

COCHRANE CORNER

This month's Cochrane Corner contains two related Cochrane reviews, which are considered jointly in Round the Corner (pp. 216–221).

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

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[†]This review is an abridged version of a Cochrane review previously published in the Cochrane Database of Systematic Reviews, 2015, Sep 23, Issue 9: CD011612 (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.

Background

Considering the ample evidence of involvement of the glutamate system in the pathophysiology of depression, pre-clinical and clinical studies have been conducted to assess the antidepressant efficacy of glutamate inhibition, and glutamate receptor modulators in particular. This review focuses on the use of glutamate receptor modulators in unipolar depression.

Objectives

To assess the effects - and review the acceptability - of ketamine and other glutamate receptor modulators in comparison to placebo (or saline placebo), other pharmacologically active agents, or electroconvulsive therapy (ECT) in alleviating the acute symptoms of depression in people with unipolar major depressive disorder.

Search methods

We searched the Cochrane Depression, Anxiety and Neurosis Review Group's Specialised Register (CCDANCTR, to 9 January 2015). This register includes relevant randomised controlled trials (RCTs) from: the Cochrane Library (all years), MEDLINE (1950 to date), EMBASE (1974 to date), and PsycINFO (1967 to date). We did not apply any restrictions to date, language or publication status.

Selection criteria

Double- or single-blind RCTs comparing ketamine, memantine, or other glutamate receptor modulators with placebo (or saline placebo), other active psychotropic drugs, or electroconvulsive therapy (ECT) in adults with unipolar major depression.

Data collection and analysis

Three review authors independently identified studies, assessed trial quality and extracted data. The primary outcomes for this review were response rate and adverse events.

Main results

We included 25 studies (1242 participants) on ketamine (9 trials), memantine (3), AZD6765 (3), D-cycloserine (2), Org26576 (2), atomoxetine (1), CP-101,606 (1), MK-0657 (1), N-acetylcysteine (1), riluzole (1) and sarcosine (1). Twenty-one studies were placebo-controlled and the majority were two-arm studies (23 out of 25). Twenty-two studies defined an inclusion criteria specifying the severity of depression; 11 specified at least moderate depression; eight, severe depression; and the remaining three, mild-moderate depression. Nine studies recruited only treatment-resistant patients. We rated the risk of bias as low or unclear for most domains, though lack of detail regarding masking of treatment in the studies reduced our certainty in the effect for all outcomes. We rated three studies as having high risk for selective outcome reporting. Many trials did not provide information on all the prespecified outcomes and we found no data, or very limited data, on very important issues like suicidality, cognition, quality of life, costs to healthcare services and dropouts due to lack of efficacy. Among all glutamate receptor modulators, only ketamine (administered intravenously) proved to be more efficacious than

placebo, though the quality of evidence was limited by risk of bias and small sample sizes. There was low quality evidence that treatment with ketamine increased the likelihood of response after 24 hours (odds ratio (OR) 10.77, 95% confidence interval (CI) 2.00 to 58.00; 3 RCTs, 56 participants), 72 hours (OR 12.59, 95% CI 2.38 to 66.73; 3 RCTs, 56 participants), and one week (OR 2.58, 95% CI 1.08 to 6.16; 4 RCTs, 131 participants). The effect of ketamine was even less certain at two weeks, as data were available from only one trial (OR 0.93, 95% CI 0.31 to 2.83; 51 participants, low quality evidence). This was consistent across all efficacy outcomes. Ketamine caused more confusion and emotional blunting compared to placebo. There was insufficient evidence to determine if this increased the likelihood of leaving the study early (OR 1.90, 95% CI 0.43 to 8.47; 5 RCTs, 139 participants, low quality evidence). One RCT with 72 participants reported higher numbers of responders on ketamine than midazolam at 24 hours (OR 0.36, 95% CI 0.14 to 0.58), 72 hours (OR 0.37, 95% CI 0.16 to 0.59), and one week (OR 0.29, 95% CI 0.08 to 0.49). However, midazolam was better tolerated than ketamine in terms of blurred vision, dizziness, general malaise and nausea/vomiting at 24 hours post-infusion. The evidence contributing to these outcomes was of low quality. We found better efficacy of sarcosine over citalopram at four weeks (OR 6.93, 95% CI 1.53 to 31.38; 1 study, 40 participants), but not at two weeks (OR 8.14, 95% CI 0.88 to 75.48); fewer participants in the sarcosine group experienced adverse events (OR 0.04, 95% CI 0.00 to 0.68; $P=0.03$, 1 study, 40 participants). This was based on low quality evidence. No significant results were found for the remaining glutamate receptor modulators. In one study with 18 participants, ketamine was more effective than ECT at 24 hours (OR 28.00, 95% CI 2.07 to 379.25) and 72 hours (OR 12.25, 95% CI 1.33 to 113.06), but not at one week (OR 3.35, 95% CI 0.12 to 93.83), or two weeks (OR 3.35, 95% CI 0.12 to 93.83). No differences in terms of adverse events were found between ketamine and ECT, however the only adverse events reported were blood pressure and heart rate. This study was rated as very low quality.

Authors' conclusions

We found limited evidence for ketamine's efficacy over placebo at time points up to one week in terms of the primary outcome, response rate. The effects were less certain at two weeks post-treatment. No significant results were found for the remaining ten glutamate receptor modulators, except for sarcosine being more effective than citalopram at four weeks. In terms of adverse events, the only significant differences in favour of placebo over ketamine were in regards to confusion and emotional blunting. Despite the promising nature of these preliminary results, our confidence in the evidence was limited by risk of bias and the small number of participants. Many trials did not provide information on all the prespecified outcomes and we found no data, or very limited data, on very important issues like suicidality, cognition, quality of life, costs to healthcare services and dropouts due to lack of efficacy. All included studies administered ketamine intravenously, which

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.

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

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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.

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[†]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.

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