

can pose practical problems in clinical practice. Very few trials were included in the meta-analyses for each comparison; the majority of comparisons contained only one study. Further RCTs (with adequate blinding) are needed to explore different modes of administration of

ketamine with longer follow-up, which test the comparative efficacy of ketamine and the efficacy of repeated administrations.

Assessed as up to date: 9 January 2015

doi: 10.1192/apt.22.4.214

Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults[†]

Tayla L. McCloud, Caroline Caddy, Janina Jochim, Jennifer M. Rendell, Peter R. Diamond, Claire Shuttleworth, Daniel Brett, Ben H. Amit, Rupert McShane, Layla Hamadi, Keith Hawton & Andrea Cipriani

Background

There is emerging evidence that glutamatergic system dysfunction might play an important role in the pathophysiology of bipolar depression. This review focuses on the use of glutamate receptor modulators for depression in bipolar disorder.

Objectives

1. To assess the effects of ketamine and other glutamate receptor modulators in alleviating the acute symptoms of depression in people with bipolar disorder. 2. To review the acceptability of ketamine and other glutamate receptor modulators in people with bipolar disorder who are experiencing acute depression symptoms.

Search methods

As described in the related review (CD011612).

Selection criteria

RCTs comparing ketamine, memantine, or other glutamate receptor modulators with other active psychotropic drugs or saline placebo in adults with bipolar depression.

Data collection and analysis

At least two review authors independently selected studies for inclusion, assessed trial quality and extracted data. Primary outcomes for this review were response rate and adverse events. Secondary outcomes included remission rate, depression severity change scores, suicidality, cognition, quality of life, and dropout rate. We contacted study authors for additional information.

Main results

Five studies (329 participants) were included in this review. All included studies were placebo-controlled and two-armed, and the glutamate receptor modulators – ketamine (two trials), memantine (two trials), and cytidine (one trial) – were used as add-on drugs to mood stabilisers. The treatment period ranged from a single intravenous administration (all ketamine studies), to repeated administration for memantine and cytidine (8 to 12 weeks, and 12 weeks, respectively). Three of the studies took place in the USA, one in Taiwan, and in one, the location was unclear. The majority (70.5%) of participants were from Taiwan. All participants had a primary diagnosis of bipolar disorder, according to the DSM-IV or DSM-IV-TR, and were in a current depressive phase. The severity of depression was at least moderate in all but one study. Among all glutamate receptor modulators included in this review, only ketamine appeared to be more efficacious than placebo 24 hours after the infusion for the primary outcome, response rate (odds ratio (OR) 11.61, 95% confidence interval (CI) 1.25 to 107.74; $P=0.03$; $I^2=0\%$, 2 studies, 33 participants). This evidence was rated as low quality. The statistically significant difference disappeared at three days, but the mean estimate still favoured ketamine (OR 8.24, 95% CI 0.84 to 80.61; 2 studies, 33 participants; very low quality evidence). We found no difference in response between ketamine and placebo at one week (OR 4.00, 95% CI 0.33 to 48.66; $P=0.28$,

1 study; 18 participants; very low quality evidence). There was no significant difference between memantine and placebo in response rate one week after treatment (OR 1.08, 95% CI 0.06 to 19.05; $P=0.96$, 1 study, 29 participants), two weeks (OR 4.88, 95% CI 0.78 to 30.29; $P=0.09$, 1 study, 29 participants), four weeks (OR 5.33, 95% CI 1.02 to 27.76; $P=0.05$, 1 study, 29 participants), or at three months (OR, 1.66, 95% CI 0.69 to 4.03; $P=0.26$, $I^2=36\%$, 2 studies, 261 participants). These findings were based on very low quality evidence. There was no significant difference between cytidine and placebo in response rate at three months (OR, 1.13, 95% CI 0.30 to 4.24; $P=0.86$, 1 study, 35 participants; very low quality evidence). For the secondary outcome of remission, no significant differences were found between ketamine and placebo, nor between memantine and placebo. For the secondary outcome of change scores from baseline on depression scales, ketamine was more effective than placebo at 24 hours (MD -11.81 , 95% CI -20.01 to -3.61 ; $P=0.005$, 2 studies, 32 participants) but not at one or two weeks after treatment. There was no difference between memantine and placebo for this outcome. We found no significant differences in terms of adverse events between placebo and ketamine, memantine, or cytidine. There were no differences between ketamine and placebo, memantine and placebo, or cytidine and placebo in total dropouts. No data were available on dropouts due to adverse effects for ketamine or cytidine; but no difference was found between memantine and placebo.

Authors' conclusions

Reliable conclusions from this review are severely limited by the small amount of data usable for analysis. The body of evidence about glutamate receptor modulators in bipolar disorder is even smaller than that which is available for unipolar depression. Overall, we found limited evidence in favour of a single intravenous dose of ketamine (as add-on therapy to mood stabilisers) over placebo in terms of response rate up to 24 hours; ketamine did not show any better efficacy in terms of remission in bipolar depression. Even though ketamine has the potential to have a rapid and transient antidepressant effect, the efficacy of a single intravenous dose may be limited. Ketamine's psychotomimetic effects could compromise study blinding; this is a particular issue for this review as no included study used an active comparator, and so we cannot rule out the potential bias introduced by inadequate blinding procedures. We did not find conclusive evidence on adverse events with ketamine. To draw more robust conclusions, further RCTs (with adequate blinding) are needed to explore different modes of administration of ketamine and to study different methods of sustaining antidepressant response, such as repeated administrations. There was not enough evidence to draw meaningful conclusions for the remaining two glutamate receptor modulators (memantine and cytidine). This review is limited not only by completeness of evidence, but also by the low to very low quality of the available evidence.

Assessed as up to date: 9 January 2015

doi: 10.1192/apt.22.4.215

[†]This review is an abridged version of a Cochrane review previously published in the Cochrane Database of Systematic Reviews, 2015, Sep 29, Issue 9: CD011611 (see www.cochranelibrary.com for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

We thank the Cochrane Review Group for their support in publishing these reviews.

See commentary on pp. 216–221, this issue.