Ketamine for suicidal ideation in adults with psychiatric disorders:

A systematic review and meta-analysis of treatment trials

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ABSTRACT

Objective: Ketamine may reduce suicidal ideation in treatment-resistant depression. But it is not known how quickly this occurs and how long it persists. We undertook a systematic review and meta-analysis to determine the short and longer-term effectiveness of ketamine for suicidality. ***Method:*** CENTRAL, EMBASE, Medline, and PsycINFO were searched until 12 December, 2018. Randomised controlled trials of ketamine or esketamine reporting data on suicidal ideation, self-harm, attempted or completed suicide in adults diagnosed with any psychiatric disorder were included. Two reviewers independently extracted data and certainty of evidence was assessed using GRADE. Standardised mean difference (SMD) was used for continuous outcomes. ***Results:*** Twenty-five reports from 15 independent trials, with a total of 572 participants diagnosed with predominately affective disorders, were included. The evidence was rated moderate to low. In most trials ketamine was administered at 0·5mg/kg via a single intravenous infusion over a 30-45 minute period. Only a single trial of intransal esketamine was identified. At 4 hours post-infusion, treatment with ketamine was associated with a significant reduction in suicidal ideation scores (SMD -0·51, 95% CI -1·00 to -0·03), which persisted until 72 hours post-infusion (time-points between 12 and 24 hours: SMD -0·63, 95% CI -0·99 to -0·26; between 24 and 72 hours: -0·57, -0·99 to -0·14), but not thereafter. However, there was marked heterogeneity of results. In a single trial of esketamine, marginal effects on suicidal ideation were observed. In terms of actual suicidal behaviour there were virtually no data on effects of ketamine or esketamine. ***Conclusion:*** A single infusion of ketamine may have a short-term (up to 72 hours) beneficial impact on suicidal thoughts. While confirmation of these results in further trials is needed, they suggest possible use of ketamine to treat acute suicidality. Means of sustaining any anti-suicidal effect need to be found.

Keywords: suicide, suicidal ideation, ketamine, esketamine, depression.

INTRODUCTION

Suicidal ideation and self-harm are frequent and potentially life-threatening major public health problems, especially for people with severe mental health issues and mood disorders (Malhi et al., 2015). People presenting to hospital services for self-harm have a considerable risk of new episodes of self-harm [an average of 16·3% within a year in one review (Carroll et al., 2014), but well over 20% in other recent studies (Geulayov et al., 2016)], and also of completed suicide (1·6%) within a year (Carroll et al., 2014). Although fewer studies have focused on those presenting to clinical services for suicidal ideation only (i.e., without concurrent self-harm), patients hospitalised for clinically significant levels of suicidal ideation are also at increased risk of suicide (Hubers et al., 2018). Effective interventions in people presenting with suicidal ideation or self-harm are therefore a priority in order to contribute to efforts to reduce rates of self-harm and completed suicide.

Although there is currently no evidence that psychological treatments reduce suicide rates in self-harm patients (Crawford et al., 2007), brief cognitive behavioural-based psychological therapy has been shown to be effective in reducing repetition of self-harm at six and 12 months follow-up (Hawton et al., 2016a; Hawton et al., 2016b). However, psychological treatments for suicidal patients, although they are brief, require between three and 10 sessions (Hawton et al., 2016a), making them unsuitable for emergency treatment of suicidal patients. Currently, the only potential treatment available for acutely suicidal patients is ECT (Malhi et al., 2015), but there is little evidence to support this (Bergfeld et al., 2018). Otherwise treatment relies on close monitoring or hospitalisation (Griffiths et al., 2014).

Recent studies in both treatment-resistant unipolar and bipolar patients showed promising effects of ketamine in reducing depression scores (Caddy et al., 2015; McCloud et al., 2015). Although

some reviews investigating the effectiveness of ketamine as an emergency treatment have been conducted, often they include only brief mention of the efficacy of ketamine in reducing suicidal ideation in these populations of patients without specific details (Caddy et al., 2015; McCloud et al., 2015; Naughton et al., 2014).

One small systematic review, including data from nine studies, showed that overall ketamine appeared to be associated with a reduction in suicidal ideation at 40 minutes with effects appearing to persist up to 10 days post-infusion (Reinstatler and Youssef, 2015). A second older review also found that ketamine may be associated with beneficial effects on suicidal ideation (Fond et al., 2014). However, as both of these reviews included studies of diverse designs the authors did not calculate an overall pooled effect of ketamine on suicidal ideation. A further systematic review did not consider effects for ketamine beyond the four-hour post-administration window (Bartoli et al., 2017b). A fourth systematic review (Xu et al., 2016), and an individual patient data meta-analysis (Wilkinson et al., 2018), both found that ketamine was associated with a reduction in suicidal ideation, but that the effect was less durable at the seven day follow-up assessment.

Recently, there has been attention to intranasal treatment with esketamine for patients with treatment resistant depression. This has recently received approval from the Food and Drug Administration (FDA) in the USA for use as an adjunctive treatment to antidepressant therapy (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632761.htm).

Because of the increasing emphasis on finding effective interventions to reduce suicides (Zalsman et al., 2016), and the publication of new trials designed *a priori* to include patients with clinically significant levels of suicidal ideation and using specific suicidal ideation rating

scales, we undertook a systematic review to identify all studies reporting information on the effect of ketamine or esketamine on suicidality and conducted a meta-analysis for a number of time points between an immediate effect and up to more than one month.

METHODS

The protocol of this systematic review was registered with PROSPERO (CRD42017070591).

Search strategy and inclusion/exclusion criteria

We searched CENTRAL, EMBASE, Medline, and PsycINFO until 12 December, 2018 using the strategy outlined in Supplementary Table 1 in the Appendix. All published and unpublished randomised controlled trials (RCTs), comparing ketamine or esketamine as monotherapy or add-on treatment with placebo or active comparator in adult patients (i.e., 18 years and over) with a primary diagnosis of any major psychiatric disorder were eligible for inclusion in this review. Cross-over trials were also included; however, to protect against the carry-over effect only data for the period prior to cross-over were considered. Studies were excluded if the drugs under investigation were administered as an analgesic and/or anaesthetic agent, or data on suicidality were not available.

Data extraction

Abstracts and full texts were screened independently by two authors (KW and JP) and any disagreements were discussed with a third member of the team (AC and KH). Two reviewers (KW and JP) independently extracted data from included trials using a standardised form. We extracted outcome data at seven clinically-relevant time points, as follows: (1) *immediate effect* (within 4 hours); (2) *very ultra-rapid effect* (greater than 4 but less than/equal to 12 hours); (3) *ultra-rapid effect* (greater than 12 hours but less than/equal to 24 hours); (4) *rapid effect* (greater than 24 but less than/equal to 72 hours); (5) *early effect* (greater than 72 hours but less than /equal to 2 weeks); (6) *acute effect* (greater than 2 but less than/equal to 4 weeks); and (7) *longer-term effect* (greater than 4 weeks).

Outcome measures

The primary outcome was the mean change in suicidal ideation as assessed by the Beck Scale for Suicidal Ideation (BSSI), the Columbia Suicide Severity Rating Scale (C-SSRS), or from the suicidal ideation item of a depression rating scale such as the Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI, versions one or two), or the (Quick) Inventory of Depressive Symptomatology (IDS/QIDS).

We also extracted data on the following secondary outcomes where these were reported in the included studies: (1) repeat self-harm episodes; (2) further episodes of attempted suicide; (3) suicide deaths; and (4) deaths from any cause.

Statistical analysis

Where possible we synthesised quantitative data between studies using meta-analysis (Witt et al., 2017). For continuous outcome data we calculated the standardised mean difference (SMD) with corresponding 95% confidence intervals (CI). For dichotomous outcome measures we calculated the pooled odds ratio (OR) with corresponding 95% CI (Higgins et al., 2011). We used data from the intention-to-treat analyses for both continuous and dichotomous outcomes. The DerSimonian-Laird random effects model, as implemented by RevMan version 5.3 (http://handbook-5-1.cochrane.org/), was used to synthesise both continuous and dichotomous outcome data.

We also planned, *a priori*, a series of subgroup and sensitivity analyses. For details of these, see the review protocol in PROSPERO (CRD42017070591).

Risk of bias assessment and GRADE

The risk of bias of included studies was assessed by two reviewers independently (KW, JP) using the Cochrane Risk of Bias Tool (https://methods.cochrane.org/bias/resources/cochrane-risk-bias-tool). Any disagreements were discussed and, if necessary, involved a third reviewer (KH, AC). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was also used to assess the overall certainty of evidence (Schünemann et al., 2013). Further information is available in the Appendix.

Role of the Funding Source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. KH, AC, JP, and KW had full access to all the data in this study and all authors had final responsibility for the decision to submit for publication.

RESULTS

A total of 5,547 potentially relevant records were obtained from the electronic search, whilst a further 30 were identified by hand search and personal correspondence. 3,962 records remained after removing duplicates. Following a review of their titles and abstracts, a total of 3,898 records were excluded, whilst a further 39 were excluded following a review of their full texts for the reasons as outlined in Figure 1.

Where necessary, we clarified methodological or data queries with study authors; however, not all replied (Burger et al., 2016). One further trial was excluded due to the study design as trial participants were randomised to one of two different dosing regimens (either two doses per week or three doses per week) (Singh et al., 2016). As participants therefore received multiple doses, and data could not be obtained prior to the second dose, we concluded that the results could not be pooled with the results of the other trials in a meta-analysis. One further trial identified as awaiting assessment at the time of the initial systematic search was subsequently published and we were therefore able to include this study from personal correspondence. This therefore left a total of 25 studies, representing 15 independent trials, eligible for inclusion in the review (see Table 1 for study characteristics, and the Appendix for full reference list).[a1-a15]

** INSERT FIGURE 1 HERE **

** INSERT TABLE 1 HERE **

Overall, 572 adult participants (range: 15 to 80) between 37·7 and 65·6 years of age at randomisation (Mean: 46·1 years, SD: 11·2 years) were analysed. Most studies recruited participants with a diagnosis of unipolar major depression (10 studies),[a2,a4-a8,a11,a12,a14,a15] followed by uni- or bi-polar depression (2 studies),[a1,a10] bipolar depression (2 studies),[a3,a13] any mood and/or anxiety disorder (1 study).[a9] Of the 14 trials included, only six included patients with clinically significant levels of suicidal ideation.[a3-a5,a9,a14,a15] In three other trials, patients at high risk of suicide were excluded from participation.[a2,a8,a11]

Over half of the sample was female in the eight of the 13 trials (61·5%) that included information on gender. Scores on a measure of suicidal ideation at baseline (reported in nine trials) indicated moderate levels of suicidal thoughts. In the nine trials that reported information on suicidal behaviour, between 11·1% and 62·5% of the sample had a history of self-harm and/or attempted suicide prior to randomisation.

Interventions and comparisons

Most trials included in this review (14 trials) investigated the impact of ketamine on suicidal ideation. Ketamine was administered as a primary treatment for the acute relief of depression and/or suicidal ideation in all but three of these trials, where ketamine was used alongside electroconvulsive therapy (ECT) for the rapid relief of treatment-resistant depression.[a1,a6,a10] In most trials, ketamine was administered at 0·5mg/kg (8 trials; n=288),[a1,a3-a5,a8,a9,a13,a15] whilst in two further trials escalating doses up to 0·5mg/kg were used (n=32).[a2,a7] For the remaining trials, a number of different doses were used ranging from 0·27mg/kg[a11] to 1·0mg/kg.[a6,a10] In one further trial, ketamine was administered at two different doses, 0·2mg/kg and 0·5mg/kg.[a12] As these two conditions each had its own control group, data

from both comparisons could be used. In a single trial of esketamine, the overall dosage was 84mg.[a14]

In nine trials, including one in which ketamine was administered alongside electroconvulsive therapy (ECT), ketamine was administered on one occasion only,[a3-a6,a8,a9,a11-a13] whilst in two further trials in which ketamine was used alongside ECT, participants could receive up to five infusions of ketamine (i.e., once per ECT session).[a1,a10] In the remaining four trials, participants could receive multiple doses across the intervention period.[a2,a7,a14,a15] To protect against potential effects of repeated doses, for those trials in which the drug was administered on more than one occasion, only data prior to the second dose were extracted and included in any meta-analysis.

Ketamine was administered intravenously in all but three trials, where it was either administered subcutaneously,[a2] or where intravenous, intramuscular, and subcutaneous routes of administration were possible.[a7] For most studies (11 trials), ketamine was administered via an infusion over a 30 to 45 minute period. For two trials ketamine was infused via bolus,[a1,a10] and for one trial the duration of infusion was not clearly reported.[a6] In a single trial of esketamine, only the intranasal route of administration was used.[a14]

The majority of included studies compared ketamine with another drug (9 trials), most commonly midazolam as active placebo,[a2-a4,a7-a9] propofol and fentanyl,[a6] and methohexital,[a10] as active comparators. The remainder compared the effects of ketamine with a placebo control (i.e., saline solution).[a1,a5,a11-a15]

Effect of ketamine on suicidal ideation scores

By the immediate effect time point (i.e., within 4 hours), ketamine was associated with a significant reduction in suicidal ideation scores (SMD -0·51, 95% CI -1·00 to -0·03, 10 studies, I^2 73·0%; Figure 2). No study included data on the effect of ketamine on suicidal ideation scores by the very ultra-rapid effect time point (i.e., greater than 4 but less than/equal to 12 hours); however, effects in favour of ketamine for suicidal ideation were found at the ultra-rapid effect (i.e., greater than 12 hours but less than/equal to 24 hours) time point (SMD -0·63, 95% CI -0·99 to -0·26, 10 studies, I^2 63·0%; Figure 2), and the rapid effect time point (i.e., greater than 24 but less than/equal to 72 hours) time point (SMD -0·57, 95% CI -0·99 to -0·14, 8 studies, I^2 50·0%; Figure 2). These results were associated with considerable heterogeneity.

By the early effect time point (i.e., greater than 72 hours but less than/equal to 2 weeks), ketamine was no longer associated with a significant treatment effect for suicidal ideation (Figure 2).

** INSERT FIGURE 2 HERE **

Effect of ketamine on self-harm, attempted suicide, suicide, and all-cause mortality

One study of two different doses of ketamine (i.e., 0·2mg/kg *vs.* 0·5mg/kg) found that no participant in either the ketamine or control group engaged in a further episode of self-harm in either dosing group over the course of the follow-up period (up to 28 days).[a12]

This same study also reported data on the proportion with a suicide attempt by the longest time point (up to 28 days); no participant attempted suicide in either the ketamine or control

arms in this trial. [a12] There were also no suicide deaths in this trial. [a12] No included trial reported data on all-cause mortality.

Risk of Bias and GRADE

An overall summary of the risk of bias for all 15 trials is provided in Supplementary Figures 1 and 2 in the Appendix alongside an assessment of overall outcome quality. Overall, the certainty of the evidence was low to moderate (Supplementary Table 2, Appendix).

Sub-group and sensitivity analyses

Results from the sensitivity analyses excluding those studies in which a full-scale measure of suicidal ideation, as opposed to a single item measure, was used did not show material differences in terms of the observed effect of ketamine at any time-point (Supplementary Figure 3, Appendix). We also added one further (post-hoc) subgroup analysis. Specifically, given recent findings that ketamine may accelerate effect of ECT in patients with treatment-resistant depression (Jankauskas et al., 2018), we excluded those studies in which ketamine was administered as part of ECT treatment.[a1,a6,a10] Excluding these trials did not materially affect either the direction or magnitude of effect for ketamine for any time point. Given its influence on the results, we also conducted a further *post-hoc* sensitivity analysis excluding the Ionescu and Zarate trials which showed the strongest effects in favour of ketamine,[a13,a15] but found no material difference in either the direction or magnitude of the effect for ketamine for any time point.

Small study effects

The sample sizes of some of the included trials were relatively small, with eight trials (53.3%) including under 30 participants. We therefore performed Egger's test to examine the

impact of small study effects on the results. There was no evidence of small study effects for the immediate (i.e., within 4 hours; p=0.616), ultra-rapid (i.e., greater than 12 hours but less than/equal to 24 hours; p=0.816), rapid (i.e., greater than 24 but less than/equal to 72 hours; p=0.240), or early (i.e., greater than 72 hours but less than/equal to 2 weeks; p=0.219) effect time points. However, as there were fewer than 10 studies included in both the acute and longer-term effect time points, formal tests for small study effects could not be undertaken for these analyses.

DISCUSSION

This review, combining data from 15 independent randomised controlled trials involving 572 participants, shows evidence of effects in favour of a single treatment of ketamine for suicidal ideation in adult psychiatric patients predominately diagnosed with mood disorders; and principally unipolar major depression. These effects were apparent up to 72 hours post-infusion, in line with some previous work (Xu et al., 2016; Wilkinson et al., 2018), although considerable heterogeneity was associated with the estimates. The results suggest that ketamine can potentially be used in the emergency treatment of acute suicidal ideation. It is notable that effects in favour of ketamine for suicidal ideation would appear to be more time-limited than its effects on depression more broadly, as recent reviews have indicated positive effects of ketamine on depression scores up to one week post-infusion (Caddy et al., 2015; Xu et al., 2016).

These results are broadly in line with those of a recent individual participant data (IPD) meta-analysis in which ketamine was found to be associated with significant reductions in suicidal ideation in patients who were predominately diagnosed with major depression, although most of the eight trials analysed did not specifically target patients with clinically significant suicidal ideation (Wilkinson et al., 2018). However, we included 15 trials and doubled the number of participants (*n*=572). Furthermore, we were able to examine more clinically relevant time-points, which allowed us to identify more precisely the duration of impact of ketamine on suicidal ideation.

In terms of diagnosis, while we included studies of participants diagnosed with any psychiatric disorder, the diagnoses of participants were almost always mood disorders. This raises the issue of whether ketamine might have benefits for suicidality in patients with non-

affective disorders, especially those with borderline personality disorder, in whom repeated self-harm is a common feature (Hawton et al., 2016b). The average levels of suicidal ideation at baseline in our review were moderate in those trials in which it was reported. However, in the nine trials with information about actual suicidal acts substantial proportions of the participants had a history of self-harm and/or attempted suicide before trial entry, suggesting that they constituted patients at considerable risk. There is some evidence suggesting that the anti-suicidal effect of ketamine is independent from the antidepressant effect,[14,30] but larger studies including a variety of disorders are needed before we can draw clinically meaningful conclusions.

A number of the analyses included in this review were associated with high levels of heterogeneity owing to differences in dosing and route of administration. Ketamine dosing in the trials included in this review ranged from 0.27 to 1.0mg/kg, although we would note that higher doses were not necessarily associated with a superior effect of ketamine. In terms of route of administration, in most of the trials included in the review, ketamine was administered intravenously. Although we identified three recently published trials investigating the effectiveness of esketamine delivered via intranasal administration as an adjunct to oral antidepressant therapy which suggested a significant treatment effect in favour of esketamine for symptoms of depression at up to two months post-treatment (Daly et al., 2018; Gálvez et al., 2018),[a14] we were able to include data from only one of these trials,[a14] finding only a modest and non-significant effect at the immediate time point (i.e., up to four hours) in reducing suicidal ideation (and suicide risk as defined by a score of between zero and one on the clinician-administered Suicide Ideation and Behavior Assessment Tool).[a14] We were unable to obtain data on suicidal ideation to include a second of these trials in the present review (Daly et al., 2018), and for a third, the trial was discontinued prematurely due

to tolerability problems (Gálvez et al., 2018). Absorption via the nasal mucosa was variable, leading to high peak serum levels of esketamine in some participants. Notably, due to adverse effects, no participant was able to achieve the necessary 10 pump actions required to administer the full esketamine dose in the treatment protocol. There is therefore a need to evaluate both the safety and effectiveness of esketamine post-market before recommendations can be made as to both the safety and effectiveness of esketamine as an emergency treatment for suicidality. Whilst giving ketamine intravenously to suicidal patients in an accident and emergency department complicates the logistics of the administration of the intervention, it can guarantee that the drug is properly delivered. Other routes of delivery (such as intramuscular) also require further research.

In terms of mechanisms of the effect of ketamine on suicidality, the most obvious is through its impact on depression, although, as noted above, the two may not be completely correlated (Wilkinson et al., 2018), and the treatment effect for depression appears to last longer than that for suicidality (Caddy et al., 2015; McCloud et al., 2015), although it is still relatively short-term (Ibrahim et al., 2012). Other potential mechanisms of the anti-suicidal ideation effect of ketamine includes amelioration of symptom clusters associated with reduction of suicidal thoughts such as subjective symptoms of depression (e.g. sadness, pessimism, loss of interest) (Keilp et al., 2018) or improvement in neurocognitive domains such as memory (Gorlyn et al., 2015). These potential mediators require further research.

Limitations

The main limitation in our review is related to an intrinsic limitation in the available information from included studies. The assessment of suicidal ideation mainly relied on use of a single item on a depression rating scale, and the scales used varied across studies. Whilst there is some evidence of excellent correlation (around $r = 0.80$) between the suicidal ideation items of the HAM-D and MADRS (which the majority of the trials included in this review used) and suicide items in the BSSI (Ballard et al., 2015), it is perhaps questionable if these constitute a satisfactory and sensitive indicator of suicidality, especially when used to assess relatively rapid changes in suicidal ideation over a fairly short time span. Furthermore, only one study investigated effects for repeated self-harm behaviour, attempted suicide, and suicide, but no participant in either the ketamine or control arms experienced these outcomes by the final follow-up assessment, likely due to insufficient statistical power (Su et al., 2017). One further issue is that there is considerable uncertainty about the degree of association between overt expression of suicidal ideas and actual suicide risk, in that many patients who have died by suicide have not admitted to suicidal ideas when questioned in the weeks before their deaths (Berman, 2018).

A second limitation relates to the choice of the control group in the majority of included studies. The trials either used another anaesthetic agent (most commonly midazolam) or placebo, which are not effective in the treatment of depression or suicidality. Therefore, it may be that the effect of ketamine observed here could be masked if future trials were to compare the effectiveness of ketamine against other active antidepressant agents. In addition, ethical considerations relating to the off-label use of ketamine, including questions around the representativeness of participants included in these trials to date, and potential longer-term side effects of ketamine use, including the potential for rapid rebound of suicidal ideation

after ketamine treatment, requires further consideration before ketamine can be recommended for its anti-suicidal potential (Singh et al., 2017).

A further limitation is that in the included trials there was no reporting of potential adverse effects (e.g., dissociation, blurred vision, dizziness, malaise, nausea, or possible emergence psychosis) beyond the few hours after treatment, even in studies where ketamine was administered at relatively high doses (e.g., 1.0mg/kg). This problem was also highlighted in a recent review, which found limited reporting of safety or tolerability outcomes in trials of ketamine for the treatment of depression (Short et al., 2018). This is a key point also considering that previous studies have shown that ketamine effects on depression might be mediated by, or related to, both dissociative (Luckenbaugh et al., 2014) and psychotomimetic (Sos et al., 2013) effects. Consistently, the need of strategies to mitigate adverse effects of ketamine have been recently reported (Bartoli et al., 2017a; Cooper et al., 2017). This is an issue that requires careful consideration in future trials, especially when ketamine is used as an off-label treatment (Sanacora et al., 2017).

We also had to exclude some studies either because they did not report information on suicidality [e.g., (Abdallah et al., 2012; Alizadeh et al., 2015; Berman et al., 2000; Daly et al., 2018; Feder et al., 2014; Gálvez et al., 2017; Lai et al., 2014; Lapidus et al., 2014; Li et al., 2016; Ochs-Ross et al., 2019; Phillips et al., 2017; Popova et al., 2018; Rodriguez et al., 2013; Yoosefi et al., 2014; Zhong et al., 2016)], or because they were secondary publications of studies we had already included in the review [e.g., (DiazGranados et al., 2010; Lally et al., 2014; Zarate Jr. et al., 2006)]. Inconsistent reporting of clinical trials numbers in these secondary publications complicates the identification of duplicated studies in this field. Additionally, for studies in which information on suicidal ideation was not reported, although

we attempted to contact corresponding authors on three occasions to obtain these data, we received responses from few. These problems highlight the need for greater transparency in trials of ketamine or esketamine on adverse outcomes, and particularly those relating to suicidal ideation and behaviour. Stricter adherence and enforcement of CONSORT reporting guidelines in these trials would represent an important first step to help overcome these problems.

Sample sizes of the included trials were also relatively small, with eight trials including under 30 participants. This contributed to heterogeneity and uncertainty of the estimated effects in individual trials, as there were often too few participants to detect clinically significant effects of ketamine, particularly for rarer outcomes such as suicidal behaviour.

Finally, whilst we had planned, *a priori*, secondary analyses relating to possible differential effect in males compared with females and by suicidal ideation severity at baseline, the trials included in our analysis did not report disaggregated data by these factors so we could not carry out these subgroup/sensitivity analyses.

Clinical implications

The results of this review suggest that ketamine may have a role in acute treatment for suicidality. However, there is clearly a need for clinical measures to ensure persistence of any benefits. One possibility is combining some sort of acute psychosocial intervention, such as brief psychological therapy with ketamine treatment. Adaptations of psychosocial treatments which have been shown to have impacts on suicidality, for example cognitive-behavioural therapy (CBT) approaches (Hawton et al., 2016b), could provide a basis for the development

of acute therapy in this setting. Another is the use of multiple treatments with ketamine, which in practice is common (Caddy et al., 2015), and yet most studies included in the current review evaluated the effects of ketamine as a single treatment. These possible approaches to maximising the potential benefits of ketamine in the clinical management of people with suicidal ideation are well worth pursuing in order to determine the place of ketamine in contributing to current efforts to reduce suicide.

Conclusions

The results of this review suggest that a single dose of ketamine (0.5 mg/kg) may have short-term benefits in the acute treatment of suicidal ideas, but that ways, including possible psychosocial interventions, need to be found to maintain these effects. There is a clear need for more research focused on the effects of ketamine in suicidal patients, including in those with psychiatric disorders other than affective disorders. In such research there needs to be close monitoring of suicidal ideation, perhaps using digital and frequently repeated recording of patient's thoughts (e.g. ecological momentary assessment). There is also a need to closely monitor side effects of the medication to ensure patient safety, including beyond the immediate post-treatment period. We conclude that currently there is considerable uncertainty about the use of ketamine specifically as a treatment for suicidal ideas, but that current results of trials suggest that this drug may have a potential place in the clinical care of suicidal patients.

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DECLARATION OF CONFLICTING INTERESTS

The following were involved in trials included in this review: MFG, JWM, and CL. All other authors declare that there is no conflict of interest.

Table 1. Study characteristics for all trials included in the review. Full reference list for included trials available in the Appendix.

Study ID	Registration number	Country	Sample size	Methods	Participants	Intervention	Control	Duration	Outcomes
Anderson 2017[a1]	ISRCTN 14689382	UK	72	Multicentre, parallel, randomised study comparing ketamine with placebo in the acute treatment of patients with uni- or bi-polar depression.	Adult males and females with a primary diagnosis of uni- or bipolar depression of moderate severity as defined by the DSM-IV. Additional inclusion criteria required eligible participants to have: (1) a verbal IQ score of 85 or greater, and; (2) an American Society of Anaesthesiol-ogists score of 1, 2, or 3. Patients were excluded if: (1) they spoke a language other than English; (2) were detained under the Mental Health Act; (3) were unable to give informed consent; (4) were diagnosed with psychosis, schizoaffective disorder, obsessive-compulsive disorder, or anorexia; (5) had a history of alcohol or drug dependence as defined by the DSM-IV; (6) had received ECT in the three months prior to trial entry; (7) had known hypersensitivity to ketamine; (8) had a contraindication to ketamine; (9) were diagnosed with an organic brain disease; (10) had a history of using etomidate or other induction agents; (11) were pregnant or not using contraception; (12) were breastfeeding, or; (13) had a score of less than 24 on the Mini Mental Status Examination.	Ketamine: 0·5mg/kg, delivered by intravenous (IV) bolus (duration of administration not reported). Participants received one dose each electroconvulsive therapy (ECT) session, for a maximum of four doses (i.e., once per ECT session).	Control (placebo): saline (dose not reported), delivered by IV bolus (duration of administration not reported). Participants received one dose each ECT session, for a maximum of four doses (i.e., once per session).	Unclear.	Suicidal ideation: MADRS, suicidality item (obtained by correspondence). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
George 2017[a2]	NCT 01441505	Australia	16	Single centre, cross-over, RCT comparing ketamine with midazolam in the acute treatment of older adults (Mean: 65·6 years, SD: 5·7 years) with treatment resistant depression.	Males and females over 60 years of age with a primary diagnosis of major depression as defined by the DSM-IV-TR and clinician-conducted interview. Additional inclusion criteria required eligible participants to have: (1) a score of 20 or greater on the MADRS, and (2) insufficient therapeutic response to more than one adequate trial of an antidepressant during the current depressive episode as defined by Anti-depressant Treatment Response Questionnaire. Patients were excluded if they: (1) were judged to	Ketamine: ascending doses from 0·1 mg/kg, 0·2mg/kg, 0·3mg/kg, 0·4mg/kg to 0·5mg/kg, delivered by subcutaneous infusion (duration of administration not reported). Participants received five doses separated by a week.	Control: midazolam, 0·01mg/kg, delivered by subcutaneous infusion (duration of administration not reported). Participants received one dose. Dose was randomly inserted within the first three treatment sessions.	Up to five weeks.	Suicidal ideation: single item from the MADRS (obtained by correspondence). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.

					be at high suicide risk necessitating urgent management; (2) were pregnant; (3) had a diagnosis of schizophrenia, drug abuse or dependence within the last six months; (3) had current psychotic symptoms; (4) known hypersensitivity or medical contraindication to ketamine; (5) had a history of ketamine abuse.				
Grunebaum 2017[a3]	Not reported.	USA	16	Single centre, parallel, randomised study comparing ketamine with midazolam in the acute treatment of patients with bipolar depression.	Males and females between 18 and 65 years of age with a primary diagnosis of bipolar depression as defined by the DSM-IV. Additional inclusion criteria required eligible participants to have: (1) a score of 16 or greater on the HDRS-17, and; (2) a score of 4 or greater on the Scale for Suicidal Ideation. Patients were excluded if they: (1) had an unstable medical and/or neurological illness; (2) had an electrocardiogram (ECG) abnormality; (3) had current psychosis; (4) had a history of ketamine abuse/dependence; (5) had a history of alcohol and/or drug dependence in the past six months; (6) had drug induced suicidality; (7) had a treatment failure or other adverse reaction to ketamine or midazolam; (8) used opioids daily; (9) had a score of greater than 25 on the Mini Mental Status Examination (MMSE); (10) were unable to provide informed consent, or (11) spoke a primary language other than English.	Ketamine: racemic, 0·5mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Control: midazolam, 0·02mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Unclear.	Suicidal ideation: Scale for Suicidal Ideation, clinician-rated version. Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Grunebaum 2018[a4]	NCT 01700829 .	USA	80	Single centre, parallel, randomised study comparing ketamine with midazolam in the acute treatment of patients with major depression.	Males and females between 18 and 65 years of age with a primary diagnosis of major depression (unclear how defined). Additional inclusion criteria required eligible participants to have: (1) a score of 16 or greater on the HDRS. Participants were excluded if: (1) they were diagnosed with an unstable medical or neurological illness; (2) were pregnant or lactating; (3) had current psychosis; (4) had a history of ketamine use or dependence; (5) had a history of alcohol or drug dependence in the past six	Ketamine: 0·5mg/kg, delivered by IV infusion over 40 minutes. Participants received one dose.	Control: midazolam, 0·02mg/kg, delivered by IV infusion over 40 minutes. Participants received one dose.	Unclear.	Suicidal ideation: Scale for Suicidal Ideation, clinician-rated version. Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.

					months; (6) had suicidal ideation due to substance use or withdrawal; (7) had previous ineffective use of ketamine or midazolam, or; (8) a score of greater than 25 on the MMSE (for participants over 60 years of age).				
Hu 2016[a5]	Not reported.	China	27	Single centre, parallel, randomised study comparing ketamine with escitalopram in the acute treatment of patients with major depression without psychotic features.	Males and females between 18 and 60 years of age with a primary diagnosis of major depression without psychotic features as defined by the DSM-IV. Additional inclusion criteria required eligible participants to have: (1) a score of 24 or greater on the HDRS; (2) a score of one or greater on item three (suicide risk) of the HDRS, and; (3) sufficient language ability to be able to understand the study aims and to provide informed consent to participate in the study. Patients were excluded if they: (1) had a lifetime history of alcohol or drug dependence; (2) a lifetime diagnosis of psychosis, bipolar disorder, obsessive-compulsive disorder, or any Axis 1 disorder other than major depression; (3) a history of non-response or intolerance to escitalopram; (4) were pregnant or breastfeeding; (5) had attempted suicide in the current depressive episode; (6) had any contraindication to ketamine or escitalopram; (7) had received ECT or any NMDA antagonist medication in the past six months.	Ketamine: 0·5mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Control: placebo (saline solution; dose not specified), delivered by IV infusion (duration of administration not specified). Participants received a maximum of one dose.	Unclear.	Suicidal ideation: QIDS-SR, suicidality item. Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Kudoh 2002[a6]	Not reported.	Japan	70	Single centre, parallel, randomised study comparing ketamine with propofol plus fentanyl in the acute treatment of patients with major depression.	Males and females between 35 and 63 years of age with a primary diagnosis of major depression as defined by the DSM-IV. No specific exclusion criteria were reported.	Ketamine: 1·0mg/kg, route of administration not reported, duration of administration not reported. Participants received one dose.	Control: propofol (1·5mg/kg) and fentanyl (2·0 nanograms/kg), route of administration not reported, duration of administration not reported. Participants received one dose.	One day	Suicidal ideation: HDRS, suicidality item. Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Loo 2016[a7]	NCT 01441505.	Australia	15	Single centre, cross-over, randomised study	Males and females over 18 years of age with a primary diagnosis of major depression as defined by the SCID-R	Ketamine: ascending doses from 0·1 mg/kg, 0·2mg/kg,	Control: midazolam, 0·01mg/kg, (route of administratio	Up to five weeks.	Suicidal ideation: single item from the MADRS (obtained by correspondence).

				comparing ketamine with midazolam in the acute treatment of patients with treatment resistant depression.	for DSM-IV-TR and as verified by a face-to-face psychiatric interview. Additional inclusion criteria required eligible participants to have: (1) a score of 20 or greater on the MADRS, and (2) insufficient therapeutic response to more than one adequate trial of an antidepressant during the current depressive episode as defined by the Maudsley Staging of Treatment Resistance. Patients were excluded if they: (1) were pregnant; (2) had a diagnosis of schizophrenia, bipolar disorder, or drug abuse or dependence within the last six months; (3) had current psychotic symptoms; or (4) had received ECT within the four weeks preceding trial entry.	0·3mg/kg, 0·4 mg/kg to 0·5mg/kg, delivered either by intravenous, intramuscular, or subcutaneous bolus over approximately five minutes. Participants received five doses separated by a week.	n and duration of administratio n not reported). Participants received one dose. Dose was randomly inserted within the first three treatment sessions.		Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Murrough 2013[a8]	NCT 00768430	USA	73	Single centre, parallel, randomised study comparing ketamine with midazolam in the acute treatment of patients with major depression.	Males and females between 21 and 80 years of age with a primary diagnosis of major depression as defined by the SCID for DSM-IV-TR. Additional inclusion criteria required eligible participants to have: (1) a history of inadequate response to at least three therapeutic trials of an antidepressant as defined by the criteria of the Antidepressant Treatment History Form; (2) a history of at least one previous episode of major depression before the current episode, or, a chronic episode of at least two years duration, and; (3) a score of 32 or greater on the Inventory of Depressive Symptomatology-Clinician Rated. Patients were excluded if they: (1) had a lifetime diagnosis of psychosis or bipolar disorder; (2) were diagnosed with alcohol or substance dependence in the past two years; (3) were diagnosed with an unstable medical illness; (4) were at serious and imminent risk of suicide or homicide; (5) had a score of less than 27 on the MMSE; (6) were prescribed and were taking any contraindicated medications.	Ketamine: racemic, 0·5mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Control: midazolam, 0·045mg/kg, delivered by IV infusion (duration of administratio n not specified). Participants received a maximum of one dose.	One week.	Suicidal ideation: single item from the MADRS (obtained by correspondence). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Murrough 2015[a9]	NCT 01507181	USA	24	Single centre, parallel,	Males and females between 18 and 80 years of age with a primary	Ketamine: racemic, 0·5mg/kg,	Control: midazolam, 0·045mg/kg,	One week.	Suicidal ideation: single item from the MADRS

				randomised study comparing ketamine with midazolam in the acute treatment of patients with any mood and/or anxiety disorder.	diagnosis of any mood and/or anxiety disorder as defined by the DSM-IV-TR. Additional inclusion criteria required eligible participants to have: (1) clinically significant suicidal ideation as defined by a score of four or greater on the suicidal ideation item of the MADRS. Patients were excluded if they: (1) scored five or greater on the C-SSRS (for outpatients only); (2) had a lifetime diagnosis of schizophrenia or any other psychosis; (3) had current psychosis symptoms; (4) had current mania symptoms; (5) had a diagnosis of substance use disorder in the past one month; (6) had a positive urine screen for any drug; (7) had a lifetime history of abuse of ketamine or phencyclidine, or (8) were diagnosed with an unstable medical illness.	delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	delivered by IV infusion (duration of administration not specified). Participants received a maximum of one dose.		(obtained from correspondence). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Ray-Griffith 2017[a10]	Not reported.	USA	16	Single centre, parallel, randomised study comparing ketamine with methohexital in the acute treatment of patients with uni- or bi-polar depression.	Adult males and females with a primary diagnosis of uni- or bi-polar depression as defined by the SCID for DSM-IV. Additional inclusion criteria required eligible participants to have: (1) a score of 20 or greater on the HDRS. Patients were excluded if they: (1) spoke a primary language other than English; (2) had a history of any adverse event whilst receiving ketamine or methohexital anaesthesia; (3) were pregnant, or; (4) had a Body Mass Index of greater than 40.	Ketamine: 1·0mg/kg, delivered by IV bolus. Participants received a maximum of five doses (once per ECT session).	Control: methohexital, 1·0 mg/kg, delivered by IV bolus. Participants received a maximum of five doses (once per ECT session).	One week.	Suicidal ideation: HDRS, suicidality item and BDI, suicidality item (from authors). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Sos 2013[a11]	EudraCT 2009-010625-39.	Czech Republic	27	Single centre, parallel, randomised study comparing ketamine with placebo in the acute treatment of patients with major depression.	Males and females between 18 and 65 years of age, primary diagnosis of major depression as defined by the MINI (DSM-IV). Additional inclusion criteria: (1) a score of 20 or greater on the MADRS; (2) be on a stable dose of antidepressant(s) for three or more weeks prior to study entry, and; (3) be right handed. Patients were excluded if: (1) at imminent risk of suicide (according to clinical examination); (2) diagnosed with an Axis 1 or 2 co-morbidity; (3) diagnosed with a serious, unstable medical illness	Ketamine: racemic, 0·27mg/kg, delivered by IV infusion over 30 minutes. Participants received a maximum of one dose.	Control (placebo): saline, 0·09mg/kg, delivered by IV infusion (duration of administration not specified). Participants received a maximum of one dose.	One week.	Suicidal ideation: MADRS, suicidality item (obtained by correspondence). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.

					or neurological disorder (e.g., epilepsy, head trauma with loss of consciousness); (4) lifetime diagnosis of psychosis or psychosis symptoms (including in any first- or second-degree relative), and; (5) had received ECT within three months prior to study entry.				
Su 2017a[a12]	Not reported.	Taiwan	71	Single centre, parallel, randomised study comparing ketamine at two different dosages (0·2mg/kg and 0·5mg/kg) with placebo in the acute treatment of patients with major depression.	Adult males and females with a primary diagnosis of major depression as defined by the MINI. Additional inclusion criteria required eligible participants to have: (1) previous failure to respond to at least two trials of antidepressants. Patients were excluded if they: (1) were diagnosed with bipolar depression, psychosis, substance dependence (other than nicotine); (2) had mild depressive symptoms (defined as a score of less than 18 on the HDRS), or (3) were diagnosed with hypertension or hyperglycaemia.	Ketamine (0·2mg/kg): ketlar, 0·2mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Control (placebo): saline, delivered by IV infusion over 40 minutes (duration of administration not specified). Participants received a maximum of one dose.	Unclear.	Suicidal ideation: single item from the HDRS (from authors). Suicide attempt: not reported. Suicide: measure used not reported. All-cause mortality: not evaluated.
Su 2017b[a12]	Not reported.	Taiwan	71	Single centre, parallel, randomised study comparing ketamine at two different dosages (0·2mg/kg and 0·5mg/kg) with placebo in the acute treatment of patients with major depression.	Adult males and females with a primary diagnosis of major depression as defined by the MINI. Additional inclusion criteria required eligible participants to have: (1) previous failure to respond to at least two trials of antidepressants. Patients were excluded if they: (1) were diagnosed with bipolar depression, psychosis, substance dependence (other than nicotine); (2) had mild depressive symptoms (defined as a score of less than 18 on the HDRS), or (3) were diagnosed with hypertension or hyperglycaemia.	Ketamine (0·5mg/kg): ketlar, 0·5mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Control (placebo): saline, delivered by IV infusion over 40 minutes (duration of administration not specified). Participants received a maximum of one dose.	Unclear.	Suicidal ideation: single item from the HDRS (from authors). Suicide attempt: not reported. Suicide: not reported. All-cause mortality: not evaluated.
Zarate 2012[a13]	NCT 00088699	USA	15	Single centre, cross-over, randomised study comparing ketamine with placebo in the acute treatment of patients with bipolar disorder, types I or II.	Adult males and females, between 18 and 65 years of age, with a primary diagnosis of bipolar disorder, types I or II, as defined by the SCID-P for DSM-IV, and as verified by clinical interview. Additional inclusion criteria: (1) a current duration of a major depressive episode of at least four weeks; (2) a MADRS score of 20 or greater; (3) history of inadequate treatment response to at least one adequate antidepressant	Ketamine (0·5mg/kg): ketamine hydrochloride, 0·5mg/kg, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	Control (placebo): saline, delivered by IV infusion over 40 minutes. Participants received a maximum of one dose.	40 minutes	Suicidal ideation: MADRS item (estimated from graphics in the original trial report). Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.

					trial as defined by the Antidepressant Treatment History Form, modified, and (4) history of inadequate treatment response following a prospective open trial of a mood stabiliser (lithium or valproate) for at least four weeks at minimum therapeutic levels (serum lithium: 0·6—1·2mEq/L; valproic acid: 50—125 nannograms/mL). Patients were excluded if: (1) diagnosed with comorbid substance abuse or dependence for at least three months prior to trial entry; (2) any serious unstable medical condition; (3) previous treatment with ketamine; (4) concomitant treatment with psychotropic medications other than lithium or valproate in the two weeks preceding trial entry (or five weeks for fluoxetine); or (4) pregnant or breast-feeding.				
Canuso, 2018[a14]	NCT 02133001	USA	68	Multicentre, parallel, randomised controlled trial comparing esketamine with placebo in the acute treatment of patients with major depression.	Adult males and females, between 19 and 64 years of age, with a primary diagnosis of major depression without psychotic features as defined by the DSM-IV-TR and as verified by the MINI. Additional inclusion criteria: (1) current suicidal ideation as defined by an affirmative response to the MINI question B5 ("Think about suicide?") and question B9 ("Intend to act on thoughts of killing yourself within the next 24 hours?"); (2) in need of immediate psychiatric hospitalisation due to imminent risk of suicide; and (3) a score of ≥22 on the MADRS. Patients were excluded if they: (1) were diagnosed with bipolar disorder, moderate to severe substance use disorder, intellectual disability, antisocial or borderline personality disorder; or (2) had a current or past diagnosis of any psychosis.	Esketamine (up to 84mg): esketamine dissolved in 100µL of saline solution delivered by intranasal spray. Participants received a maximum of six sprays (i.e., three 'devices' per session, separated by 5 mins) delivering a maximum of 84mg of esketamine over the 4-week study period.	Control (placebo): saline with added embittering agent, delivered by intranasal spray. Participants received a maximum of six sprays (i.e., three per session, separated by 5 mins) over the 4-week study period.	15 minutes	Suicidal ideation: single item from the MADRS and the 21-item Beck Scale of Suicidal Ideation. Suicide attempt: not evaluated. Suicide: not evaluated. All-cause mortality: not evaluated.
Ionescu, 2019[a15]	NCT 01582945	USA	26	Single centre, parallel, randomised controlled trial comparing ketamine	Adult males and females, between 18 and 65 years of age, with a primary diagnosis of major depression as defined by the SCID for DSM-IV. Additional inclusion criteria required eligible	Ketamine (0.5mg/kg): ketamine, 0.5mg/kg, delivered by IV infusion over 45 minutes.	Control (placebo): saline, delivered by IV infusion over 45 minutes. Participants	45 minutes.	Suicidal ideation: Columbia Suicide Severity Rating Scale (C-SSRS) total score. Suicide attempt: not evaluated.

		with placebo in the acute treatment of patients with major depression.	participants to have: (1) a score of ≥20 on the HDRS; (2) history of ≥3 failed trials of antidepressant treatment of adequate dosage and duration during the current episode of depression as measured by the Antidepressant Treatment History Questionnaire; (3) suicidal ideation for ≥3 months as measured by a score of ≥1 on the C-SSRS; (4) a score of ≥2 on the suicide item of the HDRS on at least three assessments; (5) ability to remain on an adequate, stable antidepressant regimen for ≥4 weeks prior to trial entry; (6) access to a secure, reliable adult chaperone after each ketamine infusion; (8) able to maintain treatment by a psychiatrist aware of the safety plan of the trial protocol, and; (9) physically healthy as determined by a physical exam, blood laboratory testing, electro-cardiogram, and medical history obtained from a board-certified physician. Patients were excluded if they: (1) were pregnant; (2) were diagnosed with an unstable medical illness; (3) were diagnosed with bipolar disorder or psychosis; (3) had been diagnosed with a substance use disorder within the past year; (5) had positive urine toxicology; (6) had past multiple adverse drug reactions; (7) had a history of ketamine abuse, (8) had suicidal ideation requiring immediate hospitalisation and/or indicating immediate suicide risk, or use of any of the following within the 6 months prior to trial entry: St John's wort, theophylline, tramadol.	Participants could receive up to six doses over the three-week study period.	could receive up to six doses over the three-week study period.	Suicide: not evaluated. All-cause mortality: not evaluated.

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