Investigating the Anti-Depressant Effects of Sub-Anaesthetic Ketamine in People with Chronic Pain

Joe Kibble

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Thesis declaration form

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

Signature: 

Name: Joe Kibble

Date: 10/07/2020

Overview

Part one of this thesis is a meta-analysis examining the evidence for an association between ketamine's antidepressant and dissociative effects. 12 studies were included in this analysis. Correlations between change scores on dissociation and depression were used to calculate the effect sizes. Overall there was a significant, albeit small, negative correlation between change scores ($r = -0.16$). Results indicate that increased dissociation is associated with reduced depression in ketamine treatment, although the effect is small

Part two of the thesis describes an empirical study that aimed to explore the acute effects of sub-anaesthetic ketamine in a chronic pain population on mood, subjective experience, and pain. Measurements were taken at baseline, mid-point, post-infusion and follow-up. Ketamine resulted in lower pain scores during the infusion, however, at one-week follow-up some of the pain scores returned to baseline for ketamine, whereas for lidocaine these reductions were sustained. Ketamine did not show superior antidepressant effects compared to lidocaine. Whilst ketamine did produce greater rewarding experiences, it did not appear to lead to greater desire for taking more of the drug in this setting.

Part three of the thesis presents a critical appraisal of the research. It reflects on the various factors that influenced my approach to the research and my experiences of conducting research in a clinical setting.

This thesis is a joint project with Georgia Halls, who investigated the effects of ketamine on cognitive function in the same sample. Additionally, this is a continuation of a previous project started by two UCL Doctorate in Clinical Psychology trainees, Catherine Trotman and Matt Knox, in 2016.

Impact Statement

This thesis consisted of two parts: a meta-analysis examining the evidence for an association between ketamine's antidepressant and dissociative effects, and a non-randomized between subjects study exploring the acute effects of ketamine in a chronic pain population on mood, subjective experience, and pain.

Major depressive disorder (MDD) is thought to effect up to 350 million people across the globe and is the leading cause of disability worldwide. Ketamine has been shown to be an effective rapidly-acting antidepressant. Dissociation is a commonly found acute psychological experience induced by ketamine. It is currently unclear whether there is an association between ketamine's antidepressant and dissociative effects. Understanding the nature of this relationship has important implications for the future of ketamine's therapeutic application. Given the lack of clarity of findings within the literature, a meta-analysis is well placed to provide a clearer quantitative estimate of the presence of an association.

The results of the meta-analysis found that increased dissociation is associated with reduced depression in ketamine treatment, although the effect was small. The findings of this meta-analysis indicate that dissociation does play a role in ketamine's antidepressant effects, suggesting a need for further exploration of this relationship. This analysis also uncovered that there is currently a lack of research in this area. Therefore, recommendations are made for further research with *a priori* hypotheses and appropriate designs to be conducted in order to specifically investigate this association.

Chronic pain also represents a global health concern, with current treatments only showing efficacy for a minority of patients. Furthermore, people with chronic pain are at increased risk of experiencing depression and the presence of co-morbid

chronic pain and depression significantly impacts the effectiveness of interventions. Ketamine has been shown to provide effective relief from both symptoms of depression and chronic pain and therefore represents an exciting prospect as a dual treatment for these co-morbid conditions. At the same time, there are concerns about the abuse potential of ketamine and this presents a potential limitation to its clinical application.

The findings of the empirical paper suggest that ketamine does produce acute reductions in pain but that some of these are not apparent at one week after infusion. Additionally, ketamine did not produce superior antidepressant effects over lidocaine. A further finding was that whilst ketamine appeared to produce more rewarding effects than lidocaine, it did result in greater desire for more of the drug. This would suggest that potential for ketamine abuse is mitigated by having the drug administered in a clinical setting. These findings should be understood in the context of the doses and durations of infusions used in this study. Therefore, further research should investigate the effects of varying drug doses, frequency, and duration of infusions in order to best harness the therapeutic benefits of ketamine in a chronic pain population.

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Part 1: Literature Review

Are the Acute Dissociative Effects of Ketamine Associated with the Antidepressant Response? A Meta-analysis

Abstract

Aim: The role of ketamine's acute psychoactive effects, such as dissociation, in the drug's antidepressant efficacy remains unclear. The current meta-analysis aimed to examine the evidence for an association between ketamine's antidepressant and dissociative effects.

Method: Following a systematic review of the literature, data were extracted from 12 studies (n = 414). Correlations between change scores on dissociation and depression were used to calculate the effect sizes, and the analysis was performed using a random effects model. Subgroup analyses were performed on the covariates of diagnosis, blinding, concomitant psychiatric medication, and study quality.

Results: Overall there was a significant, albeit small, negative correlation between change scores (r = -0.16). There was evidence of significant heterogeneity between studies and this was estimated to be moderate (I^2 = 48%). Subgroup analyses were unable to explain this heterogeneity.

Conclusions: Results indicate that increased dissociation is associated with reduced depression in ketamine treatment, although the effect is small. These findings should be interpreted with caution however, due to the small number of studies included, marginal significance of effect, and unexplained heterogeneity. Future primary research would benefit from assessing this association with *a priori* hypothesis testing and adequate measures for capturing ketamine induced psychoactive effects. This would allow for a larger scale meta-analysis to be undertaken so as to establish the reliability of the current findings.

1. Introduction

1.1 Ketamine and Depression

Ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to be an effective rapidly-acting antidepressant (Berman et al., 2000; Murrough et al., 2013; Zarate et al., 2006). In recent years an enantiomer of the drug, S-ketamine (esketamine), has gained approval from both the Food and Drug Administration (FDA) and the European Drug Agency (EDA) for treatment resistant depression (TRD). The anti-depressant effects of ketamine are thought to arise from a cascade of increased glutamate activity and synaptogenic intracellular signalling (Abdallah et al., 2016). Despite the well-established efficacy of the drug for depression and several theories on biological mechanisms (Zanos & Gould, 2018), there is still much uncertainty about whether the acute psychoactive effects of ketamine play a role in its therapeutic benefits (Grabski, Borissova, Marsh, Morgan, & Curran, 2020). Understanding the potential psychological mechanisms underlying ketamine's antidepressant effects is important for the development of the drug's therapeutic use.

1.2 Psychoactive Effects

Through antagonism of the NMDA receptor ketamine is thought to produce a range of acute psychoactive effects, including dissociative and hallucinatory experiences (Short, Fong, Galvez, Shelker, & Loo, 2018). These shifts in consciousness have been compared to the psychedelic effects of classic hallucinogens, such as psilocybin (Kolp et al., 2014). Research has shown that these drugs have the potential to provide a range of psychological benefits (Griffiths & Grob, 2010; Johnson & Griffiths, 2017). Furthermore, the altered states of

consciousness produced by these substances are thought to play a key role to their efficacy (Mithoefer, Grob, & Brewerton, 2016). Ketamine has been shown to cause similar shifts in consciousness and there is some evidence to suggest that these psychedelic experiences can lead to positive changes in worldview that facilitate abstinence from heroin and alcohol addiction (Krupitsky et al., 2002; Krupitsky & Grinenko, 1997). Despite this, there has been relatively little research on the psychedelic and other subjective effects of ketamine compared to classic psychedelics. Instead, much of the literature has measured subjective response as a means of assessing tolerability, as these symptoms are largely regarded as adverse side effects (Morgan & Curran, 2012).

1.3 Dissociation

The most widely studied aspect of the acute psychological experience of ketamine is dissociation. Symptoms of dissociation include disorientation, loss of memory, and detachment from one's own body, sense of self, and the external world (Bremner et al., 1998). Ketamine induced dissociation is usually mild to moderate in severity and tends to have a short duration, with premorbid mental state returning within hours of administration (Abdallah et al., 2016). These symptoms can be experienced as extremely aversive (Ding & White, 2002). However, others find them rewarding, leading to ketamine being used recreationally (Morgan & Curran, 2012).

A number of studies have found a correlation between acute dissociative experiences and the antidepressant effects of ketamine (Luckenbaugh et al., 2014; Niciu et al., 2018; Pennybaker, Niciu, Luckenbaugh, & Zarate, 2017). This has been theorised to be a product of the two effects sharing similar underlying biological mechanisms (Luckenbaugh et al., 2014). In particular, increased levels of glutamate

are thought to be responsible for the emergence of both ketamine induced dissociative symptoms (Zorumski, Izumi, & Mennerick, 2016), and its effects on depression (Krystal, Sanacora, & Duman, 2013). This theory has been further supported by research showing an association between depression and reduced prefrontal glutamate levels (Sanacora, Treccani, & Popoli, 2012).

It is also possible that the dissociative effects of ketamine are correlated with reductions in depression due to their ability to disrupt the psychological process of rumination, which is thought to be a maintaining factor in depression (Nolan, Roberts, & Gotlib, 1998; Verplanken, Friborg, Wang, Trafimow, & Woolf, 2007). This break in rumination may help individuals to employ an external focus, as opposed to a self-focus, which has been found to reduce depressive symptoms (Fennell, Teasdale, Jones, & Damlé, 1987; Lyubomirsky & Nolen-Hoeksema, 1995). Rumination has been linked to high functional resting state activity in areas of the brain known as the default mode network (DMN) (Raichle et al., 2001). One recent study found that, in the context of being presented with negative stimuli, specific regions of the DMN were deactivated after ketamine administration compared to placebo, and that these changes in connectivity were correlated with the psychoactive effects of ketamine (Lehmann et al., 2016). These neurobiological processes may underpin a break in rumination that is made possible by the dissociative effects of ketamine.

1.4 Views on Dissociation

Developing a clearer understanding of the nature, strength and direction of the relationship between the antidepressant and dissociative effects of ketamine has important implications for the future of its therapeutic application. In much of the

research to date, dissociation has been viewed mostly as an adverse side-effect (Morgan & Curran, 2012). This has led many in the field to consider methods for minimising the dissociative experience (Krystal, Abdallah, Sanacora, Charney, & Duman, 2019). Furthermore, other NMDA receptor antagonists have been investigated in order to find an alternative without the same dissociative effects (Lener, Kadriu, & Zarate, 2017). However, it should be noted that these other substances have been unable to replicate the same antidepressant response as ketamine (Newport et al., 2015).

Whilst some researchers seek to reduce the impact of the dissociative effects of ketamine, others see this psychological experience as integral to its clinical application. It has been suggested that dissociation, caused by higher doses of ketamine, can be used to help initiate profound psychedelic experiences, e.g. near death or ego-dissolving transcendental experiences (Kolp et al., 2014). Researchers from this perspective claim that these experiences can spontaneously lead to some resolution of psychological difficulties through the development of spiritual growth and moral character (Kolp et al., 2007).

1.5 Ketamine Psychedelic Psychotherapy

Higher doses have also been recommended as a useful adjunct to psychotherapy, and a particular intervention called ketamine psychedelic psychotherapy (KPP) has been developed to optimize the therapeutic potential of such experiences (Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007). KPP consists not only of administration of ketamine but also a preparation phase beforehand, support during the experience, and integration phase afterwards. Each

stage is facilitated by a psychotherapist to help the subject interpret and integrate their experiences into day-to-day life.

Proponents of this intervention argue that ketamine's ability to block thalamo-cortical projections, and thus disconnect the self from objective reality, help to set up the conditions for an ego-dissolving 'transpersonal' or 'mystical' experience (Kolp et al., 2014). This disconnection from reality is thought to be key to deriving psychological benefits from the drug experience. Although predominantly applied to people with addictions issues, KPP has also been shown to be an effective treatment for depression, as well as a wide range of other psychological disorders, such as anxiety disorders and PTSD (Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007).

1.6 Importance of Exploring a Possible Association

Whether or not an association can be demonstrated between the dissociative and antidepressant effects of ketamine will have important implications for both the psychotherapeutic and more medicalised approaches to ketamine outlined above. If such an association were established, then this could indicate a need for treatment protocols to be developed that aimed to enhance the quality of the experience, such as those already being used in the clinical use of other psychedelic drugs (Mithoefer et al., 2016).

Further questions could also be asked about the impact of "set and setting" and whether creating a comfortable environment or working with the client's motivations before administration of the drug could help augment the antidepressant effects. This has been seen as an important component to the therapeutic use of classic psychedelics (Carhart-Harris et al., 2018), and recent research has shown it to

be predictive of improved outcomes (Haijen et al., 2018) Preliminary research within the KPP approach suggests that attending to the psychoactive experience of the patient can help to not only increase the therapeutic response but also prolong the duration of this effect (Kolp etl., 2014). This latter point is especially pertinent to ketamine given its antidepressant effects are limited to one to two weeks (Corriger & Pickering, 2019), and the potential for repeated long term use to result in negative side effects, such as impairments in cognition and damage to the bladder (Morgan, Muetzelfeldt, & Curran, 2009).

Alternatively, it may be that any relationship found between dissociation and anti-depressant response is simply a result of a shared underlying biological mechanism, such as an increase in glutamate activity. If this were the case, then dissociation could be used as a tool for identifying which clients are most likely to benefit or when they have received an adequate dose. This would be helpful given that it is still unclear as to what dose sizes are optimal for individual patients (Krystal et al., 2019).

On the other hand, if we are able to determine that there is no significant relationship between dissociation and anti-depressant response, then further efforts could be made to develop similar NMDA antagonist medications that do not cause dissociative effects. This would be important as some patients find these experiences to be extremely unpleasant (Ding & White, 2002). Furthermore, dissociative symptoms are one of the obstacles to ketamine being self-administered at home, as reduced connection to sensory experiences could make the individual more at risk of self-injury. Whilst there are other concerns around the prospect of self-administration, such as the potential for abuse, it may be useful to have this method

as an option to particular individuals, e.g. those living in rural areas or with limited mobility.

1.7 Systematic Reviews

Recently, two separate systematic reviews have been conducted to investigate the relationship between the acute psychoactive effects of ketamine and various treatment outcomes (Grabski et al., 2020; Mathai, Meyer, Storch, & Kosten, 2020). Both reviews found the available evidence to be inconsistent in their findings related to this relationship. One review focused solely on treatment response in major depressive disorder (MDD) after exposure to a single dose of ketamine (Mathai et al., 2020). They found that of the five studies that measured an association between the antidepressant response and dissociation, as measured by the Clinician Administered Dissociative States Scale (CADSS) (Bremner et al., 1998), only two of these found a significant correlation. The other review, conducted by Grabski et al. (2020), was also unable to find a consistent association between the CADSS and antidepressant outcomes, and highlighted the difficulty in drawing clear conclusions from the current data.

1.8 Rationale for Meta-analysis

Given the lack of clarity and apparent inconsistency of findings within the literature, a meta-analysis would be well suited to provide a clearer quantitative estimate of the presence of an association. There are a number of advantages that a meta-analysis has over a narrative review. A systematic review without a meta-analysis often relies on a process of 'vote counting', whereby the number of statistically significant studies are counted and compared against the number of

studies that do not show statistical significance. This is problematic as a lack of statistical significance does not necessarily indicate a lack of an effect. By using a meta-analysis to aggregate and synthesise the data from all available studies one can get a clearer estimate of the true effect size across these studies. This then provides a clearer sense of whether this overall effect size is statistically significant.

Even if significant limitations are present when conducting a meta-analysis, this is often preferred to inviting the reader to make intuitive ad hoc conclusions through 'vote counting' (Borenstein, Hedges, Higgins, & Rothstein, 2011). This also allows for the limitations of the statistical summary to be explicitly named and provides a clear idea of what is possible with the current data. Furthermore, a meta-analysis allows us to move beyond questions of simply whether an effect exists and allows us to assess the magnitude of this effect. Finally, it allows us to explore if and even why there are inconsistencies in the effects across studies.

1.9 Aims

In the current paper I have chosen to focus on the dissociative aspect of the acute psychoactive experience of ketamine as this is the most widely measured effect in the current literature (Grabski et al., 2020). I did not feel that including other aspects of the psychoactive experience, such as psychotomimetic or mystical effects, would be appropriate as it is possible that these effects relate to distinct underlying mechanisms, both neurologically and psychologically. Thus, inclusion of these additional experiences could obfuscate the role that each of them play in the antidepressant effect of ketamine.

To my knowledge, no meta-analysis has been conducted on the nature of the relationship between these two variables. Therefore, I propose to investigate the

presence and magnitude of any association between the acute dissociative experience and the anti-depressant effects of ketamine.

2. Method

2.1 Search Strategy

The literature review for this study was partially based on the results of the search strategy carried out by Grabski et al., (2020), in their systematic review. As the scope of their review was broader than the current paper, it included all the studies of interest for this meta-analysis. Therefore, the results of their identification and screening stages of the literature review were used. However, at the eligibility and inclusion stages, separate criteria were used to the Grabski review, and assessment and selection of papers at these stages were performed by the present author.

In the Grabski review, three reviewers conducted a literature search using Medline, Embase and PsychInfo up to June 11th, 2019 for peer reviewed papers published in English. The following terms were used for the search: ketamine, esketamine, arketamine, experienc*, dissoc*, mystic*, psychedel*, psycho*, effect*, react*, anxi*, respon*, hallucin*, CADSS, BPRS, HMS, altered states of consciousness, spiritual, mental, depress, mood, psychiatric, addict*, abus*, misus*, dependen*, substance, suicide*, schizo*, psycho*, trauma*, dement*. Further details on this search can be found in Grabski et al., (2020).

2.2 Selection Criteria

Studies were eligible for inclusion if they met the following criteria: 1) participants were aged 18 years or older; 2) participants had received one or more

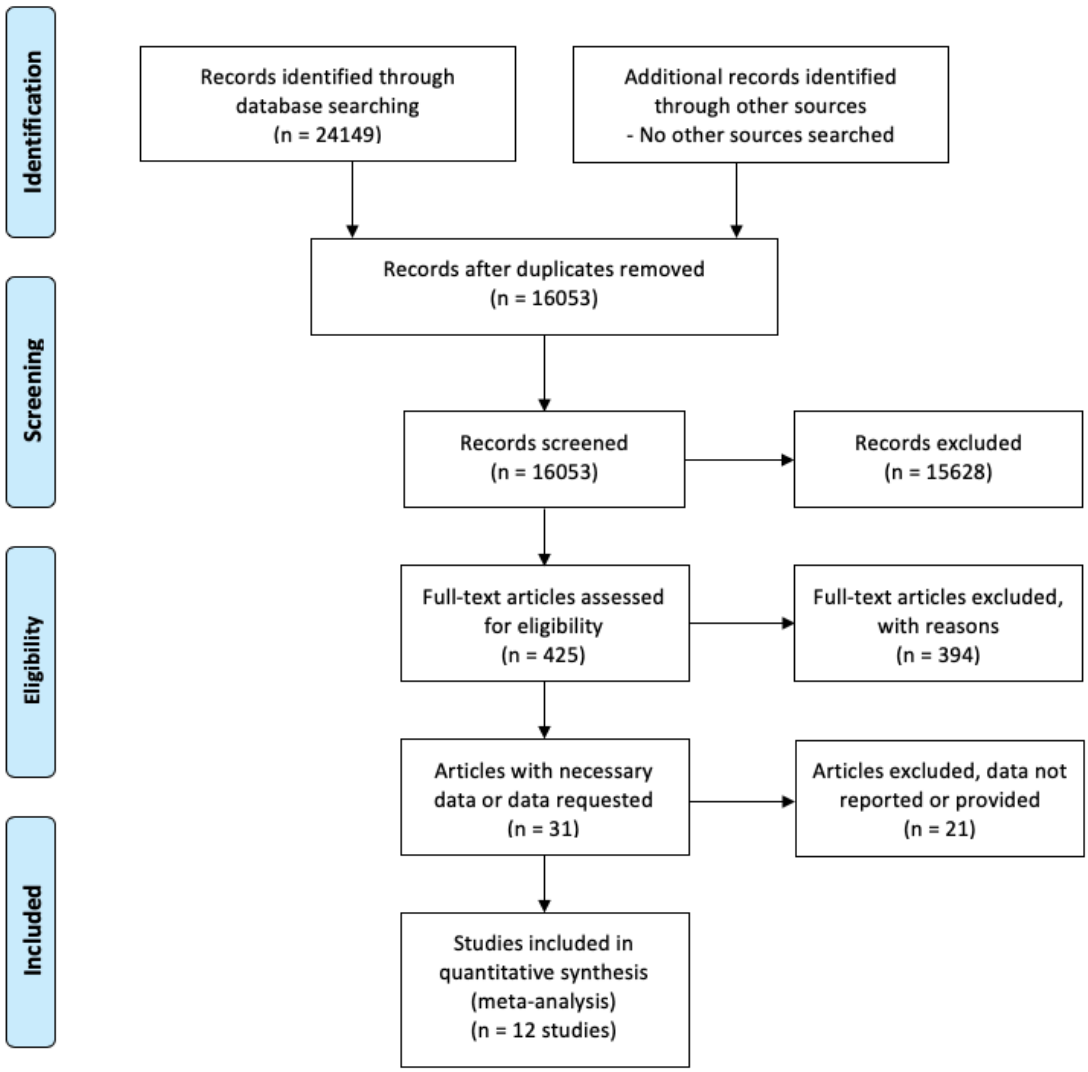
doses of ketamine (any dose size, number of doses, and administration route were accepted); 3) participants had a clinical diagnosis of a MDD or bipolar disorder (BD) at the time of the study; 4) depression was measured using a validated scale at baseline and at 24-48 hours post infusion; 5) changes in dissociation from baseline to during or immediately after treatment administration were measured using a validated scale.

Studies were excluded if they investigated other disorders of primary interest, unless participants with an MDD or BD diagnosis were included (e.g. patients with suicidality and MDD). No lower limit was made for study sample size due to the small number of studies available in relation to this research question and the ability of a meta-analysis to weight the influence of studies in the estimate of an overall effect size based on sample size.

Several studies were identified as being potentially eligible but had key missing data. In many of these studies, measures of dissociation and depression were taken, however, as the association between these variables was not of primary interest, no correlation coefficient was reported. In such cases data was requested by contacting corresponding authors. If after three attempts at contact data could not be obtained, then such studies were subsequently excluded from the meta-analysis. A summary of the selection process is provided in Figure 1.1.

Figure 1.1

Study selection PRISMA flowchart



2.3 Data Extraction

One of the final 10 articles included in the meta-analysis was a secondary data-analysis made up of three separate studies (Niciu et al., 2018). As we were able to extract the necessary data for each of these individual studies this was included as three separate papers, bringing the total studies included to 12.

Each of the 12 studies included were reviewed and the following data was coded: number of participants in the calculation of the association between dissociation and depressive response, mean age, gender distribution, primary diagnosis, administration route, dose, duration of infusion, number of infusions used in the calculation of the association, measure of depression, measure of dissociation, time points of measurements, study design, and whether concomitant psychiatric medication was permitted.

2.4 Study Quality

In order to assess the quality of each study a modified version of the quality checklist proposed by Kmet and colleagues (2004) was used. The checklist was adapted in order to be specific to each paper's relevance to answering the question of the level of association between dissociation and depression in ketamine treatment (see Appendix 1.A for a template of the checklist). This was done as many of the studies were not primarily interested in this association and therefore a measure of the overall quality of the paper would not have been indicative of the quality of evidence in relation to the association this meta-analysis aims to explore.

Studies were scored on 12 criteria, with a score of 0 given for criteria not met, 1 for partial, and 2 for yes. The total sum of scores was divided by the total possible sum, providing a quality score ranging from 0 (worst) to 1 (best).

2.5 Effect Size Calculation

As the research question was focused on an association between two variables, the Pearson product moment correlation was used as the main effect size. In order to calculate the correlation between acute dissociative response and anti-depressant effect we operationalised these two terms using change scores at particular time points for each.

Acute dissociate response was measured as the change score from baseline CADSS scores to scores 40 minutes post start of the infusion. This time point was picked as it was often the peak of the dissociative experience. We also included CADSS measurements made after this time point if this was retrospectively assessing the acute experience.

Anti-depressant response was measured by calculating the difference between baseline depression score and scores 24-48 hours after infusion, with 24 hours being the preferred time point. This time point was picked as research has shown antidepressant response to peak at 24 hours after infusion (Albott et al., 2018). We were also reluctant to use a time point any earlier than 24 hours as it is possible that acute psychoactive effects of the drug are still present and could be directly influencing levels of depression.

To test significance of correlations, Fisher's Z transformation of the correlation coefficient was used, and all analyses were performed using the transformed scale (Hedges & Olkin, 2014). The results of this analysis were then transformed back to correlation coefficients.

2.6 Data Analysis

Analyses were performed using R (Team, 2013). A random effects model was used as true effect sizes likely varied between studies due to differences in methodology (Riley, Higgins, & Deeks, 2011). In order to calculate the pooled effect sizes, weights were applied using the inverse variance method. The correlation coefficients had also been converted to the Fisher's Z scale so as to provide accurate weights for each study.

2.7 Statistical Heterogeneity

The heterogeneity variance was calculated using the Restricted Maximum Likelihood (REML) method. This method was used instead of the more common DerSimonian and Laird method as the latter can be negatively biased when the meta-analysis contains studies with a small sample size, leading to an underestimation in the heterogeneity of variance (Langan et al., 2019)

Heterogeneity was assessed using the I^2 value, which estimates what proportion of the observed variance reflects real differences in effect sizes between studies (Borenstein et al., 2011). An I^2 value of 0% to 40% indicates that heterogeneity may not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% indicates considerable heterogeneity. The Q-test was also used to test the hypothesis that all studies were measuring the same effect, with a p-value of $p < .10$ indicating study heterogeneity (Bornstein et al., 2011).

2.8 Subgroup Analysis

In order to investigate sources of heterogeneity, I conducted a series of subgroup analyses. These analyses were performed to determine the potential impact of diagnosis (MDD vs BD vs MDD/BD), blinding (blinded vs non-blinded vs both), concomitant psychiatric medication (medication permitted vs not permitted), and study quality (high vs low) on effect size estimates.

To test differences between the subgroups a fixed effects (plural) model was used. This model was used because each of these subgroup comparisons used groups that represented fixed levels of characteristics I wanted to examine and were not randomly sampled from larger population of potential subgroups. The pooling of effects within the groups was still conducted using a random effects model. The above combination of models for the subgroup analyses were therefore using a mixed-effects model.

The results of the subgroup analysis were interpreted by considering the significance of the test for interaction. This provides a superior estimate of whether effect sizes differed significantly across subgroups, as compared to simply considering whether each subgroup reached significance separately (Higgins & Green, 2008). A meta-regression was not conducted due to the low number of studies in this meta-analysis.

2.9 Publication Bias

Small sample bias methods were used to examine the risk of publication bias (Borenstein et al., 2011). This involved the assessment of a funnel plot to determine the presence of asymmetry and the use of Egger's test of the intercept (Egger, Smith, Schneider, & Minder, 1997).

3. Results

3.1 Study Selection

In total, 12 studies from 10 publications were considered to fit the inclusion criteria and either reported or responded to requests for the necessary data, i.e. correlation coefficients, (details in Figure 1.1).

Two of the included studies were secondary data analysis of multiple primary studies (Niciu et al., 2018; Wan et al., 2015). One of the authors was able to provide individual effect sizes for each of studies analysed in their paper. This request was made as each study had slightly different characteristics. These individual studies are referenced in this paper as 'Niciu BD' (Diazgranados et al., 2010; Zarate et al., 2012), 'Niciu Riluzole' (Ibrahim et al., 2012), and 'Niciu MOA' (Nugent et al., 2018).

The remaining studies all used samples relating to one primary study (Albott et al., 2018; Esterlis et al., 2018; Fava et al., 2018; Grunebaum et al., 2017; Grunebaum et al., 2018; Phillips et al., 2019; Shiroma et al., 2014; Williams et al., 2018). Including the three Niciu papers this brought the total number of studies (K) to 12.

3.2 Study Characteristics

Table 1.1 displays the characteristics of all the included studies. A total of 414 participants were included in the analysis, with a weighted average mean age of 44.8, and with 48% being women. For each study ketamine was administered intravenously. All but two of the studies provided a dose of 0.5mg/kg over 40 minutes. One study administered an initial bolus of 0.23mg/kg over 1 minute and then a constant infusion of 0.58 mg/kg over 1 hour (Esterlis et al., 2018). Another

study used a range of doses at 0.1, 0.2, 0.5 and 1 mg/kg over 40 minutes, as they were trying to determine the optimal antidepressant dose (Fava et al., 2018).

The majority of the studies were conducted with patients with a diagnosis of MDD, with only two using a BD sample, and another sample being a combination of the both. Seven of the studies were double blind randomised controlled trials, with three others being open-label, and one a between subject non-randomised study. The secondary analysis study that we were not able to get individual study effect sizes for contained one between subject design and two open label studies. Only one study systematically included a sample with a comorbid diagnosis, which was PTSD comorbid with MDD (Albott et al., 2018).

To calculate the association between dissociation and depression, change in depression was measured from baseline to one day post-infusion in all but one study. In Shiroma et al. (2014), depression was measured at baseline on day one and again at day three, meaning the change score had to be from baseline to two days post-infusion. Each study used the CADSS to measure dissociation. Similarly, all but one of the studies used change in dissociation between baseline to 40 minutes, in order to calculate the association. In Esterlis et al. (2018), dissociation was measured as baseline and then again at 100 minutes, however, participants were asked to retrospectively report on their acute experience.

Table 1.1

Characteristics of included studies

Author	Diagnosis	N*	Sex (%f)	Age	Study Design	Dose + Duration	Number of Infusions	Depression Measure	Psychiatric Medication Permitted	Association Reported
Albott et al., 2018	MDD (with PTSD)	15	33	52.1	open label	0.5 mg/kg over 40 minutes	1 infusion	MADRS	Yes	No
Esterlis et al., 2018	MDD	14	54	35.6	between, NB, non-rand	0.23 mg/kg bolus + 0.58 mg/kg infusion over 1 hour	1 infusion	MADRS	No	No
Fava et al., 2018	MDD	80	53	46.3	between, DB, rand	0.1 mg/kg (n = 18), 0.2 mg/kg (n = 20), 0.5 mg/kg (n = 22), 1.0 mg/kg (n = 20) over 40 minutes	1 infusion	HAM-D 6-item	Yes	Yes
Grunebaum et al., 2017	BD	7	43	39	between, DB, rand	0.5 mg/kg over 40 minutes	1 infusion	HDRS-17	Yes	No
Grunebaum et al., 2018	MDD	40	55	38.4	between, DB, rand	0.5 mg/kg over 40 minutes	1 infusion	HDRS-17	Yes	No
Niciu et al., 2018 BD	BD	39	59	45.7	crossover, DB, rand	0.5 mg/kg over 40 minutes	1 infusion	HAM-D 17-item	No	Yes

Niciu et al., 2018 MOA	MDD	35	66	36.2	crossover, DB, rand	0.5 mg/kg over 40 minutes	1 infusion	HAM-D 17-item	No	Yes
Niciu et al., 2018 Riluzole	MDD	52	37	47.9	open label	0.5 mg/kg over 40 minutes	1 infusion	HAM-D 17-item	No	Yes
Phillips et al., 2019	MDD	22	not known	not known	crossover, DB, rand	0.5 mg/kg over 40 minutes	1 infusion	MADRS	Yes	Yes
Shiroma et al., 2014	MDD	14	0	54	open label	0.5 mg/kg over 40 minutes	1 infusion	MADRS	Yes	Yes
Wan et al., 2015	MDD	84	46	47.2	2 x open label, 1 x between	0.5 mg/kg over 40 minutes	2 x 1 infusion, 1 x up to 6 infusions	MADRS	No	Yes
Williams et al., 2018	MDD/BD	12	43	41.3	crossover, DB, rand	0.5 mg/kg over 40 minutes	1 or 2 infusions	HAM-D 17-item	Yes	Yes

* N is provided only for participants in the study involved in the calculation for association between dissociation and depression

3.3 Study Quality

Table 1.2 summarises the study quality scores for each study. This score was used to provide an idea of the quality of evidence for this particular meta-analysis. The main difference between those studies scoring highly, i.e. closer to 1, to those lower scoring studies was whether they had aimed to explore the association between dissociation and depression in ketamine. Other problems with the studies included small sample sizes and not fully reporting analytic methods or statistics.

Table 1.2

Quality Assessment Scores

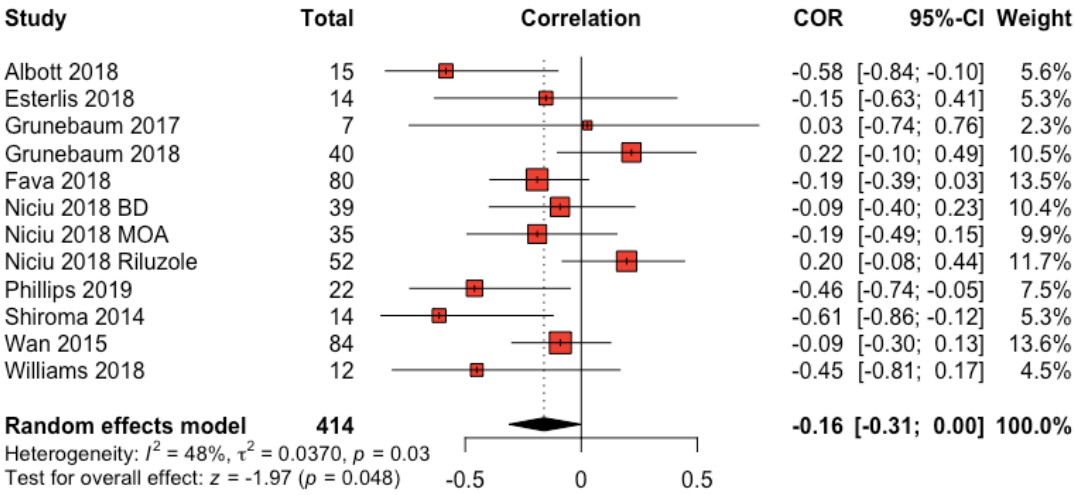
First Author	Quality Score
Albott 2018	0.50
Esterlis 2018	0.28
Fava 2018	0.79
Grunebaum 2017	0.50
Grunebaum 2018	0.58
Niciu BD	0.96
Niciu MOA	0.96
Niciu Riluzole	0.94
Phillips 2019	0.83
Shiroma 2014	0.78
Wan 2015	0.83
Williams 2018	0.71

3.4 Overall Pooled Effect Size

Effect sizes and 95% confidence intervals are provided in Figure 1.2. Nine out of 12 of the studies included reported a negative correlation. The pooled effect size of r = -0.16, 95% CI 0.31 – 0.00 indicated a small correlation and was significant (z=1.97, p = .048). There was evidence of heterogeneity between studies (Q=21.34, df=11, p=.030). The I^2 heterogeneity in this sample was 48% (95% CI 0.0% – 73.5%), indicating moderate heterogeneity, although the 95% confidence intervals indicate that low or high heterogeneity for this sample is also possible.

Figure 1.2

Forest plot for correlation coefficient for all studies and overall effect size



3.5 Subgroup Analysis

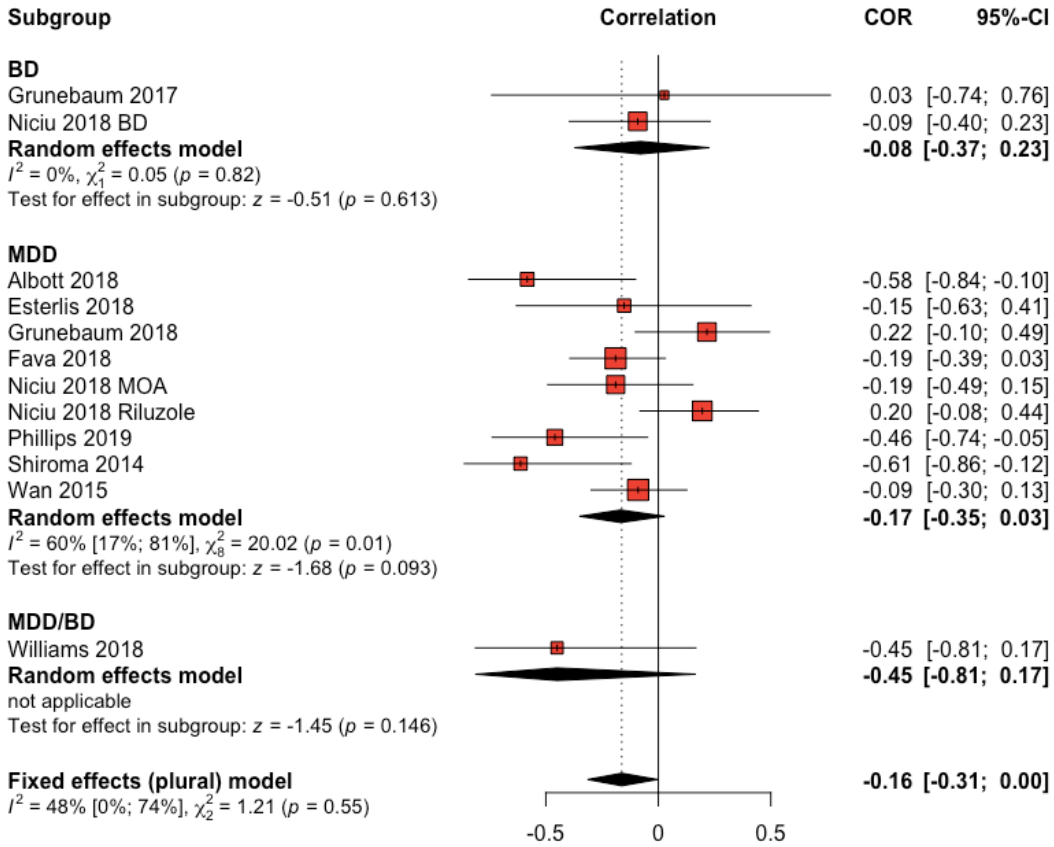
3.5.1 Diagnosis

Comparisons of diagnosis between subgroups MDD, BD, and MDD/BD showed no significant group difference (Q = 1.21, p = .546; Figure 1.3). A smaller number of studies and participants contributed data to the BD subgroup (2 studies, 46

participants), and MDD/BD subgroup (1 study, 12 participants), than to the MDD subgroup (9 studies, 356 participants), which could have introduced uncontrolled bias to the analysis.

Figure 1.3

Forest plot for subgroup analysis of diagnosis



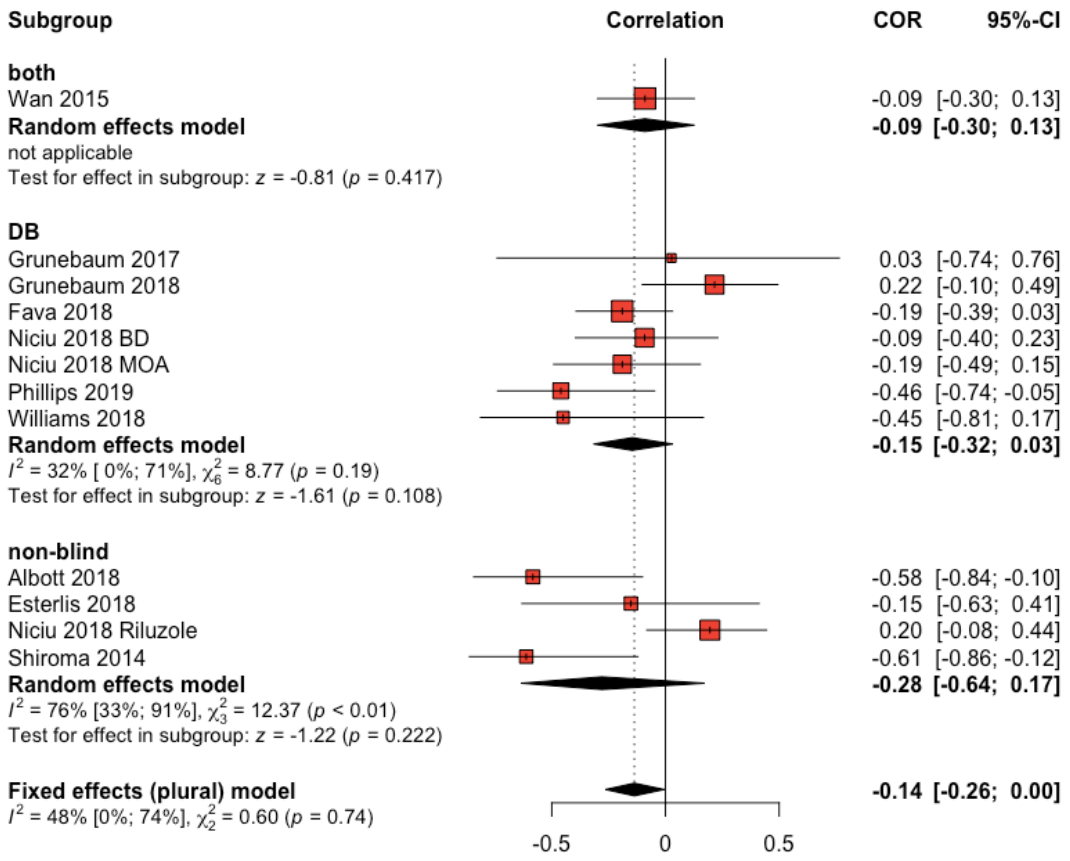
3.5.2 Blinding

Comparisons of blinding between subgroups double-blind, non-blind, and both, i.e. effect sizes taken from analysis including both double-blind and non-blind studies, showed no significant group difference (Q = 0.60, p = .741; Figure 1.4). A smaller number of studies and participants contributed data to the non-blind subgroup (4 studies, 95 participants), and both subgroup (1 study, 84 participants),

than to the double-blind subgroup (7 studies, 235 participants), which could have introduced uncontrolled bias to the analysis.

Figure 1.4

Forest plot for subgroup analysis of blinding

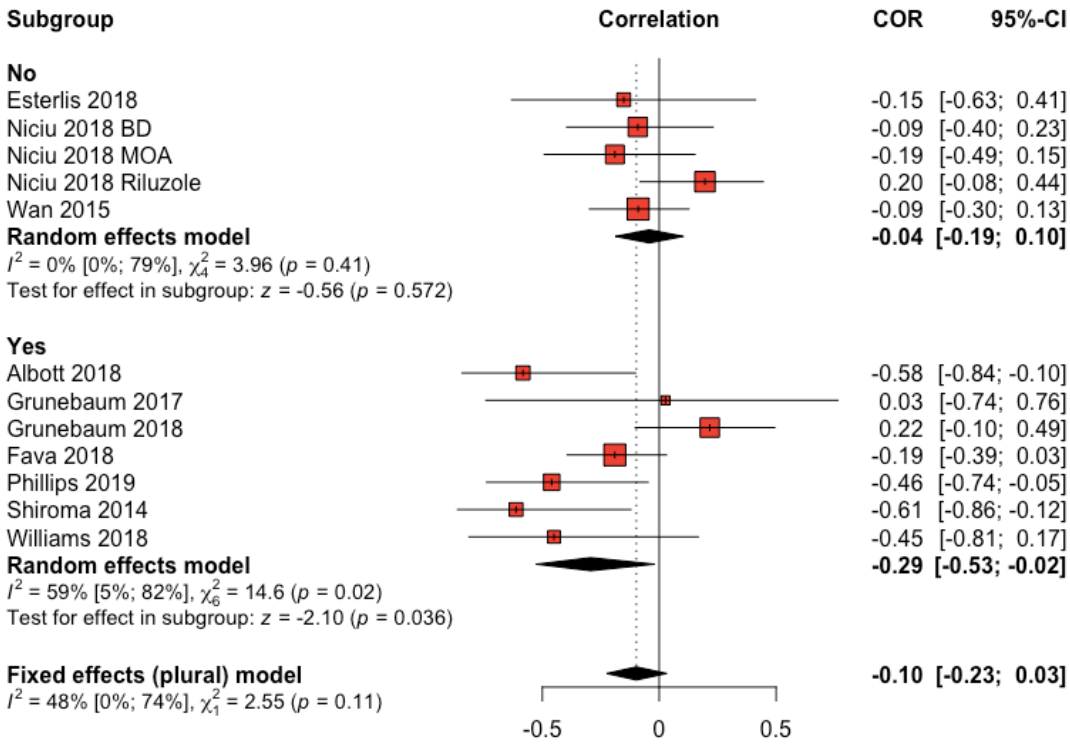


3.5.3 Concomitant psychiatric medication

Comparisons of concomitant psychiatric medication between subgroups 'Yes' and 'No' showed no significant group difference (Q = 2.55, p = .111; Figure 1.5). The number of studies and participants contributing data to the 'Yes' subgroup (7 studies, 190 participants) and 'No' subgroup (5 studies, 224 participants) were roughly similar, so the covariate distribution was not concerning for this subgroup analysis.

Figure 1.5

Forest plot for subgroup analysis of concomitant psychiatric medication

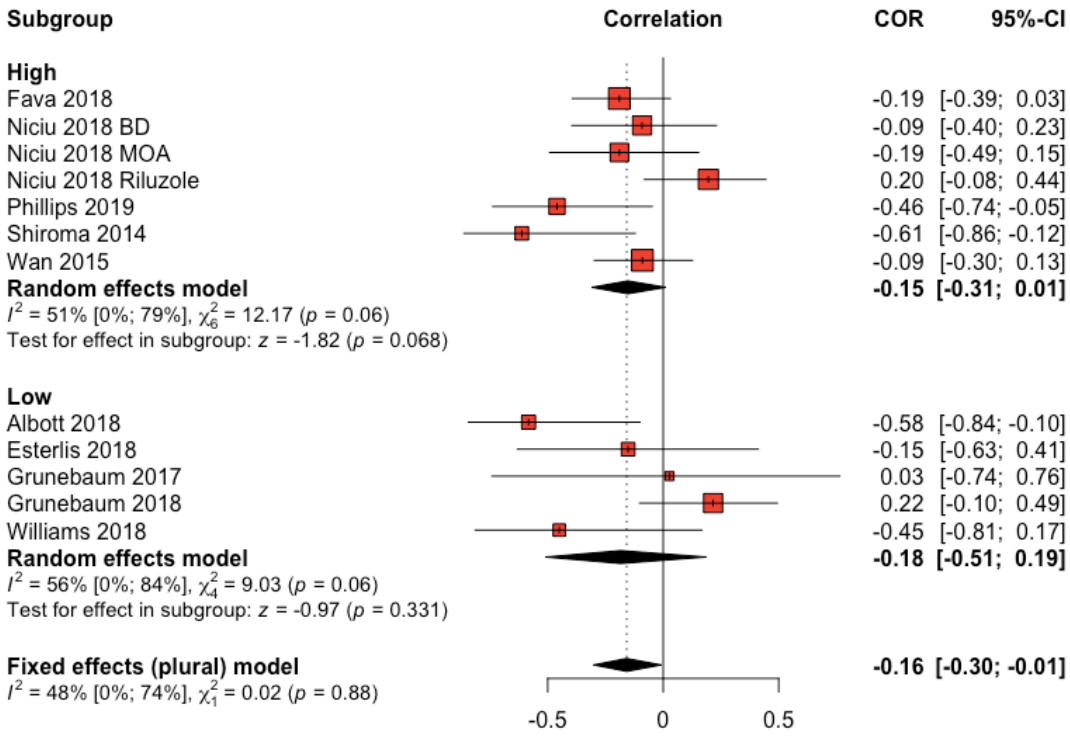


3.5.4 Study quality

Comparisons of study quality between subgroups 'High' and 'Low' showed no significant group difference (Q = 0.02, p = .878; Figure 1.6). A smaller number of studies and participants contributed data to the 'Low' subgroup (5 studies, 88 participants) than to the 'Yes' subgroup (7 studies, 326 participants), which could have introduced uncontrolled bias to the analysis.

Figure 1.6

Forest plot for subgroup analysis of study quality



3.6 Publication Bias

The risk of publication bias was examined using Egger's test of the intercept (Egger et al., 1997). For the correlation coefficients the intercept was -1.52 and was non-significant (t=1.57, p=.147). This indicates that there was no relationship between the size of the studies and their effects sizes, thus providing no evidence for the presence of publication bias. Furthermore, the inspection of the funnel plot showed broadly symmetrical distributions, suggesting a marginal risk of publication bias (Appendix 1.B).

4. Discussion

4.1 Main Findings

The findings of this meta-analysis suggest that there is an association between acute dissociation and antidepressant response at around one- or two-days post infusion. However, the estimated size of this overall correlation was only small ($r = -0.16$), suggesting that only 2.56% of variance was shared between the two measures. This estimate is smaller than that found in some of the previous research collating multiple independent studies in order to explore this association (Luckenbaugh et al., 2014; Pennybaker et al., 2017). This difference in effect sizes may be a consequence of the fact that we conducted a systematic search of the literature and were able to include a larger and broader range studies.

4.2 Understanding the Overall Effect

As the correlation between dissociation and anti-depressant effect was only small it seems there are likely many other factors that play a role in determining the efficacy of ketamine. Furthermore, it is still unclear whether these dissociative experiences are necessary for anti-depressant effects to emerge. Nevertheless, the results of this study provide evidence for an association between increased acute dissociation and reductions in depressive symptoms. This association could be explained in a number of different ways.

4.3 Expectation Effects

It is possible that the association we found across studies was a result of expectation related effects. As the dissociative effects of ketamine alert the patient to the drugs action within the body, this may create a chain of expectations that lead to

reductions in depression (Rasmussen, 2016). The effects of expectation and placebo have been observed in research on other anti-depressants. In an analysis of placebo-controlled trials for Fluoxetine, expectations of improvement were thought to be responsible for much of the observed changes in depression (Rutherford, Wall, Glass, & Stewart, 2014). As many of the studies in the current meta-analysis relied on advertising and volunteers for subject selection, an expectation of improvement could have been amplified for individuals who had prior knowledge about ketamine's utility as an antidepressant.

This expectation effect would be applicable not only to open label studies but also to blinded control trials, as the perceptible shifts in consciousness caused by dissociation would likely unblind participants. Six of the seven blinded control studies used midazolam as an active placebo, however, it has been pointed out that this is imperfect as a match for ketamine due to its lack of dissociative effects (Murrough et al., 2012; Phillips et al., 2019). Three of the studies included in this meta-analysis checked for unblinding, although one study only had a sample of seven, making it difficult to run any meaningful analysis on unblinding (Grunebaum et al., 2017). One of these studies did not find any evidence for unblinding, with both participants and clinicians only correctly guessing treatment assignment around half of the time in both the ketamine and placebo groups. However, the other study by Fava et al. (2018) did find evidence for unblinding as they reported that guesses of both clinicians and participants for treatment assignment were significantly related to actual treatment group. This was true of those receiving 1.0 mg/kg and 0.5 mg/kg, but not for those receiving 0.2 mg/kg, 0.1 mg/kg, or placebo.

On the other hand, if unblinding and expectancy effects were solely responsible for the correlation between reductions in depression and increased

dissociation, then one might expect the same to be true of other acute psychoactive effects. Psychotomimetic symptoms are another widely reported effect, yet previous research has failed to find an association between this experience and reductions in depression (Luckenbaugh et al., 2014; Grabski et al., 2020). This indicates that there may be some unique mechanism responsible for the association between depression and dissociation that is separate from unblinding and increased expectancy of benefit.

4.4 Glutamate Activity

A further potential cause for this association is a shared neurobiological mechanism via increases in glutamate activity for both the emergence of dissociative symptoms (Zorumski et al., 2016) and antidepressant effects (Krystal et al., 2013). It is possible that dissociation could serve as a clinical biomarker for these effects on glutamate and therefore for predicting ketamine's antidepressant response (Luckenbaugh et al., 2014). This is useful as it is often difficult to determine optimal therapeutic doses for patients due to individual differences in sensitivity to ketamine. Thus, dissociation could be used an indicator for adequate target engagement by the drug at a particular dose (Krystal et al., 2019).

4.5 Reduction in Rumination

Another explanation for the current finding could be that dissociation disrupts the cycles of self-focus and rumination often found in depression (Verplanken et al., 2007). These ruminative processes are thought to be related to high functional connectivity in regions of the DMN (Raichle et al., 2001). Activity in such regions have been found to reduce after ketamine administration (Scheidegger et al., 2012).

It has been proposed that the severity of acute dissociative effects induced by ketamine may reflect the amount of disruption to these networks (Walter, Li, & Demenescu, 2014). Furthermore, there is some evidence of a correlation between changes in neural connectivity and psychoactive effects (Lehmann et al., 2016). This neurobiological process may appear psychologically as the experience of reduced rumination and improved ability to engage in the external world. An increase in external focus has been shown to reduce depressive symptoms (Fennell et al., 1987; Lyubomirsky & Nolen-Hoeksema, 1995), and this may allow the individual to engage in pleasurable and absorbing activities that further reduce feelings of depression (Nolen-Hoeksema & Morrow, 1991).

As well as reducing rumination through increased capacity for distraction it is also possible that ketamine may help to disrupt and rewrite maladaptive memories. Reconsolidation is a memory maintenance process involving the destabilisation of long term memories in order to update their content with newly available information. Das et al. (2019) demonstrated that ketamine was able to interfere with reconsolidation of maladaptive reward memories related to harmful drinking, and subsequently reduced the reinforcing effects of alcohol. These beneficial changes were only found when maladaptive memories were activated during a brief 'reconsolidation window'. The authors suggested that similar processes may occur with depression. It could be that severity of dissociative experiences reflects a heighted potential for a disruption of salient maladaptive memories related to depression. This could subsequently result in reduced depression if such memories were then activated and disrupted during the reconsolidation window.

4.6 Psychedelic Experience

It is also possible that dissociation acts as a marker for profound psychedelic experiences that have been hypothesised to be responsible for ketamine's antidepressant effects (Krupitsky & Grinenko, 1997; Kolp et al., 2014). Although much of the research into the clinical application of such experinces, when induced by ketamine, has been conducted alongside the use of KPP, it may be that even without the assistance of a therapist some patients are able to gain benefit from these experiences. If the quality of psychoactive experiences and a person's ability to integrate them afterwards are partly responsible for ketamine's antidepressent effects, then one would expect studies where these factors have been addressed to have improved outcomes and larger associations between depression and dissociation. However, as all of the studies we included in our analysis took place in a more medicalised treatment context, and did report any further detail on quality of expereince, it was not possible to determine the relevance of such factros to the association we found.

It is worth noting that a neurobiological explanation of shared glutamate activity and a psychological explantion of psychedelic experiences are not necessarily mutually exclusive. Increased glutamate, or other neurobiological processes, may well underpin the manifestation of dissociation and other psychedelic aspects of the ketamine induced expereince. This idea, of both neurobiological and psychological interpretations being relevant and seen as 'two sides of the same coin', has been considered in previous research on classic psychedelics (Haijen et al., 2018; Roseman, Nutt, & Carhart-Harris, 2018). On a wider scale, there is a growing understanding of the importance of context and environment in innate neurbiological processes, for example at the level of gene expression (Caspi, Hariri, Holmes, Uher,

& Moffitt, 2010). The impact of context has also been observed in the pharmacology of drugs in animal studies (Alexander, Beyerstein, Hadaway, & Coambs, 1981), and a recent review of how SSRIs work in humans included environment and cognitive appraisal into their model for therapeutic efficacy (Harmer, Duman, & Cowen, 2017). This may point to the relevance of context and appraisal of expereince in the antidepressent effects of ketamine via underlying neurobiological processes.

4.7 Exploring Heterogeneity

The finding of an overall effect also needs to be understood in light of the presence of the significant heterogeneity between the correlations found in the studies we included. This indicates that the true effects varied between the different studies. Furthermore, the magnitude of this dispersion was estimated to be moderate as the I^2 heterogeneity was 48%. This would suggest that variation in certain characteristics, potentially related to individuals or the interventions, result in differing associations between depression and dissociation in ketamine.

In an attempt to explain some of this heterogeneity, subgroup analyses were performed on a number of covariates that were selected for *a priori*. Separate subgroup analyses were performed for the variables of diagnosis, blinding, concomitant psychiatric medications, and study quality, however, each of them failed to find any evidence of subgroup differences. There was also as much heterogeneity within the specified subgroups as there was across all the studies. The above suggests that these covariates do not modify the association between depression and acute dissociation in ketamine treatment.

It should be noted that subgroup analyses are limited in their ability to detect meaningful difference between studies and require sufficient power to do so (Higgins

& Thompson, 2004). The number of papers included in this meta-analysis was only just over the recommended number of K = 10. Furthermore, there was an uneven covariate distribution amongst the subgroups for all but one of the subgroup analyses, with the analysis on concomitant psychiatric medication being the exception, limiting the ability of the analysis to detect subgroup differences. Therefore, it may be that with a larger number of studies, and more evenly distributed studies and participants, some of these covariates may have shown evidence of significant differences between the subgroups.

4.8 Patient Characterises

Despite the subgroup analyses not finding any explanations for differences in the correlations between studies, it is worth considering what other factors may account for these differences. It is possible that heterogeneity amongst patient characteristics may have played a role. There is huge variation in how users respond to ketamine, with recreational users reporting both incredibly aversive and rewarding experiences (Muetzelfeldt et al., 2008). There is some evidence to suggest that factors such as family history of alcohol dependence may influence how people experience the drug (Yoon, Pittman, Limoncelli, Krystal, & Petrakis, 2016). Other explanatory factors here could relate to age, severity of depression, symptom profile, and previous exposure to ketamine.

Additionally, differences in personality domains could be responsible for some of the variation. In one study on classic psychedelics, the personality trait ‘absorption’, which is a person’s propensity to become immersed in experiences, was predictive of acute psychoactive experiences, whilst openness to experience was predictive of improved outcome (Haijen et al., 2018). It may be that for ketamine,

such personality traits may also play a role in the dissociative experience and antidepressant effect. In fact, researchers have previously reported an ability to predict the acute psychoactive effects experienced by patients receiving ketamine using Eysenck's Personality Inventory (Khorramzadeh & Lofty, 1973), although this has not been replicated since.

4.9 Intervention Characteristics

It is interesting to note that many aspects of the intervention, such as dose, administration, and duration, were broadly similar between studies suggesting these characteristics are not responsible for the observed heterogeneity. However, it is possible that other aspects of intervention, such as co-interventions, clinical setting, and after care, are responsible for the differences in association. As these factors are rarely reported in the studies included in this meta-analysis it was not possible to do any further analyses on their relation to ketamine's antidepressant and dissociative responses. In much of the research on KPP such factors are seen as integral to the benefits found with this approach (Krupitsky & Grinenko, 1997; Krupitsky & Kolp, 2007). Furthermore, feeling comfortable with the environment and the people present has been shown to be predictive of therapeutic response when it comes to the use of classic psychedelics (Haijen et al., 2018). Therefore, future research on ketamine's use as an antidepressant should look to further explore and report on these contextual and interpersonal factors. In particular, the potential for ketamine and psychological therapies to interact is an interesting avenue for further investigation. There is some preliminary evidence to suggest that cognitive behavioural therapy may sustain the antidepressant effects of ketamine (Wilkinson et al., 2017). Any future research on ketamine in conjunction with therapies like CBT may benefit from investigating the

potential role of dissociation, or other subjective experiences induced by ketamine, in sustaining antidepressant effects.

4.10 Limitations

There a number of limitations to this meta-analysis. Firstly, the finding of a significant overall effect was not robust and the addition of only one study with a neutral or positive correlation between dissociation and depression would be enough to make the results non-significant. This is especially the case in light of the number of studies included in this meta-analysis being relatively small (K = 12). We were not able to include all the studies we had identified due to missing data. Despite many studies collecting data on dissociation and depression measures in response to ketamine, most did not report a correlation between the two. As very few studies were set up to test an *a priori* hypothesis on this association, the lack of data may be a consequence of reporting bias, where non-significant results have not been reported. We attempted to manage this by requesting source statistics from authors but were unable to obtain the missing data from all the papers we identified. Furthermore, we did not find any evidence for publication bias when testing for this, although this does not rule out this bias influencing the findings.

There was a great deal of heterogeneity in methodology between the studies used in this meta-analysis. As previously mentioned, it is possible that the associations found in the open-label studies are a result of expectancy effects, although this may also be relevant to blinded trials due to the unblinding effects of the psychoactive effects of ketamine. No clear differences were found between open-label and blinded studies when conducting a sub-group analysis. The results of the quality assessment also revealed a wide range of quality of evidence that each study

was able to provide to the research question of this analysis. This was a result of some papers not exploring the association between depression and dissociation in ketamine. However, this did not appear to significantly influence the results of these studies as no evidence for differences between high and low quality of evidence studies were found in a sub-group analysis.

It should also be mentioned that antidepressant outcome was defined at the 24-48-hour time point. It is possible that the correlation between acute dissociation and depression scores changes when considering later time points for assessing depression. Ketamine's antidepressant effects are thought to peak at 24-72 hours and last up to 2 weeks (Krystal et al., 2013; Zarate et al., 2006). Future meta-analysis could be conducted in order to investigate the presence and size of associations between depression and dissociation at these later time points.

A further limitation relates to the suitability of the CADSS for capturing the acute psychoactive effects induced by ketamine. This measure was initially developed to discriminate individuals with dissociative disorders from other psychiatric disorders (Bremner et al., 1998). In an analysis of the CADSS's ability to capture the psychoactive effects of ketamine it was found many of the items were not relevant to the ketamine experience (van Schalkwyk, Wilkinson, Davidson, Silverman, & Sanacora, 2018). After conducting qualitative analysis, they also found that there were prominent aspects of the ketamine experience that are not captured by the CADSS, principally 'sense of peace' and 'disinhibition'. Furthermore, the CADSS does not include a valence dimension, indicating whether symptoms were experienced as positive or negative, and previous research has found this to be important for predicting anti-depressant response (Aust et al., 2019).

All of the studies included in this meta-analysis used the CADSS to measure dissociation. In light of the limitations of this measure presented above it is possible that some aspects of ketamine induced dissociative experience were not adequately captured and that the effect size we found may have been different had they been. Therefore, future research into this subject may benefit from using an improved measure of dissociation that still captures aspects of the CADSS shown to be relevant to ketamine, such as depersonalisation (Niciu et al., 2018), along with other aspects identified as being important, such as sense of peace, disinhibition and valence of the experience (van Schalkwyk et al., 2018; Aust et al., 2019).

Finally, it may be that other acute psychoactive effects of ketamine are associated with its antidepressant effects. For example, there is some research suggesting that the psychotomimetic effects of ketamine, as measured by the Brief Psychiatric Rating Scale (BPRS), are correlated with antidepressant response (Carlson et al., 2013; Sos et al., 2013). Additionally, research on ketamine's application to cocaine addiction found that mystical experiences, but not dissociative effects, were associated with motivation to quit following treatment (Dakwar, Levin, Foltin, Nunes, & Hart, 2014). Unfortunately, it was not possible to include these effects in the current meta-analysis, partly due to fact that there were an inadequate number of studies collecting data on them (Grabski et al., 2020). Similar to the CADSS, some of the measures of these effects commonly used in research, such as the BPRS, are administered to assess tolerability and were not designed to capture drug-induced psychoactive experiences. Future research may benefit from considering tools that are specifically designed to measure the whole spectrum of psychoactive experiences induced by ketamine, in order to assess how they may relate to the drug's therapeutic properties.

4.11 Conclusion

The presence of an association between depression and dissociation found in this meta-analysis has important clinical implications. Treatments using ketamine as a therapeutic tool appear to be splintering off into two almost opposing directions based on their assumptions around this association. One branch views dissociation and other acute psychoactive effects as adverse side effects to be minimized, whilst the other treats them as essential experiences to be harnessed for therapeutic benefit. The present meta-analysis provide evidence for the presence of an association. However, this finding should be taken with caution due to the low number of studies that met criteria for inclusion in this analysis, marginal significance of the effect, and unexplained heterogeneity. Therefore, we would recommend further research with *a priori* hypotheses and appropriate designs to be conducted in order to specifically investigate this association. This would allow for more powerful meta-analyses to be conducted in future to confirm or disconfirm the results of this study. Consideration should also be given to designing studies that are able to unpick what neurobiological or psychological mechanisms may be underlying such an association.

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Part 2: Empirical Paper

Investigating the Anti-Depressant Effects of Sub-Anaesthetic Ketamine in People with Chronic Pain

Abstract

Aims: This study aimed to explore the acute effects of sub-anaesthetic ketamine in a chronic pain population on mood, subjective experience, and pain. The associations between these three effects were also examined.

Method: A non-randomized between subjects design was used with an active control group of participants receiving acute lidocaine. Both pain and subjective drug effects were measured using visual analogue scales (VAS). Mood was measured with the Hospital Anxiety and Depression Scale (HAD), Physical Health Questionnaire-2 (PHQ-2) and a single VAS. Measurements were taken at baseline, mid-point, post-infusion and follow-up. Data were primarily analyzed using mixed ANOVAs and associations were then explored using Pearson correlation.

Results: 43 participants were administered ketamine and 56 were administered lidocaine, with a total n = 99. Participants in the ketamine group had lower pain scores than those in the lidocaine group in the acute phase, although at one-week follow-up some of these scores had returned to baseline for ketamine. No significant differences were found in mood scores between ketamine and lidocaine. A number of subjective drug effects were found to be higher following ketamine compared to lidocaine. Reduction in pain scores were generally associated with reduction in mood scores.

Conclusion: Within a chronic pain population ketamine does not appear to produce an antidepressant effect at the doses and infusion durations used in this study. Ketamine may provide superior acute analgesic effects compared to lidocaine, although this does not appear to be sustained at one week follow up. Despite producing greater rewarding experiences, ketamine does not appear to lead to desire for taking more of the drug in this setting. Future research should focus on

developing drug regimens that optimize the therapeutic benefits of ketamine in the chronic pain population.

1. Introduction

1.1 Depression and Current Medication

Major depressive disorder (MDD) is thought to effect up to 350 million people across the globe and is the leading cause of disability worldwide (Collins et al., 2011). The standard antidepressant medications currently administered today have been shown to work in only 50% of those treated (Undurraga & Baldessarini, 2012). Additionally, in those that do respond, there is a delay in the onset of action of 3-4 weeks (Quitkin et al., 1987), prolonging the functional impairment and risks of suicidality. There is thus a need for more rapid-acting antidepressant drugs. The standard anti-depressant medications primarily target the monoamine system. A number of studies have implicated the glutamate system in the pathophysiology of depression and therefore an area of focus for new treatments (Deschwanden et al., 2011; Lapidus, Soleimani, & Murrough, 2013)

1.2 Ketamine

Ketamine is a non-competitive antagonist at the receptor N-methyl d-aspartate (NMDA) and is thought to increase the presynaptic release of glutamate (Moghaddam, Adams, Verma, & Daly, 1997). As the glutamate system plays an important role in neuroplasticity it is possible that ketamine may target the deficits in synaptic structure and function that have been implicated in depression (Kang et al., 2012). Specifically, Ketamine's inhibition of NMDA receptors leads to increased production of brain-derived neurotrophic factor (BDNF), which has been shown to be at reduced levels in depressed patients and is related to synaptogenesis (Strasburger et al., 2017).

1.3 Ketamine and Depression

Ketamine was first shown to have antidepressant effects in patients with MDD in 2000 (Berman et al., 2000). Since then the efficacy of ketamine for improving mood has been demonstrated in a number of randomized control trials (Caddy et al., 2015). It is worth noting that most of these trials have been conducted on individuals with treatment resistant or severe depression and there is limited evidence for these effects in milder presentations. Further research is thus needed to explore its antidepressant effects in mildly depressed and non-clinical populations.

One of the major advantages of ketamine over other anti-depressants is the rapid onset of its initial effects when administered intravenously, 40 minutes after infusion (Zarate et al., 2012). Although ketamine has generated a lot of excitement due to its rapid antidepressant effects, research has shown that these effects rarely last beyond 7 days after a single infusion (Diazgranados et al., 2010; Murrough et al., 2012). Therefore, there is a need to explore methods of lengthening its duration of action. An obvious candidate for such a method is to administer repeated doses and there is some preliminary evidence suggesting that this could increase the time to relapse (aan het Rot et al., 2010). However, there is still a large gap in the literature here and a Cochrane review of ketamine's effects on depression has called for further research to be done investigating the effects of repeated doses on relapse (Caddy et al., 2015).

1.4 Ketamine and Pain

Increasingly research is demonstrating the efficacy of ketamine as an analgesic for chronic pain, including neuropathic pain, when used at subanesthetic doses (Niesters, Martini, & Dahan, 2014; Nourozi et al., 2010). Neuropathic pain can

be defined as pain which is "initiated or caused by a primary lesion or dysfunction in the nervous system" (IASP, 1994). Subsequent alterations to the structure or function of the nervous system can lead to pain occurring spontaneously or in response to normally non-painful stimuli (Niesters et al., 2014). Despite a multimodal treatment approach, current treatments for neuropathic pain have limited efficacy with the majority of patients showing either limited or no response (Dworkin et al., 2010; Finnerup, Otto, McQuay, Jensen, & Sindrup, 2005).

When administered at sub-anaesthetic doses ketamine has been found to produce analgesic effects in patients with neuropathic pain. Similar to depression, the pathway for this effect on pain is thought to be based on its inhibition of the NMDA receptor (Fisher, Coderre, & Hagen, 2000). In chronic pain, activation of the NMDA receptor leads to central sensitization or 'wind-up', which results in increased sensitivity to pain (Truini & Cruccu, 2006). Through ketamine's inhibition of the NMDA receptor it helps to decrease this sensitization to painful stimuli. Other possible pathways for these analgesic effects, such as anti-inflammatory effects at central sites, are also being explored (Niesters et al., 2014).

1.5 Pain and Depression

People with chronic pain are at increased risk of experiencing depression and evidence suggests that the incidence of depression increases with the duration of the pain (Bair, Robinson, Katon, & Kroenke, 2003). Despite a clear link between neuropathic pain and depression (Torta, Ieraci, & Zizzi, 2017), the reason for this association is not well understood, although there are multiple theories that attempt to explain it. The presence of co-morbid chronic pain and depression significantly impacts the effectiveness of interventions (Ohayon & Schatzberg, 2003). As there is

little evidence that treating pain leads to remission of depression it has been suggested that targeting both may considerably enhance treatment outcomes (Linton & Bergbom, 2011). Therefore, the potential for ketamine to be used as dual treatment for co-morbid depression and chronic pain is an exciting prospect.

1.6 Abuse Potential

There are many concerns about the use of ketamine as a treatment for both pain and depression. Research has shown that frequent use of the drug is associated with ulcerative cystitis and impairments in memory (Morgan & Curran, 2012). The psychotomimetic effects of ketamine have led to it being used as a recreational drug. A large number of recreational users have reported concerns about addiction to ketamine (Muetzelfeldt et al., 2008), and have described difficulties with stopping due to cravings (Morgan, Rees, & Curran, 2008). Furthermore, compulsive use and rapid development of tolerance have been shown in animal studies (Lu, France, & Woods, 1992; Moreton, Meisch, Stark, & Thompson, 1977). As such, it has been suggested that the risk of dependency, especially with repeated use, may limit the clinical application of ketamine for depression (Short et al., 2018).

1.7 Moderating Factors

It is currently unclear how concomitant medication may interact with the antidepressant effect of ketamine. It has been suggested that the antidepressant effects of ketamine could be sustained beyond its current limited duration through the use of other medications (Caddy et al., 2015). In one study, ketamine was shown to accelerate and enhance the antidepressant effects of a selective serotonin reuptake inhibitor (SSRI) when taken concurrently (Hu et al., 2016). Furthermore, there is a

possibility that ketamine could interact with other medications in a way that alters their analgesic effects. For example, some researchers have suggested that ketamine may help to prevent opioid tolerance in chronic pain patients due to its antagonistic action on NMDA receptors, which have been implicated in in the development of opioid tolerance (Weber, Yao, Binns, & Namkoong, 2018).

One of the most commonly experienced acute side effects of ketamine is dissociation (Short et al., 2018). This is characterized by out of body experiences and disconnection from one's surroundings. When initiated by ketamine infusion, these experiences are often transient in duration and mild-moderate in severity. There is evidence to suggest that the severity of dissociative effects induced by ketamine are correlated with its antidepressant effects (Luckenbaugh et al., 2014; Niciu et al., 2018). This was hypothesized to be a result of both effects being linked to increased glutamate activity.

Another potential factor moderating the effects of ketamine is family history of alcohol dependence. Several studies have found an association between family history of alcohol dependence and improved antidepressant response with ketamine (Luckenbaugh et al., 2012; Niciu et al., 2014; Phelps et al., 2009). Additionally, research has found that individuals with this family history were less sensitive to the subjective effects of ketamine (Petrakis et al., 2004), and experienced greater rewarding reactions to ketamine than those without this risk (Yoon et al., 2016). It has been hypothesized that these differences are mediated by altered functioning of NMDA receptors in individuals with a family history of alcoholism. As ketamine's effects on the NMDA receptor are the proposed mechanisms for not just its antidepressant effects, but also for its analgesic effects, it is possible that an individual's family history of alcohol use could moderate both of these outcomes.

1.8 Aims

There is now a large body of evidence demonstrating the efficacy of sub-anaesthetic ketamine as an analgesic and as a rapid acting antidepressant. This study aimed to explore whether these effects can be replicated in a chronic pain population by comparing patients administered ketamine to an active 'control' group of patients administered with lidocaine in the same UCLH Pain Clinic. The subjective experiences initiated by ketamine were also compared to those of lidocaine. Further investigation was undertaken to explore the influence of a number of potential moderating factors. These factors included the severity of depressive symptomology, number of previous doses, concomitant medications and family history of alcohol dependence. Due to the lack of prior research related to these questions this aspect of the research will be exploratory in nature.

2. Method

2.1 Power Calculation

The power calculation was based on the findings of (Coyle & Laws, 2015) who carried out a meta-analysis finding large effect sizes for the effects of single infusions of ketamine on depressive symptoms. Assuming equal group sizes, the power calculation was performed on "G*Power 3" computer program (Faul, Erdfelder, Lang, & Buchner, 2007), specifying alpha=5% and desired power =80%. The effect size was conservatively estimated down from large to medium and the required sample size was estimated at 52 total or 26 individuals per group.

2.2 Joint Working

This thesis is a joint project with Georgia Halls, who investigated the effects of ketamine on cognitive function in the same sample. Additionally, this is a continuation of a previous project started by two UCL Doctorate in Clinical Psychology trainees, Catherine Trotman and Matt Knox, in 2016. (More information is available in Appendix 2.A)

2.3 Ethics

Ethical approval was granted by the University College London (UCL) Research Ethics Committee and by the South Central Berkshire NHS Research Ethics committee (IRAS Project ID: 214864; see Appendix 2.B).

2.4 Participants

A convenience sample was taken from patients receiving specialist treatment for chronic pain at UCLH. Participants were recruited from patients who had moderate to severe chronic pain and were receiving intravenous infusions of either ketamine or lidocaine as part of their treatment. Participants were men and women between the ages of 18-70 and native English speakers. Exclusion criteria included diagnosis of a psychiatric condition, record of serious head injury, record of learning disability, suspected allergy to ketamine, pregnancy or currently breast feeding, or unable to provide informed consent.

2.5 Design

A non-randomized, between subjects, active control design was used. The independent variables were ketamine and lidocaine, the latter being the control. It

was not possible to blind the participants as the independent variable of drug was already prescribed as part of their treatment. Neither was it possible to blind the researchers due to the difference in duration of infusion between the two drugs.

2.6 Measures

2.6.1 Mood

Depressive symptomology was measured primarily using the Hospital Anxiety and Depression Scale (HADS), which is a validated self-report measure used to assess depression and anxiety in non-psychiatric hospital settings (Zigmond & Snaith, 1983; see Appendix 2.E). The 2-item Patient Health Questionnaire depression module (PHQ-2) was also used to assess depression (see Appendix 2.E). This measure was added firstly due to its past use in studies exploring the antidepressant effects of ketamine and secondly due to its brevity.

2.6.2 Pain

Three aspects of pain were measured using three 0-10 Visual Analogue Scale (VAS) (see Appendix 2.F). These scales were used to measure pain intensity, pain distress, and pain interference.

2.6.3 Subjective Rating Scales

Subjective drug effects were measured using a 13 item 0-10 VAS (Curran & Morgan, 2000) (see Appendix 2.G). The aspects of subjective drug effects measured by this scale can be broadly split into four categories: a) Bodily Symptoms (dizziness, drowsiness, nausea), b) Cognitive/Mood Symptoms (mental confusion, depression, feel stressed), c) Perceptual Symptoms (visual distortions, out of body

experience) and d) Reinforcing Drug Effects (liking the drug, disliking the drug, feeling high, feeling a drug effect, want to drink alcohol).

2.6.4 Repeated Dose

The number of previous doses of ketamine or lidocaine that had been administered to the participants as part of their treatment whilst at the UCLH Pain Clinic were gathered from the UCLH database.

2.6.5 Family History of Alcohol Dependence

Participants' familial risk of alcohol dependence were measured by assessing how many of their first and second-degree relatives have a history of alcohol use disorder. This method has been suggested by Krystal et al. (2017) as it allows for the examination of the relationship between increasing familial risk of alcohol dependence and various other measures.

2.6.6 Alcohol Use

The Alcohol Use Disorders Identification Test (AUDIT) was used to measure participants' alcohol use. This is a 10-item questionnaire shown to have good validity and reliability (Babor, de la Fuente, Saunders, & Grant, 2001; see Appendix 2.H).

2.6.7 Medication

We collected information about the medication participants were prescribed and had taken in the last 24 hours. If they had taken an SSRI, SNRI, or atypical anti-

depressant in the last 24 hours they were coded as taking an antidepressant. If they had taken any opioid in the last 24 hours they were coded as taking an opioid.

2.6.8 Demographic Details

Participants were asked to provide information about their age, gender and highest educational attainment (see Appendix 2.H).

2.7 Procedure

2.7.1 Pre-participation

Once possible study participants were identified by the direct clinical care team, they were then contacted by the researchers in order to determine eligibility. Patients who agreed to take part in the research were sent an information sheet before the day of their treatment at the clinic (see Appendix 2.C). After participants arrived at the pain clinic for their appointment, they were asked to provide informed consent and their demographic details (see Appendix 2.D & 2.H). They were also given the chance to ask any further questions at this point.

2.7.2 Pre-infusion Baseline

Participants were initially asked to complete baseline measures of depressive symptomology (HADS and PHQ-2), the three pain VAS, and the subject drug effects VAS. Once these measures were complete the medical staff were informed, and the patient was admitted to the ward for treatment.

2.7.3 Infusion

Ketamine infusions usually lasted between 30-60 minutes, whereas lidocaine infusions lasted between 1-3 hours. Protocol for treatment doses are around 0.15 – 0.6 mg per kg for ketamine participants and 2 – 3mg per kg for lidocaine.

2.7.4 Mid-infusion

Infusion mid-point was calculated for each participant based on anticipated infusion duration. At this point participants were asked to complete the three pain VAS and the subjective effects VAS.

2.7.5 Post-infusion

Immediately after the infusion was completed participants were administered the three pain VAS and the subjective effects VAS. Following this, they were debriefed and provided the opportunity to ask questions. At this point a one-week follow-up phone call was arranged.

2.7.6 One-week Follow-up

One-week after their infusion each participant was contacted by telephone and completed the same battery of measures administered at baseline: the measures of depressive symptomology (HADS & PHQ-2), three pain VAS, and subjective drug effects VAS. Participants were then given the chance to ask any additional questions.

2.8 Statistical Analysis

All statistical analyses were performed using SPSS Version 26 (IBM Corp, New York, NY, USA). Descriptive statistics were calculated to summarise demographic variables. Baseline differences for demographic and outcome variables were assessed using chi-square tests for categorical variables and t-tests for continuous variables.

Data were examined for the assumption of normal distribution. Visual examination of quartile-quartile plots indicated that the data was linear, however evaluation of histograms suggested non-normality in some of the data due to skew and kurtosis. Where data was not normally distributed transformations were attempted. However, these transformations were not retained as they did not improve the distribution of the data.

According to central limit theorem, in samples of 40 or more the sampling distribution is usually normal (Field, 2013). Furthermore, Field (2013) states that the F-test in the ANOVA is a robust measure and recommends its use where possible, especially when data is affected by skew or kurtosis but is linear. Therefore, mixed ANOVAs were used to explore the differences between ketamine and lidocaine on the domains of pain, mood and subjective drug effects over time. Many of acute effects VAS were analysed using a 2x4 mixed ANOVA, including baseline, mid-point, post-infusion and follow-up time points. When baseline measure was not taken a 2x3 mixed ANOVA was used including the other three time points. One-week follow-up effects for mood were analysed using a 2x2 mixed ANOVA, including the baseline and follow-up time points. This 2x2 mixed ANOVA was performed again for the HADS-D after selecting for cases with baselines scores at the clinical cut-off

and then the more severe ‘abnormal’ cut-off, in order to see if the anti-depressant effects of ketamine were different depending on severity of symptoms.

Homogeneity of variances was assessed using Levene’s test, and homogeneity of covariances was assessed using Box’s test. Where these assumptions have been violated the decision to carry on with analysis has been made due to the robustness of the F-test (Field, 2013). Assumptions of sphericity was assessed using Mauchley’s test and where this assumption was violated this has also been noted and the Greenhouse-Geisser correction has been applied.

Secondary analysis was performed in order to explore the association between variables. Correlations were run to compare change scores in the domains of pain (intensity, distress, interference) and mood (HADS Depression, HADS Anxiety, PHQ2, Depression VAS) from baseline to follow-up. Correlations were also run for the subjective drug effects of feeling a drug effect and out of body experience from baseline to mid-point as these were the peak of these experiences. Finally, participant characteristics of opioid use, antidepressant use, family history of alcohol dependence and number of previous of infusions were included in the correlation analysis. These subjective drug effects and participant characteristics were selected due to previous research indicating that they may moderate the effects of ketamine on mood (aan het Rot et al., 2010; Hu et al., 2016; Weber et al., 2018).

Visual examination of quartile-quartile plots and histograms of the change scores suggested that the data for the change scores met the assumption of normal distribution. Furthermore, examinations of scatter plots of all significant correlations showed that the assumption of linearity was met. Therefore, Pearson correlation analysis was used.

3. Results

3.1 Demographics and Baseline Scores

In total there were 99 participants: 43 were administered ketamine (29 female, 14 male) and 56 were administered lidocaine (43 female, 13 male). This figure includes all participants who completed measures at multiple timepoints; those who dropped out after the first measures were collected were not included in the final data analysis (Figure 2.1). Demographic details on age, gender and years in education were collected. Baseline comparisons were made to assess for differences in demographic characteristics and baseline scores for the primary outcome measures (Table 2.1).

There was a significant difference in age between the two groups, with participants in the ketamine group being older than participants in the lidocaine group. No baseline comparisons were made between dosage as doses of these different drugs are not equivalent. All other baseline characteristics were statistically similar.

Figure 2.1

Study flow chart

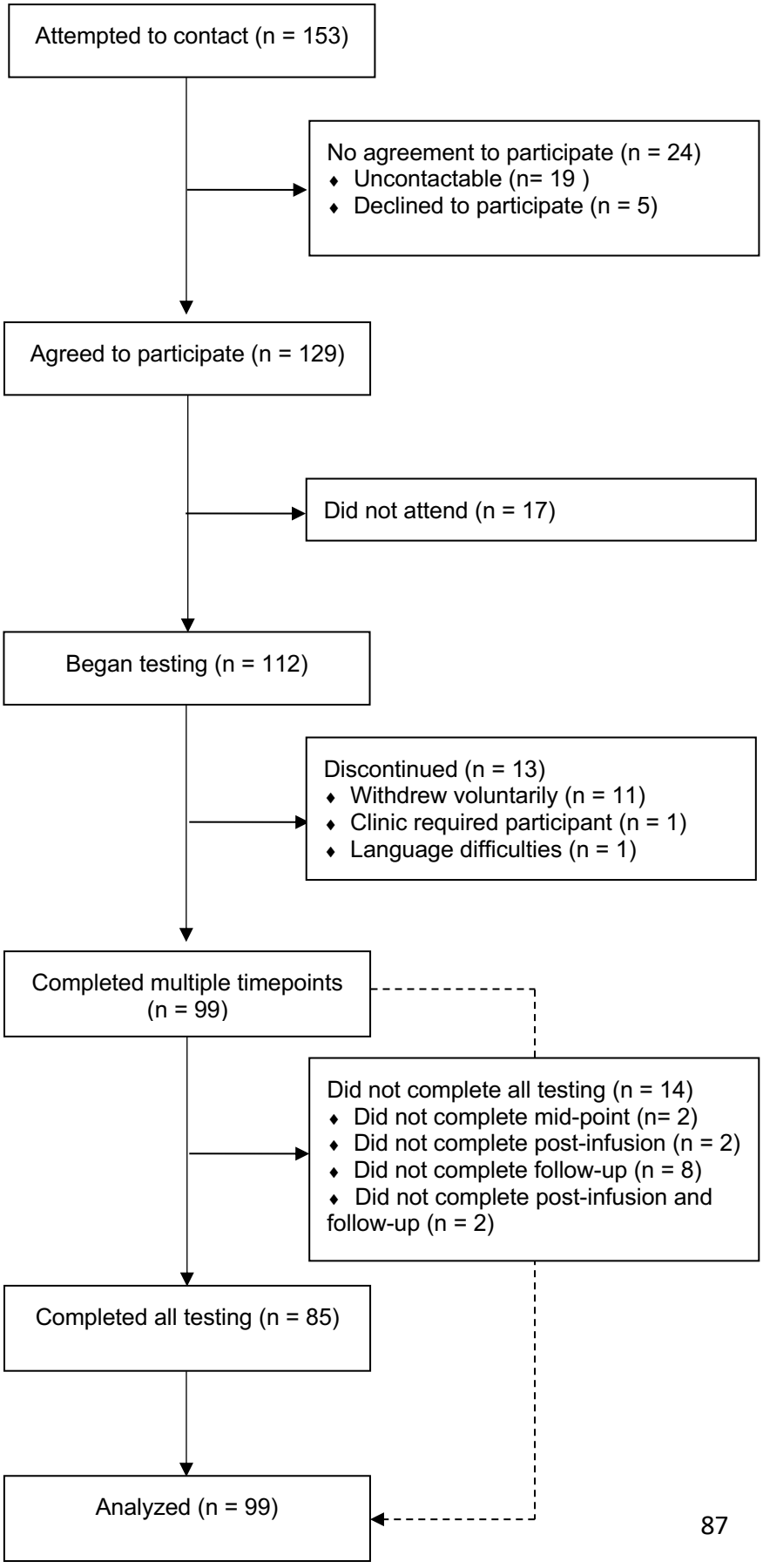


Table 2.1

Demographic characteristics and results of baseline comparisons

	Ketamine (n = 43)	Lidocaine (n = 56)
Age, years*	51.19 ± 11.70	45.93 ± 13.93
Gender, female	67%	77%
Education Years	13.59 ± 2.73	14.24 ± 2.60
Dosage, mg per kg	0.21 ± 0.09	2.61 ± 0.49
Baseline Scores		
HADS-Depression	2.05 ± 0.90	2.02 ± 0.87
HADS-Anxiety	2.16 ± 0.90	2.17 ± 0.89
Pain Intensity	6.79 ± 2.19	6.54 ± 2.24
Pain Distress	5.72 ± 3.01	5.52 ± 2.84
Pain Interference	6.97 ± 2.52	6.87 ± 2.85

* Significant baseline differences

3.2 Acute Effects: Pain

As there were baseline differences in age, ANCOVAs were run for each of the ANOVA analysis, with age being added as a covariate. As this did not change any of the significance levels, the original ANOVA analyses have been presented here. The mean and standard deviations for the data used in these ANOVAs can be found in Appendix 2.I.

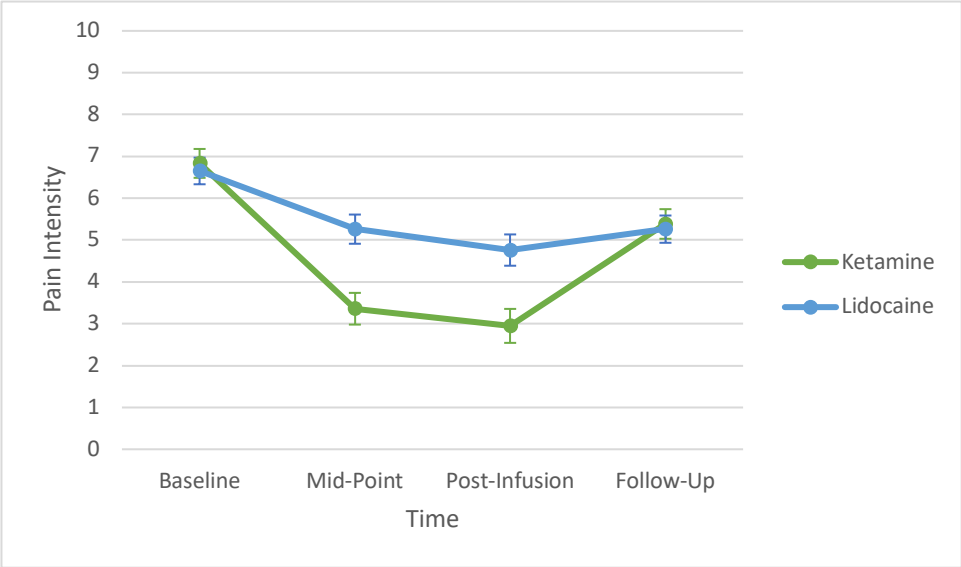
3.2.1 Pain Intensity VAS

There was an interaction between the drug group and time on pain intensity scores, $F(2.61, 216.40) = 10.41$, $p < .001$. Post-hoc tests using Bonferroni correction showed that the ketamine group scored lower than the lidocaine group at the mid-point, $F(1,83) = 13.60$, $p < .001$, and at post-infusion, $F(1,83) = 10.78$, $p = .001$.

Further analysis found that for the ketamine group, pain intensity was reduced from baseline to mid-point ($\Delta M = 3.47$, $SE = .33$, $p < .001$), post-infusion ($\Delta M = 3.89$, $SE, = .40$, $p < .001$), and follow-up ($\Delta M = 1.45$, $SE = .38$, $p = .002$). For the lidocaine group, pain intensity was reduced from baseline to mid-point ($\Delta M = 1.39$, $SE = .30$, $p < .001$), post-infusion ($\Delta M = 1.89$, $SE, = .37$, $p < .001$), and follow-up ($\Delta M = 1.39$, $SE = .35$, $p = .001$).

Figure 2.2

Mean pain intensity scores across all time points; bars represent standard errors



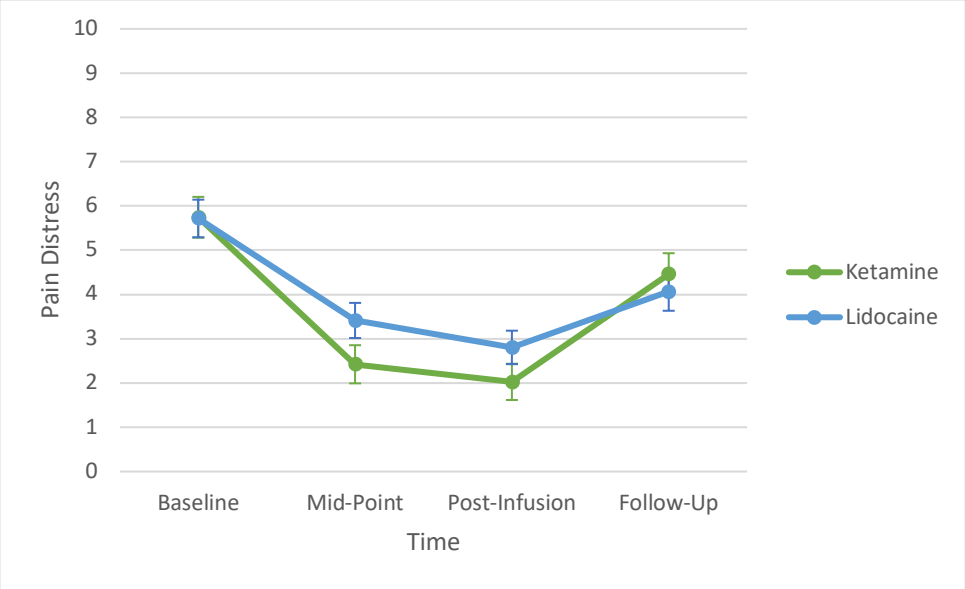
3.2.2 Pain Distress VAS

There was no interaction between the drug group and time on pain distress scores, $F(3, 249) = 2.25$, $p = .083$. There was a main effect of time showing a reduction in mean pain distress score, $F(3,249) = 46.22$, $p < .001$. There was no main effect of drug group $F(1, 83) = 0.51$, $p = .475$.

Post-hoc tests using Bonferroni correction found that for the ketamine group, pain distress was reduced from baseline to mid-point ($\Delta M = 3.32$, SE, = .42, $p <$ .001) and post-infusion ($\Delta M = 3.72$, SE, = .46, $p < .001$). For the lidocaine group, pain distress was reduced from baseline to mid-point ($\Delta M = 2.30$, SE = .38, $p <.001$), post-infusion ($\Delta M = 2.91$, SE, = .42, $p < .001$), and follow-up ($\Delta M = 1.65$, SE = .46, $p = .003$).

Figure 2.3

Mean pain distress scores across all time points; bars represent standard errors



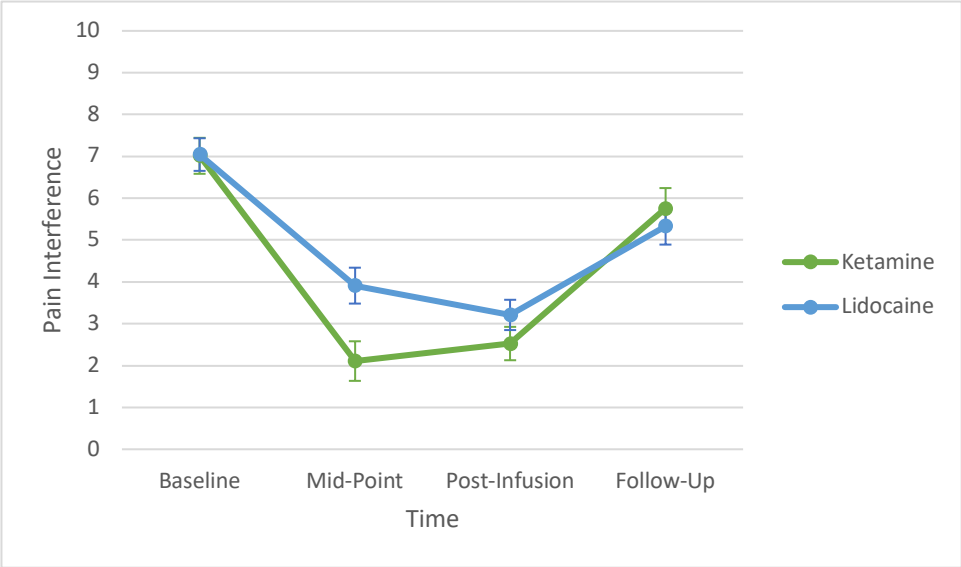
3.2.3 Pain Interference VAS

There was an interaction between the drug group and time on pain interference scores, $F(2.71, 216.53) = 3.99$, $p = .011$. Post-hoc tests using Bonferroni correction showed that the ketamine group scored lower than the lidocaine group at the mid-point, $F(1,80) = 7.99$, $p = .006$.

Further analysis found that for the ketamine group, pain interference was reduced from baseline to mid-point ($\Delta M = 4.91$, $SE = .54$, $p < .001$) and post-infusion ($\Delta M = 4.49$, $SE, = .50$, $p < .001$). For the lidocaine group, pain interference was reduced from baseline to mid-point ($\Delta M = 3.13$, $SE = .49$, $p < .001$), post-infusion ($\Delta M = 3.83$, $SE, = .45$, $p < .001$), and follow-up ($\Delta M = 1.71$, $SE = .48$, $p = .004$).

Figure 2.4

Mean pain interference scores across all time points; *bars represent standard errors*



3.3 Acute Effects: Subjective Drug Effects

3.3.1 Want to Drink Alcohol VAS

There was no interaction between the drug group and time on want to drink alcohol VAS scores, $F(2.19,179.43) = 0.63$, $p = .548$. There was a main effect of time showing a difference in mean want to drink alcohol VAS score at the different time points, $F(2.19,179.43) = 6.80$, $p = .001$. There was no main effect of drug group $F(1, 82) = 2.84$, $p = .096$.

3.3.2 Dizziness VAS

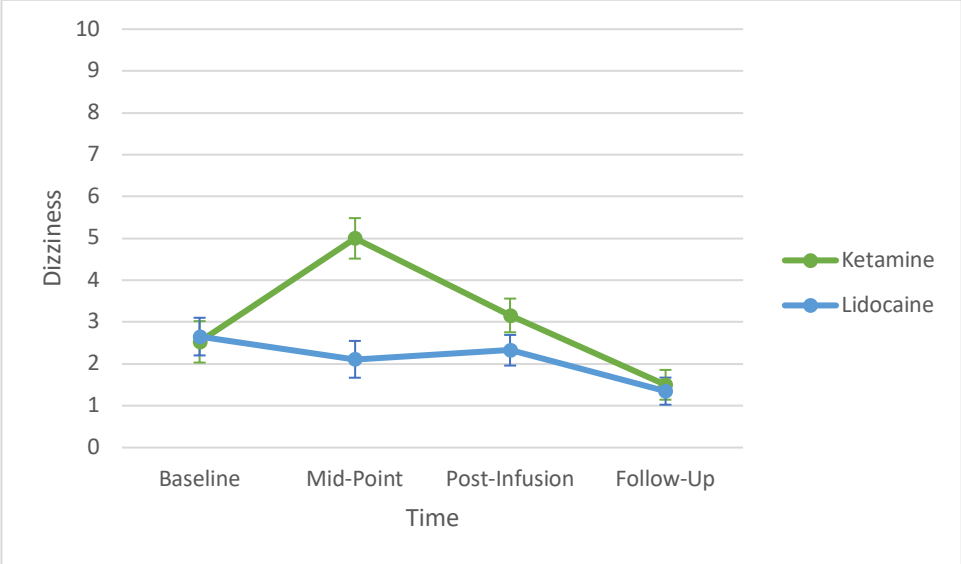
There was an interaction between the drug group and time on dizziness VAS scores, $F(3, 246) = 8.91$, $p < .001$. Post-hoc tests using Bonferroni correction showed that the ketamine group scored higher than the lidocaine group at the mid-point, $F(1,82) = 19.53$, $p < .001$.

Further analysis found that for the ketamine group, dizziness VAS was increased from baseline to mid-point ($\Delta M = -2.47$, $SE = 0.48$, $p < .001$), and then

decreased from mid-point to post-infusion (ΔM = 1.84, SE, = 0.42, p <.001) and follow-up (ΔM = 3.50, SE = 0.54, p < .001). There was also a reduction from post-infusion to follow-up (ΔM = 1.67, SE = 0.47, p = .004). For the lidocaine group, dizziness VAS was reduced from baseline to follow-up (ΔM = 1.30, SE = 0.42, p = .016).

Figure 2.5

Mean dizziness VAS scores across all time points; bars represent standard errors



3.3.3 Feel a Drug Effect VAS

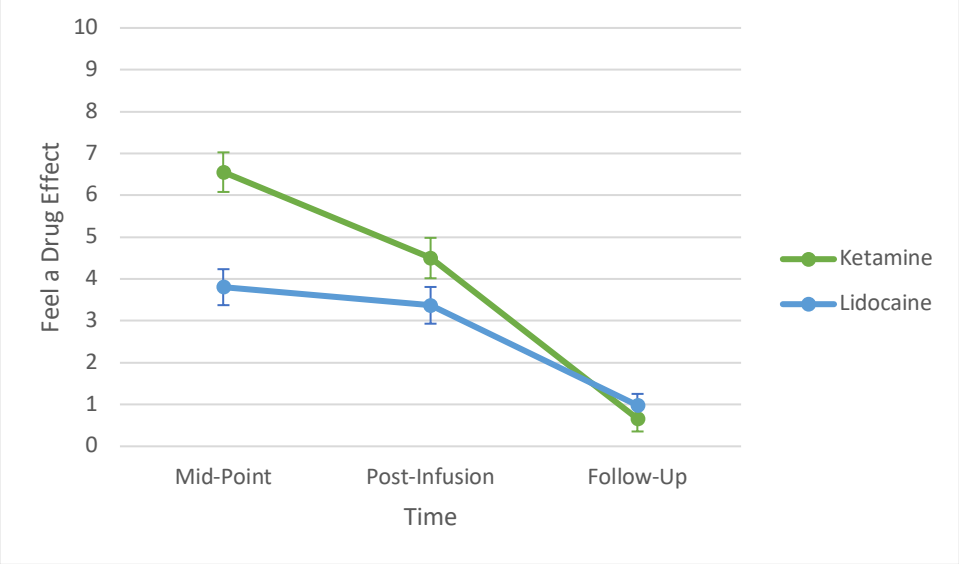
There was an interaction between the drug group and time on drug effect VAS scores, $F(2, 164) = 9.43$, $p < .001$. Post-hoc tests using Bonferroni correction showed that the ketamine group scored higher than the lidocaine group at the mid-point, $F(1,82) = 18.50$, $p < .001$.

Further analysis found that for the ketamine group, drug effect was reduced from mid-point to post-infusion (ΔM = 2.05, SE = 0.54, p = .001) and follow-up (ΔM = 5.90, SE = .51, p < .001). There was also a reduction from post-infusion to follow-up (ΔM = 3.84, SE = .51, p < .001). For the lidocaine group, drug effect VAS

was reduced from mid-point to follow-up (ΔM = 2.83, SE = 0.47, p < .001) and from post-infusion to follow-up (ΔM = 2.39, SE = 0.47, p < .001)

Figure 2.6

Mean feel a drug effect VAS scores across all time points; bars represent standard errors



3.3.4 Drowsiness VAS

There was no interaction between the drug group and time on drowsiness VAS scores, $F(2.61,213.84) = 1.32$, $p = .271$. There was a main effect of time showing a difference in mean drowsiness VAS score at the different time points, $F(2.61,213.84) = 22.35$, $p < .001$. There was no main effect of drug group $F(1, 82) = 0.17$, $p = .682$

3.3.5 Feeling High VAS

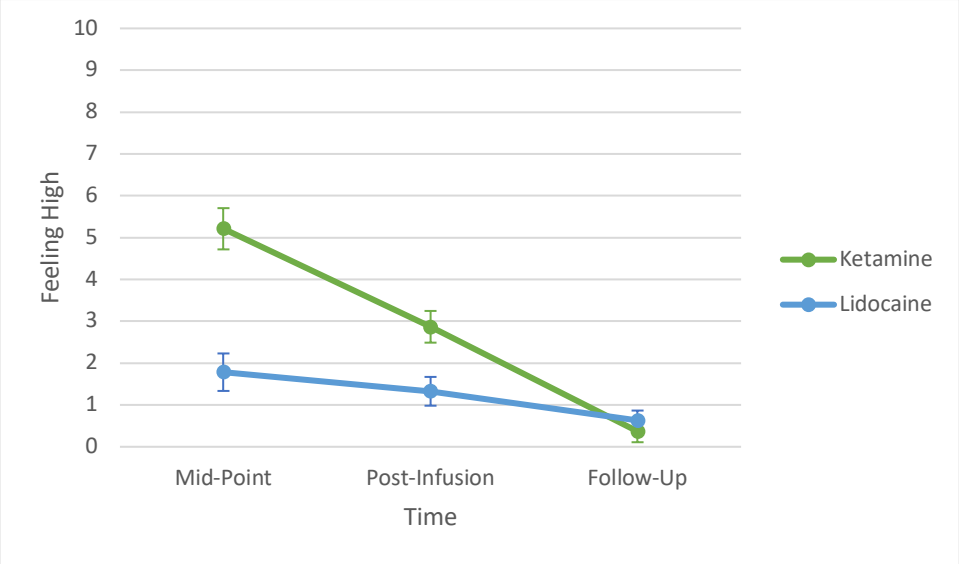
There was an interaction between the drug group and time on feeling high VAS scores, $F(1.74, 142.81) = 17.31$, $p < .001$. Post-hoc tests using Bonferroni correction showed that the ketamine group scored higher than the lidocaine group at

the mid-point, $F(1,82) = 26.45$, $p < .001$ and at post-infusion, $F(1,82) = 9.09$, $p = .003$.

Further analysis found that for the ketamine group, feeling high VAS was reduced from mid-point to post-infusion ($\Delta M = 2.34$, $SE = 0.47$, $p < .001$) and follow-up ($\Delta M = 4.84$, $SE = 0.54$, $p < .001$). There was also a reduction from post-infusion to follow-up ($\Delta M = 2.50$, $SE = 0.38$, $p < .001$). No such effects were found for the lidocaine group.

Figure 2.7

Mean feeling high VAS scores across all time points; bars represent standard errors



3.3.6 Nausea VAS

There was no interaction between the drug group and time on nausea VAS scores, $F(2.42,198.21) = 2.64$, $p = .063$. Neither was there a main effect of time, $F(2.42,198.21) = 1.86$, $p = .150$, or drug group, $F(1, 82) = 1.21$, $p = .275$.

3.3.7 Dislike the Drug VAS

There was no interaction between the drug group and time on dislike drug VAS scores, $F(1.83,146.01) = 1.36$, $p = .260$. Neither was there a main effect of time, $F(1.83,146.01) = 1.37$, $p = .256$, or drug group, $F(1, 80) = 0.15$, $p = .698$.

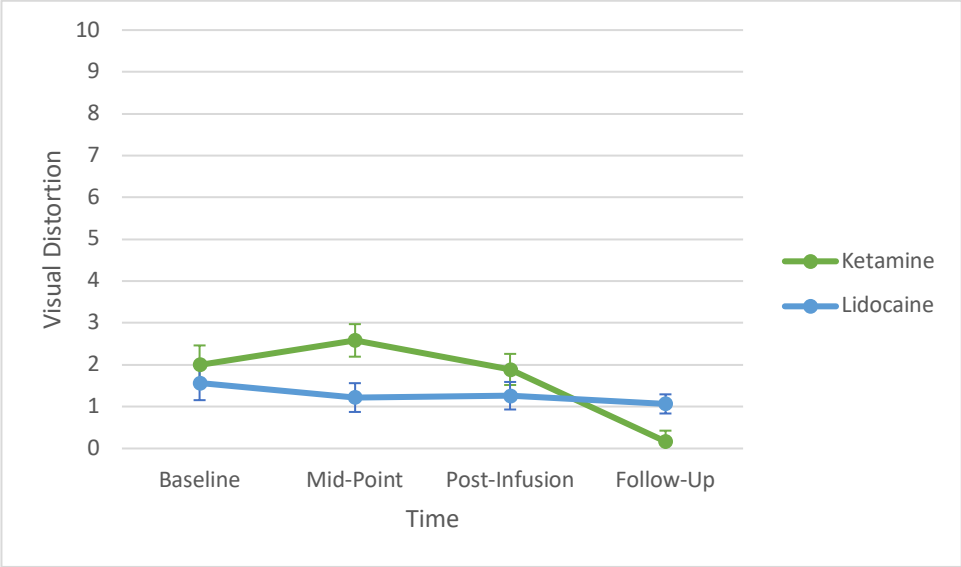
3.3.8 Visual Distortion VAS

There was an interaction between the drug group and time on visual distortion VAS scores, $F(3, 240) = 5.50$, $p = .001$). Post-hoc tests using Bonferroni correction showed that the ketamine group scored higher than the lidocaine group at mid-point, $F(1,80) = 6.91$, $p = .010$, and then lower than the lidocaine group at the follow-up, $F(1,80) = 6.73$, $p = .011$.

Further analysis found that for the ketamine group, visual distortion VAS was reduced from baseline to follow-up ($\Delta M = 1.83$, $SE = 0.43$, $p < .001$), and from mid-point to follow-up ($\Delta M = 2.42$, $SE = 0.41$, $p < .001$), and from post-infusion to follow-up ($\Delta M = 1.72$, $SE = 0.38$, $p < .001$). No such effects were found for the lidocaine group.

Figure 2.8

Mean visual distortion VAS scores across all time points; bars represent standard errors

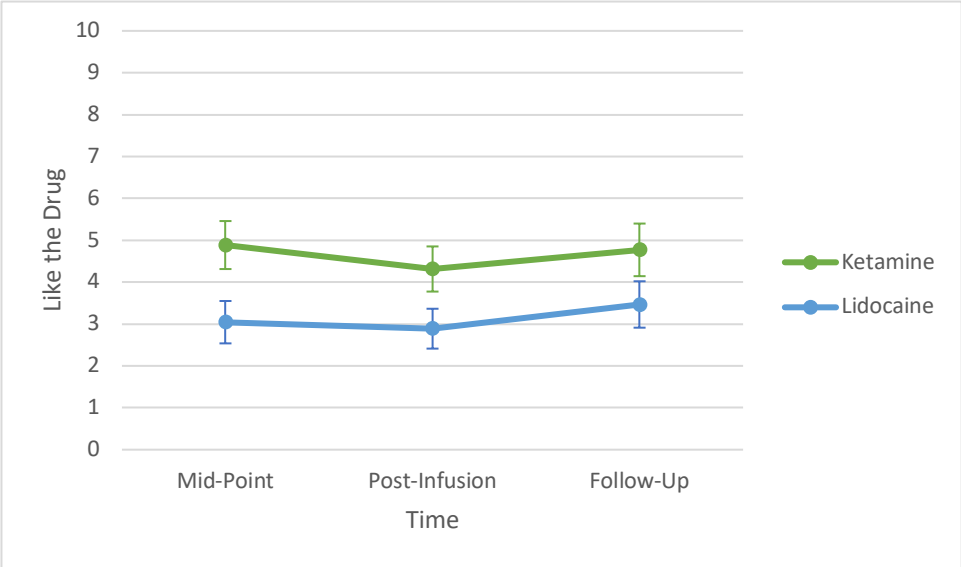


3.3.9 Like the Drug VAS

There was no interaction between the drug group and time on liking the drug VAS scores, $F(1.75,136.45) = 0.28$, $p = .728$. Neither was there a main effect of time, $F(1.75,136.45) = 0.99$, $p = .365$. There was a main effect of drug group showing a difference in mean liking the drug VAS score between drug groups $F(1, 78) = 5.65$, $p = .020$, demonstrating higher rates of liking the drug in the ketamine group.

Figure 2.9

Mean like the drug VAS scores across all time points; bars represent standard errors



3.3.10 Out of Body Experiences VAS

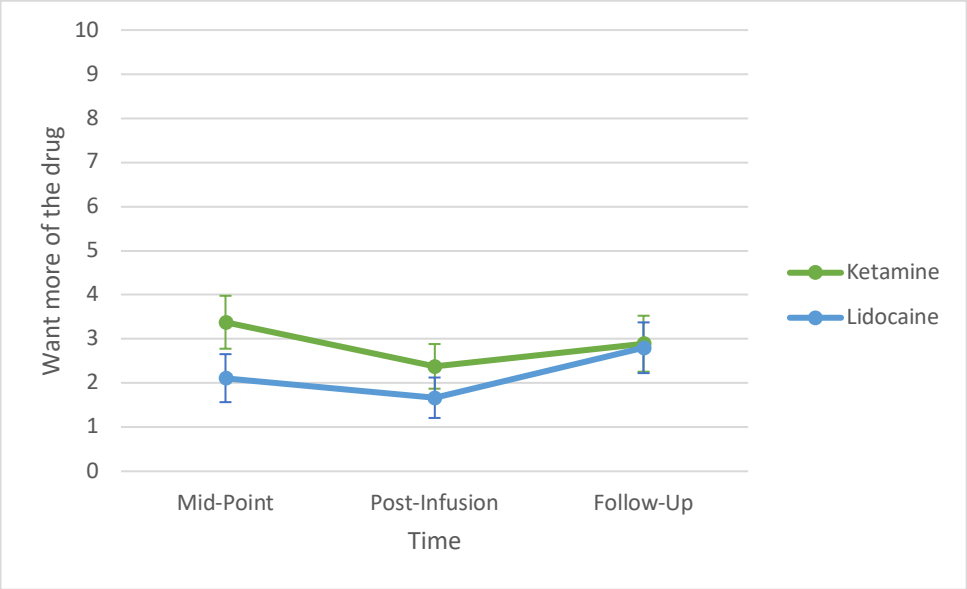
There was no interaction between the drug group and time on out of body experiences VAS scores, $F(2.71,221.86) = 1.26$, $p = .289$. There was a main effect of time showing a difference in mean out of body experiences VAS score at the different time points, $F(2.71,221.86) = 8.12$, $p < .001$. There was no main effect of drug group $F(1, 82) = 2.37$, $p = .128$

3.3.11 Want More of the Drug

There was no interaction between the drug group and time on want more of the drug VAS scores, $F(1.79,142.27) = 1.07$, $p = .341$. There was a main effect of time showing a difference in mean want more of the drug VAS score at the different time points, $F(1.79,142.27) = 2.49$, $p = .093$. There was no main effect of drug group $F(1, 80) = 1.19$, $p = .279$

Figure 2.10

Mean want more of the drug VAS scores across all time points; bars represent standard errors



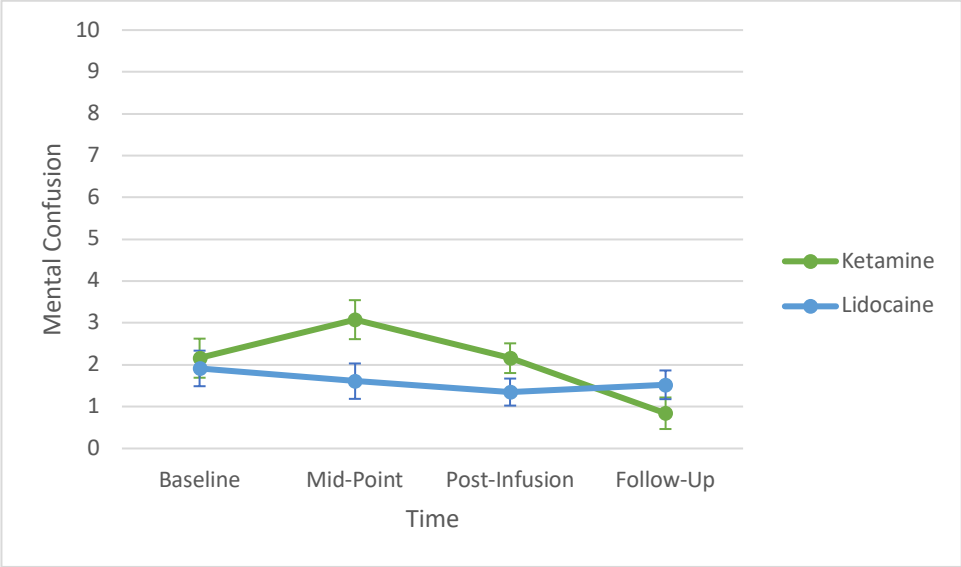
3.3.12 Mental Confusion VAS

There was an interaction between the drug group and time on mental confusion VAS scores, $F(2.58, 211.15) = 4.36$, $p = .008$). Post-hoc tests using Bonferroni correction showed that the ketamine group scored higher than the lidocaine group at the mid-point ($F(1,82) = 5.46$, $p = .022$).

Further analysis found that for the ketamine group, mental confusion was reduced from baseline to follow-up ($\Delta M = 1.32$, $SE = 0.47$, $p = .041$), mid-point to follow-up ($\Delta M = 2.24$, $SE = 0.49$, $p < .001$), and post-infusion to follow-up ($\Delta M = 1.32$, $SE = 0.38$, $p = .005$). No such effects were found in the lidocaine group.

Figure 2.11

Mean mental confusion VAS scores across all time points; bars represent standard errors



3.3.13 Feel Stressed VAS

There was no interaction between the drug group and time on feel stressed VAS scores, $F(2.32,71.92) = 0.12$, $p = .912$. There was a main effect of time showing a difference in mean feel stressed VAS score at the different time points, $F(2.32,71.92) = 9.40$, $p < .001$. There was no main effect of drug group $F(1, 31) = 0.22$, $p = .644$.

3.3.14 Depression VAS

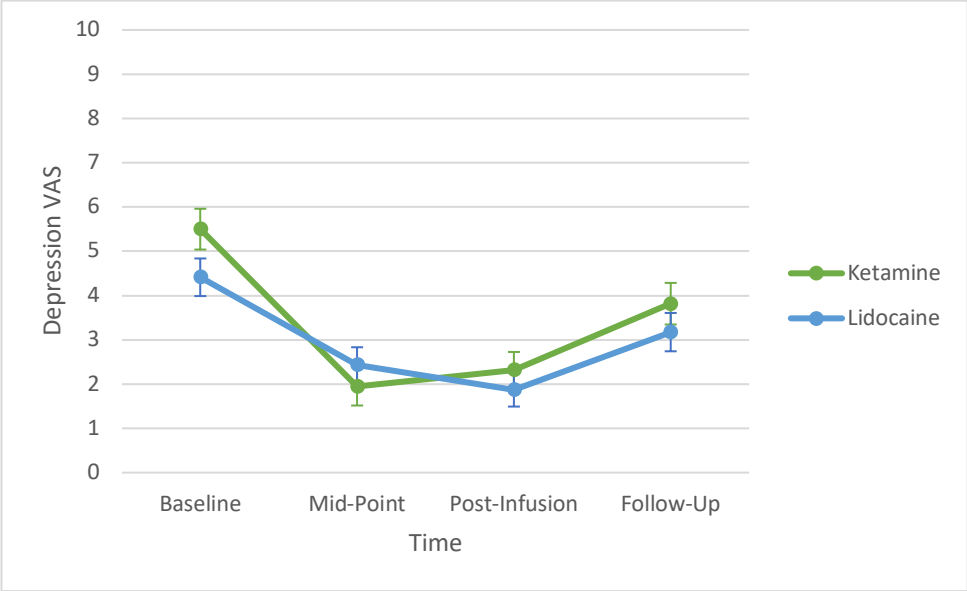
There was no interaction between the drug group and time on depression VAS scores, $F(3,246) = 2.30$, $p = .078$. There was a main effect of time showing a reduction in mean depression VAS score, $F(3,246) = 37.79$, $p < .001$. There was no main effect of drug group $F(1, 82) = 0.67$, $p = .416$.

Post-hoc tests using Bonferroni correction found that for the ketamine group, depression VAS was reduced from baseline to mid-point ($\Delta M = 3.55$, SE, = .45, $p <$

.001), post-infusion (ΔM = 3.18, SE, = .49, p < .001), and follow-up (ΔM = 1.68, SE = .43, p = .001). For the lidocaine group, depression VAS was reduced from baseline to mid-point (ΔM = 1.98, SE = .41, p <.001), post-infusion (ΔM = 2.54, SE, = .44, p < .001), and follow-up (ΔM = 1.24, SE = .39, p = .014).

Figure 2.12

Mean depression VAS scores across all time points; bars represent standard errors



3.4 One-week Follow-Up: Mood

3.4.1 HADS-D

There was no interaction between the intervention and time on HADS-D scores, $F(1, 87) = 0.20$, p = .659. Neither was there a main effect of time, $F(1, 87) = 1.29$, p = .259, or drug group, $F(1, 87) = 0.18$, p = .669.

3.4.2 HADS-A

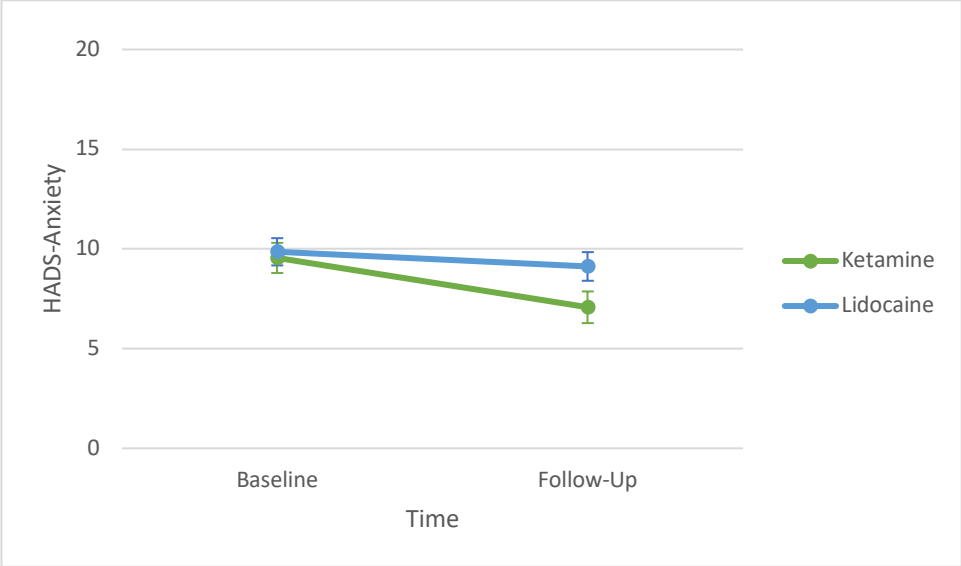
There was an interaction between the drug group and time on HADS-A scores, $F(1, 87) = 6.11$, p = .015. Post-hoc tests using Bonferroni correction showed

that the ketamine group scored lower than the lidocaine group at the follow-up, although this was not statistically significant, $F(1,87) = 3.66$, $p = .059$

Further analysis found that for the ketamine group HADS-A was reduced from baseline to follow-up ($\Delta M = 2.48$, SE, = 0.52, $p < .001$). No such effects were found for the lidocaine group.

Figure 2.13

Mean HADS-Anxiety scores across both time point; bars represent standard errors



3.4.3 PHQ-2

There was no interaction between the drug group and time on PHQ-2 scores, $F(1,87) = 0.17$, $p = .680$. There was a main effect of time showing a reduction in mean PHQ-2 score, $F(1,87) = 14.80$, $p < .001$. There was no main effect of drug group $F(1, 87) = 0.01$, $p = .925$.

3.5 Mood in a Clinical Subset

3.5.1 HADS-D for Borderline & Abnormal

There was no interaction between the intervention and time on HADS-D scores, $F(1, 54) = 0.91$, $p = .345$. Neither was there a main effect of time, $F(1, 54) = 4.01$, $p = .050$, or drug group, $F(1, 54) = 0.30$, $p = .587$.

3.5.2 HADS-D for Abnormal

There was no interaction between the drug group and time on HADS-D scores, $F(1,33) = 0.55$, $p = .465$. There was a main effect of time showing a reduction in mean HADS-D score, $F(1,33) = 6.36$, $p = .017$. There was no main effect of drug group $F(1, 33) = 0.01$, $p = .975$.

3.6 Secondary Analysis – Correlations

Table 2.2 shows the Pearson product-moment correlation coefficient for the changes in score of the pain and mood measures from baseline to follow-up, separated by drug group.

3.6.1 Ketamine Group

A significant correlation was found between changes in HADS-D and pain interference. Changes in HADS-A score were correlated with changes in pain intensity and with antidepressant use. Furthermore, significant correlations were found between changes in depression VAS and each of pain intensity and distress. No correlations were found between subjective drug effects of feel a drug effect or out of body experiences, or any of the participant characteristics and any of the mood or pain measures.

3.6.2 Lidocaine Group

Significant correlations were found between changes in HADS-D and each of pain intensity, pain interference and feel a drug effect. No correlations were found between changes in HADS-A and any of the pain measures or other variables for the lidocaine group. Depression VAS was significantly correlated with each of pain distress and interference. No correlations were found between out of body experiences or any of the participant characteristics and any of the mood or pain measures.

Table 2.2

Pearson's correlations between changes scores and patient characteristics

	Ketamine												
		1	2	3	4	5	6	7	8	9	10	11	12	13
1. HADS-Depression	Correlation	–												
	N													
2. HADS-Anxiety	Correlation	0.30	–											
	N	40												
3. PHQ-2	Correlation	0.26	0.45**	–										
	N	40	40											
4. Depression VAS	Correlation	-0.03	0.08	0.00	–									
	N	40	40	40										
5. Pain Intensity	Correlation	0.08	0.33*	0.08	0.53**	–								
	N	40	40	40	40									
6. Pain Distress	Correlation	-0.02	0.20	0.07	0.37*	0.75**	–							
	N	40	40	40	40	40								
7. Pain Interference	Correlation	0.33*	0.38*	0.15	0.24	0.58**	0.52**	–						

	N	40	40	40	40	40	40							
8. Feel a Drug Effect	Correlation	0.02	-0.03	0.07	0.26	0.16	-0.04	0.10	–					
	N	39	39	39	39	39	39	39						
9. Out of Body Experience	Correlation	-0.31	-0.06	0.17	0.18	-0.06	-0.03	0.02	-0.09	–				
	N	39	39	39	39	39	39	39	39					
10. Opioids	Correlation	-0.12	-0.29	-0.33	0.31	-0.02	-0.05	0.08	0.29	0.35	–			
	N	16	16	16	16	16	16	16	16	19				
11. Antidepressants	Correlation	-0.46	-0.59*	-0.18	-0.11	-0.28	-0.13	-0.58*	0.18	-0.22	0.05	–		
	N	16	16	16	16	16	16	16	16	19	19			
12. Family History of Alcohol	Correlation	0.03	0.08	-0.30	0.16	0.08	0.22	0.02	-0.08	-0.16	0.34	0.027	–	
	N	16	16	16	16	16	16	16	16	19	19	19		
13. Previous infusions	Correlation	-0.01	0.13	-0.12	0.26	0.17	0.25	0.30	-0.09	0.04	0.05	-0.36	0.03	–
	N	40	40	40	40	40	40	40	39	42	19	19	19	

	Lidocaine												
		1	2	3	4	5	6	7	8	9	10	11	12	13
1. HADS-Depression	Correlation	–												
	N													
2. HADS-Anxiety	Correlation	0.45**	–											
	N	49												
3. PHQ-2	Correlation	0.27	0.16	–										
	N	49	49											
4. Depression VAS	Correlation	0.26	0.19	0.21	–									
	N	48	48	48										
5. Pain Intensity	Correlation	0.37**	0.15	0.17	0.27	–								
	N	49	49	49	48									
6. Pain Distress	Correlation	0.12	0.14	.30*	.33*	.60**	–							
	N	49	49	49	48	49								
7. Pain Interference	Correlation	0.35*	-0.07	0.09	.36*	.50**	.46**	–						
	N	48	48	48	47	48	48							
8. Feel a Drug Effect	Correlation	0.35*	0.26	0.20	0.27	0.07	0.11	0.21	–					

	N	48	48	48	48	48	48	47						
9. Out of Body Experience	Correlation	-0.13	-0.27	0.02	-0.09	0.02	-0.07	-0.18	-0.36*	–				
	N	48	48	48	48	48	48	47	48					
10. Opioids	Correlation	0.13	0.37	0.09	0.03	-0.07	0.17	0.28	-0.26	0.26	–			
	N	18	18	18	18	18	18	18	18	22				
11. Antidepressants	Correlation	0.12	-0.01	-0.04	-0.13	-0.21	0.12	0.07	-0.06	-0.09	0.033	–		
	N	18	18	18	18	18	18	18	18	22	22			
12. Family History of Alcohol	Correlation	0.027	-0.14	-0.01	0.03	0.17	-0.38	-0.19	0.38	-0.21	-0.31	-0.24	–	
	N	18	18	18	18	18	18	18	18	22	22	22		
13. Previous infusions	Correlation	0.13	0.07	0.06	-0.10	0.02	0.10	-0.14	-0.09	-0.04	-0.27	0.06	-0.06	–
	N	49	49	49	48	49	49	48	48	55	22	22	22	

*$p < .05$. **$p < .0$

4. Discussion

4.1 Overall

There is a large body of literature showing ketamine to be an efficacious treatment for both depression and pain (Kryst et al., 2020; Nourozi et al., 2010). However, there is an absence of research looking at ketamine's potential as an antidepressant in the chronic pain population. The current paper compared the effects of ketamine with lidocaine, when administered by IV infusion in a chronic pain population, on pain, subjective effects and mood.

4.2 Pain

Ketamine resulted in superior reductions to lidocaine for both pain intensity and interreference during the acute phase. A pervious study comparing these drugs in a neuropathic pain population was unable to find any differences in their acute impact on pain (Kvarnström, Karlsten, Quiding, Emanuelsson, & Gordh, 2003). It is possible that this difference in findings is a result of the current paper having a larger sample and therefore greater ability to detect an effect. The current findings reinforce previous research showing that pain relief occurs during ketamine infusion (Nourozi et al., 2010).

Despite ketamine leading to superior reductions in pain scores during the acute phase, only pain intensity scores were significantly improved at one-week follow-up, with both pain distress and interreference returning to baseline levels. In comparison, the lidocaine group showed sustained improvement on all three measures of pain at the one-week follow-up. This is partly reflective of the literature as many studies have found acute effects of ketamine on pain but comparatively less have been able to evidence longer term effects (Niesters et al., 2014). A review of

RCTs on ketamine in chronic pain found that the only studies to show analgesic efficacy over 48 hours, as measured by a >50% reduction of pain intensity, used infusions of 10 hours or more (Noppers et al., 2011). Additionally, one of these studies found that even when pain relief was sustained with longer infusion duration, there was little change to functionality (Sigtermans et al., 2009). As the infusion times in the current study were between 30 minutes to 1 hour it may be that this was not long enough to produce a significant long-term reduction in pain distress, and that even with longer infusions a significant reduction in pain interference would be unlikely.

No significant correlations were found between opioid use and reductions in pain scores for participants administered ketamine. This would suggest that opioid medication does not enhance the analgesic efficacy of ketamine. A similar finding was reported in a recent meta-analysis which found no difference in analgesic efficacy when comparing studies using ketamine alone versus studies using analgesic adjuncts, including opioids (Orhurhu, Orhurhu, Bhatia, & Cohen, 2019). It still may be the case that ketamine improves the pain relieving effects of opioids, as has been found in previous research (Niesters et al., 2014). However, the current study design did not allow for this to be investigated as it would be necessary to compare ketamine and opioid treatment to opioid only.

Reductions in each of the pain scores from baseline to follow-up appeared to be correlated with reductions on various measures of mood for both ketamine and lidocaine. This may result from a synchronicity between pain and depression/anxiety symptoms that has been demonstrated in previous research (Gerrits, van Marwijk, van Oppen, van der Horst, & Penninx, 2015). It has been suggested that both conditions may share neurobiological mechanisms (Meerwijk, Ford, & Weiss, 2013).

Therefore, it is possible that ketamine and lidocaine may have been acting on neurobiological functioning common to both conditions. In the instance of ketamine, this is likely to be inhibition of the NMDA receptor, which has been put forward as the mechanisms for the drug's analgesic and antidepressant effects (Fisher et al., 2000; Strasburger et al., 2017). It may also be that reductions in pain led to improved quality of life for some patients, thereby leading to reductions in depression and anxiety.

4.3 Depression

None of the measures for depression showed a superior effect for ketamine over lidocaine. Two of the measures, HADS-D and PHQ-2, were taken at baseline and one-week follow-up. Although the literature shows that a single dose of ketamine has a robust acute antidepressant effect, this effect reduces over time and tends to disappear at 1 – 2 weeks (Corriger & Pickering, 2019). In fact, the most recent meta-analysis of RCTs only found a marginal effect at 7 days post-infusion that was no longer significant after carrying out a sensitivity analysis (Kryst et al., 2020). It is therefore not entirely surprising that ketamine did not show an antidepressant effect at all on the HADS-D, and no difference from lidocaine on the PHQ-2, given that these measures were taken a week after the ketamine infusion.

There was also no difference found between ketamine and lidocaine on the depression VAS, which was taken at the mid-point and post-infusion stages, as well as baseline and one-week follow-up. It may be that these measures were taken both too soon and too late after administration of the drugs to capture any antidepressant superiority that ketamine may have had over lidocaine. Research shows that the peak of ketamine's antidepressant effects has been found to at 24 hours (Corriger &

Pickering, 2019). It may be that had we measured depression at this time point a difference would have been found between the drug groups.

It is also possible that ketamine is not as effective an antidepressant in the chronic pain population as it is in the treatment resistant depression population, where much of the research has previously been done. A previous study on the use of long term ketamine treatment on complex regional pain syndrome also failed to find any evidence of improvement in depression, despite improvement in pain scores (Sigtermans et al., 2009).

4.4 Severity of Depression

Analysing cases who met criteria for more severe or 'abnormal' scores for depression at baseline showed that these participants did see an improvement in HADS-D scores, whilst analysis including slightly less severe 'borderline' along with 'abnormal' participants did not. However, there was no difference in scores between ketamine and lidocaine for this more severe group, suggesting that these changes were not related to factors unique to ketamine, and instead may have been due to reductions in pain or being involved in the research.

This would suggest that even amongst more severely depressed individuals in a chronic pain population there is a lack of an antidepressant effect found in research with depressed populations without chronic pain. This points to a possibility that depression in chronic pain has distinct underlying mechanisms that are different to those in populations without pain. Evidence for this comes from research showing that chronic pain conditions, such as fibromyalgia and lower back pain, are associated with changes in regions of the brain linked with emotional stimuli, such as the prefrontal cortex and anterior cingulate cortex (Fritzsche et al., 1999).

4.5 Anxiety

In the current sample ketamine led to a significant reduction in anxiety as measured by the HADS-A, whilst no such reduction was found for lidocaine. Despite this, there was no significant difference in scores between these drug groups at the follow-up, suggesting there was only a transient effect. Although there is far less evidence in the current literature demonstrating the anxiolytic effects of ketamine compared to its antidepressant effects, these effects have been found across a range of diagnoses. Studies have demonstrated ketamine's efficacy in reducing anxiety in patients with generalized anxiety disorder (Glue et al., 2017), social anxiety (Taylor et al., 2018), and major depressive disorder (Lapidus et al., 2014; Zarate et al., 2006). The findings of this paper suggest that similar, although potentially much smaller effects, may exist within the chronic pain population.

4.6 Subjective Drug Effects

Of the bodily, cognitive, and perceptual symptoms measured in this study, ketamine appeared to result in higher scores than lidocaine on dizziness, visual distortion, and mental confusion at the mid-point of infusions. This profile of side effects is consistent with the literature both in depressed and chronic pain populations (Niesters et al., 2014; Short et al., 2018). Furthermore, all of these measures returned to baseline immediately after the infusion, again replicating previous research and demonstrating these effects are resolved shortly after administration (Noppers et al., 2011; Short et al., 2018). Visual disortion appeared to reduce below baseline levels at the one-week follow-up for ketamine. This finding may be explained by the bright lighting in the clinic and the fact that several participants reported not having their correct glasses.

When looking at the measures of reinforcing drug effects, the ketamine group scored higher than the lidocaine group on 'feel a drug effect' and 'feeling high' in the acute phase. Furthermore, participants receiving ketamine appeared to like the drug more than lidocaine across all time points, from the acute phase to one-week follow-up. The feeling of being high has been reported in previous research on healthy volunteers and it has been suggested that these rewarding properties may increase the risk of abuse (Krystal et al., 1999). However, in the current study there was no difference between ketamine and lidocaine on whether people wanted more of the drug, despite ketamine patients being more likely to report reinforcing drug effects. What's more, ratings of wanting more of the drug remained low for ketamine from the acute infusion to the one-week follow-up.

These findings indicate that although ketamine may produce noticeable psychoactive effects that some participants find enjoyable, these do not lead to craving or desire for more of the drug, as some have previously feared (Rasmussen, 2016). This is in contrast to previous findings from a study where similar doses were administered to ketamine-naïve healthy volunteers who reported both liking the drug and wanting more compared to a placebo group (Morgan, Mofeez, Brandner, Bromley, & Curran, 2004). These contradictory findings may result from a difference in populations and settings of the studies, indicating that patients receiving ketamine in the context of pain management are unlikely to develop cravings for the drug outside of the clinical setting. Given the relatively large sample we tested, this is an important finding clinically.

4.7 Repeated Infusions

There was no correlation between number of previous repeated infusions and changes in mood scores or pain measures. It should be noted that within the clinic this study took place in, repeated infusions were usually administered every three months. However, in the research on depression repeated infusions usually take place twice or thrice weekly, and it is this frequency that is correlated with further improvement in mood (Kryst et al., 2020). Furthermore, the research on pain shows that it is not only repeated infusions that are associated with reductions in pain but also longer duration of infusions (Noppers et al., 2011).

4.8 Antidepressant Medication

There was no correlation between antidepressant use and any of the depression measures. This would indicate that within our sample the administration did not enhance the effectiveness of antidepressants in the week after their infusion. This is contrast to one previous study showing ketamine enhanced the effectives of SSRIs when taken in conjunction (Hu et al., 2016). However, we did find a correlation between antidepressant use and larger reductions in anxiety as assessed by the HADS-A.

4.9 Limitations

A number of limitations with the current study should be acknowledged. Although the sample size was relatively high, some of the measures, such as ‘feel stressed’ VAS, concomitant medications, and family history of alcohol dependence, were introduced halfway through the study, meaning there was only data on these items for less than half of the sample. Therefore, these measures were especially

prone to type two error and it might be that nonsignificant findings here were a result of the analysis being underpowered, as opposed to there not actually being an effect.

One potential issue in this study was measuring depression in a chronic pain population. The HADS was picked due to it being designed specifically for use within medical settings as it includes less somatic items, and excludes severe symptoms, making it more sensitive to milder psychiatric disorders. (Herrmann, 1997; Rusu, Santos, & Pincus, 2016). The PHQ-2 and depression VAS were selected for their brevity and previous use in ketamine research (Morgan et al., 2004). Different results were found for each of the three measures of depression used and none of these measures appeared to significantly correlate with each other in the ketamine or lidocaine group. This calls into questions the construct validity of these measures in the chronic pain population, as there was little convergent validity between them, despite the fact they were all meant to measure depression. The difficulty in capturing depression in this population has been noted before. Whilst the HADS-D has been shown to capture pain related distress in previous research (Rusu et al., 2016), it may be that the VAS and PHQ-9 measures were capturing other aspects of mood.

A consequence of this study being conducted with participants receiving their usual medication treatment was that it was impossible to blind participants or medical staff to the independent variable, i.e. the drug being administered. It was also not possible blind researchers to the drug group as infusion length differed significantly between the drugs. An additional consequence of studying participants in a real-world clinical setting was that the dose and duration of infusion varied between patients within the groups, potentially leading to different effects on the variables we measured.

A further limitation related to study design was the lack of randomisation to the two groups. This opens up the possibility of systematic differences between the groups, other than the drug being administered, which could have acted as confounding variables influencing the results. Demographics and baseline scores were tested for equivalence between groups. The only difference we found was for participants in the ketamine group to be significantly older than those in the lidocaine group. One explanation for this is that patients were only usually provided ketamine after a failed course of lidocaine treatment, thus it is likely they would have been in treatment for longer and thus older. In order to account for this group difference, we ran the mixed ANOVAs and ANCOVAs with age as a covariate and found that this did not change the results. It is of course possible though that other differences existed between these groups on factors that we were unable to measure and thus control for.

4.10 Implications

There are a number of clinical and research implications that can be drawn from the present study. Our findings suggest that ketamine has superior acute analgesic effects to lidocaine, however, these effects do not appear to be completely sustained at one-week follow-up. Further research may benefit clinical practise by investigating ways of maximising the length of these analgesic effects, such as through varying the frequency and duration of infusions (Noppers et al., 2011).

A widely held concern around the clinical application for ketamine is the potential for abuse (Rasmussen, 2016). Whilst we did find that those receiving ketamine reported feeling more drug effects that could potentially be reinforcing, such feeling high and liking the drug, these effects did not seem to lead to any

significant desire for more of the drug, as these scores were low and were no different to lidocaine. This suggests that within a medical setting ketamine may not prompt the same desire to take more of the drug found in other settings (Morgan et al., 2004). However, more specific research on this subject should be conducted in order to avoid repeating previous mistakes of distributing drugs, initially thought to be "safe", such as oxycodone, that then became epidemics of substance abuse (Horowitz & Moncrieff, 2020).

The rapid-acting antidepressant properties of ketamine demonstrated in previous research were not replicated in this study. This indicates that for this population, a single dose of ketamine does not reduce symptoms of depression beyond those that might be expected with pain relief. Future research in this area may benefit from measuring mood at time points in between the acute phase and one-week, as previous studies have found most benefit here. Additionally, research using samples with co-morbid chronic pain and depression may produce different results from the current study, where the majority of participants scored below clinical threshold. Finally, this study presents some preliminary evidence of ketamine inducing a small effect of anxiety reduction in people with chronic pain. Again, further research on co-morbid chronic pain and anxiety disorders may be useful in order to see if larger and more significant effects can be found in these populations.

4.11 Conclusion

This study aimed to explore the effects of ketamine on pain, mood, and subjective drug effects in a chronic pain population. Ketamine produced superior acute analgesic effects, but these reduced after a week, especially for pain related distress and interreference. Compared to lidocaine, ketamine was associated with a

range of bodily, cognitive and perceptual experiences. Ketamine also appeared to be liked more than lidocaine, although this did not appear to result in higher desire for being given more of the drug. In contrast to research in depressed populations, ketamine did not appear to improve symptoms of depression beyond what might be expected with reductions in pain. Further research should investigate the effects of varying drug doses, frequency and duration of infusions in order to best harness the therapeutic benefits of ketamine in a chronic pain population.

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Part 3: Critical Appraisal

Overview

In this critical appraisal I will share my reflections on completing the DClinPsy thesis. This will mostly focus on my work with the empirical paper but will also touch on some elements of the literature review. Initially, I will discuss the context for why I chose this project and how these influences may have shaped my approach to the research. I will then consider my experiences of conducting the empirical research and the process of data collection in a clinical setting. Finally, I will comment on how aspects of my personality may have informed how I competed the projects.

Interest in the Subject

This first section will provide a reflection of the ideas and experiences that guided my decisions in choosing the topics for my research project. It will also hopefully give an idea of the context that may have influenced the approaches used in carrying out this research and interpreting the findings.

Since before starting the DClinPsy, I had developed an interest in the burgeoning research exploring the therapeutic utility of psychoactive substances for various mental health issues. Initially, my awareness of this had been focused on the work by Griffiths and colleagues at the John Hopkins University School of Medicine on the use of hallucinogenic substances such as psilocybin (Griffiths & Grob, 2010). They had found evidence that these substances could initiate profound spiritual experiences that led to improved sense of wellbeing and reductions in psychopathology. As someone hoping to work in psychology, I found this work of particular interest as the psychological experience was often positioned as central to the mechanism of the drug's effectiveness.

Shortly after joining the UCL DClinPsy course, I was made aware of the work being done by the university's Clinical Pharmacology Unit (CPU) into the clinical benefits of substances such as ketamine and MDMA. When the opportunity came to join a project looking at the effects of ketamine in a chronic pain population, I was quick to cite an interest and get involved. The idea of contributing to the development of knowledge of these substances and their myriad effects was exciting to me. Although one might expect that my excitement was drawn from the prospect of discovering the different benefits that a psychoactive substance like ketamine might have, I was also very open to and wary of the negative aspects of such a drug. Much of my previous experience had been working with people facing addiction issues. What's more, I had known several people in my personal life who had struggled with addiction, including addiction to ketamine. These experiences had built in me a respect for the powerful potential of such substances to do great harm to people's lives, as well as to benefit.

During my first placement I was lucky enough to have worked in a team with a prominent voice in the critical psychiatry movement, Dr Joanna Moncrieff. I became increasingly interested in her work suggesting that the scientific support for antidepressants and antipsychotics had been mis-sold to both the public and many clinicians, leading to their overuse in the treatment of mental health issues. One idea she presented that I found particularly interesting was that of the disease centred model versus the drug centred model (Moncrieff & Cohen, 2005). The disease centred model, put forward by orthodox psychopharmacology, assumes that psychotropic drugs correct imbalances in biochemistry that act as underlying mechanisms for a specific disease process. In contrast to this, the drug centred model suggests that drugs induce certain physiological and psychological states that may, or

may not, be experienced as beneficial in certain contexts. This accounts for the large variability in the effectiveness of many psychiatric medications and their potential to be experienced as profoundly unhelpful by some.

A further idea from Dr Moncrieff's work that stuck with me was her assertion that the small superiority of effect that anti-depressants like SSRIs had over placebo was potentially the result of an active placebo effect (Moncrieff, Cohen, & Porter, 2013). In other words, that heightened expectation, following the noticeable physiological and psychological changes from taking a psychotropic drug, creates a more potent placebo effect. It is clear to me that these ideas of the drug centred model and active placebo greatly influenced some of my interpretations of the results of my meta-analysis.

Due to these various influences and experiences, I felt well positioned to take a balanced and open-minded approach to the questions posed in my literature review and empirical paper. I did not feel particularly wedded to any one idea or potential outcome and felt genuinely curious to see what the results of these scientific enterprises might be. Nevertheless, the potential for my own preconceived ideas and expectations to cause bias in the interpretation and even setting up and conducting of the research was still existent. According to Bayes's theorem, prior assumptions are a necessary part of drawing inference from research to the real world (Dienes, 2011). As the subject of bias is another interest of mine, it felt important to continuously reflect on how my own preconceptions may have weighted the decisions I took with my research at each stage. For example, at the point of data collection, there was the potential to unconsciously encourage a participant to answer a question in a certain way when they expressed ambivalence about how to answer. Later on, there may have been an unconscious temptation to use certain analyses or select certain factors

in analyses that could have been more likely to produce significant results, or results that met my own expectations. In order to counter this, I aimed to set up *a priori* plans for how to deal with such situations, at the points of data collection and analysis. The use of supervision was also helpful in this regard. Interpretation of results may be biased by the limitations of knowledge or how available certain ideas are to a researcher, perhaps because they are more emotive or meaningful, otherwise known as the availability heuristic (Schwarz et al., 1991). Therefore, being able to share and discuss my findings with supervisors was invaluable in expanding my interpretation of the findings to beyond my own preconceptions and knowledge base.

Continuation of a Project

One inescapable feature of my empirical research, that presented several obstacles, was that I was picking up a project that had already been started by previous trainees. Although this was in part a blessing, as it meant spending less time on assembling the research methodology, it was also limiting in several ways. In the proposal and final write up, it meant explaining and rationalising decisions that I had not been a part of, and in some cases did not necessarily agree with. I was able to overcome this, in part, by communicating with those had been involved in the original design of the research, namely the previous trainees and my supervisors. Despite this there were still decisions that I found hard to explain, such as the inclusion of the 2-item Patient Health Questionnaire depression module (PHQ-2). This measure, along with the Hospital and Anxiety Depression Scale (HADS) and depression visual analogue scale (VAS), was used to capture depression in our sample. The inclusion of the latter two scales made sense to me. The HADS was well suited to this population as it did not include somatic items usually found in

depression measures, making it less likely to obfuscate symptoms of chronic pain with those of depression (Herrmann, 1997; Rusu et al., 2016). The depression VAS was brief and allowed us to capture the acute effects ketamine and lidocaine had on depression by administering this measure at baseline, mid-infusion, and post-infusion, and follow-up. However, the PHQ-2, whilst having the advantage of being brief, did not appear to add any extra value over these two other scales, and was only administered, along with the HADS, at baseline and post-infusion. Regardless of these doubts it was still necessary to keep the measure in the research, as data had already been collected on it, and I was therefore placed in a position of defending a choice that I did not entirely agree with.

A further difficulty that arose from continuing a project was making my own mark on the research. At the initial planning phase there was still the opportunity to make alterations to the research by considering other measures that could provide useful information in relation to the factors already being studied. This was, however, limited by the need to keep the changes to a minimum, so as to avoid having to resubmit the project to ethics, something that had cost the previous trainees a lot of time due to changes in the process for seeking ethical approval. Furthermore, there was a need to keep the list of measures as brief as possible in order to minimise disruption to the participants' usual treatment and avoid dropout through being overburdened.

The above restraints meant that it was only possible to add a select few items to the testing protocol. This could have been made more challenging by the fact I was conducting the project with a fellow trainee as a joint project. However, working with another trainee ended up being more of a help as we were able to share ideas for how best to contribute our own ideas. In order to make the most of the few changes it

was also incredibly helpful to consult with the medical team at the site where we would be conducting our research. We presented the findings from the previous trainees' efforts to the team and took questions and suggestions for changes at the end. Although we were not able to enact all of their suggestions, many of the additions we made were influenced by their ideas. This felt especially important as they had insights into the population and drugs that would have been very difficult to gain otherwise. This process of consultation with staff is something I hope to continue in my clinical and any future research work I may undertake.

Research in a Clinical Setting

Conducting research within a live clinical setting was one of the most challenging but also most rewarding aspects of the research. All of my previous experience working in psychology had been clinical and it felt strange to be taking on the more hands-off role of a researcher. I felt a strong desire to prioritise developing a good relationship with clients and reflect on any difficulties they expressed, as I would in my clinical roles. Whilst there is nothing wrong with any of these behaviours, *per se*, I was also conscious of how the inconsistency of my interactions with participants might influence the results. In order to manage this, I tried to stick to the participants' words as much possible when reflecting back and checking in with what they had said in response to an answer. Additionally, during the cognitive tasks that were administered for my fellow trainee's part of the research, many of the participants exhibited and expressed anxiety at the prospect of being tested and were self-critical when they struggled with the exercises. Here I could feel a particular urge to reassure and assist participants in doing as well as they could. This was something that I had to consciously check in and pull back from in

order to ensure that each participant had a consistent experience, so that as little bias as possible would affect the results. Discussing such instances with my fellow trainee and developing standardised responses was a useful approach to this problem.

Another balance that felt important to achieve was between encouraging patients to take part in the research and being sensitive to when patients did not feel able to engage in testing on the day. Many of the patients were in a lot of pain by the time they arrived at the clinic and I was conscious of not wanting to exacerbate their distress by having them undergo the additional stress of answering questions and completing tests. To manage this, I made sure to check before each phase of testing that they felt okay to continue and made very clear to them that it was perfectly acceptable to drop out. This felt particularly important as I was aware that some might feel uncomfortable about withdrawing from the process. I had expected dropout to be a regular occurrence but to my surprise, once people had started, only a very few asked to stop. In fact, many participants commented that it felt good to contribute to research that might help others and were glad for the opportunity to give back to the NHS and the pain management centre in particular.

As well as working with the participants, it was also of vital importance to work effectively alongside the clinical staff. I was aware of the immense pressures on the staff to deliver timely and compassionate care to their patients and was eager to cause as little disruption to their time as possible. There was also the pressure on us as researchers to maximise our time there and obtain as much data as possible with the opportunity that the staff had afforded us by allowing us entry onto their ward. This required consistent and clear communication with the ward staff about who we were hoping to involve in our research and when we would be testing them. For instance, we would try to email the team with names and times for people we

had planned to test before each visit. Furthermore, we would often be provided with information by patients that seemed helpful for the clinical staff to be aware of, in relation to treatment effectiveness and side effects. Thus, it was important to set up relationships and systems so that information could be effectively fed back to the team. This job was made all the easier by the remarkably friendly and supportive staff at the UCLH pain management centre, who were often more than happy to assist with our research where they could.

Personality

Throughout the research process, and especially at the point of data analysis and interpretation, I became aware of how aspects of my own personality were influencing my approach to the work. In particular, I noticed an almost obsessive need to understand not just the small aspect of an idea that pertained to what I was doing, but much of the surrounding context too. A limitation to this approach to learning was that tasks that could have taken relatively little time would often span over hours, if not days. An example of this was in assessing that the various assumptions were fulfilled for the statistical tests that we had planned on using. Some of my data was not normally distributed, and despite being informed by statistician colleagues at UCL that the tests I was using were robust to this, I embarked on a long journey to discover how the data could be transformed to be more normal. After reading several articles about whether such transformations were effective, or even necessary, I decided to learn and go through the procedures to transform the data. Following several more hours of performing various transformations, I came to the conclusion that the data was no better after this process than it was at the beginning. Furthermore, I also realised that due to the size

of my sample, the non-normality of the distribution in the data would unlikely be a problem due to the central limit theorem. For all my work, I had returned to where I had started and to where I had been advised to stay.

I believe that within this desire to fully understand whatever concept I am interacting with is an element of perfectionism. Within clinical research, perfectionism has been conceptualised as a personality trait that may underly numerous psychological difficulties, as well as containing some potentially adaptive features (Bieling, Israeli, & Antony, 2004). High perfectionism has been related to negative states such as worry, stress and negative affect in non-clinical populations (Chang, 2006). Furthermore, research specifically on clinical psychologists has found that those who with higher perfectionism were more likely to be stressed and subsequently experience burnout (D'souza, Egan, & Rees, 2011). It has been proposed that perfectionism may cause stress due to perfectionists' tendencies to apply rigid procedures for evaluation, focus on negative aspects of performance, and self-doubt about doing the right thing (Bieling et al., 2004; Hewitt, Flett, & Ediger, 1996). I recognised each of these factors in my own processes during my research, and a tendency for the resulting negative affect to lead to avoidance strategies that then become negatively reinforcing. For example, the excessive research that I undertook on transformations and the assumption of normality may have come from a feeling of uncertainty that I was doing the right thing, and for the many hours lost to this reading, many more were lost to procrastination.

Although much research had been conducted on the negative consequences of perfectionism (Shafran & Mansell, 2001), recent research has begun to recognise some of its more positive aspects (Bieling et al., 2004). In particular, it is thought that adaptive perfectionism is related to positive reinforcement through the

achievement of high standards and any subsequent reward from meeting these standards (Slade & Owens, 1998). In my case, there were often occasions where the process of reading further to gain a deeper understanding of a concept was ultimately rewarded, as I was able to relate these better understood concepts to other ideas I came across and to the interpretation of my results. It has been proposed that having a better understanding of perfectionism, and the distinction between its adaptive and maladaptive forms, may help in guarding people from its negative consequences (D'souza et al., 2011). As I look to embark in a career in clinical psychology, being more reflective of my own perfectionistic traits, and developing self-care strategies in response to them, will no doubt be key to achieving a sustainable and effective future in this profession.

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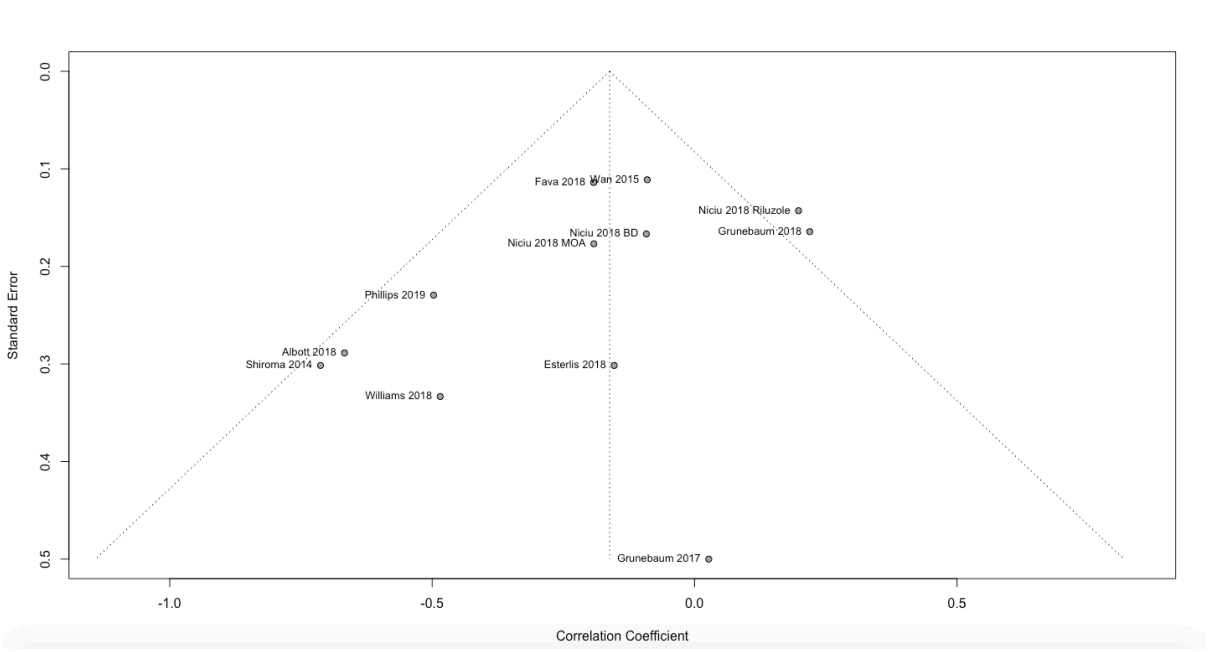
Appendix 1.A: Quality assessment tool template for the quality of evidence for this meta-analysis.

Removed due to copyright

Appendix 1B: Funnel plot of standard errors by correlation coefficient



Appendix 2.A: Details Regarding Each Individual's Contribution to the Joint Research Project

This thesis is a joint project with Georgia Halls, who investigated the effects of ketamine on cognitive function in the same sample.

Recruitment and testing were undertaken by both Georgia and I and this work was evenly split. We both also took equal responsibility for the scoring and entering of data onto a shared database.

Georgia's thesis focused on the impact of ketamine on cognitive functioning. All participants were thus tested using a range of cognitive tests, including the Story Recall Sub-Test of Rivermead Behavioural Memory Test, Serial Sevens, and a task on Verbal Fluency. Data from these tests were collected at baseline, mid-infusion and post-infusion. The data from these tests were not investigated in the current paper.

The focus of my paper was on the effects of ketamine on pain, mood and subjective drug effects. Georgia did include analysis of the pain data but data on depression and subjective drug effects were not included in her thesis.

Appendix 2.B: NHS Ethics 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

pp.

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.C: Participant Information Sheet

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

Participant Information Sheet

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

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

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

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

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

Part 1

What is the purpose of the study?

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

Why have I been invited?

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

Do I have to take part?

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

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

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

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

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

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

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

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

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

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence.
The details are included in Part 2.

Part 2 – Further Details

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

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. You can contact them by ringing on the numbers given below. If you remain unhappy and wish to complain formally you can do this by contacting the Patient Advice and Liaison service at the University College London Hospital. You can contact them by ringing 020 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 2020. You can obtain a copy of the published results by contacting us at address on the bottom of this sheet after the study has finished. You will not be identified in any report or publication resulting from this study.

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

Thank you for taking the time to read this information sheet

Contacts

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

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

Patient Advice and Liaison Service

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

Appendix 2.D: Consent Form

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

Participant Identification Number for this trial:

CONSENT FORM

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

Name of Researcher: Matt Knox and Catherine Trotman

Please initial box

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

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

Appendix 2.E: HADS & PHQ-2

Removed due to copyright

Appendix 2.F: Pain VAS

HOW ARE YOU FEELING?

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

Pain intensity

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

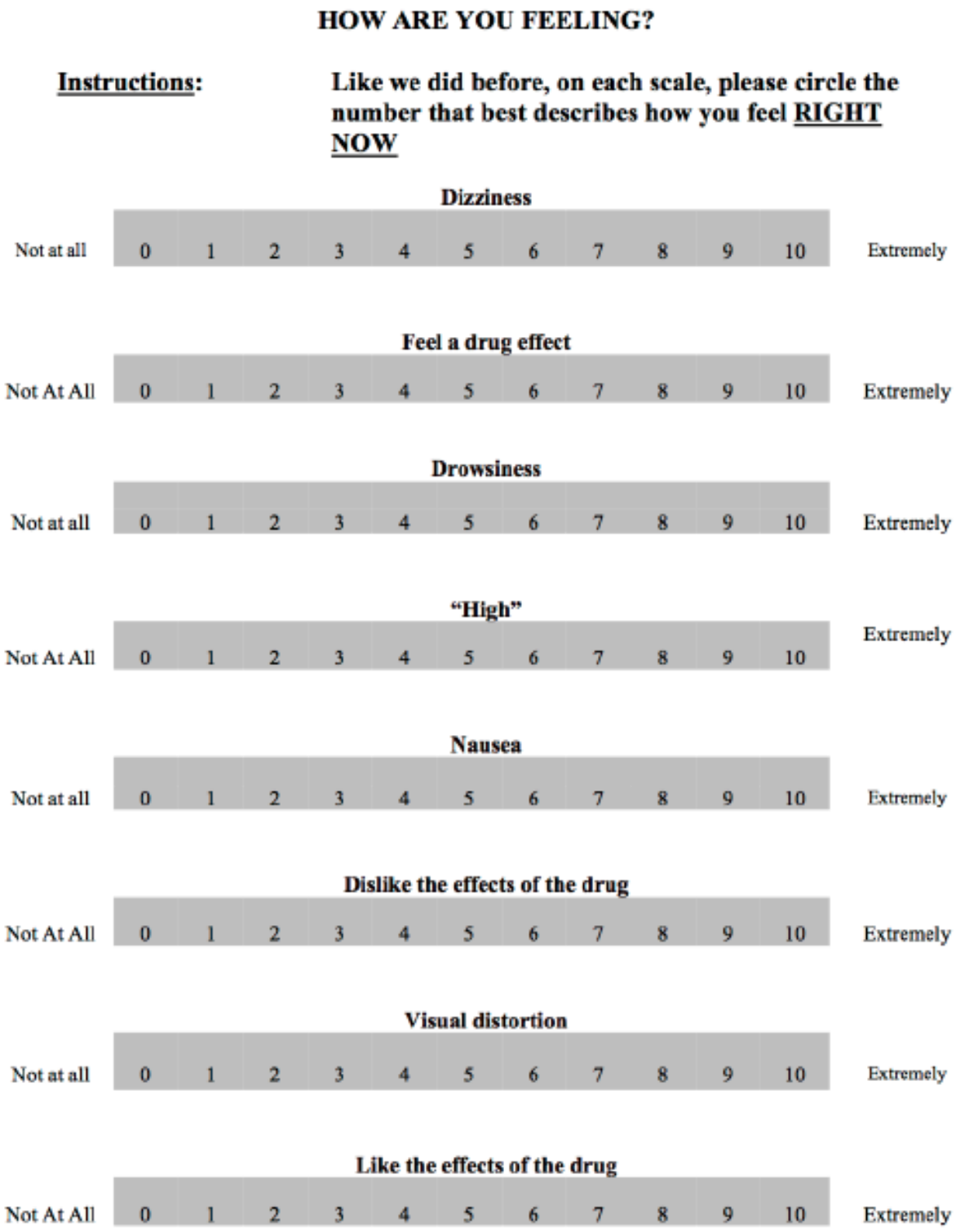
Pain distress

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

Pain interference

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

Appendix 2.G: Subjective Drug Effects VAS



Out of body experiences

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

Want more of the drug

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

Mental confusion

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

Depressed

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

Appendix 2.H: Demographic Details and AUDIT-C

AUDIT-C removed due to copyright

DEMOGRAPHIC DETAILS

Education

What is the highest level of formal education you have received? (Please circle)

GCSE (or age 16 equivalent)	A-Level (or age 18 equivalent)	Undergraduate degree (or age 21 equivalent)	Postgraduate degree

Medications

What medications have you been prescribed?

What drugs or medications have you taken over the past 24 hours?

[NURSE ONLY] Dose of Lidocaine or Ketamine administered:

Appendix 2.I: Means and Standard Deviations for ANOVA data

Pain Intensity

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Baseline Pain Intensity	Lidocaine	6.65	2.11	46
	Ketamine	6.83	2.207	39
	Total	6.74	2.144	85
Midpoint Pain Intensity	Lidocaine	5.2609	2.27239	46
	Ketamine	3.359	2.47872	39
	Total	4.3882	2.54059	85
Post Infusion Pain Intensity	Lidocaine	4.7609	2.47597	46
	Ketamine	2.9487	2.60262	39
	Total	3.9294	2.67834	85
Follow-up Pain Intensity	Lidocaine	5.26	1.994	46
	Ketamine	5.38	2.445	39
	Total	5.32	2.2	85

Pain Distress

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Baseline Pain Distress	Lidocaine	5.72	2.722	46
	Ketamine	5.74	3.058	39
	Total	5.73	2.864	85
Midpoint Pain Distress	Lidocaine	3.413	2.63798	46
	Ketamine	2.4231	2.75428	39
	Total	2.9588	2.7214	85
Post Infusion Pain Distress	Lidocaine	2.8043	2.65514	46
	Ketamine	2.0256	2.44397	39
	Total	2.4471	2.57509	85
Follow-up Pain Distress	Lidocaine	4.07	2.984	46
	Ketamine	4.46	2.873	39
	Total	4.25	2.923	85

Pain Interference

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N

Baseline NRS Alcohol	Lidocaine	0.67	1.874	46
	Ketamine	1.45	2.993	38
	Total	1.02	2.459	84
Mid-Infusion NRS Alcohol	Lidocaine	0.17	0.797	46
	Ketamine	0.45	1.826	38
	Total	0.3	1.36	84
Post-infusion NRS Alcohol	Lidocaine	0	0	46
	Ketamine	0.24	0.751	38
	Total	0.11	0.515	84
Follow-up NRS Alcohol	Lidocaine	0.3	1.28	46
	Ketamine	0.66	2.109	38
	Total	0.46	1.704	84

Want to Drink Alcohol

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Baseline NRS Alcohol	Lidocaine	0.67	1.874	46
	Ketamine	1.45	2.993	38
	Total	1.02	2.459	84
Mid-Infusion NRS Alcohol	Lidocaine	0.17	0.797	46
	Ketamine	0.45	1.826	38
	Total	0.3	1.36	84
Post-infusion NRS Alcohol	Lidocaine	0	0	46
	Ketamine	0.24	0.751	38
	Total	0.11	0.515	84
Follow-up NRS Alcohol	Lidocaine	0.3	1.28	46
	Ketamine	0.66	2.109	38
	Total	0.46	1.704	84

Dizziness

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Baseline NRS Dizziness	Lidocaine	2.65	3.086	46
	Ketamine	2.53	3.011	38
	Total	2.6	3.034	84
Mid-Infusion NRS Dizziness	Lidocaine	2.11	2.71	46
	Ketamine	5	3.288	38
	Total	3.42	3.301	84
Post-infusion NRS Dizziness	Lidocaine	2.33	2.504	46
	Ketamine	3.16	2.455	38

	Total	2.7	2.502	84
Follow-up NRS Dizziness	Lidocaine	1.35	1.935	46
	Ketamine	1.5	2.48	38
	Total	1.42	2.185	84

Feel a Drug Effect

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Mid-Infusion NRS Drug Effect	Lidocaine	3.8	2.705	46
	Ketamine	6.55	3.151	38
	Total	5.05	3.207	84
Post-infusion NRS Drug Effect	Lidocaine	3.37	3.05	46
	Ketamine	4.5	2.883	38
	Total	3.88	3.012	84
Follow-up NRS Drug Effect	Lidocaine	0.98	1.949	46
	Ketamine	0.66	1.76	38
	Total	0.83	1.862	84

Drowsiness

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Baseline NRS Drowsiness	Lidocaine	2.96	3.047	46
	Ketamine	3.45	3.202	38
	Total	3.18	3.109	84
Mid-Infusion NRS Drowziness	Lidocaine	4.57	2.964	46
	Ketamine	5.47	3.302	38
	Total	4.98	3.135	84
Post-infusion NRS Drowziness	Lidocaine	3.87	3.195	46
	Ketamine	3.63	2.665	38
	Total	3.76	2.952	84
Follow-up NRS Drowsiness	Lidocaine	2.22	3.069	46
	Ketamine	1.87	2.933	38
	Total	2.06	2.995	84

Feeling High

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Mid-Infusion NRS High	Lidocaine	1.78	2.691	46

	Ketamine	5.21	3.418	38
	Total	3.33	3.476	84
Post-infusion NRS High	Lidocaine	1.33	2.242	46
	Ketamine	2.87	2.44	38
	Total	2.02	2.444	84
Follow-up NRS High	Lidocaine	0.63	1.793	46
	Ketamine	0.37	1.324	38
	Total	0.51	1.594	84

Nausea

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Baseline NRS Nausea	Lidocaine	1.76	2.601	46
	Ketamine	2.03	2.531	38
	Total	1.88	2.557	84
Mid-Infusion NRS Nausea	Lidocaine	1.63	2.67	46
	Ketamine	1.39	1.98	38
	Total	1.52	2.372	84
Post-infusion NRS Nausea	Lidocaine	1.74	2.695	46
	Ketamine	0.89	1.269	38
	Total	1.36	2.199	84
Follow-up NRS Nausea	Lidocaine	1.96	2.683	46
	Ketamine	0.92	2.173	38
	Total	1.49	2.505	84

Dislike the Drug

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Mid-Infusion NRS Dislike	Lidocaine	1.11	2.142	46
	Ketamine	1.72	2.212	36
	Total	1.38	2.181	82
Post-infusion NRS Dislike	Lidocaine	1.67	2.899	46
	Ketamine	1.36	2.257	36
	Total	1.54	2.626	82
Follow-up NRS Dislike	Lidocaine	0.98	2.295	46
	Ketamine	1.17	2.348	36
	Total	1.06	2.306	82

Visual Distortion

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Baseline NRS Visual Distortion	Lidocaine	1.57	2.553	46
	Ketamine	2	3.043	36
	Total	1.76	2.769	82
Mid-Infusion NRS Visual Distortion	Lidocaine	1.22	2.24	46
	Ketamine	2.58	2.454	36
	Total	1.82	2.42	82
Post-infusion NRS Visual Distortion	Lidocaine	1.26	2.235	46
	Ketamine	1.89	2.227	36
	Total	1.54	2.24	82
Follow-up NRS Visual Distortion	Lidocaine	1.07	1.982	46
	Ketamine	0.17	0.697	36

Like the Drug

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Mid-Infusion NRS Like	Lidocaine	3.04	3.371	45
	Ketamine	4.89	3.419	35
	Total	3.85	3.494	80
Post-infusion NRS Like	Lidocaine	2.89	3.157	45
	Ketamine	4.31	3.234	35
	Total	3.51	3.249	80
Follow-up NRS Like	Lidocaine	3.47	3.9	45
	Ketamine	4.77	3.465	35
	Total	4.04	3.75	80

Out of Body Experiences

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Baseline NRS Out of Body	Lidocaine	0.65	1.649	46
	Ketamine	1.24	2.755	38
	Total	0.92	2.224	84
Mid-Infusion NRS Out of Body	Lidocaine	0.7	1.75	46
	Ketamine	1.53	2.957	38
	Total	1.07	2.394	84
Post-infusion NRS Out of Body	Lidocaine	0.61	1.77	46
	Ketamine	1.08	2.123	38
	Total	0.82	1.94	84

Follow-up NRS Out of Body	Lidocaine	0.07	0.327	46
	Ketamine	0	0	38
	Total	0.04	0.243	84

Want More of the Drug

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Mid-Infusion NRS Want More	Lidocaine	2.11	3.393	45
	Ketamine	3.38	3.939	37
	Total	2.68	3.681	82
Post-infusion NRS Want More	Lidocaine	1.67	2.868	45
	Ketamine	2.38	3.311	37
	Total	1.99	3.077	82
Follow-up NRS Want More	Lidocaine	2.8	3.8	45
	Ketamine	2.89	3.921	37
	Total	2.84	3.831	82

Mental Confusion

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Baseline NRS Confusion	Lidocaine	1.91	2.723	46
	Ketamine	2.16	3.063	38
	Total	2.02	2.866	84
Mid-Infusion NRS Mental Confusion	Lidocaine	1.61	2.56	46
	Ketamine	3.08	3.208	38
	Total	2.27	2.947	84
Post-infusion NRS Mental Confusion	Lidocaine	1.35	1.969	46
	Ketamine	2.16	2.433	38
	Total	1.71	2.215	84
Follow-up NRS Menatl Confusion	Lidocaine	1.52	2.528	46
	Ketamine	0.84	2.047	38
	Total	1.21	2.334	84

Feel Stressed

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Baseline NRS Stressed	Lidocaine	4.12	3.407	17
	Ketamine	3.56	3.183	16

	Total	3.85	3.261	33
Mid-Infusion NRS Stressed	Lidocaine	1.94	2.883	17
	Ketamine	1.81	2.994	16
	Total	1.88	2.891	33
Post-infusion NRS Stressed	Lidocaine	2.65	3.02	17
	Ketamine	2	2.921	16
	Total	2.33	2.944	33
Follow-up NRS Stressed	Lidocaine	4.06	3.418	17
	Ketamine	3.75	2.236	16
	Total	3.91	2.865	33

Depression

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
Basline NRS Depressed	Lidocaine	4.41	2.825	46
	Ketamine	5.5	3.261	38
	Total	4.9	3.06	84
Mid-Infusion NRS Depression	Lidocaine	2.43	2.941	46
	Ketamine	1.95	2.76	38
	Total	2.21	2.854	84
Post-infusion NRS Depression	Lidocaine	1.87	2.491	46
	Ketamine	2.32	3.05	38
	Total	2.07	2.75	84
Follow-up NRS Depression	Lidocaine	3.17	3.136	46
	Ketamine	3.82	2.884	38
	Total	3.46	3.024	84

HADS-D

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
HADS time 1 Dep	Lidocaine	9.1	3.901	49
	Ketamine	8.9	4.95	40
	Total	9.01	4.378	89
HADS follow-up Dep	Lidocaine	8.82	4.833	49
	Ketamine	8.25	4.834	40
	Total	8.56	4.815	89

HADS-A

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
HADS time 1 Anx	Lidocaine	9.86	4.34	49
	Ketamine	9.55	5.267	40
	Total	9.72	4.753	89
HADS follow-up Anx	Lidocaine	9.12	5.098	49
	Ketamine	7.07	4.932	40
	Total	8.2	5.099	89

PHQ-2

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
PHQ time 1 Total	Lidocaine	3.16	2.055	49
	Ketamine	3.05	2.136	40
	Total	3.11	2.08	89
PHQ follow-up total	Lidocaine	2.39	1.891	49
	Ketamine	2.42	2.218	40
	Total	2.4	2.032	89

HADS-D Borderline & Abnormal

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
HADS time 1 Dep	Lidocaine	11.34	2.61	32
	Ketamine	11.84	3.659	25
	Total	11.56	3.094	57
HADS follow-up Dep	Lidocaine	10.78	4.612	32
	Ketamine	10.36	3.957	25
	Total	10.6	4.305	57

HADS-D Abnormal

Descriptive Statistics

	Drug Administered	Mean	Std. Deviation	N
HADS time 1 Dep	Lidocaine	11.34	2.61	32
	Ketamine	11.84	3.659	25
	Total	11.56	3.094	57
HADS follow-up Dep	Lidocaine	10.78	4.612	32
	Ketamine	10.36	3.957	25
	Total	10.6	4.305	57