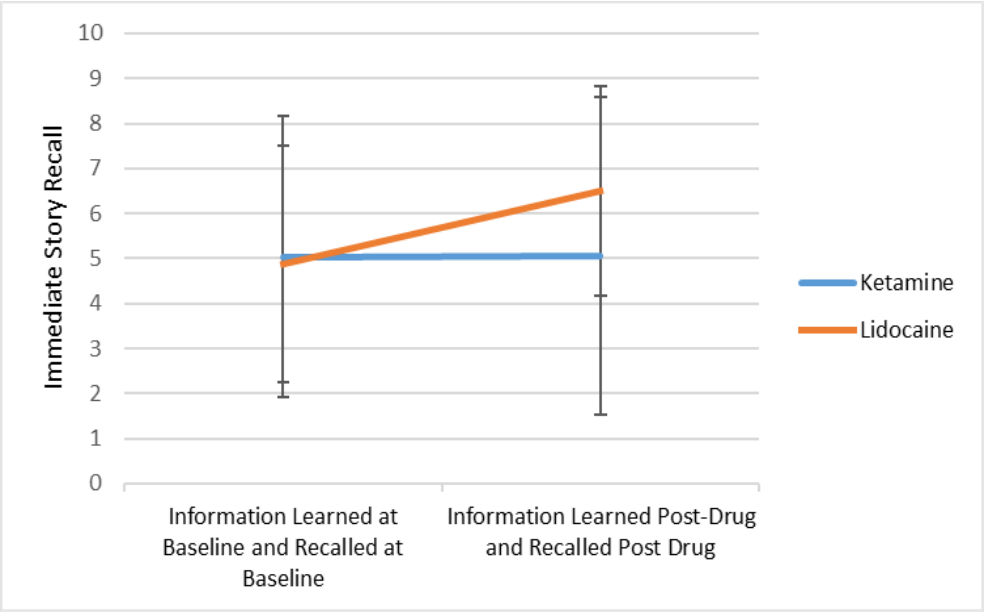

Figure 2.5: *Immediate Recall for Information Learned and Recalled at Baseline compared to Information Learned and Recalled After Drug Administration for Participants Administered Ketamine and Lidocaine*

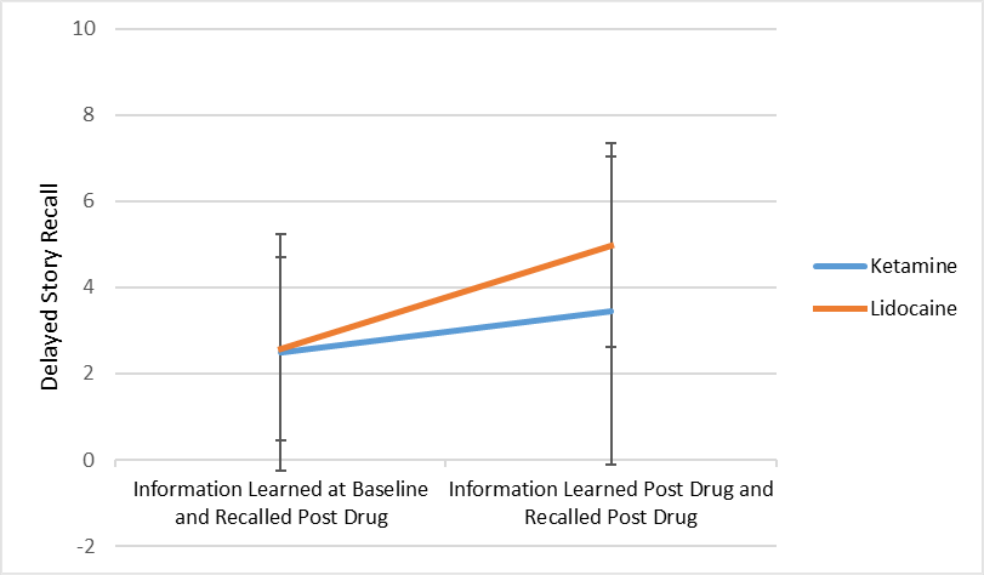

Figure 2.6: *Delayed Recall of Information Learned at Baseline and Recalled Post Drug Administration, as compared to Delayed Recall of Information both Learned and Recalled Post Drug for Participants Administered Ketamine and Lidocaine*

As with the data for pain, the cognitive data appeared to violate assumptions required for parametric analysis/ Change scores were analysed using Mann-Whitney tests and results were largely in line with results from the ANOVA's (see Table 2.7). Results of Mann-Whitney tests indicated that ketamine participants had a significant change in their post drug performance on the serial sevens task as compared to the lidocaine group. In a task of immediate recall of a story, participants receiving ketamine were significantly more impaired than lidocaine participants after drug administration. Ketamine participants were also significantly more impaired on a task requiring the delayed recall of a story than their lidocaine counterparts. No other cognitive tasks showed a significant difference in the Mann-Whitney results.

Table 2.7

Mann-Whitley tests on change scores of cognition

	Median ketamine (N)	Median lidocaine (N)	U	Z	P	r
Fluency correct	-0.50 (24)	-2.00 (33)	463.50	1.095	0.274	0.14
Fluency total errors	0.00 (24)	0.00 (34)	453.00	0.963	0.336	
Serial sevens	**2.00 (24)**	**-1.00 (33)**	**594.00**	**3.223**	**0.001***	**0.43**
Immediate recall	**-1.00 (24)**	**-1.5 (33)**	**572.00**	**2.853**	**0.004***	**0.378**
Delayed recall	**0.50 (23)**	**2.00 (33)**	**541.00**	**2.250**	**0.024***	**0.301**

*. Indicates a significant difference at the 0.05 level

2.44. Secondary Analysis – Correlations

Table 2.8 shows the means, standard deviation and Spearman's Rho correlations between changes in pain and cognitive domains by drug administered.

Lidocaine. In lidocaine participants, change in pain intensity was significantly positively correlated with change in pain distress, pain intensity was significantly positively correlated with pain interference, and pain distress was significantly positively correlated with change in pain interference. Change in pain distress was significantly negatively correlated with a change in the amount of errors on a task of verbal fluency.

Errors in verbal fluency were significantly negatively correlated with the immediate and delayed recall of story 1. The immediate and delayed recall of story 1 was significantly positively correlated with overall immediate recall, as was the immediate and delayed recall of Story 2 with overall immediate recall. Overall immediate recall was significantly positively correlated with overall delayed recall.

Ketamine. In ketamine participants, change in pain intensity was significantly positively correlated with change in pain distress, and pain intensity was significantly positively correlated with pain interference, however there was no significant relationship between pain distress and pain interference. Change in pain distress was significantly negatively correlated with performance on the immediate and delayed recall of story 1. Change in pain interference was significantly positively correlated with measures of delayed recall.

Changes in number of correct responses on a task of verbal fluency were significantly negatively correlated with errors on that same task. Immediate and delayed recall of story 1 was significantly positively correlated with overall immediate recall. However, the immediate and delayed recall of Story 2 was significantly negatively correlated with overall immediate recall.

Table 2.8.

Means, standard deviation and Spearman's rho correlations between changes in pain and cognitive domains

Drug	Measure	Mean	SD	N	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Lidocaine	1. Pain Intensity	1.59	1.74	33	-	**0.41***	**0.44***	-0.17	-0.12	-0.15	0.12	-0.04	0.17	0.062
	2. Pain Distress	2.50	2.31	33	**0.41***	-	**0.58****	-0.03	**-0.45****	-0.24	0.02	0.12	-0.13	-0.01
	3. Pain Interference	3.41	3.58	32	**0.44***	**0.58****	-	-0.04	-0.20	-0.07	-0.18	-0.02	0.06	0.27
	4. Verbal Fluency Correct	-2.51	4.99	33	-0.17	-0.03	-0.04	-	0.10	0.17	-0.19	-0.13	-0.18	-0.30
	5. Verbal Fluency Total Errors	-0.09	0.80	33	-0.12	**-0.45****	-0.20	0.10	-	0.33	**-.35***	-0.05	-0.12	-0.02
	6. Serial Sevens	-0.48	2.96	33	-0.15	-0.23	-0.07	0.17	0.33	-	0.07	-0.01	-0.01	-0.13
	7. Story 1 Recall	2.30	1.55	33	0.12	0.02	-0.18	-0.19	**-0.35***	0.07	-	0.18	**0.40***	-0.14
	8. Story 2 Recall	1.52	1.90	33	-0.04	0.12	-0.02	-0.13	-0.05	-0.01	0.18	-	**-0.52****	0.09
	9. Story Immediate Recall	-1.62	2.40	33	0.17	-0.13	0.06	-0.18	-0.12	-0.01	**0.40***	**-0.52****	-	**0.49****
	10. Story Delayed Recall	-2.41	1.82	33	0.06	-0.01	0.27	-0.30	-0.02	-0.13	-0.14	0.09	**0.49****	-
Ketamine	1. Pain Intensity	3.81	2.49	24	-	**0.72****	**0.47***	0.14	0.18	0.12	-0.04	-0.27	0.13	0.18
	2. Pain Distress	3.65	2.88	24	**0.72****	-	0.41	0.35	0.15	0.09	-0.05	**-0.43***	0.02	-0.01
	3. Pain Interference	5.50	3.22	23	**0.47***	0.41	-	0.20	0.10	0.20	-0.40	0.06	-0.22	**0.43***
	4. Verbal Fluency Correct	-0.58	4.61	24	0.14	0.35	0.20	-	**-0.45***	0.29	0.09	-0.12	-0.09	-0.04
	5. Verbal Fluency Total Errors	0.25	1.73	24	0.18	0.15	0.10	**-0.45***	-	0.04	-0.25	-0.02	0.13	0.07
	6. Serial Sevens	2.63	4.53	24	0.12	0.09	0.20	0.29	0.04	-	0.17	-0.17	0.33	0.16
	7. Story 1 Recall	2.57	2.06	23	-0.04	-0.05	-.40	0.09	-0.25	0.17	-	0.11	**0.46***	-0.37
	8. Story 2 Recall	1.76	2.40	23	-0.27	**-0.43***	0.06	-0.12	-0.02	-0.17	0.11	-	**-0.45***	0.21
	9. Story Immediate Recall	-0.02	3.10	24	0.13	0.02	-.22	-0.09	0.13	0.33	**0.46***	**-0.45***	-	0.19
	10. Story Delayed Recall	-0.96	2.87	23	0.18	-0.01	**0.43***	-0.04	0.07	0.16	-0.37	0.21	0.19	-

* Correlation is significant at the 0.05 level (2-tailed)

** Correlation is significant at the 0.01 level (2-tailed)

2.5 Discussion

This paper described a non-randomised between subjects study of the effects of sub-anaesthetic IV infusions of ketamine compared to those receiving IV infusions of lidocaine on the cognitive functioning in participants receiving the drugs for chronic pain. The study compared the two groups in terms of changes in pain, episodic memory, working memory and attention, and verbal fluency.

2.51 Summary & Interpretation of Results

Pain. Administration of ketamine significantly reduced participant levels of pain intensity, pain distress and pain interference. Indeed, ketamine was significantly more effective than lidocaine in acutely reducing pain intensity and pain interference, but not in reducing pain distress. The three domains of pain appeared to be related in both groups of participants.

These results are in line with previous research which reported that acute sub-anaesthetic ketamine leads to pain reduction in patients with chronic cancer pain and for patients with chronic neuropathic pain (Bell et al, 2017; Visser & Schug, 2006).

Some of the various biological and evolutionary factors that may contribute to cognitive disruption in persons with chronic pain have been outlined in the introduction. However it is important to again note that chronic pain itself can lead to reduced attention, decreased processing speed and decreased executive functioning (Baker et al, 2016; Moriarty et al, 2011) as well as to a reduction in the capacity and recall of working, or explicit memory, verbal memory and spatial memory (Moriarty et al, 2011). It follows therefore that some of the increased cognitive ability observed in participants in this study may be related to the corresponding decrease in the three pain domains.

Phonological fluency. Both groups of participants significantly increased in phonological fluency performance post drug administration, probably reflecting a

practice effect. Previous research on healthy volunteers indicated that simple phonological fluency does not appear to be impaired by ketamine (Fu el at, 2005). However, a study of chronic somatoform pain disorder patients indicated that pain patients were impaired in a task of verbal fluency as compared to healthy controls (Ren et al, 2017).

Working memory & attention. The ketamine group was significantly impaired post-drug on a task of working memory and attention as compared to the lidocaine group. While the lidocaine group of participants experienced a small increase in performance on this task post drug, the ketamine group of participants experienced an impairment in their post drug functioning.

Simple attention and the maintenance of information in working memory appeared to be unaffected by ketamine (Aubrun et al, 2008; Morgan & Curran, 2006; Zohar et al, 2002). However, the serial sevens task used involves the manipulation of information in working memory. More difficult tasks, and tasks which involve manipulation of working memory have been shown to be impaired by ketamine (Honey et al, 2003; Koychev et al, 2017; Morgan & Curran, 2006). Finally, as reported previously, chronic pain can impair working memory and attention, so the slight increase in ability of the lidocaine group may have been related to the decrease in pain.

Episodic memory. Participants in both the ketamine and lidocaine groups performed significantly better in the immediate recall of episodic memory than they did in the delayed recall of episodic memory.

Participants administered lidocaine performed significantly better on a task of immediate recall after drug administration than they did on this task before drug administration, whereas there was no significant change in immediate recall in the ketamine group after drug administration.

Delayed Recall – both ketamine and lidocaine groups performed better on the delayed recall of a story presented before drug administration than they did on the delayed recall of a story presented before drug administration. However, the lidocaine group exhibited significantly greater delayed recall for information presented after drug administration then the ketamine group.

Pain has been reported to impair memory (Moriarty et al, 2011), and the findings from this study imply that a reduction in pain may have led to increased memory functioning. However, while both groups experienced increased memory ability in the delayed recall of information, the lidocaine groups were significantly more improved than the ketamine groups in both the delayed recall and the immediate recall of information learned after drug administration.

Previous studies indicate that ketamine does not impair episodic memory for information learned before drug administration (Morgan & Curran, 2006; Morgan, Mofeez, Brandner, Bromley & Curran, 2004a). However, research indicates that ketamine does impair episodic memory for information learned under the influence of the drug. (Morgan & Curran, 2006; Morgan et al, 2004a).

Pain and cognition. For participants administered lidocaine, decreased pain distress was related to reduced incidence of errors on a measure of phonological fluency. In ketamine participants, as pain distress decreased, the post-drug ability to recall episodic information learned before drug administration increased. In addition, a change in pain interference was positively correlated with delayed recall of episodic memory.

Ketamine participants also experienced a decrease in their verbal fluency correlated with an increase in their errors on that task. Finally, in ketamine participants, the immediate and delayed recall of the story learned pre drug was positively correlated

with overall immediate recall, however, the immediate and delayed recall episodic information learned post drug was significantly negatively correlated with overall immediate recall.

2.52 Limitations

As this study was with patients receiving ketamine and lidocaine as part of their routine medical care, it was not possible to control drug doses, or to blind participants or medical staff to drug group. In addition, due to the variation in length of drug infusions, it was not possible to blind researchers to drug group.

A further limitation regarding infusion length relates to time elapsed between pre-drug and post-drug cognitive tests. Ketamine infusions were between 30 and 60 minutes long, with one outlier receiving a two-hour infusion, while lidocaine infusions lasted between one and two hours. Due to this, ketamine participants repeated cognitive measures after 20-40 minutes, while lidocaine participants repeated cognitive measures after 30-60 minutes. It is possible that ketamine participants may have had an advantage due to recency effects. However, it is important to note that ketamine participants were impaired compared to lidocaine participants on most cognitive tasks.

Due to the medical setting of the study, while protocols for treatment dose were 0.5mg/kg for ketamine participants and 2 or 3mg/kg for lidocaine participants, some participants received slightly higher or lower doses of drug. In addition, several participants were not naïve to these drugs and had received ketamine or lidocaine infusions previously. Further complicating matters, several participants in the ketamine group had been administered lidocaine in the past, but as they were not responsive to this drug they were then prescribed ketamine.

Other limitations include the physical area in which participants were experiencing chronic pain. While initial pain scores were similar between the two

groups, the body parts affected varied. In addition, participants had been experiencing chronic pain for different lengths of time, they had different levels of physical functioning and they were prescribed varying medications for their pain and for any other conditions.

2.53 Implications of the Research

Chronic pain is a costly burden – for the individual experiencing pain, for their families, and for the health and economic systems involved (Dueñas, Ojeda, Salazar, Mico, & Failde, 2016; Phillips, 2009). Unmanaged chronic pain can lead to absenteeism, reduced productivity and long-term incapacity – however, as many as 40% of persons experiencing chronic pain report that their pain is not managed effectively (Phillips, 2009).

Psychological interventions are useful in the management of chronic pain as they help patients understand the ramifications of their pain behaviours, to decrease unhealthy and increase healthy coping mechanisms, and to understand and modify the thought and emotional patterns associated with their chronic pain (Eccleston, 2001; Eccleston, Morley, & C. de C. Williams, 2013). More and more research is emerging which supports the notion that multidisciplinary pain management is both cost effective and effective in the reduction of pain and improvement of overall quality of life (Giusti et al, 2017). However, while there is research supporting the efficacy of psychological interventions (Cano-García, González-Ortega, Sanduvete-Chaves, Chacón-Moscoso, & Moreno-Borrego, 2017; Eccleston, Morley, & C. de C. Williams, 2013) evidence surrounding pharmacological interventions for the management of chronic pain is poor.

There are several pharmacological therapies available for patients with chronic neuropathic pain, however research has yet to find a panacea that works for all patients with all types of chronic pain (Finnerup, Otto, McQuay, Jensen, & Sindrup, 2005).

Indeed, a 2010 review of drug therapy for chronic back pain found only a small effect of non-steroid anti-inflammatory drugs and opioids as compared to placebo, and no effect of antidepressants, with all three drug categories inducing adverse effects in participants (Kuijpers, 2011). Because of this, research on the analgesic properties of ketamine and other NMDA receptor antagonists, as well as their cognitive correlates and adverse effects is important

2.54 Conclusions

Research on the pain relieving properties of NMDA receptor antagonists has been ongoing for almost three decades (Childers & Baudy, 2007). However, little is known about the cognitive effects of an acute sub-anaesthetic dose of ketamine in patients with chronic neuropathic pain. This findings of this study indicated that acute ketamine produced more short-term pain relief than lidocaine. Working memory was impaired by ketamine administration, as was episodic memory for information learned under the influence of the drug. Further research should focus on the longer term pain relieving properties of the drug, on comparisons of ketamine's efficacy to other common analgesics, and on the cognitive consequences of long term and repeated ketamine administration in persons with chronic pain.

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Part 3: Critical Appraisal

3.1 Critical Appraisal

3.11 Gaining Ethical Approval

The most frustrating aspect of this study was the time consuming process of gaining ethical approval.

The Joint Research Office. The Joint Research Office (JRO) aims to support researchers at UCL and UCLH in conforming to the regulatory requirements and safety standards set out by the university. The first steps in registering research at UCL involve notifying the JRO of intent to submit a data protection application, submitting a data protection application, completing a registration form for sponsorship of the study, and completing a UCL insurance registration form.

All of the above documents were submitted between January and February of 2017. The researchers then spent the next six months chasing a response by sending e-mails, making telephone contact and turning up physically at the JRO offices. The UCL Insurance Registration Form was submitted in February 2017 but confirmation of insurance was not given until July 2017. The UCL data protection application was submitted in January of 2017, and was granted approval in August of 2017. This six to eight month delay was unacceptable, and caused the timeline of the study to be severely disrupted as the research could not be submitted for ethical approval until the project had JRO approval. The researchers later learned that the department was undergoing restructuring, that the employee responsible for the study had left the department, and that the study had not been assigned to another JRO employee for several months.

NHS Ethics. The NHS ethics process itself was considerably more straightforward. In order to gain ethical approval for a study on NHS patients, researchers must complete a detailed research application using the Integrated Research Application System (IRAS), and then upload copies of all study documents such as

measures used, consent forms and information forms. The ethics application is then booked in, and the IRAS application is submitted online to a Research Ethics Committee.

The IRAS application form for the study was completed and submitted in October 2017. In December of 2017, two months after submission, the project received ethical approval from the South Central Berkshire Research Ethics Committee. The researchers were then able to apply for honorary contracts with the trust in question, and to begin piloting in January of 2018.

Though the submission date for this thesis was June 2018, collection of study data began in February 2018 and was not completed until the end of May 2018. Fortunately, at the beginning of the study my supervisors recommended starting the ethics process very early. If this had not been the case, the quality of the study would have been severely compromised.

3.12 Selecting Appropriate Neurocognitive Tasks

Measures used in piloting. Five cognitive measures and one measure of pain were included in the pilot participant pack. The demands of these tasks were discussed with staff at the study site who reported the belief that their patients could complete them. These measures are described below:

Spot-the-word. In order to assess participant's verbal IQ, the spot-the-word test was administered (Baddeley, Emslie, & Nimm-Smith, 1993). During this exercise, participants are given a list of paired words, one of which was a real word, the other made up. Participants are asked to identify the real word. This test was used to determine if the IQ of participants in the lidocaine and ketamine conditions are evenly matched.

N-back task. The n-back task is used to measure attention and working memory at two levels of difficulty (Braver et al, 1997). The task measures attention during the 0-back condition, where participants were asked to indicate if an image displayed on the screen was shown previously. In the easier 1-back condition, participants indicate if the image displayed on the screen was shown immediately before, and in the more difficult 2-back condition, participants determine if the image on screen was the same as the image presented two images previously.

Story recall. Episodic memory was tested using the Story Recall subtest of the Rivermead Behavioural Memory Test (Wilson, Cockburn & Baddeley, 1985). The Story Recall subtest involves measures of delayed and immediate recall. In the immediate recall condition, participants are asked to listen to a short passage of prose being read aloud, immediately after which they are 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

Hayling sentence completion. In order to assess response initiation and response inhibition, participants completed the Hayling Sentence Completion Task (Burgess & Shallice, 1997). In the response initiation condition, participants were read a sentence, and asked to finish that sentence with a congruent word. In the response inhibition condition, participants were read a sentence and asked to finish that sentence with an incongruent word.

Trail-making test. The Trail Making Test (Reitan, 1958) involves participants quickly connecting circles, and measures speed and executive functioning. In part A of the test, participants connected circles with numbers in them in increasing order, which measures attention and psychomotor speed. In part B, participants linked circles containing both numbers and letters in increasing order, a measure of working memory.

Visual analog scales. Three Visual Analogue Scales measuring participant's pain intensity, degree of distress and interference with functioning were used

Measures used in empirical study. During piloting it was evident that several changes needed to be made. This study is a joint project, and time to complete the combined measures was too lengthy. In addition, it was discovered that due to their levels of pain or disability, measures that required participants to write or interact physically with testing stimuli were not feasible. Due to time constraints, the Spot-The-Word and the Hayling Sentence Completion tasks were removed. The N-Back task, which is both time consuming and involves physical interaction with test material, was removed, and the Trail Making Task, which involves participant interaction in the form of connecting circles with a pencil was removed.

The removed tasks were measures of response initiation and response inhibition (Hayling), attention and working memory (N-Back), psychomotor speed and working memory – switching (Trails A & B), and verbal IQ (Spot the Word). The Story Recall task, a measure of immediate and delayed episodic memory was retained, and two further cognitive measures were added: A Serial Sevens Subtraction task, which measures attention and working memory, and a Verbal Fluency task. These tasks use verbal instructions, and require verbal responses from participants. They are short, and do not require physical interaction with testing materials, and so were more appropriate for the study population.

3.13 Assumptions about Quality of Life with Chronic Pain

Pain and especially chronic pain has always been of interest to me. My beloved late Grandfather suffered from years of chronic pain as a result of severe arthritis and a series of unsuccessful spinal reconstruction surgeries. He was a strong, active and independent man, who hated the reduced mobility his pain caused, and who often had

periods of low mood due to this. However he cared deeply for his family, and pushed through the pain so he could be involved in all aspects of family, work and social life. I watched him try treatment after treatment, consulting with pain experts and visiting pain management centres in several countries, but getting no real relief, and my heart broke for him.

Personally, during a period of extreme stress five years ago, I experienced a week-long episode of trigeminal neuralgia. During this relatively short period of time, I was unable to sleep or eat. By the time the neuralgia was diagnosed accurately and treated pharmacologically, I was suicidal and experiencing visual and auditory hallucinations.

Because of my pervious experiences, I expected patients with longstanding chronic pain to have a reduced quality of life, to be depressed, and to feel hopeless. Indeed, before starting this study, the researchers visited the study site in order to speak to patients, meet the medical staff, and to get an idea of the drug administration procedure. Patients at that visit spoke of significantly decreased functioning and low mood as a result of longstanding chronic pain.

However, during the course of the study, interacting with participants forced me to re-evaluate my views. While there were participants who reported feeling low and frustrated, many participants reported that they had come to terms with their pain and the limitations it caused them. Several participants receiving ketamine or lidocaine for the first time reported that while they had undergone many unsuccessful pharmacological treatments to manage their pain, they continued to be hopeful that this new treatment would be beneficial. Other participants were regularly receiving lidocaine or ketamine every few months. They reported that while the effects of the drugs wore off before they were able to have another dose they felt grateful for the

periods during which they experienced decreased pain and increased functioning. Though participants were in obvious pain during the pre-drug portion of the study, they were willing and eager to help, and reported being happy to work with researchers.

It is important to note that research has indicated that while there is a relationship between global quality of life and chronic pain, this relationship is not linear, and is in fact moderated by variables such as stress, fatigue and social support (Wahl et al, 2009). Indeed, in line with my experience of pain patients, quality of life is more associated with the patient's beliefs about their pain than it is with the intensity of that pain (Lam, Peters, Vlaeyen, Kleef, & Patijn, 2005).

3.14 Assumptions about the Pain Team

My expectations of the pain team at the study site were similar to my expectations of pain patients. I made the assumption that due to their work with people with irreversible chronic pain, they might feel negative about patient outcomes. In turn, I assumed they might feel disillusioned with the work they were doing, and experience significant job burnout. I also assumed that they would not be happy to have their workspace invaded by researchers and their valuable time spent in helping us. Indeed, research on physicians working with chronic pain patients show that persons in this field show higher levels of burnout than other physicians (Lapa, Carvalho, Valentim, Viana, & Pinto-Gouveia, 2017; Riquelme et al, 2018).

Again, working with staff at the study site made me re-evaluate my assumptions. The team was welcoming, interested in the research being carried out, and were always available to answer questions and give help if needed. Working with such a friendly team was a genuine delight, and their attitude towards patients was inspiring. They obviously cared about their patients, and did everything they could to make them

comfortable including making time for patient questions, empathically listening to patients, and explaining procedures clearly and without the use of jargon.

There are several factors which moderate burnout, such as beliefs about chronic pain, trust in and support from co-workers, levels of professional self-efficacy, low organisational cynicism and views of the working environment. (Rodrigues, Cohen, Swartout, Trotochaud, & Murray, 2018; Simha, Elloy & Huang, 2014). During the data collection period, the researchers saw staff exhibit empathy and support each other during difficult periods. The supervising nurse appeared to make every attempt to organise shifts to best suit staff, staff made each other cups of tea and brought in treats to share, and everyone I interacted with seemed to genuinely enjoy their work. I believe that the protective behaviours that the highly professional staff at the study site exhibited helped to mediate several of the negative effects of working with chronic pain.

3.2 References

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Appendix 1.A: Creation of Search Terms

Table 1.

Thesaurus Results for Memory in EMBASE, MedLine and PsycINFO

Search Term	EMBASE Thesaurus	MedLine Tree	PsycInfo Thesaurus
Memory	*Broader terms:* memory/ or brain function/ or cognition/	*Broader terms:* mental processes/ or memory/	*Related terms:* memory/ or amnesia/ or chunking/ or cognitive processes/ or cued recall/ or cues/ or declarative knowledge/ or forgetting/ or free recall/ or "generation effect (learning)"/ or hindsight bias/ or human information storage/ or information processing model/ or "interference (learning)"/ or latent inhibition/ or learning/ or matching to sample/ or "memory and learning measures"/ or memory disorders/ or memory training/ or metacognition/ or note taking/ or procedural knowledge/ or prompting/ or "recall (learning)"/ or relearning/ or retention/ or rote learning/ or serial recall/ or source monitoring/ or "tip of the tongue phenomenon"/
Brain Function	*Broader terms:* brain function/ or central nervous system function/	No Tree	Not in thesaurus
Cognition	*Broader terms:* cognition/ or mental function/	*Broader terms:* mental competency/ or mental health/ or mental processes/	*Related terms:* cognition/ or cognitive development/ or cognitive impairment/ or cognitive linguistics/ or cognitive processes/ or cognitive science/ or information processing model/ or intuition/ or metacognition/ or need for cognition/
Mental Function	*Broader terms:* mental function/ or "biological phenomena and functions concerning the entire organism"/	No Tree	Not in thesaurus
Neuropsych-ological OR neuropsych-ology	*Broader terms:* Psychology	*Broader terms:* Psycho-physiology	*Broader Terms* neurosciences, physiological psychology, psychological assessment *Related Terms* behavioral neuroscience, neurocognition, neuroeconomics, sychoneuroimmunology, social neuroscience, bender gestalt test, benton revised visual retention test, body sway testing, brain damage, cognitive assessment, diagnosis, memory for designs test, neuropsychological testing, traumatic brain injury

Table 2.

Unsuitable Search Terms Removed

Included	Removed
"memory and learning measures"	"biological phenomena and functions concerning the entire
"recall (learning)"/ or	organism"/
amnesia/ or	"generation effect (learning)"/ or
brain function/ or	"interference (learning)"/ or
chunking/ or	"tip of the tongue phenomenon"/ OR
cognition/ or	behavior and behavior mechanisms"/ or
cognitive development/ or	behavioral neuroscience
cognitive impairment/ or	bender gestalt test
cognitive processes/ or	benton revised visual retention test
cued recall/ or	body sway testing
declarative knowledge/ or	brain damage
forgetting/ or	central nervous system function/ or
free recall/ or	cognitive assessment
human information storage/ or	cognitive linguistics
latent inhibition/ or	cognitive science/ or
learning/ or	cues/ or
matching to sample/ or	diagnosis
memory disorders/ or	hindsight bias/ / or
memory training/ or	information processing model/ or
memory/ or	information processing model/ or
mental competency/ or	intuition/ or
mental function/ or	memory for designs test
mental processes/ or	mental health/ or
metacognition/ or	need for cognition/ or
neurocognition/ or	neuroeconomics
neuropsychological/ or	neuropsychological testing
neuropsychology/ or	neurosciences
procedural knowledge/ or	note taking/ or
prompting/ or	physiological psychology
recall/ or	psychological assessment
relearning/ or	psychophysiology
retention/ or	psychological phenomena/
rote learning/ or	Psychology
serial recall/ or	psychoneuroimmunology
source monitoring/	social neuroscience
	traumatic brain injury

Search Terms – Memory

"memory and learning measures"/ or "recall (learning)"/ or amnesia/ or brain function/ or chunking/ or cognition/ or cognitive development/ or cognitive impairment/ or cognitive processes/ or cued recall/ or declarative knowledge/ or forgetting/ or free recall/ or human information storage/ or latent inhibition/ or learning/ or matching to sample/ or memory disorders/ or memory training/ or memory/ or mental competency/ or mental function/ or mental processes/ or metacognition/ or neurocognition/ or neuropsychological/ or neuropsychology/ or procedural knowledge/ or prompting/ or recall/ or relearning/ or retention/ or rote learning/ or serial recall/ or source monitoring/

Appendix 1.B: Search Process

Table 1

Search Terms & Limits

	Terms	Results
1.	"memory and learning measures"/ or "recall (learning)"/ or amnesia/ or brain function/ or chunking/ or cognition/ or cognitive development/ or cognitive impairment/ or cognitive processes/ or cued recall/ or declarative knowledge/ or forgetting/ or free recall/ or human information storage/ or latent inhibition/ or learning/ or matching to sample/ or memory disorders/ or memory training/ or memory/ or mental competency/ or mental function/ or mental processes/ or metacognition/ or neurocognition/ or neuropsychological/ or neuropsychology/ or procedural knowledge/ or prompting/ or recall/ or relearning/ or retention/ or rote learning/ or serial recall/ or source monitoring/	1217324
2.	Cognit*	1458144
3.	1 OR 2	2012442
4.	Ketamine	58223
5.	3 AND 4	4468
6.	Limit 5 to english language	4260
7.	Limit 6 to human	2843
8.	limit 7 to "300 adulthood <age 18 yrs and older>" [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] ()	2720
9.	limit 8 to adulthood <18+ years> [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	2720
10.	limit 9 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in PsycINFO,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	875
11.	limit 10 to (clinical trial or randomized controlled trial or controlled clinical trial) [Limit not valid in PsycINFO; records were retained] (299)	299
12.	limit 11 to "0300 clinical trial" [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] (283)	283
13.	limit 12 to clinical trial, all [Limit not valid in Embase,PsycINFO; records were retained] (283)	283
14.	remove duplicates from 13	219

Appendix 1.C: Tool Used to Assess Studies

Checklist for Measuring Study Quality

Downs, S. H., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology & Community Health, 52*(6), 377-384.

Reporting

1. *Is the hypothesis/aim/objective of the study clearly described?*

Yes	1
No	0

2. *Are the main outcomes to be measured clearly described in the Introduction or Methods section?*
If the main outcomes are first mentioned in the Results section, the question should be answered no.

Yes	1
No	0

3. *Are the characteristics of the patients included in the study clearly described?*
In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

Yes	1
No	0

4. *Are the interventions of interest clearly described?*
Treatments and placebo (where relevant) that are to be compared should be clearly described.

Yes	1
No	0

5. *Are the distributions of principal confounders in each group of subjects to be compared clearly described?*
A list of principal confounders is provided.

Yes	2
Partially	1
No	0

6. *Are the main findings of the study clearly described?*
Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).

Yes	1
No	0

7. *Does the study provide estimates of the random variability in the data for the main outcomes?*
In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	1
No	0

8. H*ave all important adverse events that may be a consequence of the intervention been reported?*
This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).

Yes	1
No	0

9. *Have the characteristics of patients lost to follow-up been described?*
This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

Yes	1
No	0

10. *Have actual probability values been reported (e.g.0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*

Yes	1
No	0

External validity

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

11. *Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*
The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

Yes	1
No	0
Unable to Determine	0

12. *Were those subjects who were prepared to participate representative of the entire population from which they were recruited?*
The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

Yes	1
No	0
Unable to Determine	0

13. *Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?*
For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

Yes	1
No	0
Unable to Determine	0

Internal validity - bias

14. *Was an attempt made to blind study subjects to the intervention they have received?*
For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

Yes	1
No	0
Unable to Determine	0

15. *Was an attempt made to blind those measuring the main outcomes of the intervention?*

Yes	1
No	0
Unable to Determine	0

16. *If any of the results of the study were based on "data dredging", was this made clear?*
Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

Yes	1
No	0
Unable to Determine	0

17. *In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?*
Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

Yes	1
No	0
Unable to Determine	0

18. *Were the statistical tests used to assess the main outcomes appropriate?*
The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

Yes	1
No	0
Unable to Determine	0

19. *Was compliance with the intervention/s reliable?*
Where there was noncompliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

Yes	1
No	0
Unable to Determine	0

20. *Were the main outcome measures used accurate (valid and reliable)?*
For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

Yes	1
No	0
Unable to Determine	0

<u>Internal validity - confounding (selection bias)</u>

21. *Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?*
For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case control studies where there is no information concerning the source of patients included in the study.

Yes	1
No	0
Unable to Determine	0

22. *Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?*
For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

Yes	1
No	0
Unable to Determine	0

23. *Were study subjects randomised to intervention groups?*
Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.

Yes	1
No	0
Unable to Determine	0

24. *Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?*
All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.

Yes	1
No	0
Unable to Determine	0

25. *Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?*
This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.

Yes	1
No	0
Unable to Determine	0

26. *Were losses of patients to follow-up taken into account?*
If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

Yes	1
No	0
Unable to Determine	0

Appendix 1.D: Detailed Critical Appraisal of Included Studies.

Table 1.

Assessment of Reporting

Study	Hypothesis/ aim/objective clearly described	Main outcomes clearly described	Characteristics of the patients clearly described	Interventions of interest clearly described	Distributions of principal confounders clearly described? (2)	Main findings clearly described?	Estimates of the random variability for main outcomes provided?	Important adverse events reported	Characteristics of patients lost to follow-up been described	Actual probability values reported	Total (11)
1996 LaPorte	Yes Introduction	Yes Cognition	Yes See: Subjects & Table 1	Yes Ketamine (0.5 mg/kg) or placebo in a bolus injection. Drug/ placebo infused over 1 minute	Yes See: Table 1	Yes	Yes Standard deviation reported	No No attempt to measure adverse effects	Yes None lost to follow up	Yes	10
1997 Malhotra	Yes Introduction	Yes Cognition Behavioural effects	Yes See: Table 1	Yes Placebo OR ketamine bolus of 0.12 mg/kg then infusion of 0.65 mg/kg of ketamine (max dose 58 mg) over	Yes See: Table 1	Yes	Yes Standard error of mean	Yes Via clinical observations	Yes None lost to follow up	Yes	11

				one hour. Total dose of 0.77 mg/kg/hr							
1997 Murman	Yes Introduction	Yes Cognitive function Psychiatric & physical symptoms Motor signs of HD Ketamine blood levels	Yes	Yes Saline bolus + increasing IV ketamine 0.10, 0.40, and 0.60 mg/kg/hr OR Saline bolus + IV saline x3	Yes Within-subjects	Yes See Table 1 & 2 and Figure 1	Yes Standard error reported	No Adverse effects were reported, but there was no comprehensive attempt to measure them	Yes 4 patients unable to complete testing at 0.6mg/kg/hr ketamine	Yes	10
2001 Reeves	Yes Introduction	Yes Pain scale 1-5 Trail making PCA opioid consumption	Yes See Table 1 in paper	Yes. PCA morphine 1 mg/mL; PCA morphine w ketamine 1 mg/mL of each	Yes See Table 1 in paper	Yes See: Table 2. Postoperative Outcomes	Yes Standard deviations provided	Yes Nausea, sleep quality, vivid dreams, nausea, hallucinations, pruritus, respiratory depression, Acute Pain Service interventions	Yes 7 lost to follow up due to: inadequate analgesia; protocol violation; admitted to ICU	Yes	11
2002 Zohar	Yes Introduction	Yes Pain. Cognitive function - DSST; MMT	Yes See: Table 1	Yes PCA device with 0.125% bupivacaine OR 0.125% bupivacaine	Yes See: Table 1	Yes. See: Table 2	Yes Standard deviation/standard error of mean reported	Yes BP; heart rate & respiration; follow up: fever nausea vomiting	Yes None lost to follow up	No No p or t values reported	10

		Adverse effects – nausea; sleepiness; anxiety. Additional morphine used.		and ketamine (1 mg/mL). Max 9ml/hr of drug				coughing dizziness & drowsiness			
2008 Aubrun	Yes Introduction	Yes Mood Cognitive function Pain	Yes See: Table 1	Yes Patient controlled analgesia: Ketamine group: combination of morphine 1 mg/ml and ketamine 0.5 mg/ml Placebo group: morphine 1 mg/ml alone	Yes See: Table 1	Yes See: Table 4	Yes Standard deviation reported	Yes See: Table 3	Yes 12 patients excluded: 5 did not fulfil inclusion criteria; refused to participate in the study; experienced major surgical complications	Yes	11
2014 Shiroma	Yes introduction	Yes Depression symptoms Cognitive functioning	Yes See: Table 2	Yes All participants: IV infusion of 0.5 mg/Kg of ketamine hydrochloride	Yes See: Table 2	No	Yes Standard deviation reported	No Measured (Aldrete scale) but not reported	Yes Described in results	Yes	9

				6 infusions per day over 2 weeks (days: 1,3,5,8,10,12)							
2015 Murrough	Yes Introduction	Yes Change in depression severity Cognitive functioning	Yes See: Table 1	Yes Ketamine group: IV infusion of ketamine (0.5 mg/kg) over 40 min Active control group: IV infusion of midazolam (0.045 mg/kg) over 40 min	Yes See: Table 1	Yes	Yes Standard deviation reported	No Not reported	Yes Described in results	Yes	10
2017 Grunebaum	Yes Introduction	Yes Suicidal ideation Depression symptoms Cognitive functioning	Yes See: Table 1	Yes IV racemic ketamine hydrochloride 0.5 mg/kg OR midazolam 0.02 mg/kg in 100 mL of normal saline over 40 minutes	Yes See: Table 1	No	Yes Standard deviation or standard error reported	Yes Systematic Assessment for Treatment Emergent Events; Clinician-Administered Dissociative States Scale; Brief Psychiatric	Yes See: Figure 1	Yes	10

								Rating Scale (positive subscale)			
2018 Galvez	Yes Introductio n	Yes Cognitive functioning Mood Quality of life Side effects Ketamine & norketamin e plasma concentrati on	Yes See: Table 1	Yes 10 sprays of 100 mg of ketamine 3/ week for 2 weeks, then weekly for 2 weeks OR 10 sprays of 4.5 mg midazolam 3/ week for 2 weeks, then weekly for 2 weeks	Yes See: Table 1	Yes	Yes Standard deviations reported	Yes See: Table 3	No Characteristi cs not described	No No p values	9

Table 2

Assessment of External Validity

Study	Subjects invited to participate representative of the entire population	Subjects who participated representative of the entire population	Staff, places, and facilities where the patients were treated were representative	Total (3)
1996 LaPorte	No Inpatient research unit	Unable to determine Proportion of whose asked who agreed not stated	No Inpatient research unit	0
1997 Malhotra	Unable to determine	Unable to Determine Proportion of those asked who agreed not stated	No Specialist Centre	0

1997 Murman	Unable to Determine Proportion of participants to source population not reported	Unable to Determine Proportion of those asked who agreed not stated	Yes	1
2001 Reeves	Yes All patients presenting for elective major abdominal surgery involving a midline incision were identified	Unable to determine Proportion of those asked who agreed not stated	Yes	2
2002 Zohar	Yes Randomised	Unable to determine Proportion of those asked who agreed not stated	Yes	2
2008 Aubrun	Unable to determine No reporting of proportion of source population/ participants	Unable to determine Proportion of those asked who agreed not stated	Yes	1
2014 Shiroma	Unable to determine Referred by clinicians in primary care & mental health	Unable to determine Proportion of those asked who agreed not stated	No Special Diagnostic and Treatment Unit	0
2015 Murrough	Unable to determine	Unable to determine Proportion of those asked who agreed not stated	No Academic medical centre	0
2017 Grunebaum	Unable to determine Recruited via the internet, local media and clinician referral	Unable to determine Proportion of those asked who agreed not stated	No voluntary admission to an inpatient research unit at New York State Psychiatric Institute	0
2018 Galvez	Unable to determine Source population not identified	Unable to determine Proportion of those asked who agreed not stated	Unable to determine Not reported	0

Table 3

Assessment of Internal Validity - Bias

Study	Subjects blinded to intervention	Those measuring the main outcomes of the intervention blind	Results not based on "data dredging"	Analyses adjusted for differences in follow-up/ time between intervention and outcome	Appropriate statistical tests used	Reliable compliance with the intervention/s	Main outcome measures used accurate (valid and reliable)	Total (7)
1996 LaPorte	Yes	Yes	Yes No retrospective unplanned subgroups reported	Yes Follow up time same for all participants	Yes	Yes	Yes Measures clearly described	7
1997 Malhotra	Yes	Yes	Yes No retrospective unplanned subgroups reported	Yes Follow up time same for all participants	Yes	Yes	Yes Measures clearly described	7
1997 Murman	Yes	Yes	Yes No retrospective unplanned subgroups reported	Yes Follow up time same for all participants	Yes	Yes	Yes Measures clearly described	6
2001 Reeves	Unable to Determine	Unable to Determine	Yes No retrospective unplanned subgroups reported	Yes Outcome measures adjusted for length of surgery	Yes	Yes	Yes Measures clearly described	5
2002 Zohar	Yes	Yes	Yes	Unable to determine	Unable to determine	Yes	Unable to determine	4

			No retrospective unplanned subgroups reported		p & t values not reported		No description of cognitive tests used	
2008 Aubrun	Yes	Yes	Yes No retrospective unplanned subgroups reported	Yes Follow up time same for all participants	Unable to determine p values not reported	Yes	Yes Measures clearly described	6
2014 Shiroma	No	No	Yes No retrospective unplanned subgroups reported	Yes Follow up time same for all participants	Yes	Yes	Yes Measures clearly described	5
2015 Murrough	Yes	Yes Double blind	Yes No retrospective unplanned subgroups reported	Yes Follow up time same for all participants	Yes	Yes	Yes Measures clearly described	7
2017 Grunebaum	Yes	Yes Double blind	Yes No retrospective unplanned subgroups reported	Yes Follow up time same for all participants	Yes	Yes	Unable to determine Neurocognitive tasks not escribed in detail – what are the tests?	6
2018 Galvez	Yes	Yes Double blind	Yes No retrospective unplanned subgroups reported	Yes Follow up time same for all participants	Yes	Yes	Yes Measures clearly described	7

Table 4

Assessment of Internal Validity - Confounding (Selection Bias)

Study	Cases and controls recruited from the same population	Cases and controls recruited over the same period of time	Study subjects randomised to intervention groups	Randomised intervention assignment concealed from patients and staff	Adequate adjustment for confounding in the analyses	Losses of patients to follow-up taken into account	Total (6)
1996 LaPorte	Yes Same inpatient research unit	Unable to determine No time period given	No Alternate allocation used	Yes	No No adjustment to analysis	Yes None lost to follow up	3
1997 Malhotra	Unable to determine Within-subjects but two different groups (healthy & schizophrenia)	Unable to determine No time period given	Yes Within-subjects	Yes	Yes No confounding demonstrated	Yes None lost to follow up	4
1997 Murman	Yes Within-subjects	Yes Testing placebo/ketamine separated by a week	Yes Within-subjects, but placebo/ketamine randomised	Yes	Yes Within-subjects	Yes Numbers reported	6
2001 Reeves	Yes All recruited from same hospital	Unable to determine No time period given	Yes	Unable to determine	Yes	Yes	4
2002 Zohar	Yes All recruited from same hospital	Unable to determine No time period given	Yes Computer generated randomisation	Yes	Unable to determine Statistics not reported	Yes None lost to follow up	4
2008	Yes	Yes	Yes	Yes	Yes	Yes	6

Aubrun	All recruited from same hospital	The study was conducted between May 2003 and October 2004	Random number table		Intent-to-treat analysis	None lost to follow up	
2014 Shiroma	Yes Within-subjects	Unable to determine No time period given	No Within-subjects	No	Unable to determine	Yes Reported	2
2015 Murrough	Unable to determine	Unable to determine No time period given	Unable to determine Randomisation method not reported	Yes	Yes No adjustment – confounders appeared balanced	Yes Reported	3
2017 Grunebaum	Unable to determine Participants were recruited via the internet, local media and clinician referral	Yes Enrolment was from October 2013 to August 2015 with follow-up complete in December 2015	Yes Permuted block randomisation	Yes	Yes No adjustment – confounders appeared balanced	Yes No loss after randomisation	5
2018 Galvez	Unable to determine No information concerning source of participants	Unable to determine No time period given	Yes Permuted block design	Yes	No Results based on analysis of treatment not intent to treat	Yes Reported	3

Appendix 2.A: Confirmation of Ethical Approval

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

Mr David Carpenter
Chair

Email: nrescommittee.southcentral-berkshire@nhs.net

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

Copy to: *Ms Nikkayla Dixon*

Mr Joe Mirza, UCLH NHS Foundation Trust

Appendix 2.B: Information Sheet & Consent Form

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 3 (12/11/17)

Participant Identification Number for this trial:

CONSENT FORM

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

Name of Researcher: Matt Knox and Catherine Trotman

Please initial box

1. I confirm that I have read the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐
4. I agree to a follow up phone call one week after taking part in the study ☐
5. If during the course of the research, suicidal thoughts or depression are discussed this information will be passed on to your consultant to inform your care. ☐
6. I agree to take part in the above study. ☐

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

Appendix 2.C: Participant Research Pack

Participant ID			

Participant Pack V.5 16/02/2018
[EVEN Numbered Participants]

COVER SHEET

Participant ID				Test date				Test administer			

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	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

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											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

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.

6

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).

7

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.

8

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.

Appendix 2.D: Scoring Guidelines for Story Recall Task

Table 2.D.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 rates,	Interest rates were higher	1.0
		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.E: Shapiro-Wilk Tests of Normality for Baseline and Midpoint Pain and Cognition Scores

Table 2.E.1

Shapiro-Wilk Tests of Normality for Baseline and Midpoint Pain and Cognition Scores

Pain/Cognitive Domain	Drug Administered	Shapiro-Wilk		
		Statistic	Df	Sig.
Baseline pain intensity	Lidocaine	.873	34	.001*
	Ketamine	.748	24	.000*
Baseline pain distress	Lidocaine	.920	34	.016*
	Ketamine	.902	24	.024*
Baseline pain interference	Lidocaine	.845	33	.000*
	Ketamine	.832	24	.001*
Midpoint pain intensity	Lidocaine	.947	33	.107
	Ketamine	.933	24	.115
Midpoint pain distress	Lidocaine	.928	33	.030*
	Ketamine	.838	24	.001*
Midpoint pain interference	Lidocaine	.888	33	.003*
	Ketamine	.807	23	.000*
Baseline story 1 immediate recall	Lidocaine	.888	34	.002*
	Ketamine	.897	24	.018*
Baseline fluency correct	Lidocaine	.948	34	.108
	Ketamine	.922	24	.063
Baseline fluency errors	Lidocaine	.378	34	.000*
	Ketamine	.617	24	.000*
Baseline fluency repetitions	Lidocaine	.669	34	.000*
	Ketamine	.733	24	.000*
Baseline serial sevens	Lidocaine	.848	34	.000*
	Ketamine	.909	24	.034*
Midpoint story 2 immediate recall	Lidocaine	.958	33	.231
	Ketamine	.920	24	.059
Midpoint fluency correct	Lidocaine	.973	33	.576
	Ketamine	.972	24	.704
Midpoint fluency errors	Lidocaine	.328	33	.000*
	Ketamine	.598	24	.000*
Midpoint fluency repetitions	Lidocaine	.641	33	.000*
	Ketamine	.558	24	.000*
Midpoint serial sevens	Lidocaine	.934	33	.047*
	Ketamine	.903	24	.025*
Midpoint story 1 delayed recall	Lidocaine	.918	33	.016*
	Ketamine	.839	23	.002*
Midpoint story 2 delayed recall	Lidocaine	.967	33	.394
	Ketamine	.813	23	.001*

*. Indicates significance at the 0.05 level

Appendix 2.F: Shapiro-Wilk Tests of Normality for Pain and Cognition Change Scores

Table 2.F.1

Shapiro-Wilk tests of normality for pain and cognition change scores

Pain/Cognitive Domain	Drug Administered	Shapiro-Wilk		
		Statistic	Df	Sig.
Pain Intensity	Lidocaine	0.951	33	0.147
	Ketamine	0.953	24	0.317
Pain Distress	Lidocaine	0.959	33	0.243
	Ketamine	0.984	24	0.961
Pain Interference	Lidocaine	0.876	32	0.002*
	Ketamine	0.889	23	0.015*
Verbal Fluency Correct	Lidocaine	0.976	33	0.671
	Ketamine	0.940	24	0.162*
Verbal Fluency Total Errors	Lidocaine	0.837	33	0.000*
	Ketamine	0.965	24	0.537
Serial Sevens	Lidocaine	0.933	33	0.044
	Ketamine	0.761	24	0.000*
Story 1 Recall	Lidocaine	0.967	33	0.410
	Ketamine	0.935	23	0.143
Story 2 Recall	Lidocaine	0.948	33	0.114
	Ketamine	0.964	23	0.546
Story Immediate Recall	Lidocaine	0.983	33	0.867
	Ketamine	0.873	24	0.006*
Story Delayed Recall	Lidocaine	0.979	33	0.744
	Ketamine	0.940	23	0.177

*. Indicates significance at the 0.05 level

Appendix 2.G: 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, with the exception of the methods section which was a joint collaboration.

Collection of data was completed by the two trainees, with help from UCL Researcher Dr Will Lawn.

Statistical analysis and write up of this empirical paper was completed by myself alone, as was Part 1, the Literature Review.