The use of Ketamine as an Anti-Depressant:

A Systematic Review and Meta Analysis

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Abstract

***Objective**:* The current meta-analysis examines the effects of ketamine infusion on depressive symptoms over time in Major Depressive Disorder (MDD) and Bipolar Disorder (BD).

***Method**:* Following a systematic review of the literature, data were extracted from 21 studies (n = 437 receiving ketamine) and analysed at four post infusion time-points (4 hours, 24 hours, 7 days, 12-14 days). The moderating effects of several factors were assessed including: repeat/single infusion; diagnosis; open-label/participant-blind infusion; pre-post/placebo-controlled design; and the sex of patients.

***Results**:* Effect sizes were significantly larger for repeat than single infusion at 4h, 24h, and at 7d. For single infusion studies, effect sizes were large and significant at 4h, 24h and 7d. Percentage of males was a predictor of anti-depressant response at 7 days. Effect sizes for open-label and participant-blind infusions were not significantly different at any time-point.

***Conclusion**:* Single ketamine infusions elicit a significant anti-depressant effect from 4 hours to 7 days; the small number of studies at 12-14 days post infusion failed to reach significance. Results suggest a discrepancy in peak response time depending upon primary diagnosis – 24 hours for MDD and 7 days for BD. The majority of published studies have used pre-post comparison; further placebo-controlled studies would help to clarify the effect of ketamine over time.

Introduction

Most current anti-depressants act on the monoamine systems of the brain and, crucially, are slow to elicit anti-depressant effects. By contrast, ketamine is an N-methyl-D-aspartate (NMDA) antagonist with purported rapid anti-depressant properties that are sustained beyond ketamine's 3 hour half-life (Young, 2013; Salvadore & Singh, 2013). Ketamine is known to block NMDA receptors thereby affecting the action of glutamate, a major excitatory neurotransmitter in the brain (aan het Rot et al, 2012). Unlike traditional antidepressants, ketamine is administered intravenously. The first placebo-controlled study investigating ketamine for the treatment of depression was conducted by Berman et al (2000). Anti-depressant response to ketamine was maintained in four of the seven completers at the end of the 72-hour follow-up period.

The prospect of using ketamine as an anti-depressant is a fascinating and exciting one, particularly in terms of its potential for alleviating depressive symptoms in individuals with treatment-resistant depression (Zarate et al, 2006; Kollmar et al, 2008; Murrough et al, 2013; Liebrenz et al, 2007; Liebrenz et al, 2009; aan het Rot et al, 2010; Ibrahim et al, 2011; Ibrahim et al, 2012) and in reducing suicidal ideation, at least temporarily or in emergency situations (Price, 2009; DiazGranados, 2010a; Larkin & Beautrais, 2011; Price et al, 2014).

Use of Ketamine to Treat Depression in Bipolar Disorder

Ketamine has also been reported to alleviate depressive symptoms in treatment-resistant bipolar depression. DiazGranados et al (2010b) conducted a double-blind, randomised, crossover, placebo-controlled study using a single ketamine infusion combined with lithium or valproate therapy for individuals diagnosed with bipolar I or II depression. The results

indicated significantly fewer depressive symptoms within 40 minutes post-infusion and for up to 3 days in those receiving ketamine compared to placebo; after this time, depression scores began to increase, but remained below baseline level at day 14. Zarate et al (2012a) replicated the study conducted by Diazgranados et al (2010b). Analysis of the intent-to-treat sample showed a significant drug-by-time interaction for depression scores; participants receiving ketamine had significantly fewer depressive symptoms from 40 minutes to 3 days post infusion when compared to placebo. However, depression scores for placebo and ketamine did not significantly differ at days 7, 10, or 14. These findings are consistent with those of Berman et al (2000), wherein depression scores returned to baseline levels within 1-2 weeks post infusion.

Safety, Efficacy and Durability of Repeated Ketamine Infusions

Since the effects of ketamine appear to be relatively short-lived, repeated ketamine infusions may potentially increase the duration of anti-depressant response. The tolerability and safety of repeated ketamine infusions in treatment-resistant depression was investigated by aan het Rot et al (2010) alongside the efficacy and clinical benefit of ketamine in treating depression. Depression scores were assessed at baseline and up to 24 hours post infusion. At 24 hours following a single intravenous ketamine (0.5mg/kg) infusion, 90% of participants met the response criterion (≥50% reduction in MADRS score) and were eligible for the second phase. These participants received five additional infusions of ketamine. The majority of participants (89%) who had received multiple ketamine infusions were found to relapse within an average of 30 days after the first infusion (an average of 19 days after the 6^{th} infusion). Notably, one participant who had received six infusions demonstrated reduced depressive symptoms for more than four weeks and

another for almost seven weeks; another continued to have decreased depressive symptoms for over three months.

The durability of response in individuals with treatment-resistant depression following repeated ketamine infusions was recently investigated in a larger treatment group (n = 24) by Murrough et al (2012). It should be noted that the results for ten of the 24 participants in Murrough et al's (2012) study were previously reported by aan het Rot et al (2010). Participants received up to six infusions of ketamine (0.5mg/kg) on a Monday-Wednesday-Friday schedule over 12 days. Participants meeting response criteria (≥50% reduction in MADRS score) following multiple infusions were tracked for a maximum of 83 days or until relapse (<50% improvement in MADRS score compared with baseline for two consecutive assessments). Overall, approximately 71% of participants responded to ketamine. The median time to relapse after the last ketamine infusion was 18 days and so, the duration of anti-depressant effect for repeat infusions may not extend much beyond that of a single infusion as identified by Diazgranados et al (2010).

Rasmussen et al (2013) conducted an open-label study to determine whether serial infusions of ketamine elicited better response and remission rates than single infusions. Participants received up to four ketamine infusions twice-weekly (for up to two weeks). If a participant met remission criteria (MADRS score <9) on the morning after an infusion or on the morning of the next scheduled infusion, they received no further infusions. Half of participants met remission criteria during the study. Rasmussen et al (2013) inferred that serial infusions may be more successful than a single infusion in reducing depressive symptoms. Despite taking anti-depressant medication, however, throughout a four-week follow-up period, symptom remission was maintained in only 20% of participants at the end

of the follow-up period. The advantage of repeated over single ketamine infusion is questionable since the seemingly prolonged anti-depressant effect of repeated infusions is minimal in duration. Furthermore, and crucially, none of these studies (aan het Rot et al, 2010; Murrough et al 2012; or Rasmussen et al 2013) employed a control group with which to compare relapse times.

Objectives of the Current Study

To the authors' knowledge, no meta-analysis has synthesized the published clinical trial data on ketamine as an anti-depressant. The key questions are: does ketamine have an immediate effect in reducing depressive symptoms?; Are the anti-depressant effects of ketamine sustained over time?; Are repeat infusions more effective in reducing depressive symptoms?; Do primary diagnosis and experimental design moderate the impact of ketamine on depressive symptoms? Finally, some evidence from studies on rats suggests a higher sensitivity of female rats to a low dose of ketamine (Carrier and Kabbaj 2013). Thus, we will also examine for differences in the anti-depressant effect of ketamine depending upon the sex of the patient.

Method

Identification and Selection of Studies

The review was conducted in accordance with PRISMA guidelines (Moher et al, 2009). A systematic search was conducted in *Web of Science*, *Science Direct*, *and PubMed* using the terms 'ketamine' AND 'depression'. In *Web of Science* and *Science Direct*, abstracts, title, and keywords were searched; in *PubMed* all fields were searched. The subject areas in

Science Direct to which the search was restricted were: Arts and Humanities; Biochemistry, Genetics and Molecular Biology; Pharmacology, Toxicology and Pharmaceutical Science; Psychology; Social Science. As the first clinical trial of ketamine for the treatment of depression was conducted in 2000, all years from 2000 up to January 2015 were included in the search.

Criteria for Inclusion of Studies

Studies were included in the meta-analysis if at least one infusion of ketamine was administered for the treatment of depression; and primary diagnosis could include Major Depressive Disorder (MDD) or Bipolar Disorder (BD). Included studies were also required to report on depressive symptoms using a standardised measure of depression, such as the Montgomery-Åsberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale (HDRS) and to include eight or more participants. A summary of the selection process is given in Figure 1.

[Figure 1 about here]

Data Extraction

Data were extracted from studies meeting the criteria outlined above. Where data were incomplete or unclear, we contacted authors for clarification or additional data. In some cases, additional data could not be obtained after enquiring with authors and such studies were consequently excluded from the meta-analysis. Meta-analysis was conducted for four

post infusion time-points (4 hours, 24 hours, 7 days, and 12-14 days). Where studies used a control group, the effect sizes were calculated for placebo versus ketamine; where no control group was used, the effect sizes were calculated for baseline depression scores versus scores at each time point. All data analysis was conducted using Comprehensive Meta-Analysis Version 2.0 (http://www.meta-analysis.com/). Effect sizes were calculated using Hedge's g, i.e. the standardised difference between means, corrected for the tendency towards over-estimation in small studies using a random effects model. Effect sizes were described using Cohen's convention wherein an effect size of 0.20 was considered small, 0.50 moderate, and 0.80 large.

Statistical Heterogeneity

We assessed heterogeneity using the I^2 value, which estimates the amount of total variation that attributable to heterogeneity. An I^2 value of 0-40% suggests that heterogeneity may not be important, 30-60% may represent moderate heterogeneity, 50-90% may represent substantial heterogeneity, and 75-100% may represent considerable heterogeneity (see Cochrane, 2011).

Risk of Bias

Studies involved in the meta-analysis were assessed for possible bias. A study was considered to have a low risk of bias if a control group was employed, if allocation of participants to control and experimental groups was adequately randomised, and if there was no evidence of conflict of interest. Medium risk of bias was assigned if a control

condition was employed within an ABBA design (blindness may have been compromised by the 'high' associated with ketamine infusions), if there was evidence of adequate randomisation of participants to control and experimental groups (where a control group was employed), if selection of participants was randomised and if there was a potential conflict of interest. High risk of bias was assigned if a study did not employ a control group, demonstrated little evidence of random selection of participants, and a potential conflict of interest was identified.

Effects of Moderators

The effects of several factors were examined: namely, experimental design (pre-post and placebo-controlled), diagnosis (MDD, BD, mixed/unknown), number of infusions (single or repeated), and infusion delivery (open-label or participant-blind). A meta-regression was also conducted to examine whether the percentage of males (% Male) was a predictor of effect size.

Publication Bias

Publication bias was examined using Fail Safe N, Duval and Tweedie's trim and fill (Duval & Tweedle, 2000), Begg and Mazumdar's Rank Correlation Test (Begg and Mazumdar, 1994), and Egger's test of the intercept (Egger, Davey Smith, Schneider & Minder, 1997).

Results

Identification and Selection of Studies

The total number of studies (K) selected was 21, of which 17 were single infusion studies. The majority of studies collected and reported data at 4h (K = 11) and 24h (K = 13); a smaller number of studies reported data at 7d (K = 6) and at 12-14d (K = 4). For single infusion studies, results were reported for 9 studies at 4 hours, for 11 studies at 24 hours, for 5 studies at 7 days, and for 2 studies at 12-14 days post infusion.

Risk of Bias

[Table 1 about here]

Overall Pooled Effect Sizes

Overall pooled Hedge's g values were large and significant at all time-points (see Table 2). No significant differences in effect sizes emerged between any time-points (4h vs 24h: p = 0.36; 4h vs 7d: p = 0.47; 4h vs 12-14d: p = 0.55; 24h vs 7d: p = 0.45; 24h vs 12-14d: p = 0.73; 7d vs 12-14d: p = 0.31). The heterogeneity across studies was large and significant at all time-points (see Table 2). The forest plot for all time-points is given in Figure 2.

[Table 2 about here]

[Figure 2 about here]

Moderating Effect of Single and Repeat Infusions

At all time-points the effect sizes for repeat infusions were larger than for single infusions, and significant at 4 hours (-3.34 vs -1.11, p = 0.001), 24 hours (-4.16 vs -1.11, p = 0.000), and at 12-14 days (-2.95 vs -0.85, p = 0.012) post infusion, but not at 7 days (-1.96 vs -0.88, p > 0.05); however, the number of repeat infusions studies is limited at each of these time-

points (K= 2, 2, 1, and 2, respectively). Single infusion studies were significant at 4h, 24h, and at 7d. A large effect size was determined at 12-14d, but did not reach significance (possibly because of insufficient available studies; see Table 3). Comparison of single infusion studies revealed no significant differences in effect sizes between time-points (4h vs 24h: p = 0.59; 4h vs 7d: p =0.43; 4h vs 12-14d: p = 0.71; 24h vs 7d: p = 0.16; 24h vs 12-14d: p = 0.55; 7d vs 12-14d: p = 0.85).

[Table 3 about here]

Single Infusion: Moderating Effect of Diagnosis

We examined the impact of moderators for single infusion studies but insufficient data were available for repeat infusion studies to permit similar analyses (see Cochrane, 2011).

For MDD, effect sizes ranged from moderate at 7d (-0.53) to large at 4h (-1.03) and 24h (-1.35). For BD, effect sizes ranged from moderate at 24h (-0.64) to large at 4h (-0.80) and at 7d (-1.51) post infusion; a large but not significant effect size was determined at 12-14 days post infusion (see Table 4). The effect sizes for MDD and BD did not significantly differ at 4 hours post infusion (p = 0.30), but were significant at 24 hours (p < 0.001) and 7 days (p < 0.001) post infusion. The effect size for MDD was largest at 24h, whereas the effect size for BD was largest at 7d. Lack of studies permitted comparison of MDD and BD at 12-14 days since no MDD studies measured at this time-point.

[Table 4 about here]

Single Infusion: Moderating Effect of Experimental Design

For pre-post design, the effect sizes were large and significant at all post infusion time-points (see Table 5). For placebo-controlled design, effect sizes ranged from small to large; the effect sizes were significant at 4 hours, 24 hours and 7 days post infusion, but not at 12-14 days post infusion; however, only one placebo-controlled study was available at 4 hours and at 12-14 days post infusion so the results must be interpreted with caution. The difference between effect sizes for pre-post and placebo-controlled design was not significant at 4 hours (p = 0.10), 24 hours (p = 0.26) or 7 days (p = 0.41) post infusion, but was significant at 12-14 days (p < 0.001); however, only one study was available for each design at 12-14 days post infusion.

[Table 5 about here]

Single Infusion: Moderating Effect of Open-Label and Blind Infusions

For open-label infusions, the effect sizes ranged from small to large and, with the exception of 7 days post infusion, all effect sizes were significant (4h: -1.03, CI_{95} = -1.39, -0.68, K = 7; 24h: -1.57, CI_{95} = -2.32, -0.82, K = 3; 7d: -0.25, CI_{95} = -0.66, 0.16, K = 1). No open-label single infusion studies were available at 12-14 days. For participant-blind infusions, the effect sizes ranged from small to large (4h: -0.80, CI_{95} = -1.05, -0.56, K = 1; 24h: -1.00, CI_{95} = -1.29, -0.71, K = 7; 7d: -0.68, CI_{95} = -0.99, -0.36, K = 2; 12-14d: -0.21, CI_{95} = -0.44, 0.02, K = 1). The effect size at 12-14 days was not significant; effect sizes at all other time-points were significant. The difference between effect sizes for open-label and participant-blind infusions was not significant at any time-point (4h: p = 0.30; 24h: p = 0.17; 7d: p = 0.11).

Single Infusion: Effect of Sex

A meta-regression was conducted with percentage of males as a predictor of effect size, with no significant effects determined at 4h (p = 0.60) or 24h (p = 0.08). However, a significant positive relationship between percentage males and effect size was determined at 7d (p = 0.008); however, only four data points were available at this time-point. Meta-regression could not be conducted at 12-14 days post single ketamine infusion due to an insufficient number of studies.

Single Infusion: Publication Bias

Publication bias (see Table 6) was examined using Fail Safe N, Duval and Tweedie's trim and fill (Duval & Tweedle, 2000), Begg and Mazumdar's Rank Correlation Test (Begg and Mazumdar, 1994), and Egger's test of the intercept (Egger, Davey Smith, Schneider & Minder, 1997). The results across all the tests indicate publication bias at 4 hours and 24 hours for single infusion studies.

[Table 6 about here]

Discussion

The results of the meta-analysis suggest that ketamine reduces depressive symptoms with large effect sizes at every time-point analysed (4 hours, 24 hours, 7 days and 12-14 days). The relative stability of the effect size across time-points suggests a sustained anti-depressant response to ketamine at least up to two weeks post infusion as examined in clinical trials to date.

Turning to single infusion studies, large effects emerged at 4 hours and at 24 hours, confirming the reported rapid reduction in depressive symptoms, and also at 7 days; a large effect at 12-14 days failed to reach significance. The lack of longer term effect is consistent with reports of relapse within 1-2 weeks for a single infusion (Zarate et al, 2006); however, few single infusion studies have assessed up to 12-14 days post-infusion (K = 2). No significant difference in effect size emerged between any time-points for single infusions. As expected, effect sizes for repeat infusions were larger than for single infusions and differed significantly at 4 hours, 24 hours and at 7 days. It must be noted that the number of repeat infusion studies was limited and further studies are required.

Moderating Effects of Diagnosis

Although effect sizes for Major Depressive Disorder (MDD) and Bipolar Disorder (BD) were moderate to large, some differences emerged in responsiveness. Following a single infusion, the effect for MDD at 24 hours was significantly larger than for BD; at 7 days BD showed a significantly larger effect size than MDD. These findings hint that the anti-depressant effect of a single ketamine infusion may vary according to the primary diagnosis, although this interpretation is limited by the small number of studies available, particularly at 7 days (K = 3 and K = 2 for MDD and BD, respectively).

Moderating Effects of Experimental Design

Single infusion pre-post comparisons resulted in larger effect sizes than placebo-controlled designs, although the difference was significant only at 12-14 days. Interpretations are somewhat limited by the small number of placebo-controlled studies at each time-point. Furthermore, all studies employing pre-post designs also used open-label infusions and this

may have affected the outcome owing to the potential of an expectancy bias. Further blind placebo-controlled studies, such as that carried out by Murrough et al (2014), are required to confirm the findings.

Moderating Effects of Open-Label and Participant-Blind Infusions

As might be expected, effect sizes in open-label trials were larger than for participant-blind trials. The difference reached significance at 12-14 days with a large effect size for open-label infusions, although it consisted of comparing just two studies. Indeed, the lack of significant differences at other time-points may reflect the small numbers of studies being compared (with just one blind trial at 4 hours, 7 days, and 12-14 days). Consideration of further interpretations is, however, required. In particular, the larger effect sizes for open-label infusion may arise as a result of expectancy bias, with knowledge of having received ketamine impacting participants' reported decrease in depressive symptoms. Similarly, those assessing symptoms may also have an expectancy bias for open-label infusions which may affect how they make MADRS and HDRS ratings. Conversely, and noted by Berman et al (2000) in the first published trial, blinding itself is likely to be compromised given the psychotomimetic effects of ketamine, especially with the lack of any active controls in studies. Indeed, at doses comparable to those used in depression studies reported here, subanaesthetic ketamine does generate self-reported "mystical-type phenomena" (Dakwar et al, 2014). These authors remark that "An intriguing but unexplored question is whether the psychoactive effects of ketamine influence its efficacy through psychological mechanisms." (p 153). Apart from needing more placebo-controlled studies per se, future studies need to explore potential active controls to ensure that blindness to a ketamine infusion is preserved and thus provide more accurate conclusions regarding ketamine's

specific effect on depressive symptoms. Second, confounding occurs as all open-label trials have utilised a pre-post design whereas placebo-controlled design was employed in all participant-blind studies. Therefore, we cannot eliminate experimental design differences as the cause of the discrepancy in effect sizes. As it is not possible to extricate the moderating effects of experimental design from nature of administration of ketamine, we cannot currently determine if one or both factors have a moderating effect on depression scores.

Effect of Sex

A significant effect of sex was found at 7 days post-infusion, but not at any other time-point, indicating that percentage of males is a predictor of response. This finding hints at a bigger symptom reduction perhaps in men, but the finding is for only a few studies (K = 4) and only at that one time point - a finding that needs to be examined in future studies. This finding is not consistent with the higher sensitivity of female rats to a low dose of ketamine (Carrier & Kabbaj, 2013). Additional studies are required to confirm whether there is an effect of sex on the outcome of ketamine infusion and what exactly that effect is, as the current meta-analysis and the effect of ketamine in rats appear to contradict each other.

Limitations of the Current Meta-Analysis

The main limitation of this meta-analysis is the relatively small number of studies with useable data (K = 21), particularly for repeated ketamine infusion (K = 4). Although most studies reported results at 4 (K = 11) and 24 hours (K = 13) post-infusion, the results suggest an anti-depressant effect of ketamine may last for up to 14 days.

What happens beyond 14 days is unknown. The reported relapse rates have varied across studies. Ibrahim et al (2012) reported an average time to relapse of 13.2 days. Mathew et al

(2010) reported that for participants prescribed post infusion placebo the average time to relapse, as indicated by MADRS scores, was 22 days. Of the participants who received post-infusion riluzole (a glutamate-modulating agent expected to maintain the anti-depressant effects of ketamine) in Mathew et al's (2010) study, 80% relapsed compared to 50% of those taking post-infusion placebo. Furthermore, 17% of those taking riluzole and 50% of those taking placebo continued to meet response criteria at 32 days post infusion. Thus, riluzole appears to be less effective at maintaining anti-depressant response when compared to placebo. The results of Mathew et al (2010) imply that an anti-depressant response of up to 32 days post-ketamine is possible. It must be noted, however, that those assigned to the placebo/riluzole trial had maintained a post-infusion anti-depressant response for 72 hours. As this group is highly selective, it is not representative of all individuals receiving ketamine infusion and thus the likelihood is that an anti-depressant effect of 32 days duration is more likely to be the exception rather than the rule.

It is plausible that the duration of the anti-depressant effect of ketamine may extend beyond 14 days, but with most studies reporting ketamine's anti-depressant effects only up to 24 hours, we cannot currently determine if this is the case. The results of the meta-analysis show that repeat infusions elicit larger effect sizes when compared to a single infusion in the three published repeat infusion studies we examined. The larger effect sizes for repeat infusions are consistent with the exacerbated effects of ketamine with repeated exposure found in rats (Trujillo et al, 2008). Nonetheless, two of the repeat infusion studies used in this meta-analysis selected participants who had previously responded to ketamine. Specifically, participants who had responded to two prior infusions of ketamine in aan het Rot et al's (2010) study were selected to receive additional infusions. Although eight of the

nine participants in this study continued to respond for an average of 30 days from the first infusion, such an effect might not be found outside of this highly selective group. Furthermore, Price et al (2009) reported repeat infusion data for participants who had responded to a single ketamine infusion and subsequently received multiple infusions. Additional repeat infusion studies are required to ascertain the effect of multiple ketamine infusions in a larger and less selective population.

The results of the current meta-analysis indicate that the anti-depressant effects of ketamine last up to 14 days after a single infusion. For repeat infusions, the median time to relapse has been reported as 18 days (Murrough et al 2013) and 19 days (aan het Rot et al 2010) after the last in a series of 6 infusions. In both cases, the duration of response for repeat infusion studies is only slightly longer than the apparent 14-day duration for single infusion studies as assessed by this meta-analysis. Further investigation is required to see if repeat infusions, administered over a short period of time, have any significant long-term benefit over a single infusion.

Although previous experience of ketamine was used as an exclusion criterion in some trials (e.g. Zarate et al 2012a), others included patients who had participated in previous ketamine trials. Salvadore et al (2012) included 4/14 patients tested by Salvadore et al (2009 and 2010); and Salvadore et al (2010) included 7/15 patients previously assessed by Salvadore et al (2009). More notably perhaps, aan het Rot et al (2010) assessed the same 10 patients as in the trial by Mathew et al (2010). Although both studies tested the same participants using a ketamine infusion of 0.5 mg/kg over 40 min, the two studies revealed quite different effect sizes at 24 hours, an effect size of -4.8 for aan het Rot et al (2010) and -2.05 for Mathew et al (2010). The use of known ketamine responders by aan het Rot et al

(2010) may well have inflated the ketamine effect, especially as the study was also non-blind. Studies assessing those who have had prior exposure to ketamine have also employed pre-post designs and, so, are not using randomised samples or controls per se. Rather, those studies are selecting participants who have already been shown to exhibit large, albeit temporary, symptomatic reduction e.g. in aan het Rot (2010) patients had previously (in Mathew et al 2010) shown a 50% reduction in the severity of their depressive symptoms for at least 24 hours. Given the larger response to repeated administration of ketamine, this is an important limitation of non-randomised open-trials. Moreover, studies using known responders are, of course, primed to produce significant effects.

The Future of Ketamine as a Treatment for Depression

Our meta-analysis reveals peak time differences in elicited response according to primary diagnosis; this requires further investigation. If primary diagnosis affects the anti-depressant outcome of ketamine infusion, this may have an impact on how ketamine is used in the treatment of depressive symptoms and the groups for whom it will be effective. For example, Niciu et al (2013) reported two cases of suicidal ideation, dysphoria and anxiety within 24 hours of a single ketamine infusion in two patients with a diagnosis of obsessive compulsive disorder (OCD) and a history of, but not current, MDD. These findings indicate the importance of considering potential comorbid diagnoses that may occur alongside depression. The meta-analysis also highlighted a need for randomised control trials to establish the safety, efficacy, and durability of response of single and of repeated ketamine infusions. Placebo-controlled studies where the 'blindness' of the infusion is maintained**,** such as Murrough et al (2014) where midazolam was employed as a control, are particularly important to understanding ketamine's anti-depressant effects.

Although ketamine has been employed as an anaesthetic since the 1960s (Salvadore & Singh, 2013), repeated ketamine infusions in rats have elicited an escalated response consistent with sensitisation (Trujillo et al 2008). Sensitisation to ketamine was greater when rats were exposed to distinct environmental cues and this suggests that repeated exposure to ketamine could result in addiction. A 1-year longitudinal study of recreational users found that frequent users were more likely to demonstrate dissociative and delusional symptoms, along with cognitive impairments affecting spatial working memory and pattern recognition memory tasks (Morgan et al 2010). Interestingly, elevated depression scores were also reported in both frequent and abstinent ketamine users across the 12-month period (Morgan et al, 2010). A more recent study found that ketamine users showed elevated delusional, schizotypal and depressive symptoms when compared to controls (Freeman et al, 2013). The addictive potential of repeated ketamine exposure must be addressed (Morgan & Curran, 2012; Trujillo et al, 2008; Hillemacher, 2007), as should any long-term adverse effects extending beyond the infusion period (Freeman et al, 2013). None of the studies included in the current meta-analysis documented major adverse effects, but side-effects such as transient headache, dizziness and nausea were commonly reported; such side-effects reportedly dissipated fairly quickly, usually once the infusion was complete (aan het Rot et al 2010; Abdallah et al 2012; Thakurta et al, 2012; Murrough et al 2013). Many studies also documented the dissociative effects of ketamine in participants (Diazgranados et al 2010; Ibrahim et al 2011;Larkin et al 2011; Zarate et al 2012a; Loo et al 2012; Murrough et al 2012, 2013; Carlson et al 2013; Sos et al 2013; Lapidus et al 2014) and increased, if somewhat mild, psychotomimetic experiences (Salvadore et al 2009, 2010; Mathew et al 2010; Larkin et al 2011; Loo et al 2012; Murrough et al 2012, 2013 ; Sos et al 2013; Lapidus et al 2014). As most studies have not followed participants beyond 24 hours

post-infusion, any long-term side-effects and addictive potential of ketamine infusion in the treatment of depression are difficult to determine . Future studies should address this key issue.

Trapid anti-depressant effects of ketamine may be well-placed in situations where an immediate alleviation of depressive symptoms is required; however, it does not have a significant anti-depressant effect on everyone. Murrough et al (2013) found that MADRS score at 4 hours post infusion was an indicator of response or non-response; lack of a response to a single ketamine infusion was an adequate predictor of lack of response to subsequent infusions. Several studies have reported a response rate of around 40% at 4 hours post infusion (Ibrahim et al, 2012; Phelps et al, 2009; Zarate et al, 2012b; Cornwell et al, 2012; Sos et al, 2013; Lapidus et al, 2014) while some studies have reported response rates of approximately 60-70% between 4 hours and 24 hours following ketamine infusion (Zarate et al, 2012b; Duncan et al, 2013; Mathew et al, 2010; Zarate et al, 2006; Murrough et al, 2013). Conversely, Rybokowski et al (2013) determined response rates of only 4% at 6 hours post infusion and 24% at 24 hours post infusion in participants with a primary diagnosis of BD. The disparity in response rates highlights the need for future studies incorporating larger samples to determine the average response rate for the target population; primary diagnosis must also be considered. Furthermore, certain groups have shown stronger anti-depressant response to ketamine than others and this also requires consideration. For example, Phelps et al (2009) and Luckenbaugh et al (2012) reported that ketamine infusion elicited a significantly greater reduction in MADRS scores for participants with a family history of alcoholism, compared to participants without a family history of alcoholism.

Conclusion

The present meta-analysis has established ketamine as an effective and rapid treatment for depression in the short-term, impacting depressive symptoms from 4 hours and, as far as we know, for up to two weeks post infusion in participants with a primary diagnosis of MDD or BD. When time to relapse is taken into account, repeat infusion does not appear to extend the duration of anti-depressant effect. Thus, single and repeat ketamine infusions appear to be equally effective in reducing depressive symptoms; however, the small number of repeat infusion studies available hinders the interpretation of this finding. More adequately controlled studies are necessary, especially randomised control trials with a control group and, preferably, some kind of active control. The extent to which ketamine can be used as an emergency treatment and, indeed, as a longer-term treatment for depression, requires much greater investigation.

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* Studies included in meta-analysis

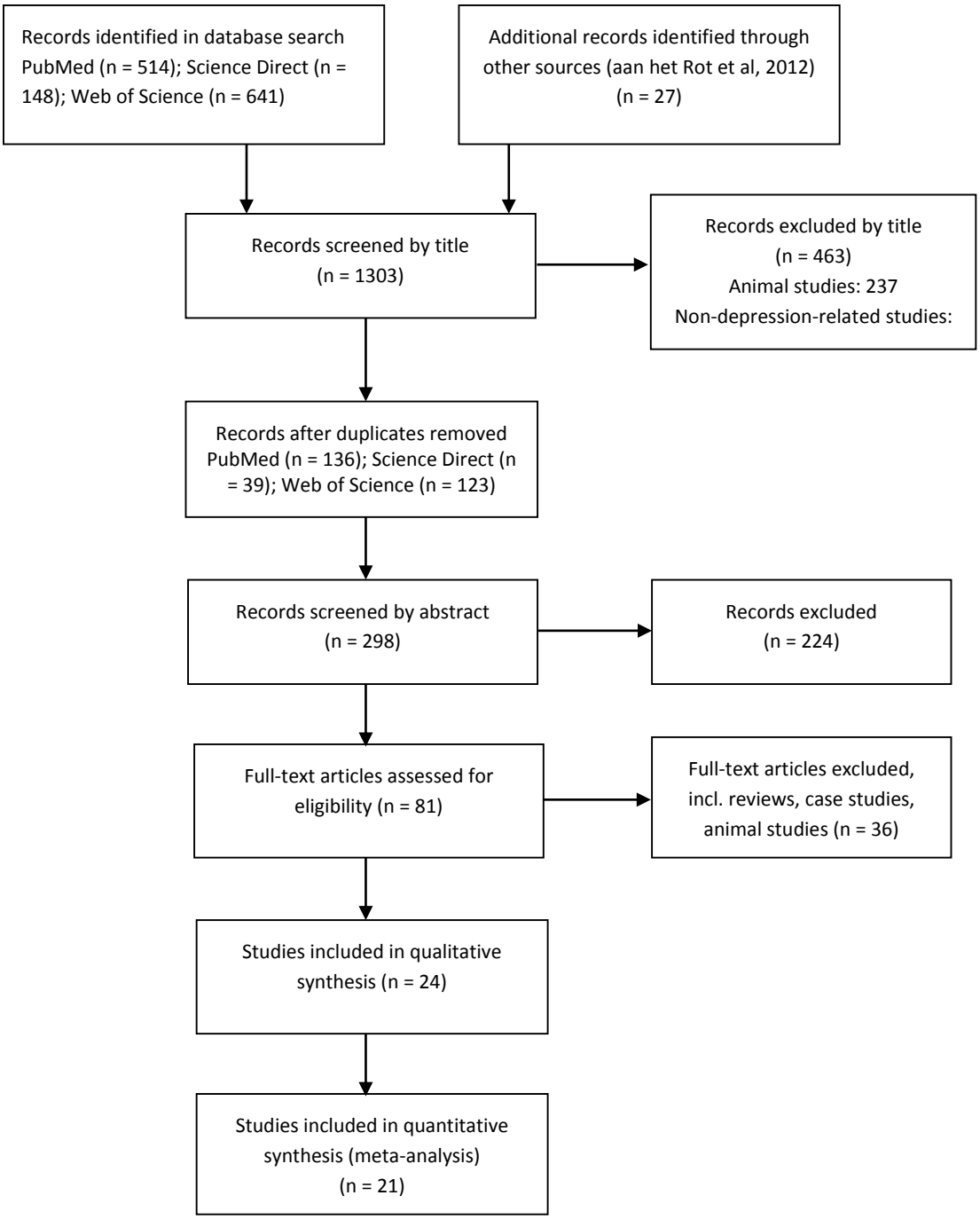

Figure 1. Flow diagram of the study selection process

Table 1 *Table of Analysis of Risk of Bias in Studies Used in the Meta-Analysis*

Study	n	% Males	4h	24h	7d	12 - 14d	Control Grp	Randomised	Rater blind	ITT Sample	Conflict of Interest	Risk of Bias
Zarate et al (2006)	18	33	N	Y	Y	N	Control condition	Yes	Yes	No	None	Low
Salvadore et al (2009)	11	64	Y	N	N	N	No	N/A	No	No	Yes	Medium
Price et al (2009)	26(S); 10(R)	61.5(S); 50(R)	N	Y	N	N	No	N/A	Unknown	No	Yes	Low
aan het Rot et al (2010)	9	50	Y	Y	N	N	No	N/A	Unknown	No	Yes	High
Salvadore et al (2010)	15	Unknown	Y	N	N	N	No	N/A	No	No	Yes	Medium
Mathew et al (2010)	26	61.5	N	Y	N	N	Yes	Yes	No	No	Yes	Medium
Diazgranados et al (2010)	18	33	N	Y	N	Y	Yes	Yes	Yes	Yes	Yes	Low
Ibrahim et al (2011)	17(E); 23(NE)	59(E); 61(NE)	Y	N	N	N	ECT-resist vs no-ECT	No	No	No	None	Medium
Larkin et al (2011)	14	Unknown	Y	N	N	N	No	N/A	Unknown	No	Unknown	Medium
Salvadore et al (2012)	14	64	Y	N	N	N	No	N/A	No	No	None	Medium
Zarate et al (2012a)	15	47	Y	Y	N	N	Yes	Yes	Yes	Yes	Yes	Medium
Thakurta et al (2012)	20	Unknown	Y	N	Y	N	No	N/A	No	No	None	Medium
Abdallah et al (2012)	8	56	N	Y	N	N	Yes	Yes	Yes	No	Unknown	Low
Loo et al (2012)	22	50	N	N	Y	Y	Yes	Yes	Yes	No	None	Low
Murrough et al (2012)	24	62.5	Y	Y	N	N	No	N/A	No	No	Yes	High
Carlson et al (2013)	20	70	Y	Y	N	N	No	N/A	No	No	Yes	Medium
Rybakowski et al (2013)	25	16	N	Y	Y	Y	No	N/A	Unknown	No	None	Medium
Permoda-Osip et al (2013)	10	0	N	N	Y	N	No	N/A	Unknown	No	Unknown	Medium
Murrough et al (2013)	47(K)	45(K)	N	Y	N	N	Yes	Yes	Yes	Yes	Yes	Medium
Sos et al (2013)	27	50	N	Y	Y	N	CO	Yes	Yes	Yes	None	Low
Lapidus et al (2014)	18	50	-	Y	Y	N	CO	Yes	Yes	Yes	Yes	Medium

ITT=Intention-To-Treat; E=ECT; NE=no ECT; S=single infusion; R=repeat infusion; K=Ketamine; O = Overall; CO= crossover design

Table 2. *Effect Sizes and Heterogeneity Values (I^2) for all studies*

Time	K	Hedge's g	CI Lower	CI Upper	p-value	I^2
4h	11	-1.29	-1.66	-0.92	<0.001	81.73
24h	13	-1.24	-1.56	-0.93	<0.001	79.81
7d	6	-1.06	-1.57	-0.55	<0.001	81.02
12-14d	4	-1.67	-2.85	-0.49	0.006	93.65

K = Number of Studies; CI = 95% Confidence Interval

Table 3. *Effect Sizes for Single and Repeated Infusions*

	Single						Repeated					
Time	**K**	**Hedge's g**	**CI Lower**	**CI Upper**	**p-value**	**I^2**	**K**	**Hedge's g**	**CI Lower**	**CI Upper**	**p-value**	**I^2**
4h	9	-1.11	-1.44	-0.78	<0.001	79.65	2	-3.34	-4.58	-2.10	<0.001	0
24h	11	-1.11	-1.38	-0.83	<0.001	75.53	2	-4.16	-5.67	-2.64	<0.001	0
7d	5	-0.88	-1.35	-0.41	<0.001	75.00	1	-1.96	-2.66	-1.25	<0.001	0
12-14d	2	-0.85	-2.17	0.46	0.203	94.50	2	-2.95	-5.65	-0.24	0.033	84.36

K = Number of Studies; CI = 95% Confidence Interval

Table 4. *Single Infusion: Moderating Effect of Diagnosis*

	MDD					BD				
Time	**K**	**Hedge's g**	**CI Lower**	**CI Upper**	**p-value**	**K**	**Hedge's g**	**CI Lower**	**CI Upper**	**p-value**
4h	7	-1.03	-1.39	-0.68	<0.001	1	-0.80	-1.05	-0.56	<0.001
24h	7	-1.35	-1.72	-0.99	<0.001	3	-0.64	-0.79	-0.49	<0.001
7d	3	-0.53	-0.82	-0.24	<0.001	2	-1.51	-1.99	-1.03	<0.001
12-14d	0	-	-	-	-	2	-0.85	-2.17	0.46	0.20

K = Number of Studies; CI = 95% Confidence Interval

Table 5. *Moderating Effects of Pre-Post Comparison and Placebo-Controlled Single Infusion Studies*

	Pre-Post					Placebo vs. Ketamine				
Time	**K**	**Hedge's g**	**CI Lower**	**CI Upper**	**p-value**	**K**	**Hedge's g**	**CI Lower**	**CI Upper**	**p-value**
4h	8	-1.21	-1.63	-0.79	<0.001	1	-0.80	-1.05	-0.56	<0.001
24h	5	-1.33	-1.91	-0.75	<0.001	6	-0.96	-1.26	-0.66	<0.001
7d	3	-1.12	-2.10	-0.13	0.03	2	-0.68	-0.99	-0.36	<0.001
12-14d	1	-1.55	-2.12	-0.98	<0.001	1	-0.21	-0.44	0.02	0.07

K = Number of Studies; CI = 95% Confidence Interval

Table 6. *Table of Publication Bias for Single Infusion Studies*

	K	Unadjusted ES (95% CI)	Trim and fill adjusted ES (95% CI)	Begg & Mazumdar's test	Egger's test
4h	9	-1.11 (-1.44, -0.78)	-1.27 (-1.69, -0.86)	z = 1.77 p = 0.04	t = 3.05 p = 0.02
24h	11	-1.11 (-1.38, -0.83)	-0.97 (-1.25, -0.70)	z = 2.65 p = 0.004	t = 4.81 p = 0.0005
7d	5	-0.88 (-1.35, -0.41)	-0.88 (-1.35, -0.40)	z = 0.73 p = 0.23	t = 2.05 p = 0.07

Note. No bias analyses were calculated for 12-14 days as only 2 studies exist**;** K = Number of Studies; CI = Confidence Interval; ES = Effect size (Hedge's g)

Group by Time point	Study name	Subgroup within study	Comparison	Outcome	Time point	Statistics for each study			
						Hedges's g	Lower limit	Upper limit	p-Value
00d4h	aan het Rot et al (2010)	Repeat infusion (Responders only)	Pre/Post	MADRS	00d4h	-3.634	-5.414	-1.855	0.000
00d4h	Zarate et al (2012a)	Single infusion	Placebo/Ketamine	MADRS	00d4h	-0.804	-1.050	-0.557	0.000
00d4h	Carlson et al (2013)	Single infusion	Pre/Post	MADRS	00d4h	-1.013	-1.538	-0.488	0.000
00d4h	Murrough et al (2012)	Repeat infusions (Responders only)	Pre/Post	MADRS	00d4h	-3.060	-4.787	-1.332	0.001
00d4h	Salvadore et al (2009)	Single infusion	Pre/Post	MADRS	00d4h	-0.989	-1.673	-0.304	0.005
00d4h	Salvadore et al (2010)	Single infusion	Pre/Post	MADRS	00d4h	-1.125	-1.750	-0.500	0.000
00d4h	Ibrahim et al (2011)	ECT-resistant (Single infusion)	Pre/Post	MADRS	00d4h	-0.476	-0.736	-0.216	0.000
00d4h	Ibrahim et al (2011)	Non-ECT (Single infusion)	Pre/Post	MADRS	00d4h	-0.966	-1.230	-0.701	0.000
00d4h	Larkin et al (2011)	Single infusion	Pre/Post	MADRS	00d4h	-3.597	-5.017	-2.176	0.000
00d4h	Salvadore et al (2012)	Single infusion	Pre/Post	MADRS	00d4h	-0.819	-1.398	-0.240	0.006
00d4h	Thakurta et al (2012)	Single infusion	Pre/Post	HDRS	00d4h	-2.510	-3.354	-1.666	0.000
00d4h						-1.290	-1.657	-0.924	0.000
01d	Rybakowski et al (2013)	Single infusion	Pre/Post	HDRS	01d	-0.620	-1.037	-0.203	0.004
01d	aan het Rot et al (2010) A	Repeat infusion (Responders/Remitters)	Pre/Post	MADRS	01d	-4.836	-7.147	-2.525	0.000
01d	Zarate et al (2012a) A	Single infusion	Placebo/Ketamine	MADRS	01d	-0.662	-0.904	-0.420	0.000
01d	Carlson et al (2013) A	Single infusion	Pre/Post	MADRS	01d	-0.906	-1.412	-0.401	0.000
01d	Murrough et al (2012) A	Repeat infusion (Responders/Remitters)	Pre/Post	MADRS	01d	-3.639	-5.651	-1.627	0.000
01d	Price et al (2009)	Single infusion	Pre/Post	MADRS	01d	-1.871	-2.501	-1.240	0.000
01d	Diazgranados et al (2010)	Single infusion	Placebo/Ketamine	MADRS	01d	-0.636	-0.850	-0.422	0.000
01d	Zarate et al (2006)	Single infusion	Placebo/Ketamine	MADRS	01d	-1.395	-1.883	-0.907	0.000
01d	Mathew et al (2010)	Single infusion	Pre/Post	MADRS	01d	-2.046	-2.840	-1.252	0.000
01d	Adballah et al (2012)	Single infusion	Pre/Post	HDRS	01d	-1.501	-2.460	-0.541	0.002
01d	Sos et al (2013)	Single infusion	Placebo/Ketamine	MADRS	01d	-0.973	-1.422	-0.524	0.000
01d	Murrough et al (2013)	Single infusion	Placebo/Ketamine	MADRS	01d	-0.817	-1.315	-0.318	0.001
01d	Lapidus et al (2014)	Single infusion	Placebo/Ketamine	MADRS	01d	-1.962	-2.740	-1.184	0.000
01d						-1.244	-1.560	-0.928	0.000
07d	Rybakowski et al (2013) A	Single infusion	Pre/Post	HDRS	07d	-1.396	-1.938	-0.854	0.000
07d	Loo et al (2012)	ECT+ketamine (Repeat infusions)	Pre/Post	MADRS	07d	-1.955	-2.659	-1.251	0.000
07d	Zarate et al (2006) A	Single infusion	Placebo/Ketamine	MADRS	07d	-0.650	-1.138	-0.161	0.009
07d	Sos et al (2013) A	Single infusion	Placebo/Ketamine	MADRS	07d	-0.698	-1.109	-0.287	0.001
07d	Thakurta et al (2012) A	Single infusion	Pre/Post	HDRS	07d	-0.247	-0.675	0.180	0.257
07d	Permoda-Osip et al (2013)	Single infusion	Pre/Post	HDRS	07d	-1.903	-2.912	-0.895	0.000
07d						-1.060	-1.572	-0.547	0.000
12-14d	Rybakowski et al (2013) B	Single infusion	Pre/Post	HDRS	12-14d	-1.551	-2.124	-0.977	0.000
12-14d	Price et al (2009) A	Repeat infusions (Responder/Remitters)	Pre/Post	MADRS	12-14d	-4.516	-6.574	-2.457	0.000
12-14d	Diazgranados et al (2010) A	Single infusion	Placebo/Ketamine	MADRS	12-14d	-0.210	-0.436	0.016	0.069
12-14d	Loo et al (2012) A	ECT+ketamine (Repeat infusions)	Pre/Post	MADRS	12-14d	-1.730	-2.381	-1.079	0.000
12-14d						-1.669	-2.850	-0.488	0.006
Overall						-1.242	-1.455	-1.028	0.000

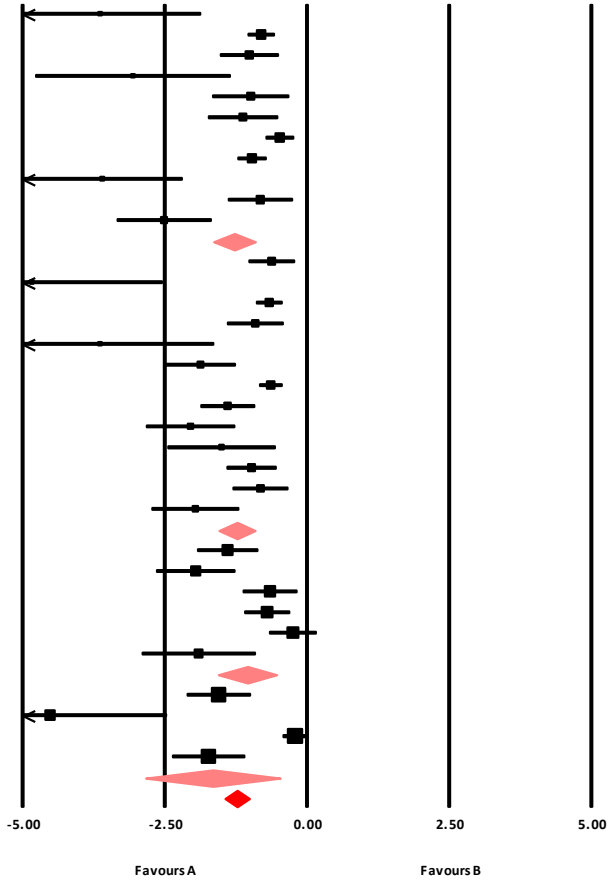

Fig. 2 Forest Plot for Moderating Effect of Time-point for All Studies