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Meta-analysis

Ketamine as a rapid-acting agent for suicidal ideation: A meta-analysis

Francesco Bartoli[a,*], Ilaria Riboldi[a], Cristina Crocamo[a], Carmen Di Brita[a], Massimo Clerici[a], Giuseppe Carrà[a,b]

[a] Department of Medicine and Surgery, University of Milano Bicocca, Monza, Italy
[b] Division of Psychiatry, University College London, London, UK

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ABSTRACT

The current systematic review and meta-analysis aimed at exploring acute effects of intravenous (IV) ketamine, an antagonist of N-methyl-D-aspartate (NMDA), in subjects with current suicidal ideation. We included clinical trials testing a single IV dose of ketamine and assessing changes in suicidal ideation within 4 h after treatment. Meta-analyses based on random-effects models, were carried out generating pooled standardized mean differences (SMDs) between endpoint and baseline scores. Heterogeneity among studies was estimated using the I^2 index. We searched main Electronic Databases, identifying five studies that met our inclusion criteria. The trials included 99 subjects treated with IV ketamine bolus or infusion. Data showed a large (SMD = −0.92; 95%CI: −1.40 to −0.44; $p < 0.001$) and consistent ($I^2 = 21.6\%$) decrease of suicidal ideation, with effects comparable between IV bolus and infusion ketamine. Additional analyses confirmed the efficacy of ketamine across different time points. However, relevant, emerging evidence should be considered as 'very low' so far. Randomized, controlled and adequately powered trials are needed.

Contents

* Corresponding author at: University of Milano Bicocca, Via Cadore 48, 20900 Monza, Italy.
E-mail address: f.bartoli@campus.unimib.it (F. Bartoli).

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1. Introduction

Although approved antidepressants act through monoaminergic mechanisms, with various affinities for serotonin and noradrenaline, it has been recently hypothesized an important role for glutamate system in mood regulation (Serafini et al., 2014; Zarate et al., 2010), also in terms of target for novel therapeutic approaches (Caddy et al., 2014; Iadarola et al., 2015; Lapidus et al., 2013). In particular, ketamine, an antagonist of N-methyl-D-aspartate (NMDA), proposed for anesthesia in the 1960s, is considered a promising option for subjects suffering from severe and treatment-resistant depression (Malhi et al., 2016). Ketamine might modulate glutamatergic receptors, enhancing neuroplasticity and neurogenesis, as well as the release of neurotransmitters involved in mood regulation (Lee et al., 2015a; Serafini et al., 2015). Preliminary, though limited, evidence for ketamine and other modulators of glutamate receptors in depression treatment has been highlighted (Caddy et al., 2015). Recent meta-analytic data have shown that, in both *unipolar* and *bipolar* depression (Lee et al., 2015b), ketamine might have a significant antidepressant effect, lasting from four hours to seven days after treatment (Coyle and Laws, 2015). Moreover, although the neurobiological basis underlying the relationship between depression and suicide is not fully understood (Rajkumar et al., 2015), it seems that the rapid onset of action of ketamine, along with an acute antidepressant effect, might reduce also suicidal ideation (Malhi et al., 2016; Mallick and McCullumsmith, 2016; Wilkinson and Sanacora, 2016). Indeed, recent systematic reviews highlighted that ketamine might be effective in reducing suicidal ideation and depressive symptoms quickly, with minimal short-term side effects, though its neurobiological correlates remain to be clarified (Mallick and McCullumsmith, 2016; Reinstatler and Youssef, 2015).

However, although a body of evidence of acceptable size has accumulated in the last few years, there are no studies that systematically pooled data of intervention studies published in this field so far. Several clinical trials have investigated the effect of ketamine in subjects with treatment-resistant (Price et al., 2009; Thakurta et al., 2012) or bipolar (Zarate et al., 2012) depression, independently by the occurrence of suicidal ideation. Nonetheless, in order to increase consistency of evidence, it seems important pooling data deriving from studies including only (Ionescu et al., 2016), or separately assessing (DiazGranados et al., 2010), subjects with current suicidal ideation, rather than depression as such. Investigating novel therapeutic options for suicidal ideation is important because a significant proportion of patients still fail to respond to standard treatment approaches (Pompili et al., 2010; Stone et al., 2009) and suicide risk prevention still represents an unmet need in psychiatric clinical practice (Wilkinson and Sanacora, 2016). We thus conducted a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines-based systematic review and meta-analysis of clinical trials (Moher et al., 2009), testing early efficacy of ketamine for suicidal ideation with the purpose of clarifying the magnitude of the effect, consistency of results, as well as quality of evidence (Schünemann et al., 2008).

2. Methods

2.1. Eligibility criteria

We included clinical trials testing a single intravenous (IV) dose of ketamine for acute treatment of suicidal ideation. To be considered, studies had (i) to recruit adults with current suicidal ideation from any inpatient and/or outpatient or emergency department settings, and (ii) to assess changes in suicidal ideation with an appropriate rating instrument and within four hours after treatment, since this is the standard time point used to assess acute responses to IV ketamine (DiazGranados et al., 2010; Ballard et al., 2014). Due to the exploratory nature of this meta-analysis, neither active comparators nor placebo were required, and single-arm clinical trials testing ketamine were considered. We excluded studies dealing with treatment-resistant depression or bipolar depression, that did not provide data for subgroups of participants reporting baseline suicidal ideation, as well as studies testing suicidal ideation changes later than four hours. Furthermore, we excluded reports with incomplete data, such as conference abstracts and dissertations, and gray literature not undergoing a peer-review process. If data from the same sample had been published in multiple works, we retained for meta-analysis only the study with more exhaustive information to avoid duplicate (multiple) publication bias (Sterne et al., 2008).

2.2. Search strategy and data extraction

We searched Pubmed and, via Ovid, Medline, Embase and PsycInfo electronic databases from inception till November 2016. We used the following search phrase: *(ketamine and (suicide or suicidal ideation)).mp.* with '*mp*' code meaning that the search included title, abstract, heading word, and keyword. Furthermore, we searched reference list of two recently published systematic reviews (Mallick and McCullumsmith, 2016; Reinstatler and Youssef, 2015). After the preliminary screening based on titles and abstracts, studies were retrieved in full text in order to test their eligibility. We developed an extraction sheet for main information from each study including year of publication; study location; setting; suicidal ideation definition and assessment; sample size; participants' characteristics; tested ketamine dose and methods for IV administration (infusion or bolus); minutes between ketamine treatment and outcome measurement; main results. Systematic searches and data extraction were performed by two authors independently (IR and CDB). Discordances were resolved by consensus with other co-authors. When reported information was incomplete or unclear, one investigator (FB) contacted the relevant corresponding author for clarification.

2.3. Data analysis

We used baseline and endpoint mean scores on suicidal ideation (with standard deviations or standard errors), or relevant paired *t*-values, to estimate standardized mean differences (SMDs) with 95% confidence interval (95%CI). Because pre- and post-treatment values are dependent, effect sizes were estimated taking into account correlation between scores at different time points. Since most of studies did not include this information, we used a conservative correlation value of 0.5 (Newby et al., 2015). Individual SMDs were pooled in meta-analyses using random effects model. Statistical significance was set at $p < 0.05$. We run a subgroup analysis based on different methods of ketamine administration (infusion or bolus) and dose (0.5 mg/kg or 0.2 mg/kg), using test for subgroup differences (Deeks et al., 2008). Additional analyses were carried out to explore effect size variations at different time points, i.e., 40, 80, 120 and 230/240 min, after IV ketamine administration, according to data available from individual studies. Heterogeneity was estimated using the I^2 index, with values of 25%, 50%, and 75%, taken to indicate low, moderate, and high levels of heterogeneity, respectively (Higgins, 2003). Publication bias was assessed using Egger's linear regression test, if at least ten studies were included in the meta-analysis, as recommended (Sterne et al., 2008). Analyses were performed using STATA statistical software package (version 13.1, 2013; Stata Corp, College Station, TX).

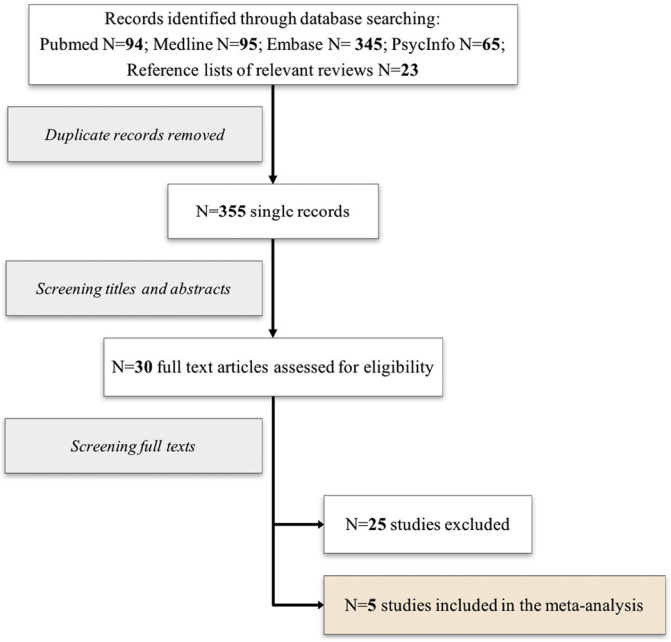

Fig. 1. Flow diagram of studies included in the meta-analysis.

3. Results

3.1. Study selection

After removing duplicates, our search generated 355 records from PubMed, Medline, Embase and PsycInfo and two relevant systematic reviews (Mallick and McCullumsmith, 2016; Reinstatler and Youssef, 2015). The preliminary screening by reading titles and/or abstracts identified 30 trials that were potentially eligible. Further screening of full texts excluded 25 trials, i.e., 14 studies because of lack of data on subgroups with baseline suicidal ideation, 4 studies without information on effects within four hours after ketamine treatment, 3 studies not considering suicidal ideation outcome, 3 case reports, and 1 proof of concept trial with limited sample size. Five trials met our inclusion criteria and were included in the meta-analysis (Ballard et al., 2015; DiazGranados et al., 2010; Kashani et al., 2014; Ionescu et al., 2016; Larkin and Beautrais, 2011). Flow chart of the study selection process is reported in Fig. 1.

All studies were written in English language, published between 2010 and 2016 and conducted in USA (DiazGranados et al., 2010; Ballard et al., 2015; Ionescu et al., 2016; Larkin and Beautrais, 2011) and Iran (Kashani et al., 2014). Three studies included inpatients and/or outpatients (Ionescu et al., 2016; DiazGranados et al., 2010; Ballard et al., 2015), whereas two studies recruited subjects from emergency departments (Kashani et al., 2014; Larkin and Beautrais, 2011). We obtained unpublished information on one study (Ionescu et al., 2016), i.e., data on changes in suicidal ideation scores after ketamine infusion. Detailed characteristics of included studies are summarized in Supplementary Table 1.

3.2. Synthesis of results

The studies included 99 subjects, 63 treated with IV ketamine 0.2 mg/kg bolus (Kashani et al., 2014; Larkin and Beautrais, 2011) and 36 with 0.5 mg/kg infusion (Ballard et al., 2015; DiazGranados et al., 2010; Ionescu et al., 2016). Considering the maximum allowed endpoint of four hours, we found a clear decrease in suicidal ideation (SMD = −0.92; 95%CI: −1.40 to −0.44; $p < 0.001$), with low heterogeneity across studies ($I^2 = 21.6\%$). Although not significantly ($p = 0.27$), the effect of ketamine bolus (SMD = −2.11; $p = 0.06$) was higher as compared with relevant effect of ketamine infusion (SMD = −0.86; $p = 0.001$). Fig. 2 shows the relevant forest plot. Additional analyses confirmed similar effects of ketamine across different time points, though with different precision and level of significance (Fig. 3). In particular, an effect was detectable after 40 min, remained significant 230/240 min after treatment, though non-significant trends were estimated at 120 and 180 min. Since included studies were less than ten, we could not assess the risk of publication bias, that should be thus considered uncertain.

4. Discussion

4.1. Summary of evidence and limitations

To the best of our knowledge, this is the first meta-analysis exploring acute effects of IV ketamine on current suicidal ideation. We included five single-arm clinical trials, comprising 99 unique subjects with current suicidal ideation. This meta-analysis produced three main findings. First, ketamine showed an overall significant efficacy in reducing suicidal ideation, considering four hours as maximum endpoint. According to standard cut-offs to evaluate effect sizes (Cohen, 1988) and heterogeneity (Higgins et al., 2003), the effect of ketamine should be considered large and consistent. Second, although effect among participants treated with ketamine bolus was slightly higher than for those treated with infusion, this difference was not statistically significant. Third, also considering different time points, we found a significant, although variable over time, effect of ketamine on suicidal ideation. This apparently contradictory finding is likely to be explained by the different number of studies involved, with related power issues, at different time points. Although this meta-analysis shows promising perspectives on ketamine efficacy for suicidal ideation, following GRADE (Grades of Recommendation, Assessment, Development and Evaluation) standard items (Schünemann et al., 2008), we could uncover several factors downgrading the quality of evidence. These include limitations in the design of clinical trial considered, imprecision of relevant results, and the overall uncertain risk of publication bias. First, the quality of trials was influenced by the lack of a placebo- or active comparator-controlled arm. Thus, studies included in this meta-analysis did not reach standard level of quality in terms of randomization, allocation concealment, and blinding of patients and assessors. Second, despite the large effect size of IV ketamine on suicidal ideation, all meta-analyses carried out were based on small sample sizes with wide confidence intervals. This might explain in particular the swinging significance at 80 and 120 minutes after treatment, since only two studies had data available at these time points (Kashani et al., 2014; Larkin and Beautrais, 2011). Third, it was impossible to assess statistical significance of publication bias (Sterne et al., 2008), inevitably leading to an overall assessment of uncertain risk of publication bias. Even if we performed a comprehensive search from four Electronic Databases, we cannot exclude that unpublished data might at least partially reduce the overall effect size. In sum, judgment about evidence from this meta-analysis should be considered 'very low' so far.

4.2. Open questions and future directions

Along with the lack of high quality, randomized, controlled clinical trials, we need to pay attention to several issues before considering ketamine as an appropriate anti-suicidal agent. First, although serious adverse effects have been reported, including dissociative and psychotomimetic symptoms (Caddy et al., 2014), not to mention common byproducts such as drowsiness, dizziness, poor coordination, and blurred vision (Wan et al., 2015), there is a paucity of systematic data on ketamine safety and tol-

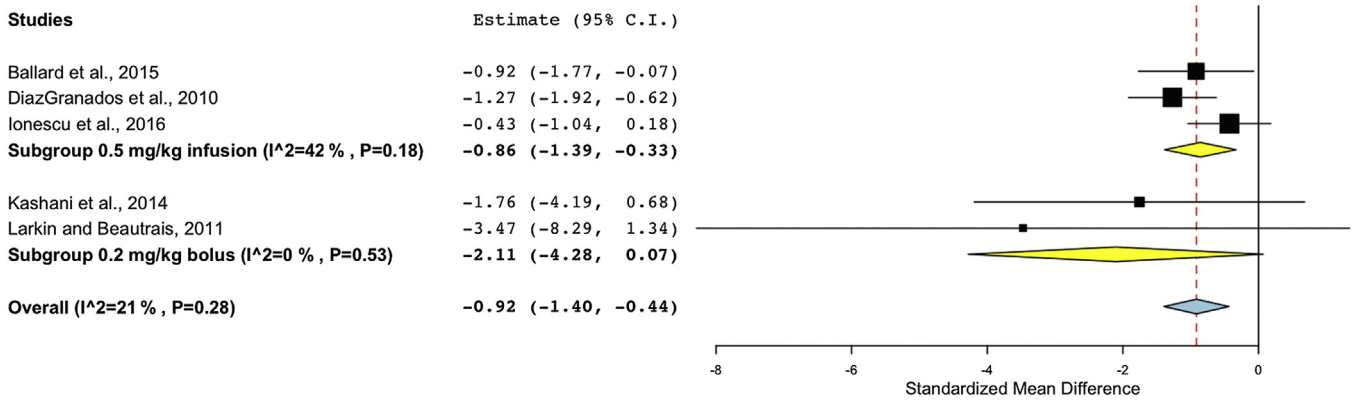

Fig. 2. Effect sizes of IV ketamine for suicidal ideation.

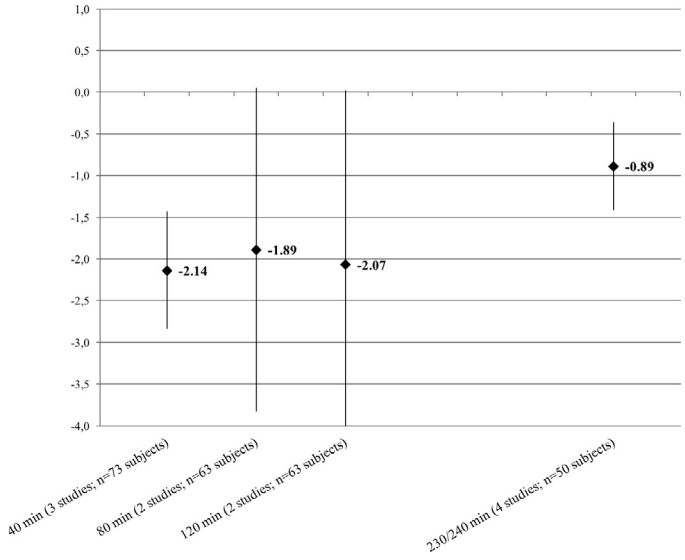

Fig. 3. Effect sizes for suicidal ideation across different time points after ketamine treatment.

erability. In addition, important issues remain unclear in terms of ketamine optimal dose, frequency and route of administration, also considering risks of tolerance, neurotoxicity (Bonnet, 2016; Zarate and Niciu, 2015) and abuse, which might be increased by long-term, multiple administration (Bartoli et al., 2014; Carrà et al., 2014; Reinstatler and Youssef, 2015; Zarate and Niciu, 2015). More importantly, we have no clear evidence on the long-term effect of ketamine on suicidal ideation, since its acute benefit might not last over a clinically meaningful timeframe (Price and Mathew, 2015).

Furthermore, underlying mechanisms by which ketamine might impact suicidal ideation remain unknown (Price and Mathew, 2015), since it is unlikely that acute infusion may drive changes in depressive and anxiety symptoms sufficient to influence self-harming thoughts (Ballard et al., 2014). Moreover, we need to better distinguish proper antidepressant and anti-suicidal characteristics of ketamine from its dissociative (Luckenbaugh et al., 2014), cognitive (Lee et al., 2016), and sleep-associated (Vande Voort et al., 2016) effects, similarly induced by ketamine. As a whole, it seems likely that several and complex clinical and biological pathways might explain response to ketamine treatment (Sanacora and Schatzberg, 2015). Indeed, ketamine antidepressant and antisuicidal mechanisms might involve NMDA receptors, but also other pathways and targets, such as HT2c receptors (Strasburger et al., 2017) and adipokines levels (Machado-Vieira et al., 2017). In addition, it should be considered that suicidal ideation is a complex phenomenon involving several underlying psychological, along with biological (e.g., Bartoli et al., 2016), mechanisms (Barzilay and Apter, 2014) that might differently respond to pharmacological treatments.

5. Conclusions

Suicide is one of the main causes of early mortality in subjects with mental disorders (Chesney et al., 2014) and acute suicidal ideation remains a clinical emergency without available, evidence-based treatments. We found a large and consistent effect of IV ketamine for the acute treatment of suicidal ideation, though based on low quality evidence. Caution should be used in interpreting our findings. Nonetheless, ketamine might be considered a prototype for the future development of similar rapid-acting anti-suicidal agents (Reinstatler and Youssef, 2015) and a thorough exploration of mechanisms by which ketamine impacts suicidal ideation (Price and Mathew, 2015) might help in elucidating also the neurobiological nature of suicidal behaviors (Mallick and McCullumsmith, 2016).

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The authors report no financial or other relationship relevant to the subject of this article.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2017.03.010.

References

Ballard, E.D., Ionescu, D.F., Vande Voort, J.L., Niciu, M.J., Richards, E.M., Luckenbaugh, D.A., et al., 2014. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J. Psychiatr. Res. 58, 161–166.

Ballard, E.D., Lally, N., Nugent, A.C., Furey, M.L., Luckenbaugh, D.A., Zarate, C.A., 2015. Neural correlates of suicidal ideation and its reduction in depression. Int. J. Neuropsychopharmacol. 18, pyu069.
Bartoli, F., Carrà, G., Brambilla, G., Carretta, D., Crocamo, C., Neufeind, J., Baldacchino, A., Humphris, G., Clerici, M., 2014. Association between depression and non-fatal overdoses among drug users: a systematic review and meta-analysis. Drug Alcohol Depend. 134, 12–21.
Bartoli, F., Crocamo, C., Dakanalis, A., Riboldi, I., Miotto, A., Brosio, E., Clerici, M., Carrà, G., 2016. Association between total serum cholesterol and suicide attempts in subjects with major depressive disorder: exploring the role of clinical and biochemical confounding factors. Clin. Biochem., http://dx.doi.org/10.1016/j.clinbiochem.2016.11.035.
Barzilay, S., Apter, A., 2014. Psychological models of suicide. Arch. Suicide Res. 18, 295–312.
Bonnet, U., 2016. How much alcohol is in ketamine's antidepressant action? Life Sci., http://dx.doi.org/10.1016/j.lfs.2016.11.003.
Caddy, C., Amit, B.H., McCloud, T.L., Rendell, J.M., Furukawa, T.A., McShane, R., et al., 2015. Ketamine and other glutamate receptor modulators for depression in adults. Cochrane Database Syst. Rev. (9), CD011612.
Caddy, C., Giaroli, G., White, T.P., Shergill, S.S., Tracy, D.K., 2014. Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a systematic review and meta-analysis of efficacy. Ther. Adv. Psychopharmacol. 4, 75–99.
Carrà, G., Bartoli, F., Crocamo, C., Brady, K.T., Clerici, M., 2014. Attempted suicide in people with co-occurring bipolar and substance use disorders: systematic review and meta-analysis. J. Affect. Disord. 167, 125–135.
Chesney, E., Goodwin, G.M., Fazel, S., 2014. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry 13 (2), 153–160.
Cohen, J., 1988. Statistical Power Analysis for the Behavioral Science. Erlbaum Associates, Hillsdale, NJ.
Coyle, C.M., Laws, K.R., 2015. The use of ketamine as an antidepressant: a systematic review and meta-analysis. Hum. Psychopharmacol. 30, 152–163.
Deeks, J.J., Higgins, J.P., Altman, G., 2008. Analysing data and undertaking meta-analyses. In: Higgins, J.P., Green, S. (Eds.), Cochrane Handbook for Systematic Reviews of Interventions. John Wiley, Sons, Ltd, Chichester, UK, pp. 243–296.
DiazGranados, N., Ibrahim, L.A., Brutsche, N.E., Ameli, R., Henter, I.D., Luckenbaugh, D.A., et al., 2010. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J. Clin. Psychiatry 71, 1605–1611.
Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560.
Iadarola, N.D., Niciu, M.J., Richards, E.M., Vande Voort, J.L., Ballard, E.D., Lundin, N.B., et al., 2015. Ketamine and other N-methyl-D-aspartate receptor antagonists in the treatment of depression: a perspective review. Ther. Adv. Chronic Dis. 6, 97–114.
Ionescu, D.F., Swee, M.B., Pavone, K.J., Taylor, N., Akeju, O., Baer, L., et al., 2016. Rapid and sustained reductions in current suicidal ideation following repeated doses of intravenous ketamine: secondary analysis of an open-label study. J. Clin. Psychiatry 77, e719–e725.
Kashani, P., Yousefian, S., Amini, A., Heidari, K., Younesian, S., Hatamabadi, H.R., 2014. The effect of intravenous ketamine in suicidal ideation of emergency department patients. Emergency (Tehran) 2, 36–39.
Lapidus, K.A., Soleimani, L., Murrough, J.W., 2013. Novel glutamatergic drugs for the treatment of mood disorders. Neuropsychiatr. Dis. Treat. 9, 1101–1112.
Larkin, G.L., Beautrais, A.L., 2011. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. Int. J. Neuropsychopharmacol. 14, 1127–1131.
Lee, E.E., Della Selva, M.P., Liu, A., Himelhoch, S., 2015a. Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative meta-analysis. Gen. Hosp. Psychiatry 37, 178–184.
Lee, J., Narang, P., Enja, M., Lippmann, S., 2015b. Use of ketamine in acute cases of suicidality. Innov. Clin. Neurosci. 12, 29–31.
Lee, Y., Syeda, K., Maruschak, N.A., Cha, D.S., Mansur, R.B., Wium-Andersen, I.K., et al., 2016. A new perspective on the anti-suicide effects with ketamine treatment: a procognitive effect. J. Clin. Psychopharmacol. 36, 50–56.
Luckenbaugh, D.A., Niciu, M.J., Ionescu, D.F., Nolan, N.M., Richards, E.M., Brutsche, N.E., et al., 2014. Do the dissociative side effects of ketamine mediate its antidepressant effects? J. Affect. Disord. 159, 56–61.
Machado-Vieira, R., Gold, P.W., Luckenbaugh, D.A., Ballard, E.D., Richards, E.M., Henter, I.D., et al., 2017. The role of adipokines in the rapid antidepressant effects of ketamine. Mol. Psychiatry 22, 127–133.
Malhi, G.S., Byrow, Y., Cassidy, F., Cipriani, A., Demyttenaere, K., Frye, M.A., et al., 2016. Ketamine: stimulating antidepressant treatment? BJPsych Open 2, e5–e9.
Mallick, F., McCullumsmith, C.B., 2016. Ketamine for treatment of suicidal ideation and reduction of risk for suicidal behavior. Curr. Psychiatry Rep. 18, 61.
PRISMA GroupMoher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339, b2535.
Newby, J.M., McKinnon, A., Kuyken, W., Gilbody, S., Dalgleish, T., 2015. Systematic review and meta-analysis of transdiagnostic psychological treatments for anxiety and depressive disorders in adulthood. Clin. Psychol. Rev. 40, 91–110.
Pompili, M., Serafini, G., Innamorati, M., Ambrosi, E., Giordano, G., Girardi, P., et al., 2010. Antidepressants and suicide risk: a comprehensive overview. Pharmaceuticals 3, 2861–2883.
Price, R.B., Mathew, S.J., 2015. Does ketamine have anti-suicidal properties? Current status and future directions. CNS Drugs 29, 181–188.
Price, R.B., Nock, M.K., Charney, D.S., Mathew, S.J., 2009. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol. Psychiatry 66, 522–526.
Rajkumar, R., Fam, J., Yeo, E.Y.M., Dawe, G.S., 2015. Ketamine and suicidal ideation in depression: jumping the gun? Pharmacol. Res. 99, 23–35.
Reinstatler, L., Youssef, N.A., 2015. Ketamine as a potential treatment for suicidal ideation: a systematic review of the literature. Drugs R. D. 15, 37–43.
Sanacora, G., Schatzberg, A.F., 2015. Ketamine: promising path or false prophecy in the development of novel therapeutics for mood disorders? Neuropsychopharmacology 40, 259–267.
Schünemann, H.J., Oxman, A.D., Vist, G.E., Higgins, J.P.T., Deeks, J.J., Glasziou, P., et al., 2008. Interpreting results and drawing conclusions. In: Higgins, J.P., Green, S. (Eds.), Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, Ltd, Chichester, UK, pp. 359–387.
Serafini, G., Gonda, X., Rihmer, Z., Pompili, M., Girardi, P., Nasrallah, H.A., et al., 2015. NMDA receptor antagonists for depression: critical considerations. Ann. Clin. Psychiatry 27, 213–220.
Serafini, G., Howland, R.H., Rovedi, F., Girardi, P., Amore, M., 2014. The role of ketamine in treatment-resistant depression: a systematic review. Curr. Neuropharmacol. 12, 444–461.
Sterne, J.A.C., Egger, M., Moher, D., 2008. Addressing reporting biases. In: Higgins, J.P., Green, S. (Eds.), Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, Ltd, Chichester, UK, pp. 297–333.
Stone, M., Laughren, T., Jones, M.L., Levenson, M., Holland, P.C., Hughes, A., et al., 2009. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ 339, b2880.
Strasburger, S.E., Bhimani, P.M., Kaabe, J.H., Krysiak, J.T., Nanchanatt, D.L., Nguyen, T.N., et al., 2017. What is the mechanism of ketamine's rapid-onset antidepressant effect? A concise overview of the surprisingly large number of possibilities. J. Clin. Pharm. Ther. 42, 147–154.
Thakurta, R.G., Das, R., Bhattacharya, A.K., Saha, D., Sen, S., Singh, O.P., et al., 2012. Rapid response with ketamine on suicidal cognition in resistant depression. Indian J. Psychol. Med. 34, 170–175.
Vande Voort, J.L., Ballard, E.D., Luckenbaugh, D.A., Bernert, R.A., Richards, E.M., Niciu, M.J., et al., 2016. Antisuicidal response following ketamine infusion is associated with decreased nighttime wakefulness in major depressive disorder and bipolar disorder. J. Clin. Psychiatry, http://dx.doi.org/10.4088/JCP.15m10440.
Wan, L.-B., Levitch, C.F., Perez, A.M., Brallier, J.W., Iosifescu, D.V., Chang, L.C., et al., 2015. Ketamine safety and tolerability in clinical trials for treatment-resistant depression. J. Clin. Psychiatry 76, 247–252.
Wilkinson, S.T., Sanacora, G., 2016. Ketamine: a potential rapid-acting antisuicidal agent? Depress. Anxiety 33, 711–717.
Zarate Jr., C., Machado-Vieira, R., Henter, I., Ibrahim, L., Diazgranados, N., Salvadore, G., 2010. Glutamatergic modulators: the future of treating mood disorders? Harv. Rev. Psychiatry 18, 293–303.
Zarate Jr., C.A., Brutsche, N.E., Ibrahim, L., Franco-Chaves, J., Diazgranados, N., Cravchik, A., et al., 2012. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol. Psychiatry 71, 939–946.
Zarate Jr., C.A., Niciu, M.J., 2015. Ketamine for depression: evidence, challenges and promise. World Psychiatry 14, 348–350.