Can compassion-based interventions (CBIs) improve depressive symptoms in patients with chronic pain? A systematic review

and

The acute and long-term effects of sub-anaesthetic ketamine on pain, mood and cognitive functioning in chronic pain patients

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Thesis Declaration Form

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

Signature:

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Date: 01/06/2021

Overview

Part one of this thesis is a systematic review examining the evidence for compassion-based interventions in reducing depressive symptoms in chronic pain patients. Eleven studies were included in the review, of which ten reported improvements in depression symptoms after the completion of a compassion-based intervention. However, there was considerable variation in the quality of the reviewed literature.

Part two of this thesis presents an empirical study comparing the acute and long-term effects of sub-anaesthetic ketamine infusions (compared to lidocaine) on pain, mood and cognitive functioning in chronic pain patients. Long-term follow-up data was collected and compared with baseline, mid-infusion, post-infusion and one-week follow-up data. Although ketamine produced superior analgesic effects over lidocaine during the acute phase, this difference between the two groups was no longer present at one-week follow-up or long-term follow-up. Ketamine did not show any specific antidepressant effects in a chronic pain population, either acutely or over the longer-term. Ketamine acutely impaired performance on tasks of episodic memory, verbal fluency and working memory and concentration which was hypothesised to be due to a practice-blocking effect. However, these impairments were no longer observed at long-term follow-up.

Part three of this thesis presents a critical appraisal of this research. It reflects on various aspects of the research process, including the impact of COVID-19 and my experiences of conducting research in a clinical setting.

This thesis is a joint project with Laura Marks, who completed qualitative analyses of interviews with ketamine patients. Additionally, this is a continuation of a previous project by past UCL DClinPsy trainees: Georgia Halls (2020), Joe Kibble (2020), Matt Knox (2018) and Catherine Trotman (2018).

Impact Statement

Chronic pain is a significant global health concern. It is estimated that 20% of adults suffer from pain globally, yet treatment is variable and many patients do not report adequate pain relief from existing treatments. Additionally, depression commonly co-occurs with chronic pain and higher levels of depression are associated with poorer outcomes in pain patients.

The literature review provides preliminary evidence indicating that compassion-based interventions may improve depressive symptoms in patients with chronic pain. These results might encourage more pain services to offer compassion-based interventions which could, in turn, improve the mental health and wellbeing of patients living with chronic pain.

The results of the empirical paper add to the growing evidence base supporting the use of ketamine in treating chronic pain, as significant reductions in pain intensity, pain distress and pain interference were observed during the acute period (at mid-infusion and post-infusion). However, despite ketamine leading to superior reductions in pain (compared to lidocaine) during the acute phase, this difference between the two groups was not present at one-week follow-up or long-term follow-up. This suggests that, over the longer-term, the effects of ketamine and lidocaine on pain are similar. It is therefore interesting that despite ketamine yielding superior short-term results and equivalent long-term results over a shorter infusion time (therefore requiring fewer resources), it is usually only considered if lidocaine has been ineffective or is not deemed medically appropriate. These findings could alter perceptions of staff at the study site about the treatment options they offer and could also contribute to ketamine becoming a more accessible treatment for pain patients on a national, or even international, scale. It is hoped that these findings will improve the quality of life of individuals currently living with chronic pain and those who go on to develop chronic pain in the future.

The findings also contribute to our understanding of ketamine's effects on mood and cognitive functioning, which should enable patients to make more informed choices about the treatments they receive. Ketamine did not show any specific antidepressant effects in the current study, either acutely or over the longer-term. Therefore, clinicians should ensure that patients receiving ketamine infusions for pain are also receiving additional treatment for low mood if this is indicated. Additionally, patients receiving ketamine infusions should be informed that their cognitive functioning may be affected in the short-term. Regarding the long-term effects on cognition, the findings tentatively suggest that the adverse cognitive effects observed in frequent recreational ketamine users do not extend to repeated (though comparatively infrequent) users for medicinal purposes. More research is needed; however, these preliminary results may be reassuring to patients receiving ketamine treatment.

To widen the impact of this research, the results will be disseminated to clinicians at the study site and to other clinicians and academics in the field through publications.

Table of Contents

List of Tables

Part 1: Systematic Review

Part 2: Empirical Paper

Appendices

List of Figures

Part 1: Systematic Review

Part 2: Empirical Paper

Appendices

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Finally, I would like to thank all the people who agreed to participate in this research project. Their strength and resilience in the face of chronic pain and other challenging circumstances was truly inspiring. Without their altruism and willingness to participate, this thesis would not exist.

Part 1: Literature Review

Can compassion-based interventions (CBIs) improve depressive symptoms in patients with chronic pain? A systematic review

Abstract

Aims: There is a high comorbidity between chronic pain and depression. Compassion-based interventions (CBIs) encourage developing compassion for oneself and/or others. Recently, interest has grown in the application of CBIs to the chronic pain population. The aim of this review was to summarise and evaluate the evidence regarding the effectiveness of CBIs in reducing depressive symptoms in chronic pain patients.

Method: Four bibliographic databases (MEDLINE via Ovid, PsycINFO, Web of Science Core Collection and Cochrane Library) were searched without date restriction, as well as the 'grey' literature. Study quality was assessed using the Risk of Bias in randomised trials (RoB 2), Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) and What Works Clearinghouse (WWC) Standards.

Results: Eleven studies met criteria for the current review. These consisted of four randomised controlled trials (RCTs), five non-randomised designs and two single case designs. One study was judged to be at low risk-of-bias. Most studies (eight) were judged to be at moderate risk-of-bias or raise some concerns. One did not meet evidence standards and one lacked sufficient information to assess quality. Ten out of eleven studies reported improvements in depressive symptoms following the completion of CBIs delivered in various formats.

Conclusions: This review provides preliminary support for the effectiveness of CBIs in reducing depressive symptoms in the chronic pain population. Higher quality studies are required. Future research should explore possible mediating factors, whether the effectiveness of CBIs differs for certain sub-populations and the length of time for which improvements are maintained.

1. Introduction

1.1 Chronic Pain

Chronic pain, defined as pain that persists for more than three months, is estimated to affect 43% of the UK population, with between 10.4% and 14.3% of the population living with chronic pain that is either moderately or severely disabling (Fayaz et al., 2016). This equates to approximately 28 million people and 7.9 million people, respectively. In addition, Fayaz et al. (2016) demonstrated that the prevalence of chronic pain rises with increasing age, affecting up to 62% of people over the age of 75. Due to the UK's ageing population, this suggests that the burden of chronic pain will only continue to grow. Moreover, it is estimated that 20% of adults suffer from pain globally and it has been declared a global public health priority (Goldberg & McGee, 2011).

Chronic pain is a challenging condition to treat as it comprises a complex combination of biological, psychological and social factors. However, most approaches to pain management usually place greater emphasis on biological interventions (such as pharmacology, nerve blocks and surgery) and therefore may not adequately address all aspects of the pain experience (Boschen et al., 2016).

1.2 Chronic Pain and Depression

It is widely recognised that chronic pain has a substantial impact on patients' physical *and* mental health, with depression being a particularly common experience. For example, a survey of 3136 people in the Republic of Ireland found that of those with chronic pain, 15% met the criteria for clinically relevant depression compared with 2.8% of those without pain (Raftery et al., 2011). Similarly, Breivik et al. (2006) conducted interviews with 4839 people with chronic pain across Europe and found that 21% had been diagnosed with depression,

which is considerably greater than the European population prevalence rate of approximately 7% (WHO, 2012). Moreover, this may have been an underestimate as it relied on a diagnosis having been made, yet many people live with undiagnosed depression. Finally, a review by Bair et al. (2003) estimated that, overall, approximately 18% of pain patients in the general population, 27% of pain patients in primary care clinics and 52% of patients seen in pain clinics or inpatient pain programmes met criteria for major depression.

Thus, in addition to the burden of chronic pain which many patients already suffer, a significant proportion also have to manage the negative consequences associated with depression, which include increased mortality risk due to suicide and cardiovascular events, greater functional impairment and disability, and decreased workplace productivity and absenteeism resulting in reduced income or unemployment (Lépine & Briley, 2011). In fact, it has been argued that the secondary consequences of living with chronic pain, such as depression, are actually more detrimental to patients' quality of life than the pain itself (Geisser et al., 2000). Furthermore, higher levels of depression are associated with poorer treatment outcomes in pain patients (Bair et al., 2003; Huffman et al., 2019).

1.3 Theories of Chronic Pain and Depression

Several theories have been proposed to explain the comorbidity of chronic pain and depression, termed the 'pain-depression dyad' (Bair et al., 2003). To provide a full account of this dyad would be beyond the scope of this review; however, the key theories that attempt to explain this comorbidity are summarised below (see Institute of Medicine (US) Committee on Pain, Disability, and Chronic Illness Behavior, 1987; Surah et al., 2014; and Van Puymbroeck et al., 2007 for a more comprehensive review). Yet, despite several potential explanations, the mechanisms underlying this complex relationship still remain unclear.

The Antecedent Hypothesis. This proposes that depression precedes, and is responsible for, the onset of pain. Early theories (e.g. Blumer & Heilbronn, 1982) conceptualised chronic pain as a form of somatisation, in which distressing feelings were expressed through bodily complaints (including pain), often without conscious awareness of the underlying feelings. However, a systematic review by Crombez et al. (2009) concluded that the construct of 'somatisation' in pain research is scientifically flawed and can be stigmatising for patients. Yet despite the repudiation of much of the early research, more recent studies have, in fact, indicated that depression does often play a significant role in the aetiology of chronic pain. One proposed mechanism is that depression may increase pain sensitivity and reduce pain thresholds (Hermesdorf et al., 2016; Torta & Munari, 2010).

The Consequence Hypothesis. On the other hand, the presence of chronic pain may worsen mood, leading to the development of depression. This is thought to be a particular risk for individuals who are physically incapacitated by pain, as this may lead to a reduction in their usual physical and social activities. This, in turn, can result in isolation, loss of purpose, and other psychological symptoms associated with depression.

A variant of the 'consequence hypothesis' is the psychological-diathesis-stress framework (Banks & Kerns, 1996) which proposes that patients with chronic pain have certain psychological vulnerabilities ('diatheses') that increase their chances of developing depression. Banks and Kerns (1996) suggest that possible psychological diatheses for depression in chronic pain patients may include negative schemas which present as negative thoughts about the self, the world and the future (Beck, 1967, 1976), a tendency to make internal, stable and global attributions when met with aversive outcomes (Abramson et al., 1978) and deficits in instrumental skills (Fordyce, 1976). For depression to develop, the

diathesis must interact with an environmental factor or life event perceived as threatening to the person's psychological wellbeing and which exceeds their abilities to cope ('stressors'). Undoubtedly, the experience of chronic pain can elicit a range of unique stressors, such as repeated aversive sensations and the distressing emotional experiences associated with these, impairment and disability, secondary losses in various areas of life (such as work, leisure and relationships) and perceived non-validating responses from the medical system. All of these factors may interact with diatheses and increase the likelihood of chronic pain patients developing depression.

Additionally, some patients may experience depressive symptoms as a side effect of the medications prescribed to relieve their pain, such as opiate analgesics and benzodiazepines (Hall et al., 1980; Perl et al., 1980). However, the idea that behavioural toxicity of analgesics underlies depression is now quite outdated, and the evidence for this notion is weak.

Common Pathogenesis. An alternative, yet perhaps complementary, theory is that chronic pain and depression share common neurobiological mechanisms. For example, it may not be coincidental that serotonin and noradrenaline (neurotransmitter systems that are dysregulated in depression) play critical roles in mediating analgesia. Moreover, areas of the brain involved in processing emotions and mood are also involved in processing and modulating pain. In particular, the anterior cingulate gyrus is a key area of interest as similar structural and functional changes have been observed in both chronic pain and depression (Nicolson et al., 2009).

1.4 Psychological Interventions for Chronic Pain

Recent draft guidance by the National Institute for Health and Care Excellence (NICE; 2020) emphasises the importance of non-pharmacological approaches to managing chronic pain, which includes psychological therapy. The evidence-base for cognitive behavioural therapy (CBT) in the management of chronic pain is already well-established (Williams et al., 2012), with CBT being recommended in The British Pain Society Guidelines for Pain Management Programmes for adults (The British Pain Society, 2013) and in recent guidance on psychological assessment and management of chronic pain during the COVID-19 crisis (American Psychological Association, 2020). However, in recent years there has been increasing interest in 'third wave' CBT approaches. These represent a shift away from the traditional focus on *what* we think and feel to *how we relate to* our thoughts and feelings. This may enable patients with chronic pain to live more meaningful lives alongside their pain.

One group of third wave interventions that has so far received comparatively little attention in pain research are compassion-based interventions (CBIs). CBIs focus on cultivating compassion for oneself and/or others, which can be understood as being 'touched by' suffering, and an accompanying motivation to alleviate this suffering. One of the most well-established CBIs is compassion-focused therapy (CFT; Gilbert, 2014).

The "three circles" model in CFT (see Figure 1) suggests there are three distinct motivational systems within our brains which interact to regulate our emotions: (1) the threat system, which is designed to detect threats and keep us safe, and involves the release of adrenaline and cortisol; (2) the drive system, which motivates us to seek resources to survive and thrive, and is associated with the release of dopamine; and (3) the soothing system, which prompts us to seek connection with others (or find other ways of soothing ourselves), leading to stimulation of the vagus nerve and the release of oxytocin and opioids which downregulate

the threat and drive systems and regulate distress. Gilbert (2014) proposes that our ability to keep these three systems in balance is compromised by our 'tricky brains', which get caught between the competing motivations of our old and new brains.

Figure 1

The 'Three Systems' Model of Affect Regulation (Gilbert, 2014)

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Penlington (2019) presents a conceptual model of how these three systems may contribute to the maintenance of chronic pain. Penlington suggests that the experience of chronic pain may be perceived as overwhelming for some patients and, coupled with the response of experiential avoidance, may result in increased activation of the threat system. Armitage and Malpus (2019) build on this model by suggesting that some patients may also engage in understandable, yet unhelpful, ways of coping which involve activation of the drive system. For example, a 'boom and bust' cycle of activity is commonly observed in which

individuals push themselves to achieve more on their 'good days' (i.e. when the pain is less severe), but then overexert themselves, leading to flare-ups of pain and more time needed to recover. This may lead to self-critical thinking, which further fuels the threat system such that patients can get stuck in a vicious cycle of threat and drive.

Therefore, it has been argued that patients with chronic pain may benefit from interventions aimed at increasing their ability to activate their soothing system by adopting a more compassionate attitude towards themselves (and others), enabling them to relate to their pain without feeling overwhelmed by threat and avoid responding in unhelpful ways.

Other interventions aimed at increasing compassion, and thus activating the soothing system, include: Mindful Self-Compassion (Neff & Germer, 2013), Compassion Cultivation Training (Jazaieri et al., 2013), Cognitively Based Compassion Training (Pace et al., 2009), Cultivating Emotional Balance (Kemeny et al., 2012) and Compassion and Loving-Kindness Meditations (e.g. Hoffmann et al., 2011).

Evidence has recently emerged that patients with chronic pain demonstrate significantly lower levels of self-compassion than healthy individuals (Narimani et al., 2020). Moreover, higher levels of self-compassion have been associated with a range of positive pain-related outcomes including lower pain-related anxiety, depression and disability, as well as greater pain acceptance, success in valued activities and utilisation of adaptive pain coping strategies (Edwards et al., 2019). Furthermore, it has been demonstrated that self-compassion can even *predict* future depressive symptoms in patients with chronic pain (Carvalho et al., 2019). Thus, the development of greater self-compassion appears to be a useful target for intervention in chronic pain.

1.5 Aims of this Review

Research evaluating interventions for chronic pain often focus on reducing pain symptoms. However, often the pain itself cannot be relieved; therefore, it is essential that we increase our understanding of which interventions can help to reduce the burdens associated with chronic pain, such as depression, as this may have a significant impact on patient's quality of life.

The aim of the present review is therefore to summarise and evaluate the evidence regarding the effectiveness of CBIs in reducing depressive symptoms in chronic pain patients. As this is a relatively new area of research, this question has (to the best of my knowledge) not been previously systematically examined.

2. Methods

2.1 Search Strategy

The review was registered with *Prospero* (ID: 198113) before searching began to avoid unplanned duplication and increase transparency. Four bibliographic databases (MEDLINE via Ovid, PsycINFO, Web of Science Core Collection and Cochrane Library) were searched without date restriction.

The terms outlined in Table 1 were searched (to appear in any field), using a combination of key word searches and subject heading searches (see Appendix A for full search strategy). These search terms were derived from previous systematic reviews on similar topics and through consultation with an informatics specialist. The search terms were purposefully kept broad (e.g. not naming specific pain-related conditions or types of pain) in order to prioritise sensitivity over specificity and thus reduce the likelihood of potentially

relevant studies being missed. The search terms for compassion were constructed in such a way that would capture empirically supported interventions that focused on the cultivation of compassion (as defined by Kirby, 2017) which included: Compassion-Focused Therapy (CFT; Gilbert, 2014), Mindful Self-Compassion (Neff & Germer, 2013), Compassion Cultivation Training (Jazaieri et al., 2013), Cognitively Based Compassion Training (Pace et al., 2009), Cultivating Emotional Balance (Kemeny et al., 2012) and Compassion and Loving-Kindness Meditations (e.g. Hoffmann et al., 2011), as well as any other CBIs that appeared relevant. Common outcome measures of depression were included as alternative search terms for 'depressive symptoms' to ensure that studies that utilised these measures would be identified, even if they did not make explicit reference to depression.

Table 1

Search Terms Used in Systematic Review

Key terms	**Chronic pain**	**Compassion**	**Depressive symptoms**
Search terms	"chronic pain"	"compassion*"	"depress*"
	"persistent pain"	"CFT"	"mood"
	"fibromyalgia"	"cultivating emotional balance"	"PHQ-9"
		"CEB"	"PHQ-2"
		"loving-kindness meditation"	"BDI"
		"LKM"	"CES-D"
		"metta"	"HADS"
			"HADS-D"
			"SDS"
			"GDS"
			"HRSD"
			"HDRS"
			"HAM-D"
			"MADRS"

In addition, the reference lists of relevant articles were screened for further eligible studies and the key terms were searched in Google Scholar. These steps were taken to ensure that all potentially relevant published and unpublished work on the topic was located to minimise the impact of publication bias.

2.2 Inclusion Criteria

Studies had to meet the following criteria for inclusion: (1) participants were adults (aged 18 or above) with chronic pain; (2) an intervention was provided and (one of) the main objective(s) of this intervention was to increase (self-)compassion; and (3) an outcome measure of depression or depressive symptoms was used.

2.3 Exclusion Criteria

Studies were excluded from the review if: (1) participants had chronic cancer pain (as this is usually treated differently to chronic non-cancer pain); or (2) they were published in languages other than English.

2.4 Outcome Measures

The primary outcome measure used in this review was a measure of depression or depressive symptoms. This could either be completed by the participants themselves (e.g. PHQ-9; BDI) or by a clinician (e.g. HAM-D; MADRS).

2.5 Study Selection

The search results were exported into EndNote X9. Following de-duplication, the titles and abstracts of all studies initially identified by the search were screened. Full-text articles of those that appeared relevant were retrieved and read in full to determine whether they fulfilled the inclusion/exclusion criteria. Relevant trial databases were checked to ascertain whether any of the eligible studies were clinical trials.

2.6 Data Extraction and Analysis

Data from the eligible studies was extracted and entered into an Excel spreadsheet. This included information about the following: author, location, study design, participant demographics, intervention and comparator (if applicable). For continuous depression outcome data, means and standard deviations were extracted pre-test and post-test. Mean change from pre-test to post-test was also calculated for each study. *P* values and effect sizes were extracted where provided. Where effect sizes were not provided, these were calculated, where possible, using Cohen's d (Cohen, 1992).

The quality of the studies was then assessed by two independent raters. Any discrepancies regarding study quality were discussed until an agreement was reached. A third independent reviewer was available to resolve any ongoing disagreements, but this did not prove to be necessary.

Following guidance published by Muka et al. (2020), RCTs were evaluated using The Cochrane Collaboration's tool RoB 2 (Sterne et al., 2019) and non-randomised intervention studies were evaluated using the ROBINS-I (Sterne et al., 2016). See Appendices B and C for RoB2 and ROBINS-I guidelines, respectively. Single-case designs were evaluated using

WWC Standards (Kratochwill et al., 2010), as recommended by Lobo et al. (2017) in their guide to assessing the quality of single-case design intervention research.

3. Results

3.1 Included Studies

A total of 112 studies were retrieved from initial electronic and reference searches after de-duplication (see Figure 2 for PRISMA diagram). The 87 studies that were screened out on the basis of their title and abstract either (1) failed to meet the population criteria (e.g. children, cancer pain); (2) did not provide an intervention or the interventions provided did not focus on increasing compassion; (3) were non-English language publications; or (4) were review articles. Subsequently, 25 studies were read in full and 14 were excluded for the following reasons: five did not include an outcome measure of depression (D'Amico et al., 2020; Dhokia et al., 2020; Gooding et al., 2020; Montero-Marin et al., 2019; Van Der Merwe et al., 2020), four were incomplete trials registered on Cochrane CENTRAL, two (Montero-Marin et al., 2020; Ziemer, 2014) included reproduced data from other included studies (Montero-Marin et al., 2018; Ziemer et al., 2015) and were used to supplement information but not duplicated, one did not sample participants from a chronic pain population (Kleinstäuber et al., 2019), one delivered an intervention that was not sufficiently focused on training compassion (Lopes et al., 2019) and one was a review (Purdie & Morley, 2016). This resulted in a total of 11 studies. See Table 2 for a summary of study characteristics.

Figure 2

PRISMA Diagram

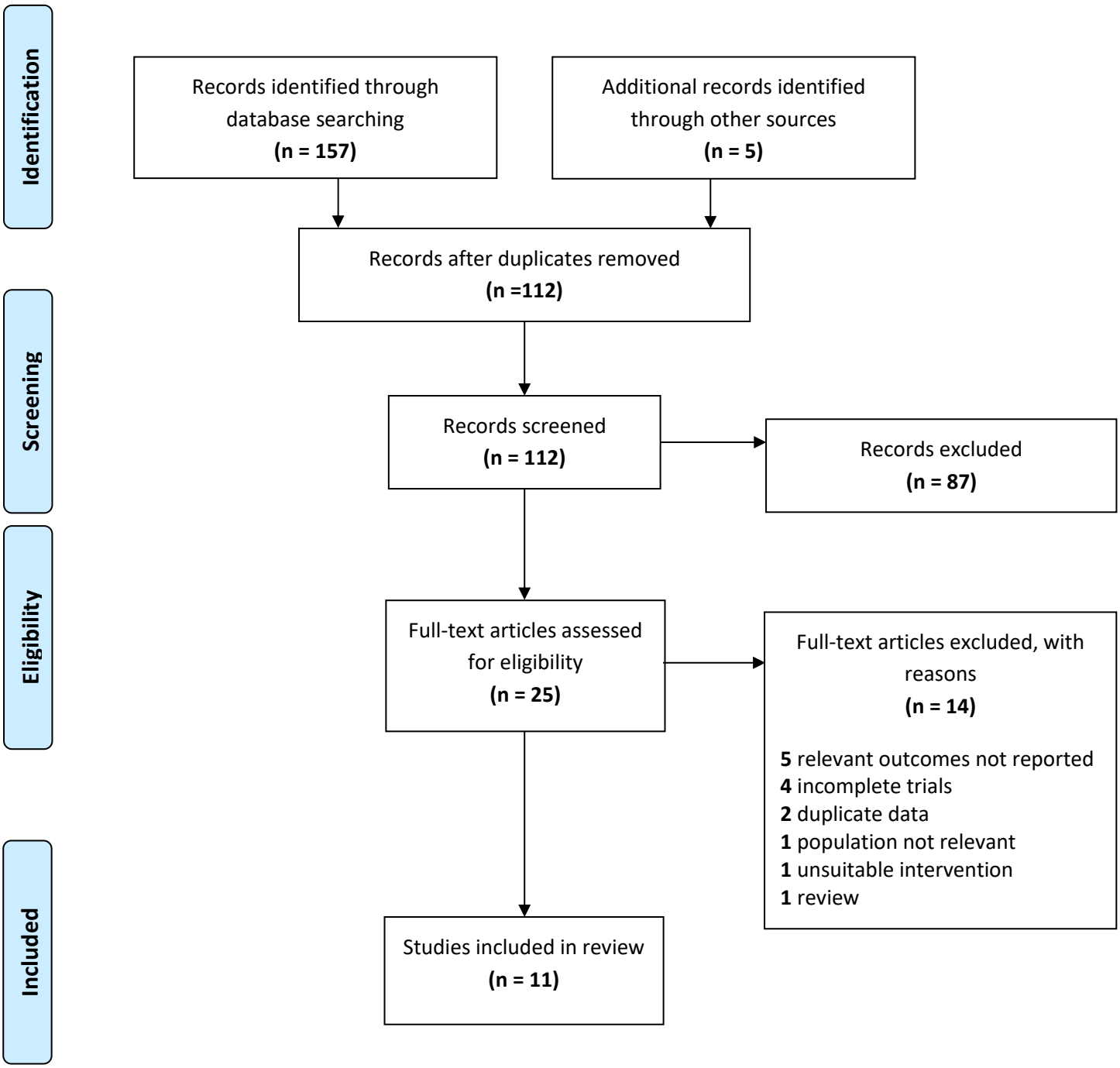

Table 2

Summary Table of Study Characteristics of Included Studies

Lead Author	Publication Date	Location	Study Design	Total Participants (% Female)	Age Group	Pain Condition	Source of Participants	Intervention Type	Intervention Duration	Comparator	Follow-up?
Armitage & Malpus	2019	UK	Pre-post	73 (NP)	NP	"Strivers" with chronic pain	Pain clinic	Group, CFT	8 sessions, 2 hours each (16 hrs total contact time)	TAU	No
Boselie et al.	2018	Netherlands	RCT	122 (96.7%)	NP; inclusion criteria 18-60	Chronic musculoskeletal pain (> 3 months)	Advertisement in magazine & website	Individual, Internet, PPI with telephone & email support	8 weeks, 1 module per week	Waitlist control	No
Flink et al.	2015	Sweden	Single case	5 (60.0%)	40-73	Chronic back pain (> 3 months)	Advertisement in newspaper	Individual, PPI	7 weeks, 1 hour sessions	N/A	3 months
Gammon	2016	USA	Pre-post	119 (71.4%)	TSC: 21-83; data not available for TAU	Chronic pain	Pain clinic	Group, TSC	12 sessions, 2 hours each (24 hrs total contact time)	TAU	No
Håkansson et al.	2015	Sweden	Single case	4 (NP)	NP	Chronic pain with comorbid anxiety & depression	Pain clinic	Individual, Internet, CFT	7 weeks, 1 module per week	N/A	No
Montero-Marin et al.	2018	Spain	RCT	42 (100%)	“Early 50s”	Fibromyalgia	Primary health-care centres	Group, ABCT	8 sessions, 2 hours each (16 hrs total contact time)	Relaxation group	3 months
Parry & Malpus	2017	UK	Pre-post	8 (NP)	NP; min = 20, max = 59	“Strivers” with chronic pain	Pain clinic	Group, CMT	8 sessions, duration not specified	N/A	No
Penlington	2019	UK	Pre-post	83 (77.6%)	NP; inclusion criteria 18+	Non-malignant chronic pain (> 3 months)	Pain clinic	Group, CFT	8 sessions, 2 hours each (16 hrs total contact time)	N/A	No
Peters et al.	2017	Netherlands	RCT	276 (85.0%)	19-83	Chronic musculoskeletal pain (> 3 months)	Advertisements in newspapers, magazines & websites	Individual, Internet, PPI with telephone & email support	8 weeks, 1 module per week	iCBT & waitlist control	6 months
Tin	2019	UK	Pre-post	122 (84.4%)	NP; inclusion criteria 18+	Chronic pain (> 3 months)	Pain clinic	Group, CFT	11 sessions, 3 hours each (33 hrs total contact time)	N/A	No
Ziemer et al.	2015	USA	RCT	116 (86.0%)	19-74	Chronic pain (> 6 months)	Advertisements on websites	Individual, self-compassion writing	3 weeks, 20min a week	Self-efficacy writing	No

NP = Not Provided; *PMP* = Pain Management Programme; *PPI* = Positive Psychology Intervention; *TSC* = Therapeutic Self-Care; *TAU* = Treatment As Usual; *ABCT* = Attachment-Based Compassion Therapy; *CMT* = Compassionate Mind Training; *iCBT* = Internet-based cognitive behavioural programme

3.2 Risk of Bias

The RoB 2 (Sterne et al., 2019) describes five domains in which bias can arise in RCTs: (i) the randomisation process; (ii) deviations from intended interventions; (iii) missing outcome data; (iv) measurement of the outcome; and (v) selection of the reported result (selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis or other synthesis). Signalling questions guide the assessor to a risk-of-bias rating in each domain and an overall risk-of-bias judgment is made: *low risk of bias* (low risk of bias for all domains); *some concerns* (some concerns in at least one domain, but not judged to be at high risk of bias for any domain); or *high risk of bias* (high risk of bias in at least one domain, or some concerns for multiple domains in a way that substantially lowers confidence in the result).

The ROBINS-I (Sterne et al., 2016) describes seven domains for judging risk of bias in non-randomised studies of interventions: (i) confounding (when factors that predict the outcome of interest also predict the intervention received at baseline, when individuals switch between the interventions being compared or when post-baseline factors that predict the outcome of interest affect the intervention received after baseline); (ii) selection of participants into the study; (iii) classification of interventions; (iv) deviations from intended interventions; (v) missing data; (vi) measurement of outcomes; and (vii) selection of the reported result. As above, signalling questions are used to guide the assessor to a risk-of-bias rating in each domain and an overall risk-of-bias judgment is made: *low risk of bias* (low risk of bias for all domains); *moderate risk of bias* (low or moderate risk of bias for all domains); *serious risk of bias* (serious risk of bias in at least one domain, but not at critical risk of bias in any domain); *critical risk of bias* (critical risk of bias in at least one domain); or *no information* (no clear indication that the study was at serious or critical risk of bias but there was a lack of information in one or more key domains).

The WWC (Kratochwill et al., 2010) provides criteria for assessing whether a single case design *meets evidence standards, meets evidence standards with reservations* or *does not meet evidence standards*. If the study *meets evidence standards* or *meets evidence standards with reservations*, there are further criteria for demonstrating evidence of a relationship between an independent variable and an outcome variable which can be *strong evidence, moderate evidence* or *no evidence*.

Risk-of-bias ratings are shown in Table 3. Columns that are not relevant for that particular study design contain an 'X'.

Table 3

Risk of Bias Ratings for Included Studies

Lead Author	Study Design	Tool Used	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Confounding	Selection of participants into the study	Classification of interventions	Overall risk of bias
Armitage & Malpus	Pre-post	ROBINS-I	X	Low	Moderate	Moderate	Moderate	Moderate	Low	Low	**Moderate**
Boselie et al.	RCT	RoB 2	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	X	X	X	**Some concerns**
Flink et al.	Single case	WWC	X	X	X	X	X	X	X	X	**Does not meet evidence standards**
Gammon	Pre-post	ROBINS-I	X	Low	Moderate	Moderate	Moderate	Moderate	Low	Low	**Moderate**
Håkansson et al.	Single case	WWC	X	X	X	X	X	X	X	X	**Not enough information available**
Montero-Marin et al.	RCT	RoB 2	Low	Low	Low	Low	Low	X	X	X	**Low**
Parry & Malpus	Pre-post	ROBINS-I	X	Low	Low	Moderate	Moderate	Moderate	Low	Low	**Moderate**
Penlington	Pre-post	ROBINS-I	X	Low	Moderate	Moderate	Moderate	Moderate	Low	Low	**Moderate**
Peters et al.	RCT	RoB 2	Some concerns	Low	Low	Some concerns	Some concerns	X	X	X	**Some concerns**
Tin	Pre-post	ROBINS-I	X	Low	Moderate	Moderate	Low	Moderate	Low	Low	**Moderate**
Ziemer et al.	RCT	RoB 2	Some concerns	Low	Some concerns	Some concerns	Some concerns	X	X	X	**Some concerns**

ROBINS-I = Risk Of Bias In Non-randomised Studies - of Interventions; *RoB 2* = Cochrane risk-of-bias tool (version 2); *WWC* = What Works Clearinghouse

3.3 Descriptive Synthesis

Populations studied. Key participant characteristics are described in Table 2 above. Four studies restricted their inclusion criteria to certain types of chronic pain: musculoskeletal pain (n = 2), back pain (n = 1) and fibromyalgia (n = 1). The majority of studies defined chronicity according to the common criterion for chronic pain (> three months); however one study specified a minimum period of six months (Ziemer et al., 2015). One study required patients to have comorbid anxiety and depression and two studies focused on a subset of chronic pain patients termed 'strivers' who typically engaged in a 'boom and bust' pattern of activity.

Overall, the number of participants in each study ranged from 4 to 276. Their ages ranged from 19 to 83, with mean age ranging between 44.6 and 63.2 years. One study had only female participants, despite males also being eligible to participate. The seven remaining studies that provided details about participants' sex all had a greater ratio of females to males, ranging from 60.0% female to 96.7% female (M = 80.2%). Only two studies (Gammon, 2016; Ziemer et al., 2015) provided any information about participants' ethnicity with both samples consisting of predominantly White participants (78.8% and 93.5%, respectively).

Intervention Format. A variety of CBIs were implemented: CFT, a positive psychology intervention (PPI) specifically targeting self-compassion, compassionate mind training, self-compassion writing, attachment-based compassion therapy (ABCT) and therapeutic self-care (TSC) in which treatment as usual (TAU) was integrated within a self-compassion framework.

Six of the eleven studies delivered the intervention face-to-face in a group setting. Each session ranged in length from 2 to 3 hours and the number of sessions offered in each

intervention varied between 8 and 12 sessions. All sessions were held on a weekly basis and total contact time ranged from 16 to 33 hours.

Three studies delivered their intervention over the internet. Participants were instructed to individually complete 7-8 online modules, at a rate of one module per week. Two of the internet-based interventions were supplemented with telephone and email support by a member of the research team.

Of the two remaining studies, one provided 1 hour individual sessions with a psychologist once a week for 7 weeks and the other provided written instructions which participants completed in a self-guided manner for 20 minutes once a week for 3 weeks.

Comparison Groups. Two studies compared outcomes against TAU. TAU was an intensive multi-disciplinary Pain Management Programme (PMP) comprising 60 hours of pain-specialist psychology and physiotherapy input (Armitage & Malpus, 2019) or 16 weeks (on average) of behavioural therapy using a mindfulness- and acceptance-based framework, biofeedback and physical therapy (Gammon, 2016).

Three studies compared outcomes with evidence-based alternative interventions that were not TAU. All three were considered to be 'active' comparators: (1) an 8-week relaxation group which had been shown to improve fibromyalgia symptoms but without clear clinical relevance (Montero-Marin et al., 2018); (2) an 8-module internet-based CBT intervention that had previously been shown to have beneficial effects for patients with chronic pain (Peters et al., 2017); and (3) a self-efficacy writing intervention which the authors thought to be particularly relevant for chronic pain based on previous research (Ziemer et al., 2015).

No studies used a no-treatment control group, although two studies did use a waitlist control. A waitlist control group is usually considered preferable to a no-treatment control group in cases such as this where it would be unethical to deny patients access to treatment. Five studies did not utilise any form of comparison or control group (although two of these were single case designs in which participants acted as their own baseline).

Table 4

Outcome Measures and Results

Author	Measure	Pre-test M (SD)	Post-test M (SD)	Mean change score	Sig. *(p)*	Standardised effect size
Armitage & Malpus	CES-D	Not reported	Not reported	-7.99	<0.001**	Unable to calculate
Boselie et al.	HADS-D	6.36 (3.98)	5.04 (3.45)	-1.32	0.01**	$np^2 = 0.07$ [medium]
Flink et al.	HADS-D	5.2 (4.55)	3.0 (1.87)	-2.2	N/A	d = 0.63 [medium]
Gammon	BDI-II	17.23 (10.84)	Not reported	Unable to calculate	<0.05*	$np^2 = 0.20$ [large]
Håkansson et al.	HADS-D	13.25 (2.36)	7.5 (0.58)	-5.75	N/A	d = 3.35 [large]
Montero-Marin et al.	HADS-D	10.35 (3.28)	4.8 (2.84)	-5.55	<0.001** [comparison with control group]	d = 0.94 [large]
Parry & Malpus	CES-D	32.75 (9.63)	20.38 (12.4)	-12.37	N/A	d = 1.11 [large]
Penlington	PHQ-2	3.42 (1.92)	2.53 (1.69)	-0.89	Not reported	d = 0.46 [small to medium]
Peters et al.	HADS-D	7.82 (4.21)	5.25 (3.77)	-2.57	<0.001** [comparison with WLC]	d = 0.777 [medium to large]
Tin	HADS-D	10.76 (3.55)	9.0 (4.2)	-1.76	<0.001**	$np^2 = 0.17$ [large]
Ziemer et al.	CES-D	13.3 (6.3)	12.8 (7.1)	-0.5	n.s.	N/A

CES-D = Center for Epidemiologic Studies Depression Scale (CES-D); *HADS-D* = Hospital Anxiety and Depression Scale – Depression subscale; *BDI-II* = Beck Depression Inventory-II, *PHQ-2* = Patient Health Questionnaire-2

n.s. = not significant

*$p < 0.05$. **$p < 0.01$.

Outcomes. A range of self-report depression outcome measures were used (see Table 4). No study used clinician administered instruments. Six studies demonstrated a statistically significant improvement in depressive symptoms following a CBI and one did not. One study (Penlington, 2019) reported only an effect size but no p-values. It is unclear why this decision was made as the sample size was sufficiently large for p-testing; possibly the author chose to place greater emphasis on the results of their qualitative analysis as this was a mixed methods study. The three remaining studies were not designed for inferential statistics as they were either single case designs (Flink et al., 2015; Håkansson et al., 2015) or a small-scale pilot project (Parry & Malpus, 2017). However, descriptive statistics indicated that there were improvements in depressive symptoms for the majority of participants.

Mean pre-post changes, p-values and standardised effect sizes are shown in Table 4. Effect sizes were reported by the authors as either Cohen's d or partial eta squared (np^2). Where effect sizes were not reported by the authors (Flink et al., 2015; Håkansson et al., 2015; Parry & Malpus, 2017) this was calculated and reported as Cohen's d (Cohen, 1992) and classified using conventional thresholds for small, medium and large effects. Reported effect sizes represented differences in depression scores before and after the intervention. However, these studies had very small sample sizes, so these effect sizes are likely to be an over-estimation and therefore unreliable.

In both studies that compared outcomes against TAU (Armitage & Malpus, 2019; Gammon, 2016), CBIs were shown to be similarly effective at significantly reducing depressive symptoms as TAU, but neither were shown to be superior to TAU. Of the studies that compared outcomes against other evidence-based active interventions, CBIs showed superior outcomes to the relaxation group (Montero-Marin et al. 2018) and comparable outcomes to the Internet-based CBT programme (Peters et al., 2017). Neither the self-compassion writing nor the self-efficacy writing had a significant effect on depressive

symptoms (Ziemer et al., 2015). In both studies that included a waitlist control, participants who received a CBI scored significantly lower on depressive symptoms post-test compared to those in the waitlist condition.

In addition to collecting outcome measures at the end of the intervention, Montero-Marin et al. (2018) demonstrated that the CBI still showed superior outcomes for depression to the relaxation group at 3-month follow-up. Similarly, Flink et al. (2015) reported that the changes remained stable at 3-months. Furthermore, Peters et al. (2017) showed that the improvement in depressive symptoms observed at post-test was maintained until 6-month follow-up.

4. Discussion

4.1 Overview

This systematic review summarises the limited but growing empirical literature on CBIs for chronic pain, specifically in relation to their effect on depressive symptoms. At this early stage of evidence synthesis, it is difficult to draw firm conclusions about the effectiveness of CBIs, although it is possible to summarise the quality of the evidence. As indicated above, the quality varies considerably and there is considerable scope for further research in this area.

4.2 Summary of Results

Ten out of eleven studies reported improvements in depressive symptoms in patients with chronic pain following the completion of a CBI (six of which were subjected to inferential statistics and were found to have statistically significant reductions). These

interventions included: CFT, a PPI specifically targeting self-compassion, ABCT and TSC. These were a mixture of group and individual interventions, delivered in-person and remotely. This suggests that various formats can be feasibly employed to deliver CBIs to patients with chronic pain. The effect sizes for these changes (as shown in Table 4) compare favourably with CBT for chronic pain. For example, a meta-analysis by Morley et al. (1999) found a mean effect size of 0.36 (small to medium) for mood/depression following CBT for chronic pain compared to waitlist control. However, as noted above, some of these effect sizes may be unreliable due to the small sample sizes of certain studies (e.g. Flink et al., 2015; Håkansson et al., 2015; Parry & Malpus, 2017).

Only one study that performed inferential statistics did not find a statistically significant reduction in depressive symptoms upon completion of a CBI. The intervention delivered in this study (self-compassionate writing) was considerably shorter in duration (20 minutes once a week for 3 consecutive weeks) than all of the other interventions included in this review (8-12 weeks). Furthermore, the writing intervention involved little input from clinicians as all participants were sent the same set of instructions to follow, whereas the majority of the other interventions involved individualised treatment and direct contact with a clinician (either in person, or telephone and email support). It is unclear whether the lack of change in depressive symptoms was due to insufficient treatment dose, absence of an individualised treatment plan, no therapist or because self-compassionate writing itself is ineffective for chronic pain (or a combination of these factors).

4.3 Comparison to Other Interventions

The two studies that compared CBIs against TAU (where TAU was either an intensive multi-disciplinary PMP comprising pain-specialist psychology and physiotherapy

input, or sessions of behavioural therapy, biofeedback and physical therapy) found that CBIs led to similar decreases on depression outcome measures as TAU. This provides preliminary evidence that CBIs for chronic pain can be as effective at reducing depressive symptoms as more well-established interventions.

These results comparing against TAU are promising as they could lead to greater patient choice regarding treatment options. This is important for several reasons. Firstly, there is evidence that patients who are offered choices about psychological treatments have better outcomes (Williams et al., 2016). Second, given the chronicity of their condition, many patients may have already tried several interventions with varying levels of success. Thus, patients who have not found TAU to be effective may welcome the opportunity to try an alternative approach. Third, the review highlighted preliminary evidence suggesting that CBIs may be particularly beneficial for a subgroup of chronic pain patients termed 'strivers'.

Armitage and Malpus (2019) describe 'strivers' as patients who tend to be highly self-critical in their thinking (and hence low in self-compassion), which pushes them to overexert themselves and become stuck in a 'boom and bust' pattern of activity. These patients often struggle with traditional pain management approaches such as pacing and activity scheduling because these approaches typically encourage patients to increase their activity levels from a low baseline, whereas 'strivers' are often continuing with inappropriately high levels of activity, despite the pain they are experiencing. This can further trigger their self-critical striving and exacerbate pain-related difficulties. As a result, it is suggested that 'strivers' may require a different psychological approach to help them pace their activity levels, improve their self-care and develop self-compassionate coping strategies (Armitage & Malpus, 2019; Parry & Malpus, 2017). Thus, following a psychological assessment, patients identified as 'strivers' could be recommended a CBI as being more suitable for their needs.

In addition, one study showed that a compassion-based group intervention had superior outcomes compared to an active control (relaxation group). This suggests that the reduction in depressive symptoms may have been due to the unique content of the CBI, rather than common factors such as being part of a group, meeting other patients with chronic pain, peer support and weekly contact with a therapist.

Finally, the two studies that included a waitlist control (Boselie et al., 2018; Peters et al., 2017) demonstrated that participants who had completed the CBI scored significantly lower on depressive symptoms than those in the waitlist condition. This study design controls for the spontaneous remission of depression, the impact of life events that occur during the intervention period, hopefulness about receiving an intervention and contact with the research team (including assessment). This increases the likelihood that it was the intervention itself that led to the improvements in depressive symptoms, and not these other common factors.

4.4 Follow-Up

Three studies included a follow-up at either 3 months or 6 months, with the results indicating that the improvements observed in depressive symptoms post-intervention were maintained over this period. Collecting follow-up data such as this is crucial as depression is a recurrent disorder and, given the long-term nature of their condition, chronic pain patients may be more vulnerable to a relapse of depressive symptoms. Indeed, Gerrits et al. (2014) followed 1122 individuals with remitted depressive or anxiety disorders over a period of 4 years and showed that pain increased the likelihood of depression recurrence (but not anxiety), largely through its association with aggravated subthreshold depressive symptoms. Therefore, it is important that we better understand the long-term effectiveness of CBIs as

these findings have reduced clinical significance if they can only demonstrate benefit in the short-term.

4.5 Mediating Relationships

Several studies hypothesised about potential variables that may be mediating the relationship between CBIs and improvements in depressive symptoms. For example, Flink et al. (2015) suggested reduced pain catastrophising (the tendency for patients to magnify their pain, ruminate on it and/or feel helpless about their ability to manage) as a possible mediator of the treatment effect; however, they did not have sufficient power to perform mediational analyses. Meanwhile, Montero-Marin et al. (2018) and Tin et al. (2019) both demonstrated that changes in psychological flexibility (defined as the willingness to experience unwanted emotions and thoughts and the ability to be in the present moment or use values-directed actions when experiencing distressing psychological events) at least partially mediated improvements in depressive symptoms in CBIs. Tin et al. (2019) was likely to have had adequate power to detect a mediation effect as the sample size of 122 participants exceeded that which was needed (as indicated by the *a priori* power analysis), to detect a mediating effect, even after 32 participants dropped out. Montero-Marin et al. (2018), with a sample size of 42, was less well-powered to detect mediating effects; however, the authors stated that they used statistical procedures to produce a test that could be applied to smaller samples in an attempt to overcome these potential limitations.

These findings tentatively suggest that increased psychological flexibility could be a key driver of the change in depressive symptoms observed following CBIs (and therefore a useful target for clinical intervention in chronic pain patients exhibiting depressive

symptoms), although further, well-powered, research is needed to corroborate these results and to explore the mediating roles of other variables related to the main ingredients of CBIs.

4.6 Strengths and Limitations of the Reviewed Studies

A strength of the studies included in this review is that they were all published within the last six years, between 2015 and 2019. This meant that the research was up-to-date and is likely to have reflected the experiences of patients currently living with chronic pain. However, the infancy of this research area also likely contributed to the mixed quality of the evidence base. This date range also avoided the possible effects of the recent COVID-19 pandemic which may have impacted on both pain and depression.

The majority of eligible studies were non-randomised pretest–posttest designs or single case designs. Although these designs do have their own strengths (particularly when new treatments are initially being developed and evaluated), it is nevertheless more difficult to draw firm conclusions about the effectiveness of CBIs from them.

Of the two single case designs, one did not report sufficient information to be able to accurately assess study quality (Håkansson et al., 2015). The other did not meet evidence standards (Flink et al., 2015) as its AB design did not include at least three different phase repetitions, and therefore could not confidently demonstrate an intervention effect. All five non-randomised pretest-posttest designs were judged to be at moderate risk of bias, indicating that they were sound for non-randomised studies but could not be considered comparable to well-performed RCTs in their ability to clearly demonstrate the effect of an intervention.

There were four RCTs eligible for inclusion in this review. One of these (Montero-Marin et al., 2018) was a registered clinical trial and was judged to be at low risk of bias. The

remaining three RCTs were not clinical trials and were judged to raise ‘some concerns’ about risk of bias.

Where ‘some concerns’ or moderate risk of bias was identified, this was largely in relation to:

(i) insufficient information about allocation sequence generation and concealment in the RCTs which meant that the reviewers could not be confident that the allocation sequence was genuinely randomised, and was therefore at risk of confounding (when there are common causes of intervention group assignment and outcome);

(ii) a lack of evidence that confounding variables were controlled for in the non-randomised studies, for example, through the use of comparison groups, matching (when participants in the intervention group are matched with a counterpart in a comparison group) or statistically controlling for potential confounders.

(iii) issues with the handling of missing outcome data, particularly as the chance that the outcome which was missing may have depended on its true value (for example, if one of the reasons participants withdrew from the study was because depressed mood was a barrier to them completing the intervention);

(iv) the use of participant-reported outcomes when the assessment of outcome was potentially influenced by knowledge of the intervention received, as the assessor (the participant) could not be blinded to their intervention status; and

(v) a lack of publicly available pre-specified analysis intentions to rule out selective reporting of particular outcome measurements or analyses.

Further studies of better quality are required, particularly more RCTs (including clinical trials). Fortunately, this does appear to be in progress. For example, whilst

conducting the search for this review, there were several clinical trials registered with the Cochrane Library that had not yet published their findings. This suggests that this is a topic of increasing interest and that this review may benefit from being updated once the findings of these studies are published.

Nevertheless, it is important to highlight that even in the most well-designed RCT there is an inherent difficulty of blinding participants to their assigned intervention (or lack thereof) in studies investigating the effects of psychological therapy. This is in contrast to the more effective placebo conditions that can be utilised in pharmacological research. This, in turn, could influence how participants respond on self-report measures of depression (e.g. responding to demand characteristics by reporting improved outcomes). Studies could also consider incorporating clinician-rated measures of depression (e.g. HAM-D, MADRS) administered by researchers who remain blinded to the participants' intervention status.

Moreover, there were also limitations regarding the representativeness of the populations sampled in these studies, particularly in terms of gender and ethnicity. For example, one study was comprised only of female participants (despite males also being eligible to participate) and the seven remaining studies that provided details about participants' sex all had a considerably greater ratio of females to males. There are several reasons why this pattern may have been observed. Firstly, Penlington (2019) suggested that an intervention focusing on compassion may appeal more to women than men (due to the connotations surrounding the word "compassion") so men may be less likely to opt for this intervention if given a choice (i.e. in non-randomised designs). However, this gender difference was also observed in systematic reviews of CBT (Williams et al., 2012) and mindfulness (Hilton et al., 2017) for pain management, so this may not be unique to CBIs. On the other hand, this may simply be a reflection of the higher prevalence of chronic pain conditions amongst females (Tsang et al., 2008), meaning that there is a larger population to

recruit from. Moreover, there is evidence to suggest that females are more likely to seek help for their pain (Cornally & McCarthy, 2013; Smith et al., 2012) in comparison to their male counterparts.

In addition, only two studies provided any information about participants' ethnicity. Both samples largely consisted of White participants (78.8% and 93.5%). This lack of information about ethnicity is problematic because differences in outcomes following pain treatment have been reported in different ethnic groups (e.g. Campbell & Edwards, 2012; Meints et al., 2019; Merry et al., 2011); however this cannot be investigated further if this data is not consistently reported. If such disparities are replicated following CBIs, there may be a crucial need to make culturally-appropriate adaptations.

Finally, assessing the psychological and emotional functioning of patients with chronic pain is inherently problematic due to the similarity of depressive symptoms (e.g. fatigue, changes in appetite and sleep, decreased concentration) and symptoms associated with chronic pain and/or the side effects of the medications used to alleviate it. For this reason, it is often helpful to separate depression scores into somatic and cognitive domains and compare each separately. Moreover, it has been demonstrated that many of the measures commonly used to assess depression may have poor validity in the chronic pain population due to criterion contamination, lack of external reference and lack of sensitivity when applied to this group (e.g. Morley et al., 2002; Pincus & Williams, 1999). Thus, there may be value in developing more valid measures for use with this specific population.

4.7 Strengths and Limitations of this Review

One strength of this review is that it endeavoured to include all relevant studies by searching four bibliographic databases, clinical trial databases as well as searching the 'grey'

literature to locate unpublished work. The inclusion of several unpublished studies in this review represents an attempt to overcome publication bias, which can impact the ability to accurately synthesise the evidence in a given research area. However, this meant that data was not always reported in the level of detail required for systematic evaluation of study characteristics and quality. In addition, some relevant studies may have been missed due to the decision to exclude non-English language publications. A further limitation is that a suitable tool for assessing the quality of pretest-posttest designs was somewhat lacking. The ROBINS-I (Sterne et al., 2016) was considered to be the most appropriate of the standardised tools; however, some adaptations were required to take into account the lack of comparison group(s) in several of the studies. The authors state that there are planned developments which it is hoped will provide clearer guidance on how ROBINS-I can be used effectively with other study designs.

Finally, there was a considerable amount of heterogeneity amongst the included studies in terms of both design and intervention type. This was largely due to the infancy of this research area, which meant that there were insufficient studies to – for example – only include RCTs or studies that delivered CFT. Moreover, it should be noted that several studies (Boselie et al., 2018; Flink et al., 2015; Peters et al., 2017) delivered a positive psychology intervention which included a composite package of techniques. Although a significant focus of the intervention was the development of self-compassion, the authors could not ascertain the effect of each component and further research is necessary to tease out which ingredients of the intervention have the greatest influence on outcomes.

This heterogeneity, together with the lack of comparison groups and unreported outcome data noted earlier, also meant that the extracted data was not particularly amenable to meta-analysis. Although this limits the conclusions that can be drawn from this review, it provides a strong starting point for future reviews in this area. For example, this review may

benefit from being updated once more studies have been published on this topic, thereby enabling the inclusion of higher quality research and greater consistency between studies.

4.8 Recommendations for Future Research

Firstly, higher quality studies are required to examine the effectiveness of CBIs in patients with chronic pain, particularly more RCTs and well-controlled non-randomised designs. These studies would benefit from having large sample sizes that provide adequate power to perform mediational analyses to explore whether changes in factors such as psychological flexibility are instrumental in determining the clinical outcomes observed. In addition, it is necessary to establish whether the effectiveness of CBIs differs for certain subgroups within the chronic pain population such as 'strivers', men and people of different ethnicities. Finally, more studies are needed that include a follow-up condition at least several months after the intervention is complete to provide a better understanding of the length of time for which any improvements in depressive symptoms are maintained.

4.9 Conclusions

This systematic review provides preliminary evidence that CBIs may improve depressive symptoms in patients with chronic pain. These results are promising as they suggest that CBIs may help to alleviate some of the emotional burden of living with chronic pain. However, this research area is still in its infancy and further research is required before any definitive conclusions can be drawn. Clinical services wishing to pilot a CBI with chronic pain patients may opt to deliver these individually or in group settings (in-person or remotely) over a number of weeks, but should be cautious about briefer interventions as there is currently limited evidence for their effectiveness.

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Part 2: Empirical Paper

The acute and long-term effects of sub-anaesthetic ketamine on pain, mood and cognitive functioning in chronic pain patients

Abstract

Aims: Ketamine can produce strong analgesia at sub-anaesthetic doses. This has led to the development of intravenous ketamine infusions as a treatment option for chronic pain. However, little is currently known about its incidental short and long-term non-analgesic effects in pain patients. This study aimed to understand the acute and long-term effects of ketamine (compared to lidocaine) on pain, mood and cognitive functioning in the chronic pain population.

Method: This study employed a non-randomised (quasi-experimental), mixed between-within subjects design. The independent variables were drug (ketamine or lidocaine) and time. Previous participants were contacted to take part in a long-term follow-up over the telephone (n = 47). Measures used were the same as in previous studies enabling comparison across time. Mixed ANOVAs compared the effects of ketamine (with lidocaine) during the acute phase (baseline, mid-infusion and post-infusion) and over the longer-term (baseline, one-week follow-up and long-term follow-up). Mean length of long-term follow up was 152 days for ketamine patients and 116 days for lidocaine patients.

Results: Ketamine acutely produced superior analgesia to lidocaine but this difference was not sustained over the longer-term. No significant differences were found in mood between ketamine and lidocaine patients at any timepoint. Ketamine, but not lidocaine, acutely impaired performance on tasks of episodic memory, verbal fluency and working memory and concentration. These cognitive impairments were no longer observed at long-term follow-up.

Conclusions: In the longer-term, the effects of ketamine and lidocaine on pain were similar. Ketamine did not show any specific antidepressant effects in a chronic pain population either acutely or over the longer-term. Acute impairments in cognitive functioning in those receiving ketamine were hypothesised to be due to a practice-blocking effect and appeared transient. Limitations and implications of the research are discussed.

1. Introduction

1.1 Overview

This study investigated the acute and long-term effects of sub-anaesthetic ketamine infusions on pain, mood and cognitive functioning in chronic pain patients, in comparison to similar patients receiving lidocaine infusions. This introduction summarises the existing literature on the relationships between ketamine and pain, mood and cognition.

1.2 Chronic Neuropathic Pain

The International Association for the Study of Pain (IASP) defines neuropathic pain as pain caused by a lesion or disease of the peripheral or central somatosensory nervous system (IASP, 1994). Chronic pain is widely defined as pain that persists for more than three months. Neuropathic pain is associated with a range of causes including: infectious disease (e.g. shingles, HIV, leprosy), autoimmune disease (e.g. diabetes); injury to the nervous system (e.g. traumatic injury, stroke, multiple sclerosis), toxic agents (e.g. alcohol, chemotherapy), inherited or genetic neuropathy (e.g. erythromelalgia, Charcot-Marie-Tooth disease, Fabry's disease) and Complex Regional Pain Syndrome (CRPS) (Niesters & Dahan, 2012).

Symptoms of neuropathic pain can include spontaneous burning or shooting pain, *hyperalgesia* (enhanced sensitivity to pain) and *allodynia* (pain from stimuli which do not normally elicit pain). Furthermore, the secondary effects are wide-ranging and can include loss of function in the affected regions, loss of independence, low mood, sleep difficulties and reduced financial income, all of which can further reduce an individual’s quality of life. Treatment is variable and often involves a trial and error approach. Randomised controlled trials have found that no more than half of patients experience clinically meaningful pain

relief in response to existing pharmacotherapy treatments, and this is almost always only partial (but not complete) relief (Dworkin et al., 2010). Thus, there is clearly a need for improved treatments for neuropathic pain.

1.3 The Neurobiology of Chronic Pain: the Role of the N-methyl-D-aspartate Receptor

Research indicates that the N-methyl-D-aspartate (NMDA) receptor plays an important role in the development and maintenance of chronic neuropathic pain (Petrenko et al., 2003). It is understood that the prolonged firing of nociceptors (sensory neurons that are sensitive to physiological changes that occur during tissue damage) triggers the excessive release of the neurotransmitter glutamate which acts on NMDA receptors in the spinal cord. Through a process known as central sensitisation, activation of NMDA receptors lowers pain thresholds and causes increased sensitivity in the pain pathways in the central nervous system, resulting in the symptoms of neuropathic pain outlined above (Bennett, 2000). Given this relationship, it has been argued that NMDA receptor antagonists (substances that inhibit the action of the NMDA receptor) might be useful in the treatment of chronic neuropathic pain.

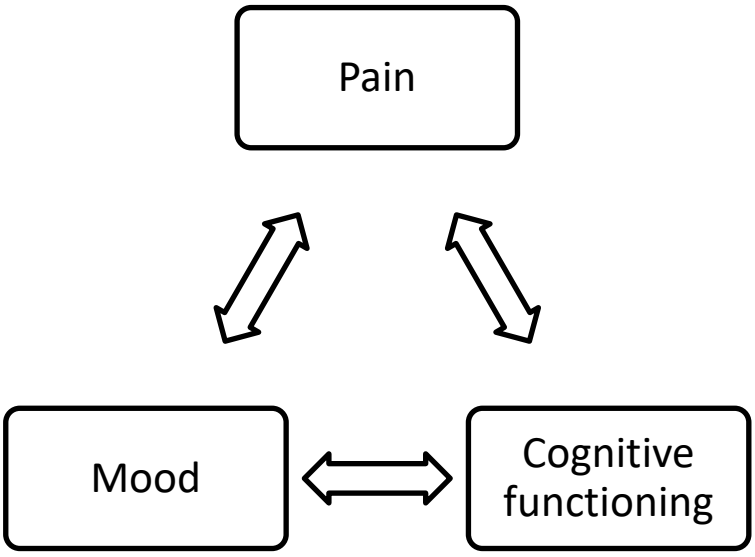
1.4 The Interactions between Pain, Mood and Cognitive Functioning

The relationship between pain, mood and cognitive functioning is considered to be dynamic (James & Ferguson, 2020), as each of these factors is thought to affect the others (see Figure 1). For example, there is a high comorbidity between pain and depression. Multiple theories have been proposed to explain this relationship, termed the ‘pain-depression dyad’ (Bair et al., 2003; see Part I of this thesis). Both pain and mood are also associated with

cognitive functioning. For example, greater severity of depression is associated with poorer cognitive functioning in domains such as episodic memory, executive functioning and processing speed (McDermott & Ebmeier, 2009). In addition, people who are in greater pain perform poorer on tests of cognitive functioning. This is hypothesised to be because the salience and potential danger of pain mean that the brain must prioritise its finite cognitive resources for processing pain signals. In doing so, other cognitive processes may become disrupted, resulting in poorer attention to other stimuli (Moriarty et al., 2011). Another hypothesis is that, through a process known as maladaptive plasticity, persistent pain signals lead to structural and neurochemical changes in the nervous system. Over time, this can result in overactivation of the amygdala and deactivation of the prefrontal cortex, leading to decreased cognitive control (Moriarty et al., 2011). Meanwhile, there is evidence suggesting that better cognitive functioning earlier in life acts as a protective factor against the development of diseases such as chronic pain later in life (Gale et al., 2012). The following sections explore how ketamine interacts with each of these variables.

Figure 1

An Illustration of the Relationship between Pain, Mood and Cognitive Functioning



1.5 Ketamine and Pain

Ketamine is an NMDA receptor antagonist that was first synthesised in 1962 as an alternative anaesthetic to phencyclidine (PCP), which produced serious psychotomimetic side effects. It is usually administered intravenously and induces dissociative anaesthesia, a trance-like state characterised by catalepsy, amnesia and analgesia (Pender, 1970). Ketamine has been on the World Health Organisation's (WHO's) Essential Medicines List since 1985 and is now one of the most widely used anaesthetics in the world (WHO, 2016). It is often preferred over other anaesthetics because of its safety profile, being less likely to suppress airway reflexes, depress breathing or lower blood pressure. In addition, it does not require expensive patient-monitoring equipment which is particularly beneficial in low-income countries and in war and disaster zones where such resources may be unavailable.

Ketamine can also produce strong analgesia when administered at sub-anaesthetic doses. Over the past two decades, this has led to the development of intravenous ketamine infusions as a treatment for chronic pain. However, concerns were reportedly raised by various sources that there was wide variation in patient selection, dosing and monitoring. This prompted the American Society of Regional Anesthesia and Pain Medicine and the American Academy of Pain Medicine to form a Ketamine Guidelines Committee which was tasked with reviewing the literature and publishing consensus guidelines (Cohen et al., 2018). These recommendations were based on the US Preventive Services Task Force (2012) grading of evidence guidelines. The Committee concluded that there was weak evidence supporting ketamine infusions for short-term improvements in spinal cord injury pain, moderate evidence supporting ketamine infusions for improvements in pain for up to 12 weeks in CRPS, and weak or no evidence supporting ketamine infusions for immediate improvements in mixed neuropathic pain, phantom limb pain, postherpetic neuralgia, fibromyalgia, cancer pain, ischemic pain, migraines or low back pain. Excluding CRPS, there

was no evidence supporting ketamine infusions for intermediate or long-term improvements in pain. However, these consensus guidelines acknowledged that most studies were small, uncontrolled and either unblinded or ineffectively blinded and called for more larger-scale studies to be conducted (Cohen et al., 2018). In addition, the studies that informed the guidelines appeared to focus on the effects of single ketamine infusions (yet the typical dosing regime in clinical settings involves multiple spaced doses) and there was substantial variation in the dose and duration of infusions.

1.6 Ketamine and Mood

Depression is a significant global health concern with more than 264 million people affected worldwide (WHO, 2020). Moreover, there is a high comorbidity between chronic pain and depression, as discussed in the literature review above (Part I of this thesis). Depression can have severe socioeconomic and health consequences and, at worst, can lead to suicide with close to 800,000 people dying by suicide each year (WHO, 2020).

In addition to its anaesthetic and analgesic properties, ketamine has also been shown to have rapid-acting antidepressant effects (see Abdallah et al., 2015 and Marcantoni et al., 2020 for reviews). A pilot study by Berman et al. (2000) found that a single sub-anaesthetic dose of ketamine had robust antidepressant effects in patients with treatment-resistant depression (TRD) within 4 hours of intravenous infusion. This finding has since been replicated in multiple randomised controlled trials (e.g. Murrough et al., 2013; Zarate et al., 2006). Moreover, there is evidence that a single infusion of ketamine can rapidly reduce suicidal thoughts in patients with mood disorders within 4 hours of administration (see Witt et al., 2020 for a review). These findings led the US Food and Drug Administration (FDA) to approve esketamine (an isomer of ketamine) for use as a rapid-acting nasal spray for TRD in

March 2019. In August 2020, the FDA added approval for patients with suicidal thoughts or behaviours.

Several mechanisms have been proposed to explain the rapid-acting antidepressant effects of ketamine and, similarly to its pain-reliving properties, the primary mechanism is thought to be via the NMDA receptor. Animal and human research suggests that these effects are mediated by a surge of glutamate (via disinhibition of inhibitory cortical neurons) that results in synaptogenesis and reversal of the negative effects of chronic stress and depression, particularly within the prefrontal cortex (see Abdallah et al., 2016 for a review).

These rapid-acting antidepressant effects give ketamine an advantage over more traditional antidepressants that target the monoaminergic system, as these typically have a lag period of several weeks before patients report experiencing any improvement in mood. In addition, the efficacy of traditional antidepressants is limited, with a large-scale clinical trial finding that a significant proportion of depressed patients did not display an adequate response to standard antidepressants and sustained remission was uncommon (Rush et al., 2006).

However, despite the promising nature of its rapid antidepressant properties, it is thought that ketamine's mood-enhancing effects are only transient. These antidepressant effects have been shown to peak at 24 hours and return to baseline levels within one to two weeks of the initial infusion (Abdallah et al., 2015; Marcantoni et al., 2020) with reductions in suicidal thoughts only lasting for up to 72 hours (Witt et al., 2020). Thus, researchers have highlighted the need for further investigation to determine the long-term effects of ketamine on mood and how these antidepressant effects can be maintained over time.

1.7 Ketamine and Cognitive Functioning

Cognition is broadly defined as the ability to acquire, process, store and retrieve information. Concerns about the adverse effects of ketamine on cognitive functioning arose from research indicating that frequent recreational ketamine use is associated with impairments in several cognitive domains including spatial working memory, pattern recognition memory, episodic memory and semantic memory (Morgan & Curran, 2011; Morgan, Muetzelfeldt & Curran, 2010; Visser & Schug, 2006). To date, the research appears to have focused largely on the relationship between recreational use of ketamine and cognitive impairment.

However, it is important to differentiate between the effects of frequent recreational ketamine use and repeated (though comparatively infrequent) sub-anaesthetic doses. Although there appear to be clear cognitive consequences related to long-term recreational ketamine use, the evidence base in pain patients is less definitive. For example, Kim et al. (2016) demonstrated that CRPS patients who received ketamine infusions twice a month for six months showed impairment in cognitive function (primarily executive function) compared to those who never or infrequently received ketamine. Thus, the authors argued that long-term frequent ketamine treatment may impair executive functioning in CRPS patients by altering the function of the dopaminergic system in the prefrontal cortex. Similarly, Reeves et al. (2001) found that patients receiving ketamine in addition to morphine for post-surgical pain performed worse on tests of attention and perception compared to patients who only received morphine. Conversely, other studies have found that working memory, attention and task-switching were unaffected when patients received either ketamine or morphine for post-surgical pain (Aubrun et al., 2008; Zohar, 2002). Thus, the cognitive effects of ketamine in the context of pain remain unclear.

1.8 Wider Research Project

This study forms part of a wider research project that began in 2017. The previous studies (written up as DClinPsy theses: Halls, 2020; Kibble, 2020; Knox, 2018; Trotman, 2018) compared the acute effects of ketamine and lidocaine infusions on pain, mood, subjective drug effects and cognition in chronic pain patients across baseline, mid-infusion and post-infusion. Additional measures of pain, mood and subjective drug effects were also taken at one-week follow-up. A total of 99 participants (43 ketamine, 56 lidocaine) took part in these previous studies. Baseline, mid-infusion and post-infusion data was collected in-person at the study site, whilst one-week follow-up data was collected over the telephone. For detailed accounts, see Halls (2020), Kibble (2020), Knox (2018) and Trotman (2018).

Lidocaine (also termed lignocaine) is a sodium channel blocker that can block nociceptors in the brain and spinal cord, thus giving it anaesthetic and analgesic properties. Lidocaine is the drug that is most commonly used as an alternative to ketamine at the study site, thereby providing a convenient comparison group. Lidocaine is also an appropriate comparator drug because it has not been found to have antidepressant properties, there is little evidence that it causes cognitive impairments and it is not abused recreationally. Hence, it provides a helpful comparison to ketamine with regard to its antidepressant, cognitive and reinforcing effects.

Previous studies found that ketamine produced greater acute analgesic effects than lidocaine (Halls, 2020; Trotman, 2018), however this difference was not sustained at one-week follow-up (Kibble, 2020; Knox, 2018). No significant differences in mood were found between ketamine and lidocaine participants during the acute phase or at one-week follow-up (Kibble, 2020). In addition, ketamine acutely impaired cognitive functioning (phonetic fluency, working memory, concentration and episodic memory for information learned under the influence of the drug), whereas an improvement in cognitive functioning was shown in

participants who received lidocaine. This result was hypothesised to be due to practice effects (Halls, 2020). Finally, despite producing greater rewarding experiences than lidocaine (feeling high, liking the drug), participants who received ketamine did not have a stronger desire for more of the drug (Kibble, 2020; Knox, 2018).

In the clinical setting within which the research was conducted, ketamine (and lidocaine) infusions are routinely administered once every three months. Its analgesic effects are therefore intended to be relatively long-lasting. However, these previous studies recommended that a more comprehensive follow-up protocol was necessary to better understand the longer-term effects of ketamine on pain (as well as on mood and cognition) in the chronic pain population.

1.9 The Impact of COVID-19

For many individuals with chronic pain, the COVID-19 pandemic has caused considerable disruption to their usual treatment. Between March and July 2020 the study site closed and staff were redeployed to other services. This meant that patients were unable to receive any ketamine or lidocaine infusions during this time. The clinic then reopened; however, to comply with social distancing measures and protect patients and staff from infection, fewer infusions could be provided. Furthermore, even when infusions could be offered, many patients were classed as clinically vulnerable and were therefore shielding and unable to travel to the study site. This has resulted in large variability in treatment, with some patients able to resume regular infusions whilst others have not received any infusions since the pandemic began.

1.10 Rationale for Current Study and Hypotheses

Given the gaps highlighted in the current literature, there is a clear need to better understand the longer-term effects of ketamine infusions in the chronic pain population. This is particularly pertinent given the interruptions to treatment patients have experienced over the past year due to the COVID-19 pandemic.

The main aim of this study was to ascertain the longer-term effects of sub-anaesthetic doses of intravenous ketamine (as compared to lidocaine) on pain, mood and cognitive functioning in patients with chronic pain. To achieve this, the current study added a fifth timepoint by contacting participants who had taken part in the previous studies and asking them to participate in a long-term follow-up. The following hypotheses were generated:

(i) Based on previous findings (Kibble, 2020; Knox, 2018) that the superior acute analgesic effects of ketamine (compared to lidocaine) were not sustained at one-week follow-up, no significant differences were expected in pain ratings between ketamine and lidocaine patients at long-term follow-up.

(ii) Based on the literature regarding the transient nature of ketamine's antidepressant properties (Abdallah et al., 2015; Marcantoni et al., 2020), it was predicted that there would be no significant differences on measures of mood between ketamine and lidocaine patients at long-term follow-up.

(iii) Based on previous findings that ketamine acutely impaired cognitive functioning in pain patients (Halls, 2020) and the literature documenting the adverse cognitive effects of frequent recreational ketamine use (Morgan & Curran, 2011; Morgan, Muetzelfeldt & Curran, 2010; Visser & Schug, 2006), it was hypothesised that ketamine patients would show impaired cognitive functioning (compared to lidocaine patients) at long-term follow-up.

2. Methods

2.1 Joint Thesis

This research is part of a joint project with fellow UCL Trainee Clinical Psychologist, Laura Marks (Marks, 2021). The current thesis analyses quantitative data from questionnaires and cognitive tasks with ketamine and lidocaine patients, while Marks (2021) involves qualitative analyses of interviews with ketamine patients. See Appendix D for details of the contributions made by each researcher.

2.2 Ethics

This study was granted ethical approval by the South Central Berkshire NHS Research Ethics Committee (IRAS ID 214864; Appendix E) in 2017. A non-substantial amendment was approved in August 2020 to adapt the study in light of restrictions on face-to-face research in the NHS (due to the COVID-19 pandemic) and add a qualitative arm to the study (Appendix F).

The study followed the ethical principles set out by the British Psychological Society (BPS, 2014) and the Declaration of Helsinki (World Medical Association, 2013). All participants received an information sheet (Appendix G) via e-mail at least 24 hours before they were due to participate and were given the opportunity to ask questions. Participants were assured that their decision whether to participate would not affect their medical care in any way and that they could withdraw from the study at any time. Participants had already provided written informed consent to participate in the first phase of the research. As this follow-up study was conducted remotely, the researcher re-read each statement of the consent form (Appendix H) aloud over the telephone. Participants confirmed verbally if they consented and the researcher initialled the statements on their behalf. Data was stored

securely and anonymously using a non-identifiable ID number (e.g. K11) and kept in a separate location to patient identifiable information.

2.3 Study Site

The study site is regarded as a centre of excellence for people with chronic pain, providing services at both a local and national level to help people get back to activities they used to enjoy and to live as full lives as possible despite pain. The clinic is staffed by a multidisciplinary team comprising doctors, nurses, physiotherapists and psychologists. It is one of only several sites nationwide that provide intravenous infusions of ketamine for chronic pain. Participants were recruited through the site; however data collection was completed remotely due to restrictions on face-to-face contact during the COVID-19 pandemic.

2.4 Participants

The inclusion criteria for the previous studies were: aged 18-70 years; fluent English speakers (no interpreter required); moderate to severe chronic neuropathic pain deemed by the clinic to require ketamine or lidocaine infusions; normal or corrected to normal vision; and normal or corrected to normal hearing. The exclusion criteria were: suspected allergy to ketamine; diagnosis of psychiatric illness(es); a record of serious head injury; a record of learning disability; pregnant or breastfeeding; and unable to provide informed consent. The previous researchers had used a convenience sample of participants who were scheduled to receive an infusion on a date that a researcher could attend the study site.

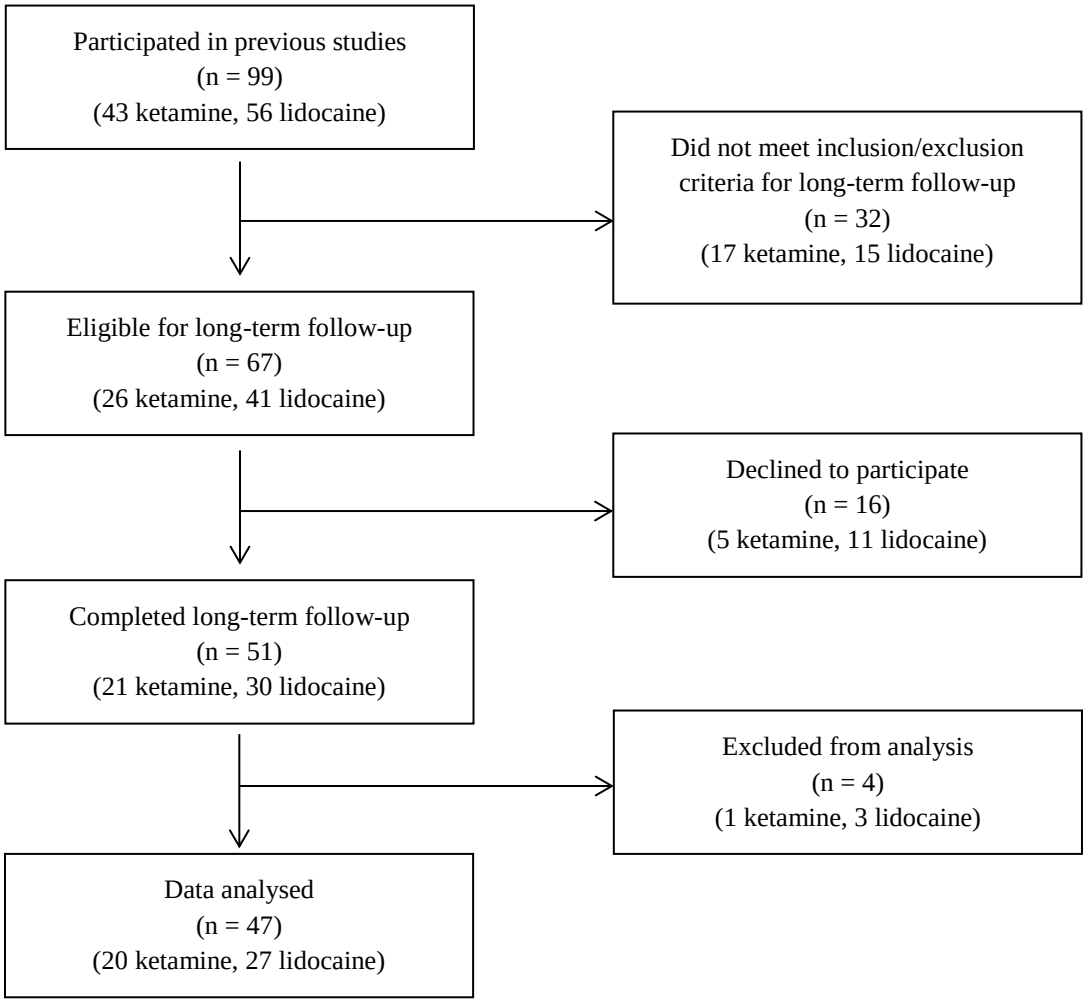
The inclusion criteria for the current study were that individuals: (1) must have participated in an earlier phase of the study; and (2) were still on the ketamine or lidocaine infusion pathway at the study site (regardless of whether they had been able to receive an infusion within the past three months). Participants were excluded if: (1) they were unable to provide informed consent; or (2) they had been discharged from the study site.

Of the 99 patients who had participated in an earlier phase of the study, 32 had discontinued the ketamine or lidocaine infusion pathway at the study site and/or had been discharged from the study site. This meant there were 67 patients eligible for long-term follow-up (26 ketamine, 41 lidocaine), of which 51 participated. Four participants were subsequently excluded from the analysis because they had received an infusion in the week prior to completing the long-term follow-up, and therefore this could have acted as a confounding variable given that this data was being compared to the one-week follow-up condition.

This left a final sample of 47 participants (20 ketamine, 27 lidocaine) between the ages of 21 and 68 years (M = 49.5, SD = 11.8). This represented a retention rate of 70%. A participant flowchart is shown in Figure 2. Full details of participant characteristics are provided in Table 2 in the Results section. Some participants did not complete every measure, therefore completion rates varied across measures.

Figure 2

Participant Flowchart to Long-Term Follow-Up



2.5 Research Design

This study employed a non-randomised (quasi-experimental), mixed between-within subjects design, conducted as part of routine care. This involved differing infusion durations (with ketamine infusions lasting 30 minutes to one hour and lidocaine infusions lasting one to three hours). As such, the study was not blind for either researcher or participant. The independent variables were drug (between subjects: ketamine or lidocaine) and time (within

subjects: baseline, mid-infusion, post-infusion, one-week follow-up, long-term follow-up). Given the naturalistic nature of the experiment, the length of long-term follow-up varied between participants due to the COVID-19 pandemic, as described in Section *1.9*.

2.6 Measures

Participants completed these measures (excluding the COVID-19 questionnaire) when they first participated in the research. The same measures were repeated in the current study for continuity. The decision to use these measures had been made in consultation with staff at the study site and through piloting in earlier studies. There were some additional measures used which are not reported here as they are not the focus of this particular study.

2.6.1 Demographic Details

Participants' age, gender and highest level of education were recorded.

2.6.2 Pain

Participants were asked to rate their current pain on three 11-point numeric rating scales (NRS; Appendix I) as follows: pain intensity from 0 ('no pain') to 10 ('extremely intense pain'), pain distress from 0 ('not distressing') to 10 ('extremely distressing') and pain interference from 0 ('does not interfere') to 10 ('interferes with everything'). NRS are a valid and reliable method of rating pain and tend to be preferred over visual analogue scales (VAS) by patients (Dworkin et al., 2005).

2.6.3 Mood

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) was used as the primary measure of depression (Appendix J). This 14-item self-report instrument was developed to detect anxiety and depression in non-psychiatric hospital settings. It consists of an anxiety subscale (HADS-A) and a depression subscale (HADS-D), each containing 7 items which are rated from 0 to 3. Scores of 0-7 in each subscale are considered normal, with 8-10 borderline and 11+ indicating clinical 'caseness'.

Compared to other commonly used measures of depression such as the Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) and the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), the HADS-D places less emphasis on somatic symptoms such as sleep disturbance, fatigue and changes in appetite. This is particularly useful in the chronic pain population given the overlap of physical symptoms in pain and depression which can make it difficult to measure these constructs independently. Moreover, in a review of 747 studies that used the HADS, a mean Cronbach's alpha of 0.82 was found for the HADS-D, demonstrating good internal consistency (Bjelland et al., 2002).

Secondary measures of depression were the Patient Health Questionnaire-2 (PHQ-2; Kroenke et al., 2003) and a depression NRS. These measures had been selected because of their use in previous studies exploring the antidepressant and reinforcing effects of ketamine, their brevity (<3 items) and their omission of somatic symptoms.

The PHQ-2 (Appendix K) is a shortened version of the 9-item PHQ-9. This 2-item self-report questionnaire asks respondents to indicate the frequency of depressed mood and anhedonia over the past two weeks from 0 ('not at all') to 3 ('nearly every day'). The PHQ-2 has been shown to have good criterion and construct validity across a sample of 6000 patients (Kroenke et al., 2003). However, due to the one-week follow-up in this research project,

previous studies adapted the PHQ-2 to ask about depressive symptoms over the past week. For the purpose of consistency, this time frame was retained in the present study. The depression NRS (Appendix L) asked participants to rate how depressed they currently felt on an 11-point NRS from 0 ('not at all depressed') to 10 ('extremely depressed').

2.6.4 Cognition

Story recall. The Story subtest of the Rivermead Behavioural Memory Test (Wilson et al., 1985) involves the immediate and delayed recall of a short passage of prose to provide a measure of verbal episodic memory. In the immediate recall condition, the researcher read a story (Appendix M) aloud and participants were immediately asked to recall as much of the passage as they could remember. In the delayed recall condition, participants were asked to recall the same story again after a 20-minute delay (Appendix N). A different story was used to those in the earlier studies so that participants had no prior knowledge of its content. See Appendix O for scoring guidelines.

Verbal fluency. Participants were asked to generate as many words as possible (excluding proper nouns) beginning with a specified letter (F) in 60 seconds (Appendix P). Each correct word scored one point. Proper nouns, words that did not begin with the target letter, and repetitions were scored as errors. Performance on this task is an indication of non-motor processing speed, semantic memory, vocabulary and executive function.

Serial sevens. The Serial Sevens Test (Appendix Q) is a measure of working memory and attention. Participants were given a number (305) and asked to successively subtract seven from it as many times as they could in 60 seconds. The number of correct subtractions was recorded.

For all three measures of cognition described above, a higher score indicated better performance. Therefore, an increase in score would represent an improvement in cognitive functioning, whereas a decrease would signify deterioration.

2.6.5 COVID-19

An 8-item self-report questionnaire was used to assess the impact of COVID-19 (Appendix R). This was adapted from a questionnaire developed by the Pain Management Collaboratory (2020) which was intended for individuals participating in ongoing clinical research during the pandemic. Several minor changes were made, such as removing superfluous items and adding a question about perceived benefits brought about by the pandemic.

The revised questionnaire asked if functioning in six domains (access to healthcare from the study site, feeling supported by staff at the study site, access to wider healthcare, social support, ability to meet basic needs, mental and emotional health) had reduced a lot, reduced a little, not been affected or improved. Participants were also asked if they had experienced any benefits arising from the pandemic (none; a little; a lot; no view) and if they thought they had contracted COVID-19 themselves (yes; no; unsure).

2.7 Procedure

Patient contact details were obtained from the study site database. Although it was originally intended that clinic staff would contact patients initially to invite them for follow-up, this did not occur due to limited resources at the study site (as a result of COVID-19). Therefore, the researchers made multiple attempts to contact all eligible participants by e-

mail or telephone between October 2020 and January 2021. All potential participants had to provide an e-mail address to which an information sheet could be sent. Those who agreed to participate were booked in for a telephone appointment.

Once consent was gained and any further questions answered, the measures were completed over the telephone. The order was as follows: immediate recall; demographics; pain NRS; depression NRS; PHQ-2; HADS; verbal fluency; serial sevens; delayed recall; COVID-19 questionnaire.

For each measure, the researcher read the instructions aloud, participants responded verbally and the researcher recorded their responses. This was chosen in preference to online questionnaires to stay as close as possible to how the previous data was collected and it was also thought that this would elicit greater engagement from participants. See Table 1 for a summary of the measures collected at each timepoint. After completing the measures, participants were debriefed and given another opportunity to ask questions. Each telephone call lasted approximately 30 minutes.

Table 1

Summary of Measures Collected at Each Timepoint

Baseline	Mid-infusion	Post-infusion	One-week follow-up	Long-term follow-up
Demographics	-	-	-	Demographics
Pain NRS	Pain NRS	Pain NRS	Pain NRS	Pain NRS
Depression NRS	Depression NRS	Depression NRS	Depression NRS	Depression NRS
PHQ-2	-	-	PHQ-2	PHQ-2
HADS	-	-	HADS	HADS
Immediate recall	Immediate recall	-	-	Immediate recall
-	Delayed recall	-	-	Delayed recall
Verbal fluency	Verbal fluency	-	-	Verbal fluency
Serial sevens	Serial sevens	-	-	Serial sevens
-	-	-	-	COVID-19

2.8 Statistical Analysis

Data was entered into Statistical Package for Social Sciences (SPSS; Version 27) for analysis. An alpha (α) level of ≤ 0.05 was used for all statistical tests. Analysis of acute and long-term drug effects was conducted only for those participants who completed the long-term follow-up (n = 47). This represented a subsample of the full sample (n = 99) recruited in earlier phases of the study. For the analysis of acute and one-week follow-up data from the larger sample (n = 99), please see Halls (2020) and Kibble (2020).

Group differences for categorical variables (ethnicity and educational level) were investigated using Chi-square tests. Fisher's Exact test (Fisher, 1922) was used for gender as this violated the assumptions of a Chi-square test due to one cell (males receiving ketamine) having an expected frequency of less than 5 and in such circumstances with a 2x2 contingency table, Field (2018) recommends reporting Fisher's instead. When testing for baseline differences on continuous variables, t-tests were used if data were normally

distributed and homogeneity of variance was assessed using Levene's test. Where data were non-normally distributed, Mann-Whitney U was used as a non-parametric alternative.

The primary analysis explored differences between ketamine and lidocaine patients on measures of pain, mood and cognition over two timeframes: acutely (baseline, mid-infusion and post-infusion) and longer-term (baseline, one-week follow-up and long-term follow up). The distribution of data was evaluated using measures of skewness and kurtosis, histograms and the Shapiro-Wilk test. Where these indicated that data were not normally distributed, the decision was made to continue with mixed analysis of variance (ANOVAs) due to the robustness of the F-test (Field, 2018).

Several mixed ANOVAs were performed: 2 (drug: ketamine; lidocaine) x 3 (time: baseline; mid-infusion; post-infusion) for acute pain and mood scores; 2 (drug: ketamine; lidocaine) x 2 (time: baseline; mid-infusion) for acute cognition scores; 2 (drug: ketamine; lidocaine) x 3 (time: baseline; one-week follow-up; long-term follow-up) for long-term pain and mood scores; and 2 (drug: ketamine; lidocaine) x 2 (time: baseline; long-term follow-up) for long-term cognition scores. The assumption of sphericity was assessed using Mauchly's test and if this assumption was violated, the Greenhouse-Geisser correction was applied. If interactions were significant, Bonferroni-corrected post-hoc tests were used to explore simple effects.

Secondary analysis explored the associations between change scores on pain, mood and cognitive measures from baseline to mid-infusion, one-week follow-up and long-term follow-up. As some change scores violated assumptions of normality, Spearman's Rho correlations were performed.

2.9 Power Analysis

This study recruited an opportunistic sample following on from previous research, in which the aim was to re-assess as many participants as possible. A post-hoc sensitivity analysis was conducted using G*Power (Faul et al., 2007) for a repeated measures ANOVA (within-between interaction). This indicated that with alpha=0.05, a sample size of n=47 provides power of 0.76 to detect an effect size of f=0.2 (i.e. small-medium by convention) for a 2 x 3 (drug x time) interaction.

3. Results

3.1 Participants

Participant details are shown in Table 2. There were no significant differences at baseline on any demographic variables (Table 2) or any dependent variables (see Table 3) ($p > .05$). See Appendix S for Shapiro-Wilk tests of normality for age and baseline scores, Appendix T for detailed results of Fisher's Exact Test and Chi-square tests, Appendix U for detailed results of independent samples t-tests and Appendix V for detailed results of Mann-Whitney U tests. Delayed recall was not measured at baseline and was therefore not included in the analysis of baseline differences.

Table 2

Demographic Details of Participants who Completed Long-Term Follow-Up

		Ketamine n = 20	Lidocaine n = 27	Total n = 47
Age M (SD) years		52.85 (9.64)	46.96 (12.73)	49.47 (11.78)
Gender	Male	4	7	11
	Female	16	20	36
Ethnicity	Asian Bangladeshi	0	1	1
	Asian British	1	0	1
	Black African	0	1	1
	Not Stated/Unknown	4	2	6
	Not Yet Asked	2	3	5
	Other White Background	2	3	5
	White British	11	15	26
	White Irish	0	2	2
Highest level of education	No formal qualifications	3	4	7
	GCSE	5	5	10
	A-Level	1	5	6
	Undergraduate degree	8	9	17
	Postgraduate degree	3	2	5
	Missing	0	2	2

Table 3

Comparison of Baseline Scores in Ketamine and Lidocaine Participants who Completed Long-Term Follow-Up

	Ketamine M (SD)	Lidocaine M (SD)	Sig. (*p*)	Total M (SD)
Pain intensity	6.95 (2.04)	6.59 (2.21)	.575†	6.74 (2.12)
Pain distress	5.30 (3.16)	5.22 (2.94)	.931◆	5.26 (3.00)
Pain interference	7.07 (2.40)	6.48 (3.11)	.564†	6.73 (2.81)
Depression NRS	4.75 (3.28)	4.19 (3.11)	.580†	4.43 (3.16)
PHQ-2	2.95 (2.28)	2.93 (2.18)	.956†	2.94 (2.20)
HADS-D	8.20 (5.21)	8.84 (4.55)	.662◆	8.56 (4.81)
HADS-A	10.60 (4.86)	10.12 (4.35)	.729◆	10.33 (4.54)
Immediate recall	5.03 (3.31)	5.11 (2.77)	.643†	5.07 (2.98)
Verbal fluency	11.00 (4.22)	10.81 (4.01)	.879◆	10.89 (4.06)
Serial sevens	6.00 (5.27)	8.89 (8.29)	.204†	7.70 (7.28)

†Mann-Whitney U. ◆Independent samples t-test

3.2 Long-Term Follow-Up

The length of long-term follow-up ranged from 23–426 days since last ketamine infusion (*M* = 151.7, *SD* = 125.4) and 9–373 days since last lidocaine infusion (*M* = 115.9, *SD* = 119.1). A Mann-Whitney U test showed no significant difference in the number of days since last infusion between patients who received ketamine (*Mdn* = 93.5) and lidocaine (*Mdn* = 49.0), *U* = 342.0, *p* = .121. Therefore the number of days since last infusion was not included as a covariate in the mixed ANOVAs.

Overall, a broad similarity was found between the results of the acute and one-week follow-up analysis for those who participated in the long-term follow-up (n = 47) and that of the full sample (n = 99; Halls, 2020; Kibble, 2020).

3.3 Acute Effects of Ketamine and Lidocaine

3.3.1 Pain

Acute changes in pain were analysed using mixed ANOVAs. As indicated in Table 4, there were significant interactions between time and drug for pain intensity (Figure 3), pain distress (Figure 4) and pain interference (Figure 5). These interactions were explored using Bonferroni-corrected post-hoc tests which are reported in Appendix W. There was a significant main effect of time on pain intensity, distress and interference and a significant main effect of drug on pain intensity and interference. There was a trend towards a main effect of drug on pain distress but this did not reach statistical significance.

Table 4

Results of Mixed ANOVAs Exploring the Acute Effects of Drug and Time on Pain

Pain Domain		Baseline M (SD)	Mid-infusion M (SD)	Post-infusion M (SD)	ANOVA Conditions	*df* 1	*df* 2	*F*	Sig. *(p)*	η_p^2
Pain Intensity[a]	Ketamine	7.05 (2.04)	2.53 (2.48)	2.11 (2.33)	**Time**	**1.636**	**67.059**	**65.214**	**< .001****	**.614**
	Lidocaine	6.58 (2.10)	5.33 (2.55)	5.23 (2.49)	**Drug**	**1**	**41**	**8.401**	**.006****	**.170**
					Time x Drug	**1.636**	**67.059**	**21.111**	**< .001****	**.340**
Pain Distress	Ketamine	5.42 (3.20)	1.26 (1.88)	1.16 (1.64)	**Time**	**2**	**82**	**41.347**	**< .001****	**.502**
	Lidocaine	5.17 (2.82)	3.21 (2.11)	3.13 (2.72)	Drug	1	41	4.022	.052	.089
					Time x Drug	**2**	**82**	**5.235**	**.007****	**.113**
Pain Interference[a]	Ketamine	7.29 (2.26)	1.32 (1.70)	1.53 (1.54)	**Time**	**1.643**	**67.361**	**83.166**	**< .001****	**.670**
	Lidocaine	6.46 (2.96)	4.04 (2.93)	3.52 (2.66)	**Drug**	**1**	**41**	**4.443**	**.041***	**.098**
					Time x Drug	**1.643**	**67.361**	**12.044**	**< .001****	**.227**

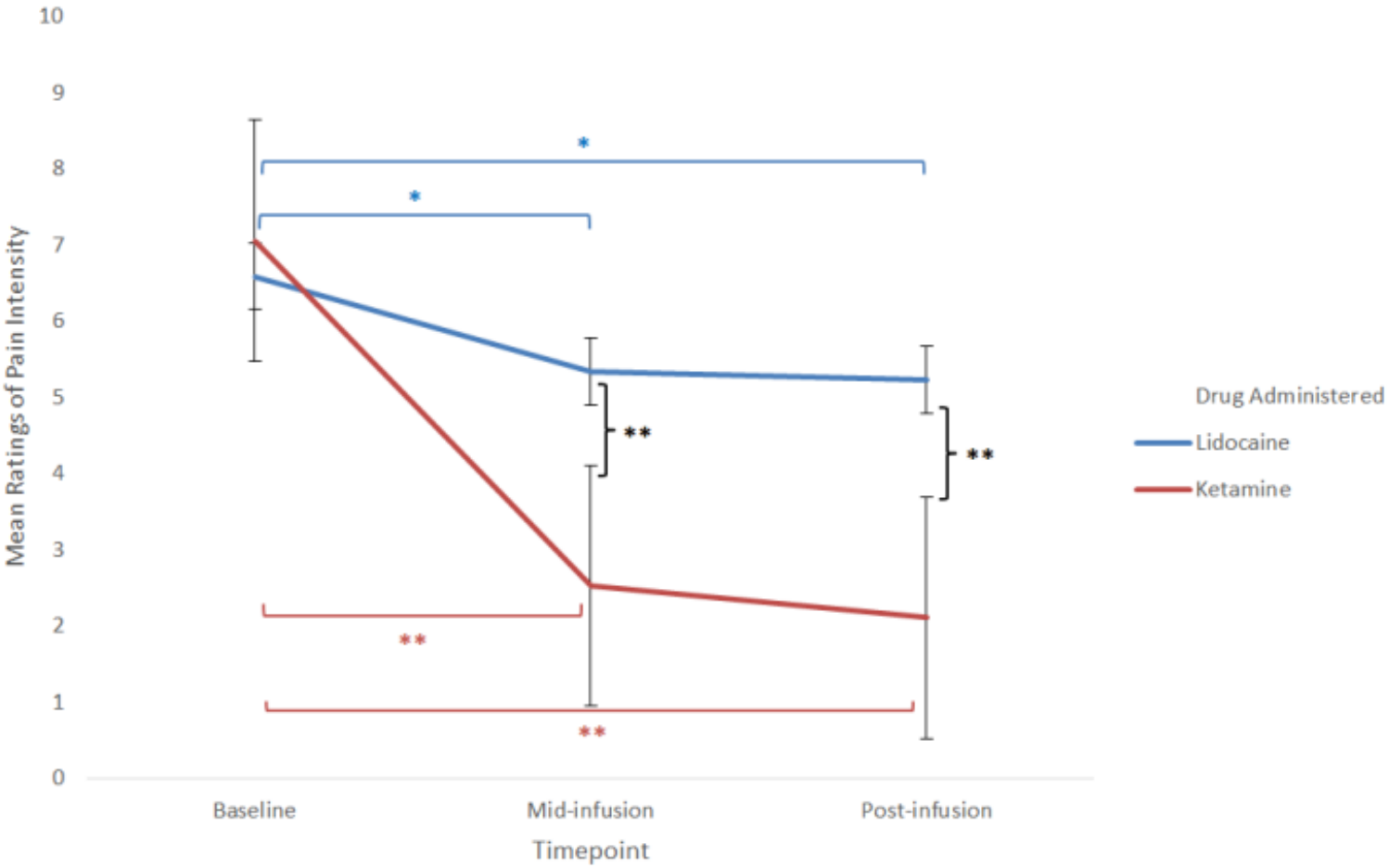
Note. Baseline scores presented here and in subsequent ANOVA tables differ slightly to those in Table 3 due to casewise deletion.

[a]. Mauchly's test of sphericity was significant, therefore sphericity could not be assumed and the Greenhouse-Geisser correction was applied.

*$p < 0.05$. **$p < 0.01$

Figure 3

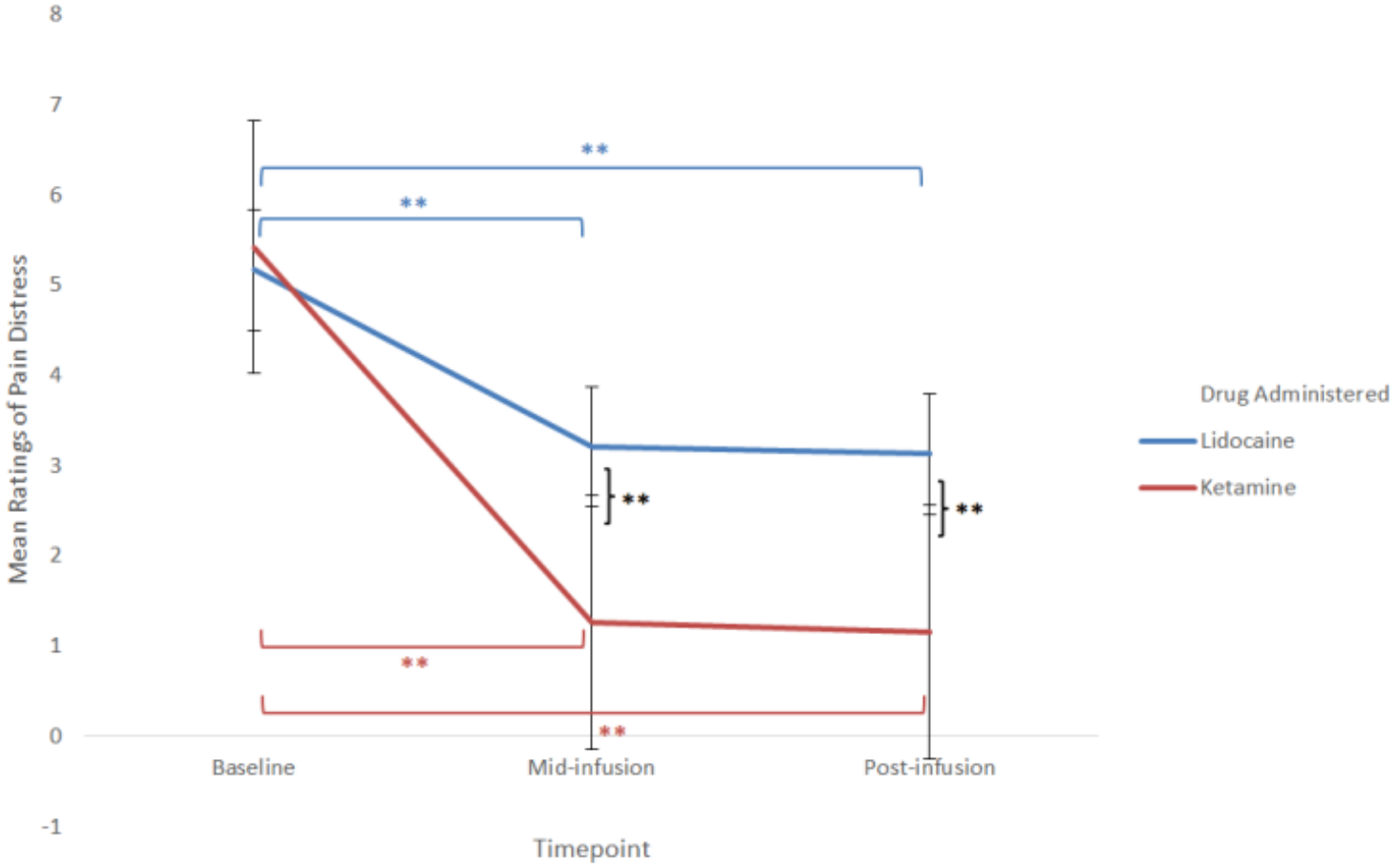
Mean Ratings of Pain Intensity (+/- Standard Error) Before, During and After Drug Administration for Participants Administered Ketamine and Lidocaine



*$p < 0.05$. **$p < 0.01$

Figure 4

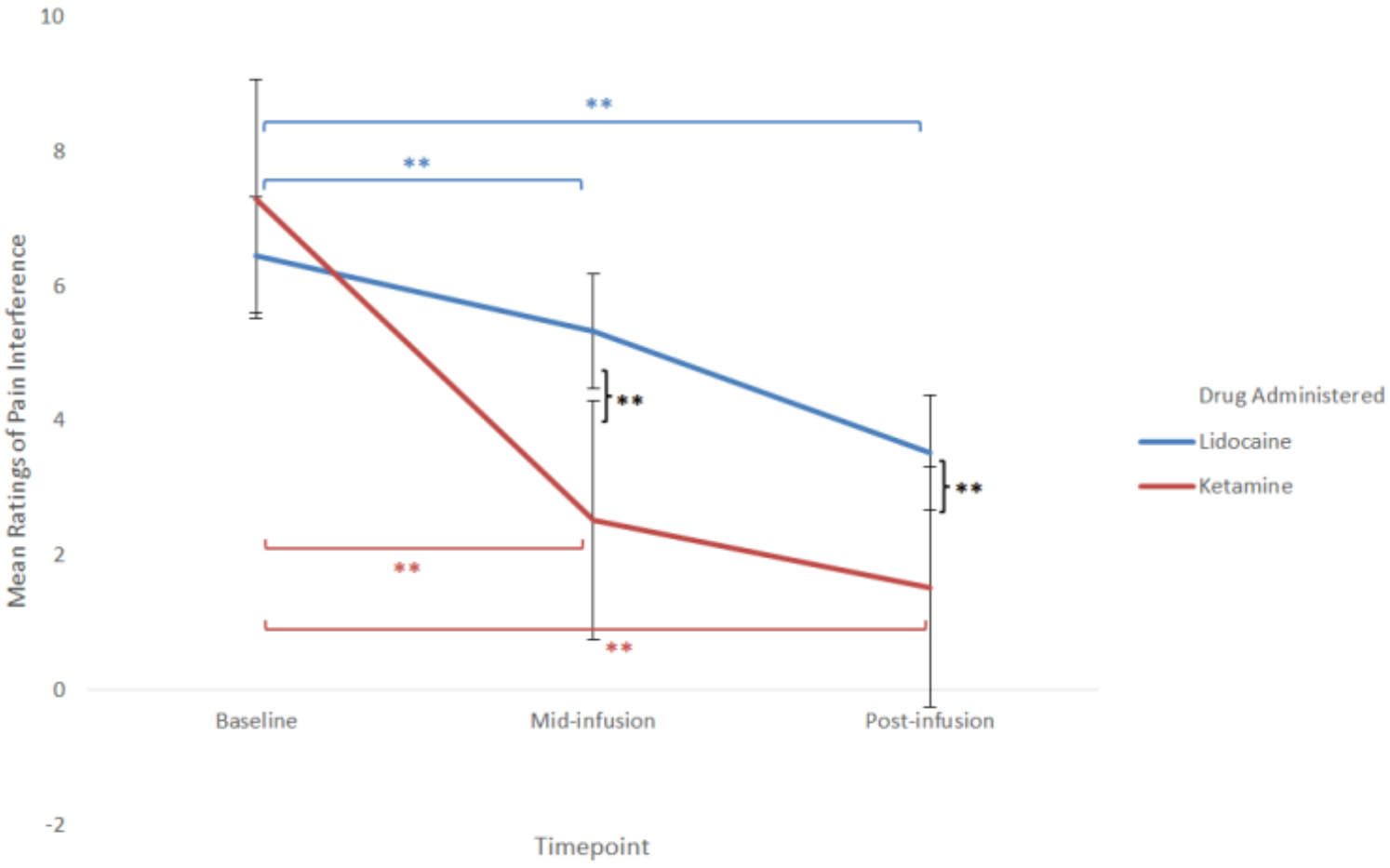
Mean Ratings of Pain Distress (+/- Standard Error) Before, During and After Drug Administration for Participants Administered Ketamine and Lidocaine



**$p < 0.01$

Figure 5

Mean Ratings of Pain Interference (+/- Standard Error) Before, During and After Drug Administration for Participants Administered Ketamine and Lidocaine



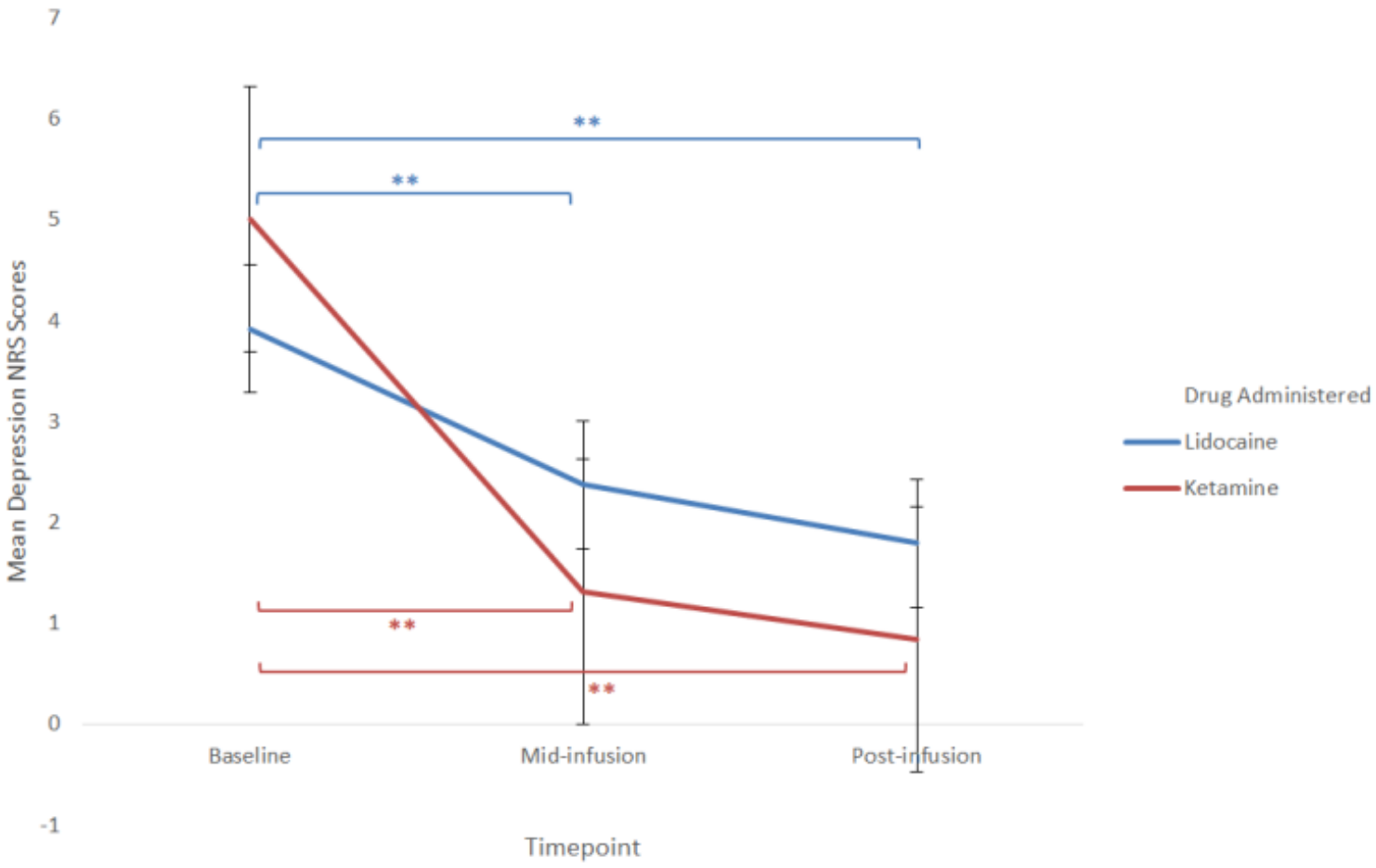
**$p < 0.01$

3.3.2 Mood

Acute changes in depression NRS were analysed using a mixed ANOVA. As indicated in Table 5, there was a significant interaction between time and drug for depression NRS scores (Figure 6). This interaction was explored using Bonferroni-corrected post-hoc tests which are reported in Appendix W. There was no significant main effect of drug but there was a significant main effect of time.

Figure 6

Mean Depression NRS Scores (+/- Standard Error) Before, During and After Drug Administration for Participants Administered Ketamine and Lidocaine



**$p < 0.01$

Table 5

Results of a Mixed ANOVA Exploring the Acute Effects of Drug and Time on Mood

Mood Domain		Baseline M (SD)	Mid-infusion M (SD)	Post-infusion M (SD)	ANOVA Conditions	*df* 1	*df* 2	*F*	Sig. *(p)*	η_p^2
Depression NRS[a]	Ketamine	5.00 (3.16)	1.32 (2.19)	0.84 (1.61)	**Time**	**1.662**	**68.129**	**50.921**	**<.001****	**.554**
	Lidocaine	3.92 (2.89)	2.38 (3.05)	1.79 (2.69)	Drug	1	41	.180	.674	.004
					Time x Drug	**1.662**	**68.129**	**6.551**	**.004****	**.138**

[a]. Mauchly's test of sphericity was significant, therefore sphericity could not be assumed and the Greenhouse-Geisser correction was applied.

**$p < 0.01$

3.3.3 Cognition

Acute changes in cognition were analysed using mixed ANOVAs. For all measures of cognition, an increase in score represented an improvement in performance, whereas a decrease indicated deterioration. As indicated in Table 6, there were significant interactions between time and drug for immediate recall (Figure 7), verbal fluency (Figure 8) and serial sevens (Figure 9). These interactions were explored using Bonferroni-corrected post-hoc tests which are reported in Appendix W. There was also a significant main effect of time on immediate and delayed recall. No other significant main effects of time or drug were found. There was a trend towards a main effect of drug on serial sevens score but this did not reach statistical significance.

Table 6

Results of Mixed ANOVAs Exploring the Acute Effects of Drug and Time on Immediate Recall, Verbal Fluency and Serial Sevens

Cognitive Domain		Baseline M (SD)	Mid-infusion M (SD)	ANOVA Conditions	*df* 1	*df* 2	*F*	Sig. *(p)*	η_p^2
Immediate recall	Ketamine	5.03 (3.31)	5.00 (3.36)	**Time**	**1**	**44**	**4.826**	**.033***	**.099**
	Lidocaine	5.17 (2.80)	7.06 (2.63)	Drug	1	44	1.969	.168	.043
				Time x Drug	**1**	**44**	**5.089**	**.029***	**.104**
Verbal fluency	Ketamine	11.00 (4.22)	10.30 (4.27)	Time	1	45	2.806	.101	.059
	Lidocaine	10.81 (4.01)	13.70 (4.67)	Drug	1	45	2.180	.147	.046
				Time x Drug	**1**	**45**	**7.543**	**.009****	**.144**
Serial sevens	Ketamine	6.00 (5.27)	4.79 (4.14)	Time	1	44	.005	.941	.000
	Lidocaine	8.89 (8.29)	10.04 (8.63)	Drug	1	44	3.727	.060	.078
				Time x Drug	**1**	**44**	**7.832**	**.008****	**.151**

*$p < 0.05$. **$p < 0.01$

Table 7

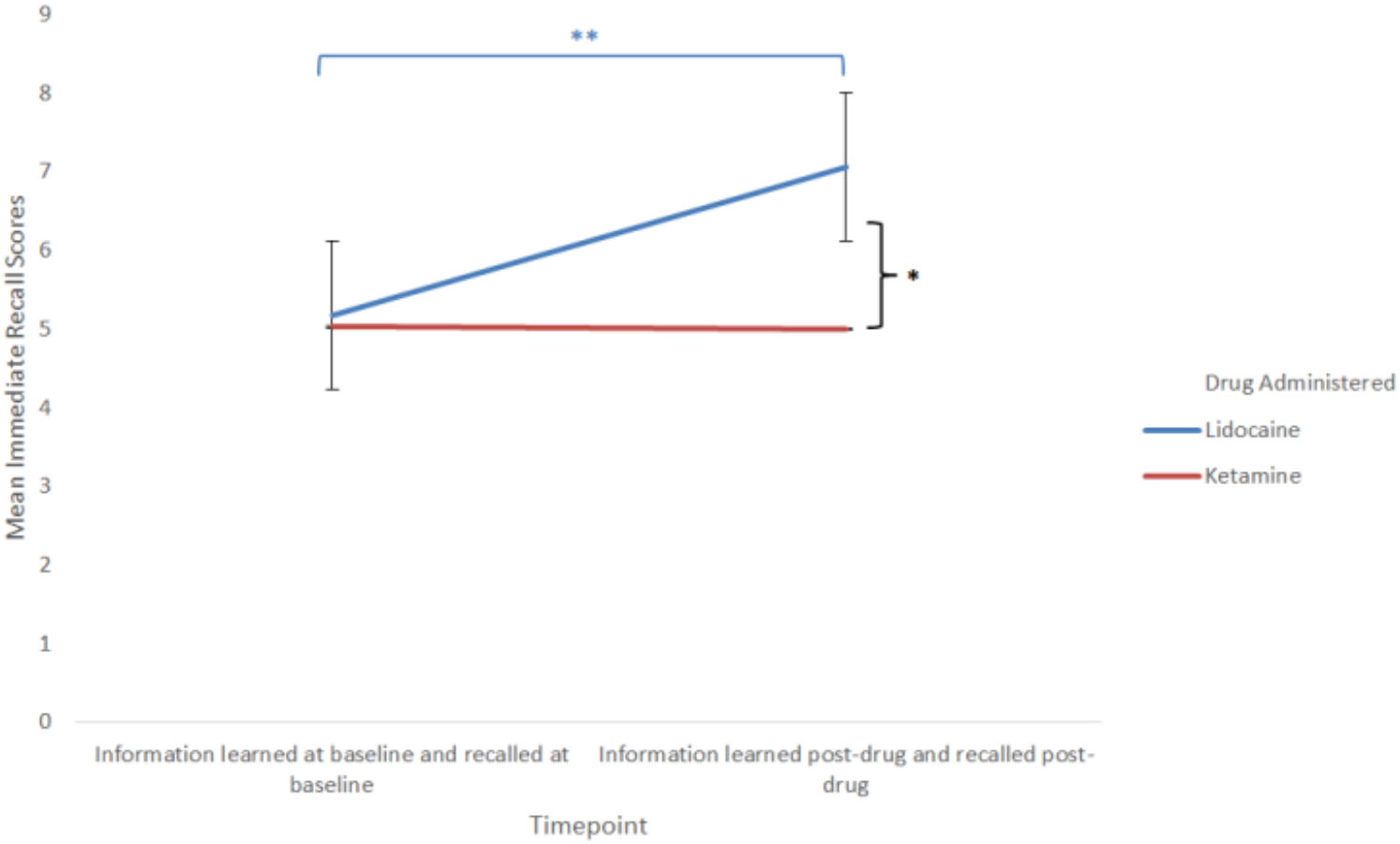
Results of a Mixed ANOVA Exploring the Acute Effects of Drug and Time on Delayed Recall

Cognitive Domain		Learned at baseline and recalled post-drug M (SD)	Learned post-drug and recalled post-drug M (SD)	ANOVA Conditions	*df* 1	*df* 2	*F*	Sig. *(p)*	η_p^2
Delayed recall	Ketamine	2.43 (2.64)	4.03 (3.61)	**Time**	**1**	**44**	**28.044**	**<.001****	**.389**
	Lidocaine	3.00 (2.19)	5.35 (2.61)	Drug	1	44	1.679	.202	.037
				Time x Drug	1	44	1.003	.322	.022

**$p < 0.01$

Figure 7

Mean Immediate Recall Scores of Information Learned and Recalled at Baseline compared to Mean Immediate Recall Scores of Information Learned and Recalled after Drug Administration (+/- Standard Error)

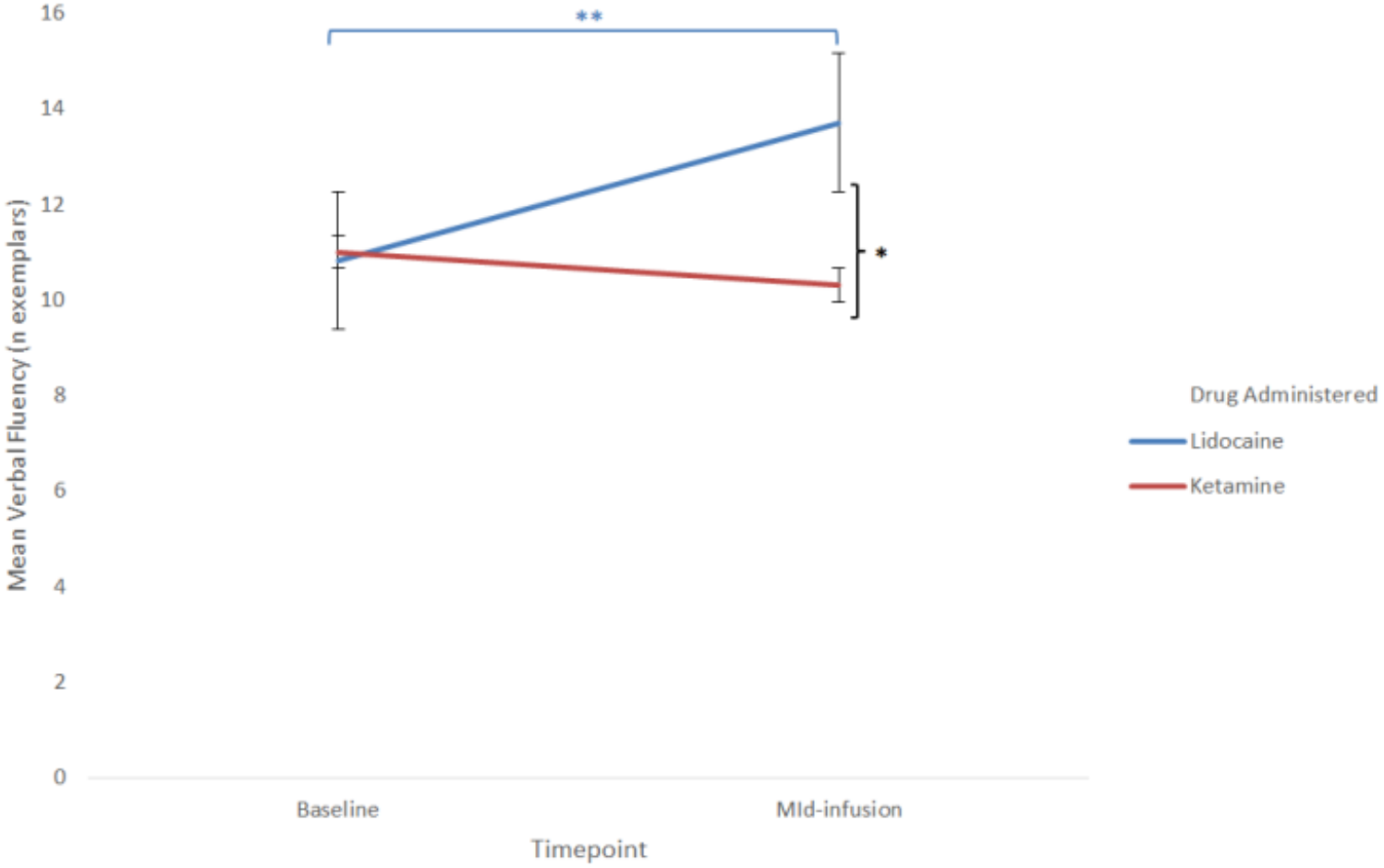


Note. Standard error bar for ketamine is displayed but is very small.

*$p < 0.05$. **$p < 0.01$

Figure 8

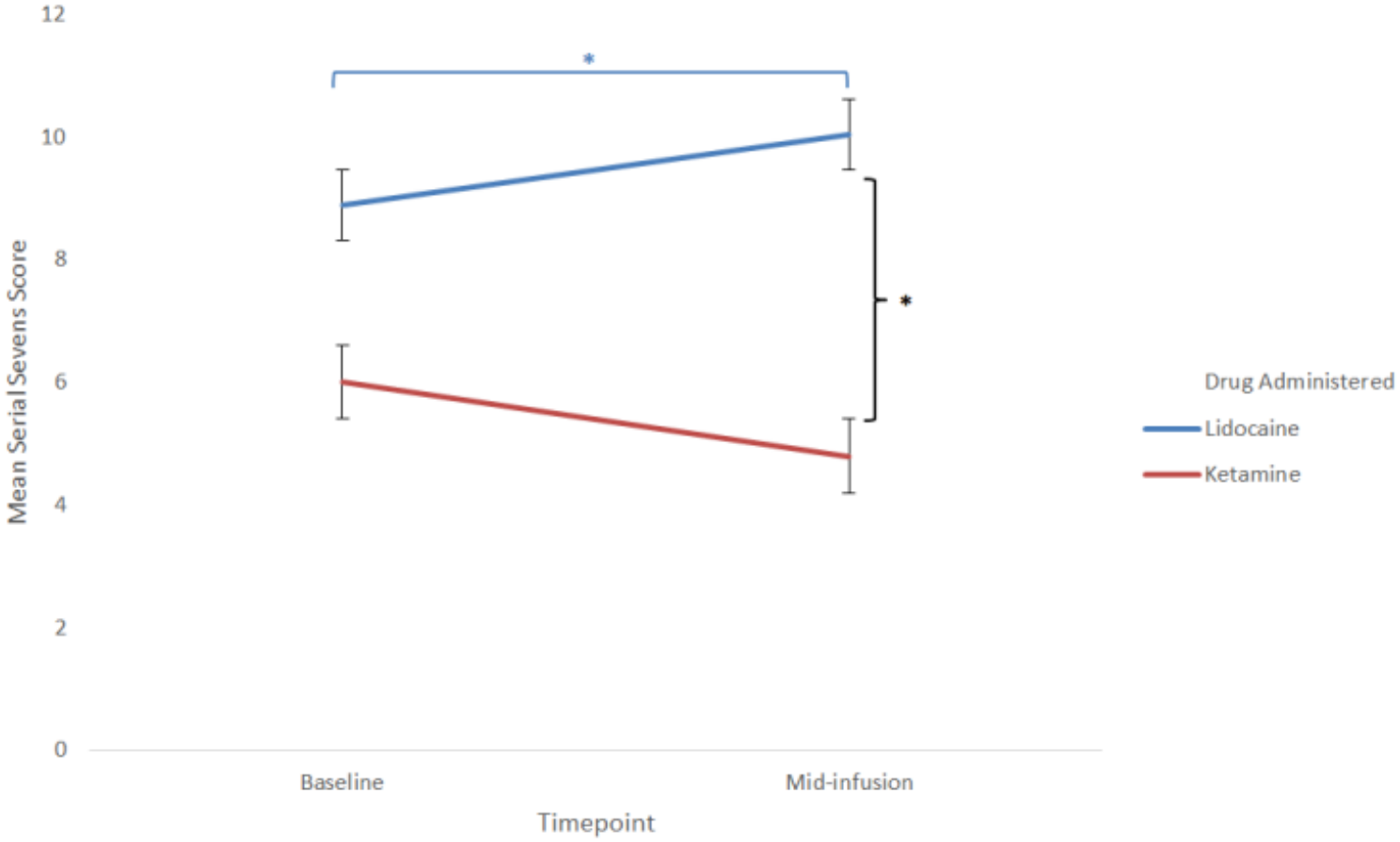
Mean Verbal Fluency (n exemplars) (+/- Standard Error) Before and During Drug Administration for Participants Administered Ketamine and Lidocaine



*$p < 0.05$. **$p < 0.01$

Figure 9

Mean Serial Sevens Scores (+/- Standard Error) Before and During Drug Administration for Participants Administered Ketamine and Lidocaine



*$p < 0.05$

3.3.4 Secondary Analysis – Correlations

Table 8 shows the Spearman's Rho correlations between acute changes in pain, mood and cognitive functioning for ketamine and lidocaine patients. Most notably, for ketamine participants, there were significant positive correlations between changes on the depression NRS and changes in pain intensity, distress and interference. Acute change scores are reported in Appendix X.

Table 8

Spearman's Rho Correlations between Acute Changes in Pain, Mood and Cognitive Functioning from Baseline to Mid-Infusion

	1	2	3	4	5	6	7
				Ketamine			
1. Pain intensity	-	**.667****	.343	**.510***	.119	.015	-.084
2. Pain distress		-	.384	**.528***	.289	.023	.008
3. Pain interference			-	**.654****	-.340	-.021	.232
4. Depression NRS				-	-.157	-.286	.075
5. Immediate recall					-	.262	.222
6. Verbal fluency						-	.296
7. Serial sevens							-
				Lidocaine			
1. Pain intensity	-	**.394***	.306	.155	.018	-.291	-.080
2. Pain distress		-	**.695****	**.459***	-.129	-.092	.064
3. Pain interference			-	.066	-.024	-.155	-.088
4. Depression NRS				-	.011	.034	.283
5. Immediate recall					-	**-.458***	-.120
6. Verbal fluency						-	**.388***
7. Serial sevens							-

Note. Delayed recall is not included as it was not measured at baseline.

*$p < 0.05$. **$p < 0.01$

3.4 Long-Term Effects of Ketamine and Lidocaine

3.4.1 Pain

Longer-term changes (between baseline and follow-ups) in pain were analysed using mixed ANOVAs (Table 9). There were no significant interactions between time and drug for any of the pain measures or any significant main effects of drug. There were significant main effects of time, such that pain intensity, distress and interference were significantly reduced at one-week follow-up compared to baseline, and pain intensity and distress were significantly reduced at long-term follow-up compared to baseline. There were no significant differences between pain intensity, distress or interference at one-week follow-up and long-term follow-up.

Table 9

Results of Mixed ANOVAs Exploring the Long-Term Effects of Drug and Time on Pain

Pain Domain		Baseline M (SD)	One-week follow-up M (SD)	Long-term follow-up M (SD)	ANOVA Conditions	*df* 1	*df* 2	*F*	Sig. *(p)*	η_p^2
Pain Intensity	Ketamine	6.89 (2.08)	5.22 (2.67)	5.83 (2.75)	**Time**	**2**	**72**	**12.659**	**<.001****	**.260**
	Lidocaine	6.95 (2.04)	5.20 (1.96)	5.40 (1.88)	Drug	1	36	.048	.828	.001
					Time x Drug	2	72	.278	.758	.008
Pain Distress	Ketamine	5.28 (3.23)	3.39 (3.26)	4.50 (3.38)	**Time**	**2**	**72**	**6.205**	**.003****	**.147**
	Lidocaine	5.60 (2.89)	4.35 (3.05)	4.50 (2.63)	Drug	1	36	.251	.619	.007
					Time x Drug	2	72	.595	.554	.016
Pain Interference	Ketamine	7.03 (2.52)	5.56 (2.33)	5.89 (3.41)	**Time**	**2**	**72**	**3.597**	**.032***	**.091**
	Lidocaine	6.55 (2.82)	5.75 (3.29)	5.65 (3.33)	Drug	1	36	.046	.831	.001
					Time x Drug	2	72	.267	.766	.007

*$p < 0.05$. **$p < 0.01$

3.4.2 Mood

Longer-term changes (between baseline and follow-ups) in mood were analysed using mixed ANOVAs (Table 10). There were no significant interactions between time and drug for any of the mood measures or any significant main effects of drug. There were significant main effects of time on all mood measures; however, the direction of this effect varied across measures. On the PHQ-2 and HADS-A, there were no significant differences between scores at baseline and long-term follow-up. However, HADS-D scores were significantly higher at long-term follow-up compared to both baseline and one-week follow-up. Finally, there was a trend towards depression NRS scores being reduced at long-term follow-up compared to baseline but this did not reach statistical significance.

Table 10

Results of Mixed ANOVAs Exploring the Long-Term Effects of Drug and Time on Mood

Mood Domain		Baseline M (SD)	One-week follow-up M (SD)	Long-term follow-up M (SD)	ANOVA Conditions	*df* 1	*df* 2	*F*	Sig. *(p)*	η_p^2
Depression NRS[a]	Ketamine	4.83 (3.43)	3.56 (2.71)	3.22 (3.93)	**Time**	**1.522**	**53.285**	**4.375**	**.026***	**.111**
	Lidocaine	3.79 (2.86)	2.95 (3.26)	3.42 (3.10)	Drug	1	35	.256	.616	.007
					Time x Drug	1.522	53.285	1.238	.290	.034
PHQ-2	Ketamine	2.83 (2.28)	1.89 (2.17)	3.17 (2.55)	**Time**	**2**	**72**	**6.096**	**.004****	**.145**
	Lidocaine	3.05 (2.24)	2.20 (2.26)	3.25 (2.31)	Drug	1	36	.105	.748	.003
					Time x Drug	2	72	.054	.948	.001
HADS-D	Ketamine	7.35 (4.82)	6.94 (4.49)	8.82 (5.54)	**Time**	**2**	**68**	**5.583**	**.006****	**.141**
	Lidocaine	8.21 (4.24)	7.63 (4.94)	9.89 (4.50)	Drug	1	34	.388	.538	.011
					Time x Drug	2	68	.043	.958	.001
HADS-A[a]	Ketamine	10.06 (4.52)	7.18 (5.32)	8.94 (5.82)	**Time**	**1.667**	**56.671**	**7.801**	**.002****	**.187**
	Lidocaine	9.63 (4.14)	8.26 (5.16)	10.84 (4.71)	Drug	1	34	.329	.570	.010
					Time x Drug	1.667	56.671	1.768	.185	.049

[a]. Mauchly's test of sphericity was significant, therefore sphericity could not be assumed and the Greenhouse-Geisser correction was applied.

*$p < 0.05$. **$p < 0.01$

3.4.3 Cognition

Longer-term changes (between baseline and follow-ups) in cognition were analysed using mixed ANOVAs. For all measures of cognition, an increase in score represented an improvement in performance, whereas a decrease indicated deterioration. As shown in Table 11, there were no significant interactions between time and drug for any of the cognitive measures or any significant main effects of drug. However, there was a significant main effect of time on immediate recall.

3.4.4 Secondary Analysis – Correlations

Table 12 shows the Spearman's Rho correlations between long-term changes in pain, mood and cognitive functioning for ketamine and lidocaine patients. From baseline to one-week follow-up, ketamine participants showed significant positive correlations between changes in pain interference and changes in depression NRS and HADS-A scores and between changes in pain intensity and depression NRS scores. At long-term follow-up these correlations were no longer significant. However, there was a significant positive correlation between changes in pain distress and changes in HADS-D scores from baseline to long-term follow-up. Long-term change scores are reported in Appendix Y.

Table 11

Results of Mixed ANOVAs Exploring the Long-Term Effects of Drug and Time on Immediate Recall, Verbal Fluency and Serial Sevens

Cognitive Domain		Baseline M (SD)	Long-term follow-up M (SD)	ANOVA Conditions	*df* 1	*df* 2	*F*	Sig. *(p)*	η_p^2
Immediate recall	Ketamine	5.21 (3.29)	7.92 (4.45)	**Time**	**1**	**42**	**28.582**	**<.001****	**.405**
	Lidocaine	5.10 (2.84)	7.98 (3.01)	Drug	1	42	.001	.977	.000
				Time x Drug	1	42	.026	.872	.001
Verbal fluency	Ketamine	11.00 (4.22)	11.50 (4.29)	Time	1	43	1.617	.210	.036
	Lidocaine	10.60 (4.09)	11.72 (4.45)	Drug	1	43	.007	.936	.000
				Time x Drug	1	43	.237	.629	.005
Serial sevens	Ketamine	6.00 (5.27)	6.47 (4.81)	Time	1	42	.359	.552	.008
	Lidocaine	8.72 (8.21)	8.84 (7.60)	Drug	1	42	1.587	.215	.036
				Time x Drug	1	42	.127	.723	.003

**$p < 0.01$

Table 12

Spearman's Rho Correlations between Long-Term Changes in Pain, Mood and Cognitive Functioning from Baseline to One-Week Follow-Up and Long-Term Follow-Up

	1	2	3	4	5	6	7	1	2	3	4	5	6	7	8	9	10
	One-week							Long-term									
Ketamine																	
1. Pain intensity	-	**.622****	**.555***	**.610****	-.025	-.098	.096	-	**.566****	.415	.159	.044	.225	-.348	.108	-.031	.032
2. Pain distress		-	.316	.177	.189	.052	.010		-	.284	.305	.431	**.483***	.156	.154	-.074	-.191
3. Pain interference			-	**.615****	.158	.236	**.471***			-	.181	-.056	.199	.100	**-.461***	-.148	.115
4. Depression NRS				-	-.160	-.276	.000				-	.269	.314	**.503***	-.048	.315	.200
5. PHQ-2					-	.418	.146					-	**.725****	**.491***	-.040	-.200	-.387
6. HADS-D						-	.283						-	**.559***	-.005	-.210	-.429
7. HADS-A							-							-	-.047	-.183	-.157
8. Immediate recall															-	-.116	.242
9. Verbal fluency																-	.235
10. Serial sevens																	-
Lidocaine																	
1. Pain intensity	-	**.578****	**.699****	**.736****	-.063	.275	.217	-	.386	.304	.245	.188	**.528****	.106	**.412***	.031	.034
2. Pain distress		-	**.618****	**.603****	.260	.350	.425		-	.300	**.590****	.145	**.545****	.262	.152	-.045	-.008
3. Pain interference			-	**.703****	-.133	**.620****	**.560****			-	.123	-.069	**.439***	.195	-.282	-.140	.133

4.	Depression NRS	-	.189	**.536***	**.532***	-	**.562****	**.669****	**.453***	.222	.155	.106
5.	PHQ-2		-	.278	.393		-	**.446***	**.668****	.146	.353	.021
6.	HADS-D			-	**.712****			-	**.453***	.102	.103	.060
7.	HADS-A				-				-	-.157	-.039	-.377
8.	Immediate recall									-	-.077	.065
9.	Verbal fluency										-	.181
10.	Serial sevens											-

Note. Delayed recall is not included as it was not measured at baseline.

*$p < 0.05$. **$p < 0.01$

4. Discussion

4.1 Overview

This paper described a naturalistic, non-randomised study exploring the acute and long-term effects of sub-anaesthetic intravenous infusions of ketamine (compared to lidocaine) on chronic pain patients. The two groups were compared in relation to changes in pain, mood and cognitive functioning. The associations between changes in these three domains were also explored.

4.2 Acute Effects

4.2.1 Pain

Both ketamine and lidocaine produced significant reductions in pain intensity, pain distress and pain interference during the acute phase (from baseline to mid-infusion and post-infusion). However, ketamine also produced significantly greater reductions in all three pain measures compared to lidocaine. These results are consistent with previous research demonstrating that ketamine is associated with significant acute pain relief (Backonja et al., 1994; Nourozi et al., 2010). However, a previous study comparing the effects of ketamine and lidocaine in 12 patients with chronic neuropathic pain did not find any significant differences between the two drugs in their acute impact on pain (Kvarnström et al., 2003). It is possible that this difference in findings is a result of the present study having a larger sample size and therefore greater power to detect an effect.

4.2.2 Mood

Depression NRS scores significantly decreased following both drugs, suggesting both groups experienced acute improvements in mood following drug administration. No differences in mood were found between ketamine and lidocaine participants mid-infusion or post-infusion. This could be because the measures were taken too soon after drug administration to capture any superior antidepressant effects that ketamine may have had over lidocaine. The antidepressant effects of ketamine have previously been shown to appear within 4 hours of administration (Berman et al, 2000; Murrough et al., 2013; Zarate et al., 2006), yet ketamine infusions only lasted 30-60 minutes and lidocaine infusions took one to three hours, meaning that the antidepressant effects may not have been captured at mid-infusion or post-infusion. If mood had been measured a little later, a difference may have been observed between the two groups. However, as this study was conducted as part of routine care, it was not possible to continue testing participants at the study site after their infusion had finished.

Correlation analyses indicated that acute reductions in depression NRS were significantly associated with reductions in pain intensity, pain distress and pain interference in ketamine patients, and with reductions in pain distress in lidocaine patients. This suggests that improvements in mood may have been a consequence of the reduced impact of pain, although it is not possible to make any causal claims based on these correlations.

4.2.3 Cognition

Lidocaine patients improved on a task of episodic memory (immediate story recall) from baseline to mid-infusion, whilst ketamine patients did not. Similarly, whereas individuals who received lidocaine improved on a verbal fluency task from baseline to mid-

infusion, the performance of ketamine patients remained the same. Finally, on a task of working memory and concentration (serial sevens), lidocaine patients showed a significant acute improvement in performance from baseline to mid-infusion. In contrast, ketamine patients performed worse at baseline (although this was not significant), and declined a little rather than improved.

The superior performance of the lidocaine group across all cognitive domains following drug administration could be explained by practice effects, whereas ketamine may have affected participants in such a way that meant they were unable to benefit from practice. Thus, at first glance there appears to be limited change in cognitive performance acutely following ketamine, however, when the results are compared against lidocaine there seems to be an acute practice-blocking effect on participants' cognitive performance once they have received ketamine. Pain reduction is not an explanation for improved cognitive performance in lidocaine patients as there were no significant associations between acute changes in pain and cognitive functioning for either drug.

4.3 Long-Term Effects

4.3.1 Pain

Results suggested that both drugs had some long-term effects on pain, as pain intensity, distress and interference were all significantly reduced in both groups at one-week follow-up compared to baseline, and pain intensity and distress remained reduced at long-term follow-up relative to baseline. However, many patients were taking other medications in addition to ketamine or lidocaine to manage their pain during this period, which could have also contributed to decreased pain ratings. A lack of significant difference between pain ratings at one-week follow-up and long-term follow-up in both groups suggests that some

improvements in pain were sustained over the longer-term; however, no further benefits were experienced after one week.

Despite ketamine leading to superior reductions in pain scores compared to lidocaine during the acute phase, this was not the case at one-week follow-up or long-term follow-up. This suggests that, over the longer-term, the effects of ketamine and lidocaine on pain were largely comparable. Given the design of the study, it was not possible to investigate how long the superior analgesic effects of ketamine were sustained after infusion, although it appeared to be less than one week.

This is partly reflected in the literature as numerous studies have demonstrated acute effects of ketamine on pain, but far fewer have shown longer-term effects (Niesters et al., 2014). There is evidence that the duration and/or frequency of infusions influences the duration of analgesic effect (Noppers et al., 2010). For example, an RCT assessing the analgesic efficacy of ketamine in fibromyalgia patients found that a 30-minute ketamine infusion produced analgesia lasting no longer than 45 minutes (Noppers et al., 2011). In contrast, Sigtermans et al. (2009) found that treating CRPS patients with a 100-hour ketamine infusion resulted in long-term pain relief for up to 10 weeks. Similar results were found in CRPS patients following daily 4-hour ketamine infusions over 10 days (Schwartzman et al., 2009). As the length of single ketamine infusions in the current study were only 30 minutes to one hour, it may be that this was not long enough to produce a significant long-term reduction in pain superior to that of lidocaine.

In addition, correlation analysis showed that, for both ketamine and lidocaine participants, reductions in pain ratings were associated with reductions in depression NRS (and, in some cases, HADS scores). It has been suggested that the neural network implicated in psychological pain (associated with depression) overlaps somewhat with brain regions

involved in physical pain (Meerwijk, et al., 2013). Thus, it is possible that ketamine and lidocaine were acting on neurobiological mechanisms common to both pain and depression. In the instance of ketamine, this is likely to be via inhibition of the NMDA receptor. It may also be that decreased pain led to improved quality of life for some individuals, leading to reductions in depression and/or anxiety. However, these correlations were not observed for PHQ-2 scores. This discrepancy may have reflected differences in the time windows of the mood measures, as the depression NRS asked participants how they felt 'right now' whereas the PHQ-2 asked about symptoms of depression over the past week.

4.3.2 Mood

Depression. Results showed a mixed picture with regard to the long-term effects of ketamine on mood. Depression NRS scores were significantly reduced at one-week follow-up relative to baseline, and this improvement in mood appeared to be maintained at long-term follow-up. However, although PHQ-2 scores were also significantly reduced at one-week follow-up compared to baseline, these had returned to baseline levels by long-term follow-up. No significant improvement in HADS-D scores was observed at one-week follow-up, and at long-term follow-up HADS-D scores were more elevated than at baseline. A similar mixed picture was also observed in lidocaine patients.

This discrepancy in findings across depression measures highlights the challenges of assessing mood in the chronic pain population. The HADS-D was originally chosen as the most suitable measure as it was developed for use in a physical health setting, whereas the depression NRS and PHQ-2 were selected to provide generalisability with research exploring the antidepressant and reinforcing properties of ketamine. A potential explanation for these inconsistent findings may be that the PHQ-2 and depression NRS lack specificity when used

with chronic pain patients. Therefore, results from these measures should be interpreted with caution.

If greater weight is placed on HADS-D scores, these were significantly higher in both groups at long-term follow-up compared to baseline. One possible contributing factor may have been the COVID-19 pandemic. This is supported by the results of the COVID-19 questionnaire (Appendix Z) which showed that the majority of participants reported negative impacts in multiple life domains as a result of the pandemic.

As predicted, none of the depression measures showed a superior effect of ketamine over lidocaine in the longer-term, which is unsurprising given the lack of evidence of a sustained antidepressant effect of ketamine in the literature. Also, just as the measures may have been administered too soon to capture ketamine's antidepressant effects (section *4.2.2*), they may also have been taken too late. The antidepressant effects of ketamine have been shown to peak at 24 hours (Abdallah et al., 2015; Corriger & Pickering, 2019; Marcantoni et al., 2020). Therefore, any antidepressant effects ketamine may have had may not have been captured at one-week follow-up or long-term follow-up.

Another possible explanation is that the frequency and/or duration of ketamine infusions were not sufficient to have a long-term impact on mood. For example, 70.8% of patients with TRD who received up to six ketamine infusions over 12 days showed a significant reduction in depressive symptoms (Murrough et al., 2013). It is important to note, however, that among responders the median time to relapse after the last ketamine infusion was only 18 days. This suggests that patients may require maintenance doses to sustain an antidepressant response to ketamine and that a single, infrequent dose may not be sufficient to have a sustained antidepressant effect.

Finally, the majority of participants in this study did not meet the threshold for clinical depression at baseline (based on HADS-D scores) so may have differed substantially from those with TRD, where most of the research on the antidepressant effects of ketamine has been conducted. Therefore, it is possible that ketamine is not as effective an antidepressant in the chronic pain population as it is in TRD.

Anxiety. There were significant decreases in HADS-A scores from baseline to one-week follow-up for both drug groups. However, by long-term follow-up, anxiety scores had returned to baseline levels for both groups, suggesting this was only a transient effect.

Improvements in anxiety at one-week follow-up may have been a consequence of reductions in pain, as correlational analyses indicated associations between reductions in anxiety scores and reductions in pain interference for ketamine and lidocaine patients. However, there were no associations between reductions in anxiety and pain for either group at long-term follow-up.

Ketamine may also have had a more direct effect on anxiety as evidence is emerging of its anxiolytic properties, with a recent review highlighting limited yet growing evidence to support the use of ketamine for anxiety disorders (Banov et al., 2020). The current findings suggest that similar, although potentially briefer effects, may exist within the chronic pain population. However, the evidence base regarding anxiety is less well-established than that of depression.

4.3.3 Cognition

Both groups demonstrated improved performance on immediate recall at long-term follow-up relative to baseline. This was possibly due to a difference in testing conditions, as

participants completed the long-term follow-up at home over the telephone where there were likely fewer distractions than at the study site where baseline measures were collected. In addition, a home environment may have been less anxiety provoking for participants, resulting in better attentional function.

The superior cognitive performance of lidocaine patients observed acutely was not sustained at long-term follow-up in any of the cognitive domains. This suggests that the hypothesised practice-blocking effect of ketamine may be transient. Due to the design of this study, it was not possible to ascertain how long this effect lasted, but this would be important for future research to establish. This finding tentatively suggests that the adverse cognitive effects seen in frequent recreational ketamine users do not extend to repeated (though comparatively infrequent) users for medicinal purposes. Furthermore, this finding differs from previous research which reported that long-term frequent ketamine treatment (twice a month for six months) may impair executive functioning in CRPS patients (Kim et al., 2016). One possible explanation for this discrepancy is that infusions at the study site are delivered less frequently (once every three months) and so may produce fewer long-term cognitive impairments when administered at this reduced frequency.

4.4 Limitations

A number of limitations with the current study should be acknowledged. Firstly, as this was a naturalistic study in which participants received ketamine or lidocaine as part of their routine medical care, it was not possible to control how many previous infusions of either ketamine or lidocaine individuals had received, nor was it possible to control drug doses. This meant that patients received slightly different doses which may have affected their responses on various outcome measures. Moreover, many patients reported that they

were regularly using other drugs or medications (in addition to ketamine or lidocaine) to manage their pain, including opioids and cannabinoids, as well as various psychotropic medications and medications for other physical health conditions (e.g. high blood pressure). It was not possible to control for all of these factors, therefore it is possible that these other substances could have also affected their pain, mood and cognitive functioning.

The naturalistic aspect of the study also meant that participants and medical staff could not be blinded to treatment condition. Differences in infusion length also prevented the blinding of researchers. Ketamine infusions lasted 30-60 minutes whereas lidocaine infusions took one to three hours. This also affected when mid-infusion measures were collected, such that ketamine and lidocaine patients repeated the cognitive tasks 15-30 and 30-90 minutes after baseline, respectively. Therefore, it could be argued that ketamine patients had an advantage due to recency effects. However, there was no evidence to support this as the lidocaine group demonstrated superior performance across all cognitive domains at mid-infusion.

A further limitation was the lack of randomisation to the between-subjects factor (drug). This increased the possibility of systematic differences between the two groups other than the drug being administered. Such differences could have been confounding variables and affected the results. Fortunately, demographics and baseline scores were compared between groups and no significant differences were found which minimised this risk.

Moreover, some patients who met the inclusion criteria for long-term follow-up declined to participate. This may have introduced bias into the results, particularly if this decision was influenced by the variables of interest (for example, if they were in too much pain or felt too depressed to complete the study). However, the broad similarity in results of the acute and one-week follow-up analysis for those who participated in the long-term

follow-up (n = 47) and that of the full sample (n = 99) suggested that the subsample included in the current study was largely representative of the wider sample and thus may reduce concerns about bias.

Nevertheless, this also reduced the sample size; therefore it may be that the failure to demonstrate significant effects over the longer-term period was a result of low power. The reduced sample size meant that the hypotheses of no effect (in relation to finding significant differences in pain and mood ratings between ketamine and lidocaine patients at long-term follow-up) were most likely underpowered. This may have meant there was low probability of detecting an effect even if one were present and that the reported null results could be false negatives (i.e. Type II error) arising from the study being underpowered. This risk could be minimised by increasing the sample size and/or increasing the significance level (e.g. α=0.10 instead of α =0.05), however this would mean that the probability of committing a Type I error (i.e. false positive) would increase. Consequently, there is always a trade-off between Type I and Type II errors.

There was also a lack of consistency between how data was collected in the acute and long-term phases. The one-week follow-up and long-term follow-up were conducted over the telephone with the researcher asking the questions verbally, whereas the baseline, mid-infusion and post-infusion data was collected in person and participants were able to read the questions themselves as they were being asked. The difference in environment may have affected participants' responses on the self-report measures and how clearly they heard and understood the cognitive tasks.

Finally, another limitation was the variation in the number of days since infusion at which the long-term follow-up occurred. However, this was not considered too problematic

as these drug treatments are intended to have long-term effects and there was no significant difference in the length of long-term follow-up between the two groups.

4.5 Implications for Clinical Practice

The current study has several implications for clinical practice. Firstly, the findings demonstrate that both ketamine and lidocaine can significantly reduce pain intensity, distress and interference in chronic pain patients during the acute period. Moreover, although ketamine showed superior analgesic effects (over lidocaine) during the acute phase, this difference was not sustained and by one week participants in the two groups were reporting similar levels of pain. Therefore, it is somewhat surprising that, despite ketamine yielding superior short-term results and equivalent long-term results over a shorter length of infusion (thereby requiring fewer resources), it is usually only considered if lidocaine has been ineffective or is not medically appropriate. These findings may encourage the study site to offer ketamine more widely to other patients, and for more sites to offer ketamine as an alternative treatment for chronic pain.

The antidepressant effects of ketamine demonstrated in previous research were not found in the present study, either acutely or in the longer-term. This suggests that, in the chronic pain population, a single ketamine infusion does not reduce depressive symptoms beyond that which might be associated with pain relief. However, it should be noted that unlike trials of antidepressant effects, the participants in the current study were not seeking treatment for depression. Nonetheless, clinicians should ensure that patients receiving ketamine infusions for pain are receiving additional treatment for low mood where this is indicated.

Finally, patients receiving ketamine infusions should be informed that their cognition may be affected in the short-term. Staff should therefore avoid discussing important information with patients once their infusion has commenced or provide it in writing so they can read it again in their own time. Regarding the long-term effects on cognition, the findings tentatively suggest that the adverse cognitive effects seen in frequent recreational ketamine users do not extend to repeated (though comparatively infrequent) users for medicinal purposes. More research is needed; however these preliminary results may be reassuring to patients receiving ketamine treatment.

4.6 Directions for Future Research

Firstly, it would be interesting to follow-up participants from the previous studies who had discontinued ketamine or lidocaine infusions (and were therefore ineligible to participate in the current study) and explore their reasons for doing so. Termination of treatment was more common in the ketamine group than the lidocaine group. Possible hypotheses could include unpleasant side-effects (including psychotomimetic effects), not finding the drug effective, cessation of pain through other means, or possible stigma associated with ketamine due to its use as a recreational drug. Secondly, future research should investigate ways of maximising the duration of ketamine's superior analgesic effects, such as by varying the frequency and duration of infusions to establish optimised treatment schedules. Finally, researchers should consider implementing a more comprehensive follow-up regime to ascertain for how long the cognitive impairments observed in the ketamine group continue. This follow-up should also involve assessing mood in-between the acute phase and one-week follow-up, as previous studies have found ketamine has most benefit here. This may require the development of new mood measures, as this study highlights the challenges of assessing mood in the chronic pain population. Further research may also wish to explore in more depth

the effect of ketamine on anxiety in this population, as there has been less attention on this subject in comparison to depression.

4.7 Conclusions

These findings indicate that ketamine infusions are effective at reducing symptoms of chronic pain. However, although ketamine produced superior analgesic effects over lidocaine during the acute phase, this advantage was not sustained over the longer-term. Ketamine did not show any specific antidepressant effects in a chronic pain population, either acutely or over the longer-term. Ketamine acutely impaired performance on tasks of episodic memory, verbal fluency and working memory and concentration. This was hypothesised to be due to a practice-blocking effect. However, these cognitive impairments were no longer observed at long-term follow-up, suggesting that they are transient.

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Part 3: Critical Appraisal

Overview

In this critical appraisal I will share my reflections on the process of completing the DClinPsy thesis, which draws on a reflective journal that I kept over the duration of the research period. This will predominantly focus on the empirical paper, but will also touch on some aspects of the literature review. Firstly, I will examine why I chose to carry out this particular research project. I will then consider the impact of COVID-19 on my experiences of conducting the empirical research, both the benefits and drawbacks. Next, I will share my reflections on two aspects of identity and difference that came to light during this process. Finally, I will discuss the challenges of being a researcher within a clinical setting and how this differed from my usual therapeutic role.

Choosing a Research Topic

I remember my interest being piqued in the area of psychopharmacology following a lecture we received in the first year of DClinPsy training. This lecture explored drug treatments for psychological disorders and was delivered by Professor Valerie Curran (who would go on to become one of my supervisors). I was particularly interested in hearing about drugs traditionally used for recreational purposes being adapted for therapeutic use, such as MDMA-assisted psychotherapy for post-traumatic stress disorder (Sessa, 2017) and psilocybin for treatment-resistant depression (Carhart-Harris et al., 2016) and I remember this lecture left me wanting to find out more. This made sense when reflecting on the subjects I had enjoyed the most at school (biology and psychology) and my decision to pursue a Master's degree in neuroscience. Thus, when it came to choosing a research topic, exploring the effects of ketamine in a physical health population appealed to me as it could combine my interests in these areas.

I was also drawn to this particular study because it was a continuation of an existing project and therefore much of the preparation had already been done (for example, obtaining ethical approval, selecting measures and establishing a recruitment pathway). As I did not have vast amounts of clinical experience prior to training, I remember at this point in the course feeling as though I had a lot of work to do with regard to developing my clinical skills. Therefore, I chose a research project that had a clear structure and direction, enabling me to focus more of my attention on my clinical work.

When selecting a topic for the literature review, I wanted to balance out the pharmacological focus of the empirical paper with a more psychologically oriented intervention. I was drawn to compassion-based approaches because, at that time, I was supporting frontline staff during the pandemic and I could see the benefits of these interventions within this population. This prompted me to explore how compassion-based interventions might also apply to patients with chronic pain.

The Impact of Covid-19

Limitations

It is difficult to critically reflect on the process of doing this research without acknowledging the role that the pandemic played at every stage of the journey. When we entered into the first national lockdown in March 2020, I underestimated the magnitude of the impact this would have on the project as we had not begun data collection at this stage and were not planning to do so until the summer. I (naively) assumed that by summer we would be able to resume our original thesis proposal, which would have involved collecting data in person at the study site. However, as the scale of the disruption became more apparent and restrictions on face-to-face research in the NHS continued, it became clear that we needed to

adapt our project in order to meet the thesis submission deadline. Whilst before the pandemic I had felt quite confident about the project, I started to feel worried. It was during this time that I felt particularly grateful to have been part of a joint project so that my research partner and I could navigate this uncertainty together.

Due to these changes, we needed to submit a non-substantial amendment to our NHS ethics. I had been warned by previous trainees that applying for NHS ethics was a complex and time-consuming process and, despite only needing an amendment, this proved to be true. This was largely due to poor communication, with e-mails being 'lost' and members of the same team delivering different messages. These issues were likely exacerbated by the pandemic, as staff had begun working from home and so were physically separated from their colleagues and harder for us to reach by telephone. Thus, despite submitting the amendment in April 2020, it was not approved until August 2020. This was a particularly frustrating period of the research process and required a lot of patience and perseverance.

Despite this desire to get started, I wish I had spent more time in the planning stage before starting recruitment and data collection. For example, if I had spent longer planning the analysis, I would have included receiving an infusion within the last week as an exclusion criteria. However, given the delays with ethics and a false belief that I was behind in comparison to other trainees, I felt a sense of urgency to 'get going' as soon as possible. Unfortunately, having not thought this through at length, it meant having to exclude four participants from the analysis who would otherwise have been eligible. After further reflection, I realised that this tendency to rush in shows up in other areas of my life and it is something I intend to be more mindful of going forwards.

Once recruitment and data collection began, one of the biggest challenges I encountered was managing risk remotely. Participants were asked directly about their mood

over the telephone and many talked about feeling depressed and/or suicidal. For one participant, this also raised safeguarding concerns about a child in their care. There appeared to be many different factors contributing to low mood, including pain, the pandemic and, for lidocaine patients, the recent introduction of a new treatment pathway at the study site which meant that they could only receive infusions for a maximum of two years before being discharged back to the care of the GP. A significant minority of lidocaine patients said that these infusions were the only thing that was keeping them going and that if they were to stop they did not think they could carry on. As such, they reported feeling increasingly hopeless about the future.

However, it had been agreed that the medical team holds the risk, not the researchers; therefore participants were required to consent to information about suicidal thoughts or depression being passed onto their consultant to inform their care. Whereas this process had been relatively straightforward in the past, as previous trainees had completed the majority of data collection at the study site and could therefore discuss this information in person with clinic staff, remote working created some additional obstacles. Fortunately, we developed a clear risk protocol such that if risk arose, the researcher immediately telephoned the clinic administrator (who was very responsive) and obtained the details of the psychologist on duty that day. The researcher would share the information with the psychologist, who would discuss with the rest of the team and follow up with the patient (of course, if a patient had been at immediate risk of harm more urgent action would have been taken, but fortunately this was not necessary). Although this process appeared to work well, managing risk was not a part of the research process that I particularly enjoyed. It was also partly for this reason that we decided not to recruit participants that had been discharged from the study site as this pathway for managing risk would not have been in place.

As well as the practicalities of managing risk remotely, there was also the emotional aspect of completing this work from home. Some participants reported considerable amounts of emotional distress and, although they were not asked directly about it, were opening up about difficult life events they had experienced. Due to my current living conditions, I had no choice but to complete these telephone calls from my bedroom. However, this meant that the boundaries between work and home were becoming increasingly blurred. This was something I had already experienced when completing two of my clinical placements from home; however, unlike my placements, there was no dedicated space to process and reflect on these conversations in supervision, nor did I have the opportunity to discuss informally with staff at the study site. Fortunately, my research partner and I were able to check-in with each other after challenging conversations. However, if I become involved in future research projects, I would perhaps consider setting up a more formal supervision/reflective space.

In addition, participants and previous trainees spoke very highly of the clinic staff. It was therefore a shame not to be able to build these relationships myself. Indeed, many participants shared how grateful they felt to be receiving care from the study site and wanted me to pass on their warm wishes to the staff.

Finally, before the study was modified in light of COVID-19 restrictions, an *a priori* power analysis was performed based on the original research proposal. The analysis indicated that this study would have been well-powered, with sufficient power to explore mediating and moderating variables. However, as a result of the changes made to the research design, the present study had less power to detect smaller effects and mediation/moderation analysis was no longer feasible.

Strengths

Despite all of the challenges that the pandemic presented for this research project, there were also some unexpected benefits. Firstly, because data collection took place during the second and third national lockdowns when the UK government slogan was to 'stay at home', many participants said that they had more time available than usual and therefore the majority of people asked were very willing to participate. This increased availability and flexibility also meant that it was relatively easy to schedule participants in for testing. Moreover, there were very few cancellations or 'did not attend' (DNA), whereas the previous trainees had cited this as an issue when testing had taken place on the day of the infusion. These factors contributed to the present study having a retention rate of 70%, which falls within the recommended follow-up thresholds of 60-80% (Kristman et al., 2004). Finally, conducting the research remotely may have also made participation more accessible for more people. For example, if the research had proceeded in person, it risked alienating a large proportion of patients who were shielding or unable to travel to the study site for other reasons and these voices would not have been captured in this research.

Social GGRRAAACCEEESSS

The Social GGRRAAACCEEESSS (Burnham, 2012) represent aspects of identity which can be visible and invisible, voiced and unvoiced. Whilst some visible characteristics were less evident over the telephone, other GGRRAAACCEEESSS came more into prominence during my conversations with participants. I will focus on two which felt particularly pertinent: (1) ability and (2) class/socioeconomic status.

One of the things that struck me the most was how many participants stated that the pandemic had given healthy individuals an insight into the lifestyles of people with chronic

pain, such as not being able to do as much or to go to as many places as they would like to, feeling stuck indoors, increased fear and uncertainty about their health, and the medical community not having all of the answers to their questions. Participants therefore spoke about feeling more prepared for the pandemic than the average person because they had already developed skills to cope with these challenges. In addition, participants said that they felt more "normal", they felt as though their way of living had been validated and they felt more understood by family and friends, which was really powerful to hear. As somebody who is fortunate not to have yet experienced chronic pain or a long-term disability, differences in ability can be a blind spot for me. I hope that, by conducting this research, this is something I will be more consciously aware of going forward.

Secondly, when completing the COVID-19 questionnaire and asking about any perceived benefits brought about by the pandemic, several participants interpreted 'benefits' to mean financial support and began discussing the payments they were receiving. Approaching this question from a position of privilege, I had failed to recognise that this language may have different connotations for some people. Although this could easily be clarified over the telephone, if this had been administered as a written questionnaire this could have affected the findings. This was an important reminder about the different meanings language can hold based on aspects of our identity.

Role as a Researcher

One part of the research process that I found particularly challenging was navigating my role as a researcher within a clinical setting. This difficulty occurred most frequently when I heard participants expressing struggles with their mental health and, although I knew I did not have clinical responsibility for these patients, I nevertheless felt compelled to do

something to help them, which was not my role. One effect of this was that I sometimes felt reluctant to enquire about mood; for fear of opening something up that I was then not in a position to adequately contain. Although I communicated this information promptly to the clinical team, I was often left with a lingering feeling of wanting to do more for these patients and a sense of guilt that I had not done enough. I also experienced feelings of hopelessness, as though there was nothing that could be done to help. Indeed, it is possible that this was a reflection of how the participants were feeling themselves.

Another challenge I encountered in my research role was managing participants' emotional responses towards the clinic. Some patients were, understandably, angry that their infusions had stopped during the pandemic and believed that they were still experiencing the effects of this even once their infusions had resumed (for example, some thought that having a longer interval between infusions meant that they did not have as strong a response to subsequent infusions). I found it was a difficult balance between empathising with patients and validating their feelings, whilst not getting drawn into criticising the clinic as I could also understand the actions they had needed to take.

Finally, despite the measures being very structured, I sometimes found myself struggling to contain participants' responses. For example, a closed, multiple-choice question would often provoke a very detailed answer. Whereas in therapy, I would normally have the opportunity to carry these conversations over to the next session where I could continue to assess and formulate, here I felt there was a pressure to capture all of the information during one session. However, several participants explained that it was difficult to reduce their complex and multifaceted experiences down into a numerical rating or multiple-choice option. This was understandable, and it was also not surprising as it was something I had seen in my clinical work when administering outcome measures. Furthermore, many participants reported having significantly reduced social contact during the pandemic and said that they

were enjoying the opportunity to connect with another person, especially those who were isolated from their loved ones. For these reasons, I did not want to curtail their responses; however, this meant that sometimes the telephone calls lasted longer than anticipated. This was only an issue when I had scheduled back-to-back appointments, as I did not want to keep the next participant waiting. I therefore began leaving longer breaks between sessions and, if the extra time was not needed, I would use it to score the previous participant's data.

Despite these challenges and additional considerations, I very much enjoyed my time in a research role. In large part, this was due to the participants themselves, who were a delight to speak with and displayed an openness, curiosity and willingness to take part in the research that I had not envisaged prior to starting recruitment. I had anticipated that recruitment would prove difficult during the pandemic, given the various stressors people were experiencing in addition to their pre-existing health conditions. However, this was not the case. The majority of people who were invited to take part were keen and willing to do so. When they declined, this was for understandable reasons, such as being unwell or increased caring responsibilities. This was perhaps all the more surprising as there was very little direct benefit for the participants themselves. Several commented that their decision to participate was driven by a desire to advance our understanding of the most effective treatments for chronic pain, in the hope that this may prevent other people from suffering in the same way they had. This is consistent with research demonstrating that the most common motivating factors for agreeing to take part in psychiatric research are to help science progress and to allow future patients to benefit from improved diagnosis and treatment (Zullino et al., 2003). It goes without saying that I am extremely grateful to these participants, without whom this thesis would not exist.

Conclusions

Completing this thesis has been a challenging – yet rewarding – experience. I have learnt a lot along the way – both in terms of developing my research skills, but also about myself and how I approach my work. Whilst I would not have chosen to carry out my major research project in the midst of a pandemic, it has taught me important lessons about tolerating uncertainty and adapting to unforeseen circumstances. These are helpful experiences I will take forward with me as I near the end of DClinPsy training and begin my first qualified role.

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Appendices

Appendix A – Search Strategy for Literature Review

MEDLINE

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to July 21, 2020>

Search Strategy:

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1 (chronic pain or persistent pain or fibromyalgia).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (58103)

2 Chronic Pain/ (14485)

3 (compassion* or CFT or cultivating emotional balance or CEB or loving-kindness meditation or LKM or metta).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (13861)

4 (depress* or mood or PHQ-9 or PHQ-2 or BDI or CES-D or HADS or HADS-D or SDS or GDS or HRSD or HDRS or HAM-D or MADRS).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (664429)

5 Depression/ (118895)

6 1 or 2 (58103)

7 4 or 5 (664429)

8 3 and 6 and 7 (30)

PsycINFO

Database: APA PsycInfo <1806 to July Week 2 2020>

Search Strategy:

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1 (chronic pain or persistent pain or fibromyalgia).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (22982)

2 Chronic Pain/ (13446)

3 (compassion* or CFT or cultivating emotional balance or CEB or loving-kindness meditation or LKM or metta).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (12152)

4 (depress* or mood or PHQ-9 or PHQ-2 or BDI or CES-D or HADS or HADS-D or SDS or GDS or HRSD or HDRS or HAM-D or MADRS).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (409829)

5 "Depression (Emotion)"/ (25568)

6 1 or 2 (22982)

7 4 or 5 (409829)

8 3 and 6 and 7 (52)

Web of Science

TOPIC: (("chronic pain" OR "persistent pain" OR "fibromyalgia")) AND TOPIC: (("compassion*" OR "CFT" OR "cultivating emotional balance" OR "CEB" OR "loving-kindness meditation" OR "LKM" OR "metta")) AND TOPIC: (("depress*" OR "mood" OR "PHQ-9" OR "PHQ-2" OR "BDI" OR "CES-D" OR "HADS" OR "HADS-D" OR "SDS" OR "GDS" OR "HRSD" OR "HDRS" OR "HAM-D" OR "MADRS"))

Cochrane Library

("chronic pain" OR "persistent pain" OR "fibromyalgia"):ti,ab,kw AND (compassion* OR CFT OR "cultivating emotional balance" OR CEB OR "loving-kindness meditation" OR LKM OR metta):ti,ab,kw AND (depress* OR mood OR PHQ-9 OR PHQ-2 OR BDI OR CES-D OR HADS OR HADS-D OR SDS OR GDS OR HRSD OR HDRS OR HAM-D OR MADRS):ti,ab,kw" (Word variations have been searched)

Appendix B – RoB 2: A revised tool for assessing risk of bias in randomised trials

Table B1

Version 2 of the Cochrane Risk-of-Bias Assessment Tool for Randomised Trials. Taken from Sterne et al. (2019).

Removed Due to Copyright

Appendix C - ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions

Table C1

Bias Domains Included in ROBINS-I. Taken from Sterne et al. (2016).

Removed Due to Copyright

Table C2

Interpretation of Domain-Level and Overall Risk of Bias Judgements in ROBINS-I. Taken from Sterne et al. (2016).

Removed Due to Copyright

Appendix D - Details Regarding Each Individual's Contribution to the Joint Research Project

This thesis was a joint project with fellow DClinPsy trainee, Laura Marks. Laura's project involved interviewing chronic pain patients whose ketamine treatment had been interrupted by the COVID-19 pandemic. These interviews explored the impact of not receiving ketamine on pain and emotion, coping strategies in the absence of ketamine, and what patients did and did not miss about receiving these infusions. This data was subjected to qualitative analysis.

Laura and I jointly contributed to the non-substantial ethics amendment and updating of participant materials (e.g. information sheet, consent form). Recruitment of ketamine patients was undertaken jointly by Laura and I but data collection was conducted separately (i.e. I collected all of the quantitative data and Laura completed all of the qualitative interviews). I recruited and tested lidocaine patients independently. I scored and entered long-term follow-up data into a database. I alone carried out statistical analysis and write up of this empirical paper, in addition to Part 1 (literature review) and Part 3 (critical appraisal).

This thesis builds on previous DClinPsy theses by Georgia Halls (2020), Joe Kibble (2020), Matt Knox (2018) and Catherine Trotman (2018). The baseline, mid-infusion, post-infusion and one-week follow-up data presented in this thesis was collected by the previous trainees.

Appendix E – NHS Ethics Approval

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

Telephone: 020 7104 8057

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

06 December 2017

Prof Valerie Curran
UCL
Gower Street
London
WC1E 6BT

Dear Prof Curran,

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

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

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

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

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

Confirmation of ethical opinion

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

Conditions of the favourable opinion

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

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

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

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

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

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

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

Registration of Clinical Trials

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

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

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

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

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

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

Ethical review of research sites

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

Approved documents

The documents reviewed and approved by the Committee are:

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

Statement of compliance

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

After ethical review

Reporting requirements

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

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

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

Feedback

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

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

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

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

Yours sincerely

[redacted]

Mr David Carpenter
Chair

Email: nrescommittee.southcentral-berkshire@nhs.net

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

Copy to: *Ms Nikkayla Dixon*

Mr Joe Mirza, UCLH NHS Foundation Trust

Appendix F – Approval of Non-Substantial Amendment

From: [redacted]
Sent: 17 August 2020 09:26
To: [redacted]
Cc: [redacted]
Subject: RE: IRAS Project ID 214864-Confirmation of Amendment Capacity & Capability

Dear [redacted],

Project ID: 17/0139 (Please quote in all correspondence)
IRAS ID: 214864
REC Ref: 17/SC/0567
Title: Comparing the Effects of Ketamine and Lidocaine
Amendment: NSA1

Confirmation of Amendment Capacity & Capability

The [redacted] acknowledges receipt of the above non-substantial amendment.

We have reviewed the amendment and the HRA Approval email dated 03/08/2020.

The [redacted] has no objections to this amendment and the study may continue at [redacted].

If applicable, you must ensure that you localise all patient facing documentation prior to consenting participants; this will be subject to random audit checks.

Please forward this email on to all relevant parties involved with this study at [redacted].

Please insert a copy of this email in your site file.

Best wishes with your research.

Kind regards,
[redacted]

I am working from home can only be reached by emails
****Please note we will NOT be issuing a separate hard copy/electronic R&D Acknowledgment letter; please accept this email as confirmation of amendment implementation at [redacted].**

Appendix G – Participant Information Sheet

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

Participant Information Sheet

(Version 7: 09/04/2020) 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 tells 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 Dr Miriam Fornells-Ambrojo 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 affects 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.

In light of the COVID-19 outbreak, the [redacted] you go to was temporarily closed. Further, our usual face-to-face methods of data collection have been replaced by telephone calls, or internet methods to reduce the risk of spreading COVID-19. However, we are very keen to hear about how well you are, and about how you may have been affected by the COVID-19 crisis.

Why have I been invited?

You are being invited because you have been 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 have previously received their normal clinical care at the [redacted].

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

The study involves completing some questionnaires either online or over the 'phone. These will ask you to rate changes in your pain since you last clinic visit, your mood, and other experiences linked to chronic pain and your current medication. You may also be asked about the impact of COVID-19 on your chronic pain. For example, how it might have affected your strategies for managing your pain or use of medication, your physical activities or other treatments.

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. Researchers 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 is 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 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 using the details below. If you remain unhappy and wish to complain formally you can do this by contacting the Patient Advice and Liaison service at [redacted]. You can contact them by ringing [redacted].

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 2021. You can obtain a copy of the published results by contacting us at the 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:

Contacts

Primary Researchers: [redacted]

Consultant Anaesthesiologists: [redacted]

Patient Advice and Liaison Service

PALS can be accessed by visiting the office at either [redacted] Monday to Friday, or [redacted] Wednesday to Friday 9am – 4pm or by telephone ([redacted])

Thank you for taking the time to read this information sheet

Appendix H – Consent Form

IRAS ID: 214864
Version 6 (09/04/2020)

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 Researchers: Laura Marks and Jenny Scott

	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. 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.	☐
5. I agree to take part in the above study.	☐
6. I would like to be notified of future studies.	YES NO (please delete)

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

Appendix I – Pain Numeric Rating Scales

HOW ARE YOU FEELING?

<u>Instructions</u>: On each scale, please tell me the number that best describes how you feel <u>RIGHT NOW.</u>

Pain intensity

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

Pain distress

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

Pain interference

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

Appendix J – Hospital Anxiety and Depression Scale (HADS)

Removed Due to Copyright

Appendix K – Patient Health Questionnaire-2 (PHQ-2)

Removed Due to Copyright

Appendix L – Depression Numeric Rating Scale

HOW ARE YOU FEELING?

<u>Instructions</u>: On each scale, please tell me the number that best describes how you feel <u>RIGHT NOW.</u>

Depressed

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

Appendix M – Immediate Story Recall Instructions

IMMEDIATE STORY RECALL

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

Twenty people / were given medical treatment / during the annual / Youth Marathon / across Dartmoor / last week. / Most of them were suffering from / exhaustion / blisters / or sprains. / More than two thousand / young people / had taken part in/ this test of navigation / and endurance. / Mr Charles / Wyatt, / the organizer / thanked / the Red Cross / for their cooperation. /

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

Appendix N – Delayed Story Recall Instructions

DELAYED STORY RECALL

Do you remember the story you heard earlier? Tell me as much of it as you can.

Appendix O – Scoring Guidelines for Immediate and Delayed Story Recall

Exact phrase	Score	Alternate	Score
1. Twenty people	1.0		
2. were given medical treatment	1.0	required medical treatment	1.0
		were treated	0.5
		medical	0.5
3. during the annual	1.0	after	0.0
		takes place every year	0.5
4. Youth Marathon	1.0	marathon	0.5
		Race	0.5
		Run	0.5
		event	0
		exercise	0
		trek	0
		sports match/sporting event	0
5. across Dartmoor	1.0		
6. last week	1.0		
7. Most of them were suffering from	1.0	mainly suffering from	1.0
		most of them had	1.0
		injuries included	0.5
8. exhaustion	1.0	tired(ness)	0.5
		Fatigue	0.5
9. blisters	1.0		
10. or sprains	1.0		
11. More than two thousand	1.0	two thousand	0.5
		x-thousand	0
		large group of	0
12. young people	1.0	people/participants	0.5
13. had taken part in	1.0	took part in	1.0
		were taking part in	1.0
14. this test of navigation	1.0	navigation(al)	0.5
15. and endurance	1.0		
16. Mr Charles	1.0	Mr	0.5
		Charles	0.5
		man	0.5
		gentleman	0.5
17. Wyatt,	1.0		
18. the organizer	1.0	(person) in charge	0.5
19. thanked	1.0	commented	0.5
20. the Red Cross	1.0	emergency services	0.5
		paramedics/first responders	0.5
21. for their cooperation	1.0	for their help	0.5
		for their assistance	0.5
		for their work	0.5
		for their participation	0

Appendix P – Verbal Fluency Instructions

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

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

For example, if I said 'L' you could say lion, lucky, love, list and so on.

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

When I say the letter, I'll start the timer, ok?

The letter is F (for Freddie) (*Immediately start timing & write down all responses.)*

Appendix Q – Serial Sevens Instructions

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

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

So if I said 207, you would say 207, 200, 193, 186 and so on for 60 seconds. Does that make sense? When I say the number, I'll start the timer, OK?

The number is 305

Immediately start timing & write down all responses.

Appendix R – COVID-19 Questionnaire

Removed due to Copyright

Appendix S – Table of Shapiro-Wilk Tests of Normality for Age and Baseline Pain, Mood and Cognition Scores

Table S1

Shapiro-Wilk Tests of Normality for Age and Baseline Pain, Mood and Cognition Scores

Variable	Shapiro-Wilk		
	W	*df*	Sig. *(p)*
Age	.957	47	.079
Pain intensity	.917	47	**.003****
Pain distress	.952	47	.051
Pain interference	.902	47	**.001****
Depression NRS	.924	47	**.005****
PHQ-2	.884	47	**<.001****
HADS-D	.963	45	.166
HADS-A	.979	45	.583
Immediate recall	.923	47	**.004****
Verbal fluency	.971	47	.285
Serial sevens	.816	46	**<.001****

***p* < 0.01

Appendix T – Table of Fisher's Exact Test and Chi-square Tests Comparing Distribution of Gender, Ethnicity and Educational Level by Drug

Table T1

Fisher's Exact Test and Chi-square Tests Comparing Distribution of Gender, Ethnicity and Educational Level by Drug

		Fisher's Exact Test	
		Sig. *(p)*	
Gender		.737	
		Chi –square	
	χ^2	*df*	Sig. *(p)*
Ethnicity	5.767	7	.567
Educational level	2.544	4	.637

Appendix U – Table of T-tests Comparing Age and Baseline Scores in Ketamine and Lidocaine Participants Who Completed Long-Term Follow-Up (Normally Distributed Variables)

Table U1

T-tests Comparing Age and Baseline Scores in Ketamine and Lidocaine Participants who Completed Long-Term Follow-Up (Normally Distributed Variables)

Domain	Ketamine M (SD)	Lidocaine M (SD)	Levene's test for Equality of Variances		t-test for Equality of Means		
			F	Sig. *(p)*	*T*	*df*	Sig. (*p)*
Age	52.85 (9.64)	46.96 (12.73)	1.588	.214	-1.731	45	.090
Pain distress	5.30 (3.16)	5.22 (2.94)	.264	.610	-.087	45	.931
HADS-D	8.20 (5.21)	8.84 (4.55)	.656	.422	.440	43	.662
HADS-A	10.60 (4.86)	10.12 (4.35)	.144	.706	-.349	43	.729
Verbal fluency	11.00 (4.22)	10.81 (4.01)	.274	.603	-.153	45	.879

Appendix V – Table of Mann-Whitney U Tests Comparing Baseline Scores in Ketamine and Lidocaine Participants Who Completed Long-Term Follow-Up (Non-Normally Distributed Variables)

Table V1

Mann-Whitney U Tests Comparing Baseline Scores in Ketamine and Lidocaine Participants who Completed Long-Term Follow-Up (Non-Normally Distributed Variables)

Domain	Ketamine *Mdn*	Lidocaine *Mdn*	*U*	N	Sig. *(p)*
Pain intensity	7.00	7.00	295.5	47	.575
Pain interference	7.25	7.00	296.5	47	.564
Depression NRS	5.00	4.00	295.5	47	.580
PHQ-2	2.50	3.00	272.5	47	.956
Immediate recall	4.25	4.50	248.5	47	.643
Serial sevens	5.00	5.00	200.0	46	.204

Appendix W – Table of Bonferroni-Corrected Post-Hoc Tests for Significant Time x Drug Interactions during the Acute Phase

Table W1

Results of Bonferroni-Corrected Post-Hoc Tests for Significant Time x Drug Interactions During the Acute Phase

Domain	Time	Mean difference (Ketamine – Lidocaine)	Standard error difference	Sig. *(p)*
Pain intensity	Baseline	.469	.638	.466
	Mid-infusion	**-2.807**	**.773**	**.001****
	Post-infusion	**-3.124**	**.774**	**<.001****
Pain distress	Baseline	.254	.920	.784
	Mid-infusion	**-1.945**	**.617**	**.003****
	Post-infusion	**-1.967**	**.710**	**.008****
Pain interference	Baseline	.831	.822	.318
	Mid-infusion	**-2.726**	**.757**	**.001****
	Post-infusion	**-1.995**	**.687**	**.006****
Depression NRS	Baseline	1.083	.925	.248
	Mid-infusion	-1.059	.830	.209
	Post-infusion	-.950	.699	.182
Immediate recall	Baseline	-.148	.902	.870
	Mid-infusion	**-2.058**	**.883**	**.024***
Verbal fluency	Baseline	.185	1.209	.879
	Mid-infusion	**-3.404**	**1.329**	**.014***
Serial sevens	Baseline	-2.889	2.160	.188
	Mid-infusion	**-5.248**	**2.139**	**.018***

*$p < 0.05$. **$p < 0.01$

Appendix X – Table of Acute Change Scores from Baseline to Mid-infusion

Table X1

Acute Change Scores from Baseline to Mid-Infusion

Domain	Drug	M	SD
Pain intensity	Ketamine	-4.35	2.72
	Lidocaine	-1.28	1.89
Pain distress	Ketamine	-4.10	2.85
	Lidocaine	-2.09	2.74
Pain interference	Ketamine	-5.83	2.65
	Lidocaine	-2.52	3.38
Depression NRS	Ketamine	-3.50	2.65
	Lidocaine	-1.70	1.88
Immediate recall	Ketamine	-.025	2.48
	Lidocaine	1.88	3.09
Verbal fluency	Ketamine	-.700	4.78
	Lidocaine	2.89	4.15
Serial sevens	Ketamine	-1.21	2.44
	Lidocaine	1.15	3.05

Appendix Y – Table of Long-Term Change Scores from Baseline to One-Week Follow-Up and Baseline to Long-Term Follow-Up

Table Y1

Long-Term Change Scores from Baseline to One-Week Follow-Up and Baseline to Long-Term Follow-Up

Domain	Drug	Baseline to one-week follow-up		Baseline to long-term follow-up	
		M	SD	M	SD
Pain intensity	Ketamine	-1.67	2.74	-1.10	2.02
	Lidocaine	-1.71	1.79	-1.40	1.76
Pain distress	Ketamine	-1.89	3.46	-.650	2.58
	Lidocaine	-1.29	2.69	-1.12	1.86
Pain interference	Ketamine	-1.47	2.57	-1.13	2.81
	Lidocaine	-.905	2.61	-1.24	2.20
Depression NRS	Ketamine	-1.28	1.60	-1.20	3.16
	Lidocaine	-.762	1.58	-.750	3.00
PHQ-2	Ketamine	-.944	2.07	.450	1.93
	Lidocaine	-.762	1.76	.200	2.38
HADS-D	Ketamine	-.611	4.51	1.26	3.87
	Lidocaine	-.524	3.43	1.52	3.03
HADS-A	Ketamine	-2.94	3.24	-.684	4.28
	Lidocaine	-1.10	2.98	.826	3.41
Immediate recall	Ketamine	-	-	2.71	3.88
	Lidocaine	-	-	2.88	3.06
Verbal fluency	Ketamine	-	-	.500	4.44
	Lidocaine	-	-	1.12	4.09
Serial sevens	Ketamine	-	-	.474	3.60
	Lidocaine	-	-	.120	2.98

Appendix Z – Results of COVID-19 Questionnaire

Over the last *X* months, how has the coronavirus pandemic affected your...? (n = 47)

Figure Z1

Ability to access ordinary healthcare from the [study site]

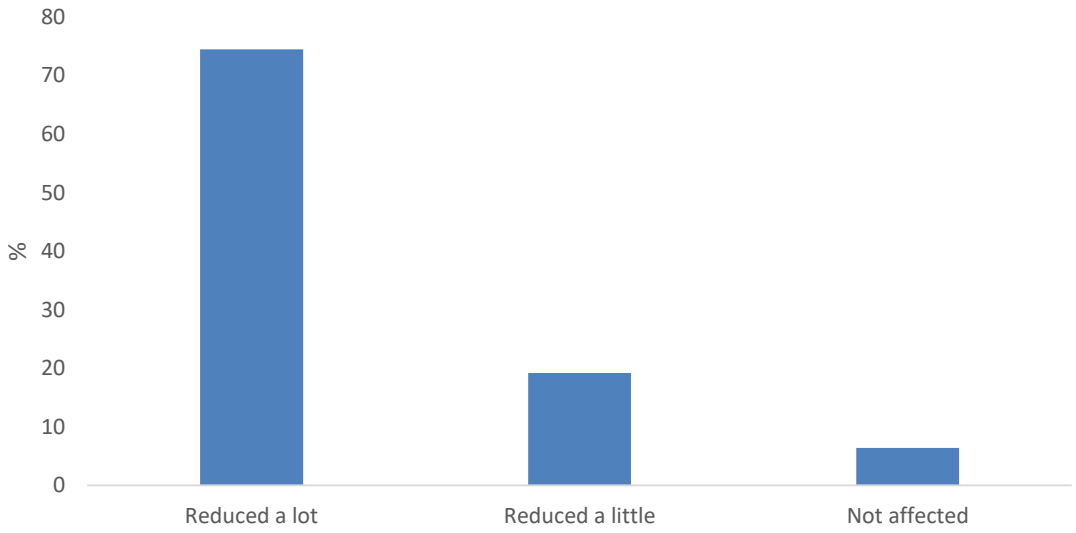

Figure Z2

Feeling supported by my medical team at the [study site] despite lockdown restrictions

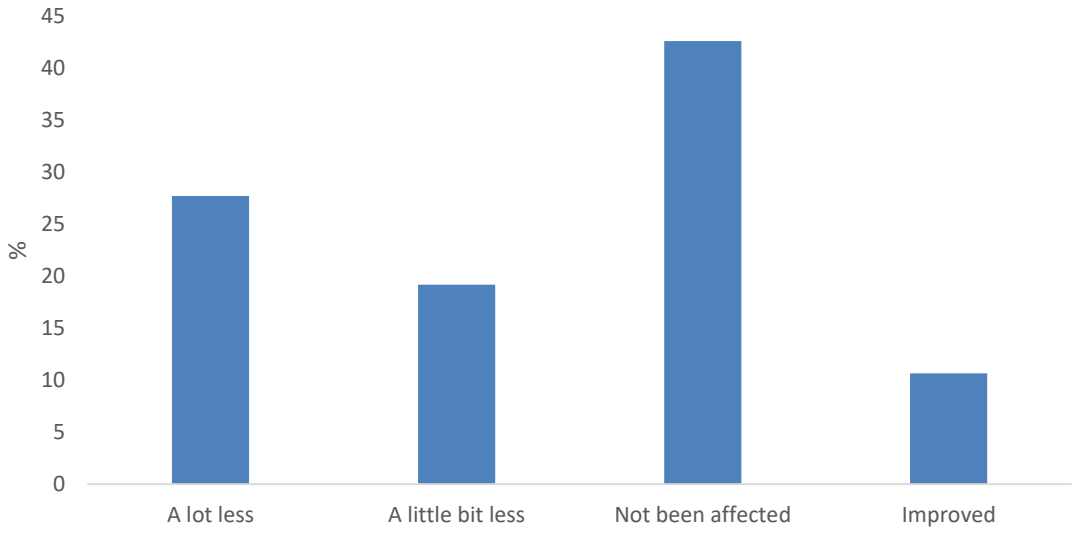

Figure Z3

Ability to access wider healthcare (including other pain treatment, prescription and over-the-counter medications, GP, medical and mental health visits, other treatments)

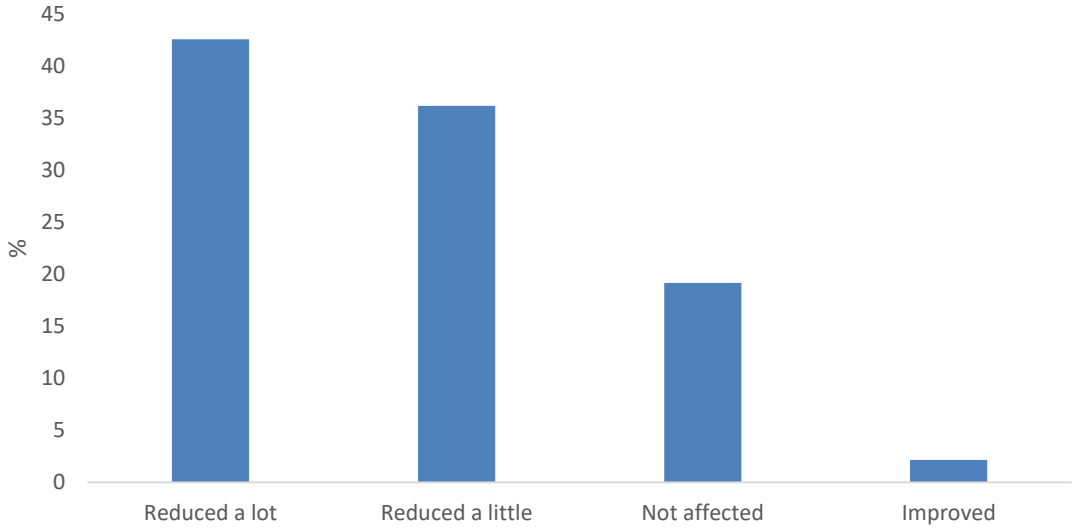

Figure Z4

Social support, or the support you get from others in your community

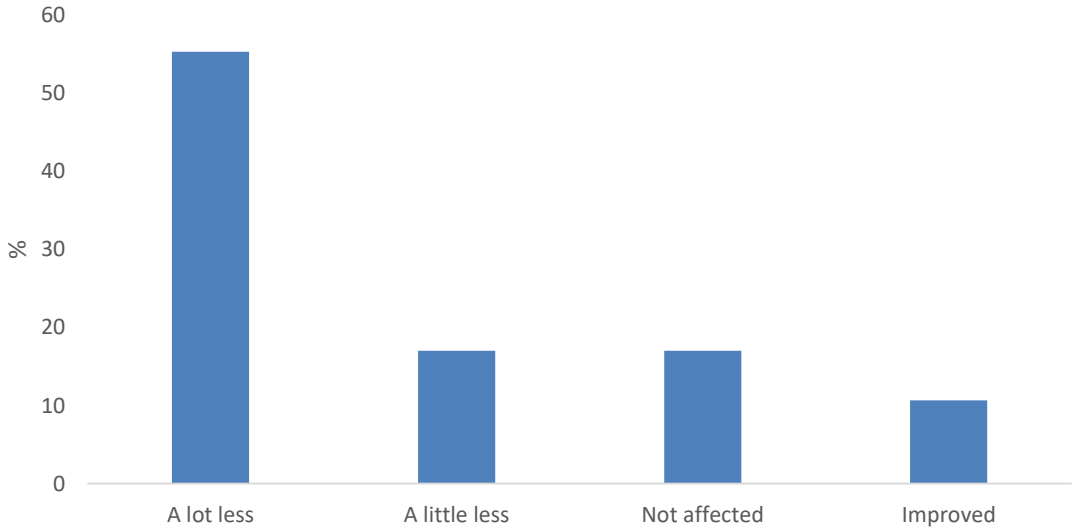

Figure Z5

Ability to meet your basic needs (including housing, food, essential supplies, transportation, childcare)

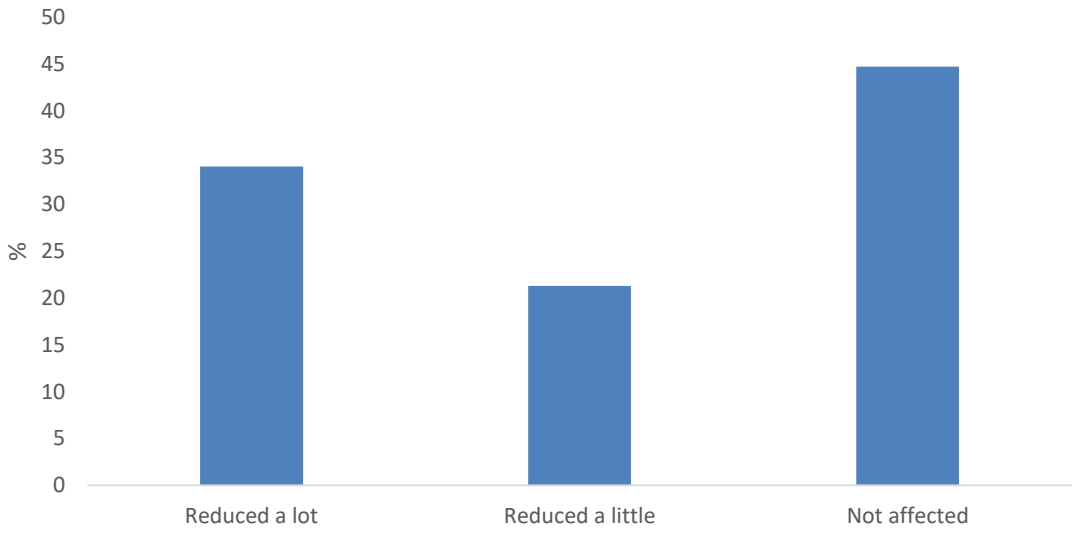

Figure Z6

Mental and emotional health (including worry, stress, anxiety, depression, mood)

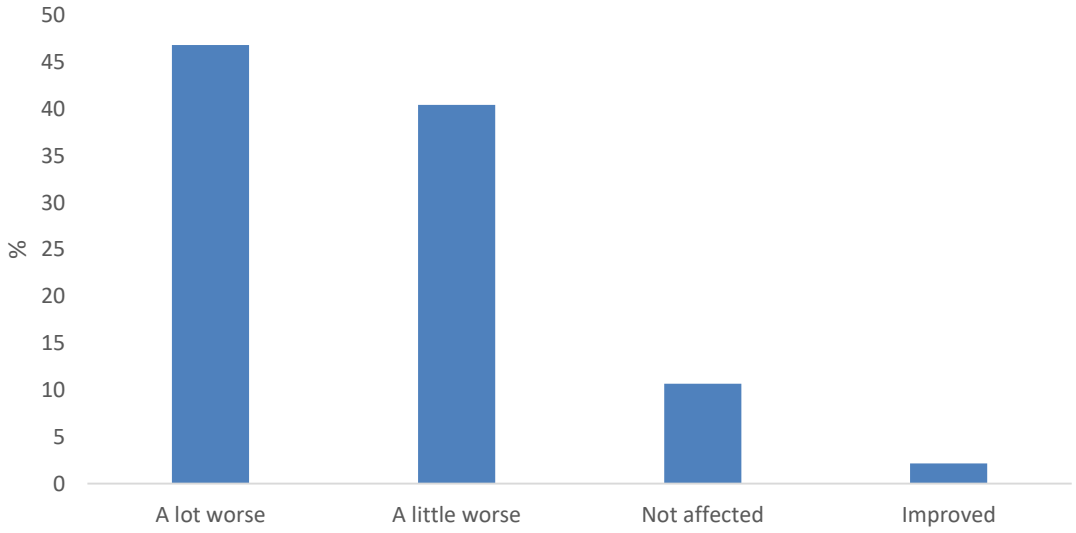

Figure Z7

Perceived benefits brought about by the pandemic (such as appreciation for family, friends, and life in general)

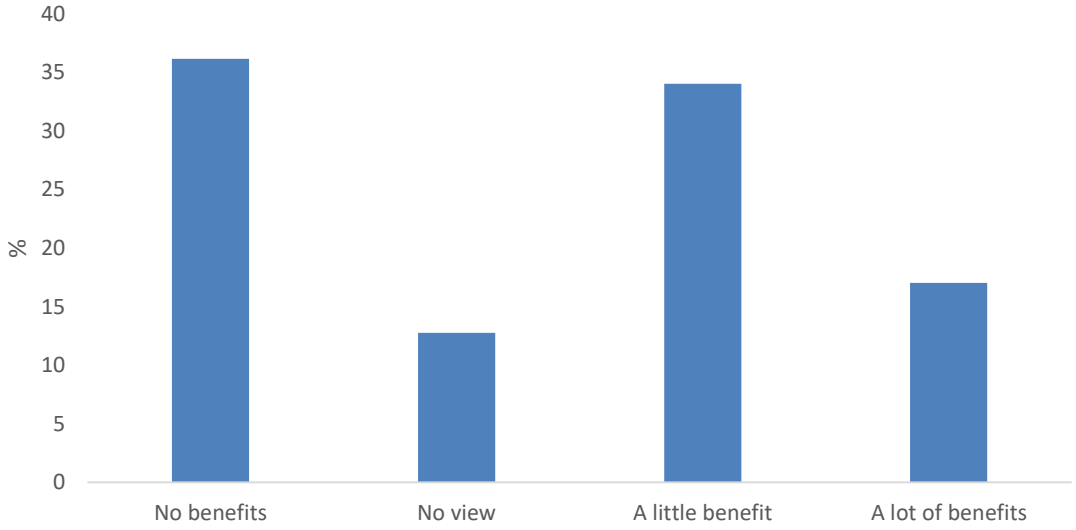

Figure Z8

Personal experience with the coronavirus