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Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults (Review)

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[Intervention Review]

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

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ABSTRACT

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

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 cross-checked reference lists of relevant papers and systematic reviews. We did not apply any restrictions to date, language or publication status.

Selection criteria

Randomised controlled trials (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.

PLAIN LANGUAGE SUMMARY

Ketamine and other glutamate receptor modulators for bipolar depression

Why is this review important?

Bipolar disorder is one of the most severe psychiatric disorders, which is characterised by a chronic pattern of relapse into mania (abnormally elevated mood or irritability and related symptoms with severe functional impairment or psychotic symptoms for seven

days or more), or hypomania (same symptoms with decreased or increased function for four days or more) and major depression. The depressive phase of the illness is associated with a greatly increased risk of self harm and suicide. Current treatments for depressive symptoms are of limited efficacy and onset of action is generally slow. Among the most promising alternatives with a different mechanism of action, is a new class of drugs, called glutamate receptor modulators. New compounds have been tested, mainly in unipolar depression, but recent studies have focused on bipolar depression. There are some recent reviews that have tried to summarise the evidence about glutamate receptor modulators, but they either focused only on ketamine or did not include relevant data from the most recent trials. For these reasons, a comprehensive and updated synthesis of all the available studies is needed.

Who will be interested in this review?

- People with bipolar disorder, their friends, and families.

- General practitioners, psychiatrists, psychologists, and pharmacists.

- Professionals working in adult mental health services.

What questions does this review aim to answer?

1. Is treatment with ketamine and other glutamate receptor modulators more effective than placebo or other antidepressants?

2. Is treatment with ketamine and other glutamate receptor modulators more acceptable than placebo or other antidepressants?

Which studies were included in the review?

We searched medical databases to find all relevant studies (specifically randomised controlled trials) completed up to 9 January 2015. To be included in the review, studies had to compare ketamine or other glutamate receptor modulators with placebo or other medicines in adults. We included five placebo-controlled studies, involving a total of 329 participants. The studies investigated three different glutamate receptor modulators: ketamine (two trials), memantine (two trials) and cytidine (one trial). All trials in the present review included participants who were also receiving another medication (either lithium, valproate, or lamotrigine). In the majority of studies, the included participants were already taking (and showing an inadequate response to) these treatments. We rated the quality of the evidence 'very low' to 'low' across different comparisons.

What does the evidence from the review tell us?

Efficacy was measured primarily as the number of patients who responded to treatment. A single intravenous dose of ketamine proved to be better than placebo, but this was based on very limited evidence (two studies with 33 participants), and its effect only lasted for up to 24 hours. This finding was based on evidence rated as low quality. In terms of adverse events, no differences were found between ketamine and placebo, despite common reports of trance-like states or hallucinations. The very small population under investigation in this review could have limited the ability to detect any real difference. No differences were found between memantine or cytidine and placebo in terms of number of people who responded to treatment or who experienced adverse effects.

What should happen next?

Ketamine may be an effective medication as add-on therapy to mood stabilisers in people with acute bipolar depression, but due to the small amount of data usable for analysis we are unable to draw any firm or reliable conclusions. The effects of ketamine may be very quick, but they are likely to last for less than three days. All trials that examined the efficacy of ketamine used only intravenous administration, which could potentially restrict its applicability in clinical settings. Future research should focus on studies which compare long-term use of ketamine (also with other active interventions), in order to draw reliable conclusions about comparative efficacy between treatments. Unfortunately, the present review did not find any reliable information about tolerability of glutamate receptor modulators; however adverse effects, particularly of repeated exposure to ketamine, still remain a major concern in this area.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Ketamine compared to placebo for depression in bipolar disorder in adults

Patient or population: adults with bipolar disorder (currently experiencing a depressive episode)
Setting: inpatient
Intervention: ketamine
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with ketamine				
Response rate - at 24 hours	Study population		OR 11.61 (1.25 to 107.74)	33 (2 RCTs)	⊕⊕◯◯ LOW[1,2]	
	0 per 1000	0 per 1000 (0 to 0)				
Response rate - at 3 days	Study population		OR 8.24 (0.84 to 80.61)	33 (2 RCTs)	⊕◯◯◯ VERY LOW[1,3]	
	0 per 1000	0 per 1000 (0 to 0)				
Response rate - at 1 week	Study population		OR 4.00 (0.33 to 48.66)	18 (1 RCT)	⊕◯◯◯ VERY LOW[1,3]	
	111 per 1000	333 per 1000 (40 to 859)				
	Moderate					
	111 per 1000	333 per 1000 (40 to 859)				
Remission rate - at 1 week	Study population		OR 3.35 (0.12 to 93.83)	18 (1 RCT)	⊕◯◯◯ VERY LOW[1,3]	

	0 per 1000	0 per 1000 (0 to 0)			
Depression rating scale score at 1 week	The mean depression rating scale score at 1 week was 0	The mean depression rating scale score at 1 week in the intervention group was 0.88 undefined fewer (5.88 fewer to 4.12 more)	-	28 (2 RCTs)	⊕◯◯◯ VERY LOW[1,3]
Acceptability - total dropouts	Study population		OR 3.48 (0.56 to 21.74)	33 (2 RCTs)	⊕◯◯◯ VERY LOW[1,3]
	118 per 1000	318 per 1000 (71 to 741)			
	Moderate				
	118 per 1000	319 per 1000 (71 to 742)			
Acceptability - dropouts due to adverse effects	No data available	No data available	-	-	-

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __OR:__ odds ratio; __RCT__: randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one point because no studies described the outcome assessment as masked.
[2] Downgraded by one point because of small sample size overall. Although wide, the confidence interval does exclude no effect and so we have not downgraded a second level for imprecision.

[3] Downgraded by two points because of small sample size overall and wide confidence intervals across the line of no difference.

BACKGROUND

Description of the condition

Bipolar disorder is a severe and chronic psychiatric disorder with a lifetime prevalence in the order of 2.4% (Merikangas 2011). Symptoms usually appear in late adolescence or early adulthood and can blight both education and early employment opportunities, with lifelong implications. The disorder is characterised by episodes of mania (abnormally elevated mood or irritability and related symptoms with severe functional impairment or psychotic symptoms for seven days or more), or hypomania (abnormally elevated mood or irritability and related symptoms with decreased or increased function for four days or more), and episodes of depressed mood (APA 2000; APA 2013; WHO 1992). Previous studies have shown that depressive symptomatology (syndromal and subsyndromal) dominates the longitudinal course of both bipolar I and II disorder (Judd 2002; Judd 2003). Bipolar depression and unipolar depression (major depressive disorder) have a number of symptoms in common, including low mood, sadness, feelings of guilt, lack of motivation, anxiety, and suicidal thoughts. However, there are distinct differences both in presentation and in response to treatment. People with bipolar depression can experience both hypersomnia (excessive daytime sleeping) and increased appetite, symptoms that are not typical features of unipolar depression. In addition, depressive symptoms can co-occur with manic symptoms, and depressive episodes can be followed immediately by manic episodes. Switches from depression to mania (and vice versa) are recognised features of the disorder but may also be precipitated by treatment (Salvadore 2010). Bipolar disorder also carries an increased risk of suicide and self harm. In a World Health Organization survey, between 20% and 25% of patients reported a history of suicide attempts (Merikangas 2011); this risk is greatest during the depressive phase. Even though lithium seems to be effective in reducing the risk of suicide in people with mood disorders (Cipriani 2013a), there are no fast-acting treatments proven to reduce suicidal ideation or behaviour, and therefore current practice is admission to hospital with close monitoring. Consequently there is an urgent need to identify effective treatments for bipolar depression that are fast-acting and reduce the risk of self harm and suicide.

Description of the intervention

Treatment of bipolar depression usually involves medicines and may include psychological therapies (Geddes 2013). However, response to pharmacological treatments for bipolar depression is often slow and incomplete and may precipitate a switch from depression to mania (Howland 1996). Currently approved treatments for bipolar depression include lithium, quetiapine, and the combination olanzapine and fluoxetine. In addition to these, lamotrigine, antidepressants, and new second-generation antipsychotics (such as lurasidone) are also prescribed. Understanding of the mechanisms of action of these medicines is incomplete, but is thought to involve a number of different neurotransmitters including serotonin, dopamine, and norepinephrine. There is emerging evidence that glutamatergic system dysfunction might play an important role in the pathophysiology of bipolar depression. Glutamate, one of the most common neurotransmitters, is involved in memory, learning, and cognition. Recent research suggests that drugs targeting a specific type of glutamate receptor in the brain (the NMDA (N-methyl-D-aspartate) receptor) may have antidepressant effects. When used to treat epilepsy, lamotrigine is thought to inhibit the release of glutamate, but its mechanism of action in bipolar depression has not been established. Evidence of aberrant glutamate conduction in depression is substantial (Altamura 1995), including demonstration of antidepressant effects following administration of ketamine, an NMDA antagonist (Zarate 2006), or agents inhibiting glutamate secretion, such as riluzole (Kendell 2005). Ketamine is a chiral arylcyclohexylamine (RS)-2-(2-chlorophenyl)-2-methylaminocyclo-hexanone, initially developed for the induction of anaesthesia (Reich 1989). Ketamine has a half-life of 2 to 2.5 hours, and undergoes hepatic metabolism by CYP2B6, CYP3A4 and, less importantly, CYP2C9, to norketamine and dehydronorketamine. Both ketamine and norketamine are noncompetitive antagonists of the NMDA receptor (Mathew 2012). Ketamine has low bioavailability when administered orally, estimated at 16%, associated with a prolonged effect (Mathew 2012). Therefore, the most common routes of administration are intravenous and intranasal (Abrams 1993).

How the intervention might work

It has been suggested that several molecular mechanisms contribute to the antidepressant effects of modulation of glutamate conductance (Browne 2013; Kavalali 2012; Mathew 2012). Antagonism of the NMDA receptor is associated with an increased glutamate secretion (Homayoun 2007), and activation of the 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid (AMPA) receptors. Agonists of the AMPA receptor have been shown to have an antidepressant effect in animal models of depression, synergistic with ketamine administration (Akinfiresoye 2013), providing further support for a role for AMPA receptors in the antidepressant response to NMDA antagonists. The role of brain-derived neurotrophic factor (BDNF) in the antidepressant action of ketamine has been demonstrated by evidence of increased hippocampal BDNF, increased tropomyosin receptor kinase B (TrkB) phosphorylation, and an abolished antidepressant effect in both BDNF and TrkB knockout mice following administration of ketamine (Autry 2011).

Imaging studies have provided further insight into the potential antidepressant effects of ketamine and NMDA antagonists. While positron emission tomography studies have demonstrated

increased metabolic activity in the frontomedial and anterior cingulate cortex, possibly associated with the psychotic effects of ketamine administration (Vollenweider 1997), reduced limbic responses to emotional stimuli following ketamine administration were observed by functional magnetic resonance imaging (Abel 2003), possibly accounting for its antidepressant effect. A systematic review found some evidence that acute administration of ketamine may provide rapid (within hours) antidepressant effects that may protect people from suicidal thinking or acute dysphoria (Aan Het Rot 2012). However, the effects appear to be short-lived (seven to 10 days), and treatment requires patients to be admitted to hospital for several hours to receive ketamine intravenously under the care of an anaesthetist.

Why it is important to do this review

Bipolar disorder is one of the most severe psychiatric disorders and ranks in the top 10 causes of medical disability worldwide (Murray 2014). It has an early age of onset and is characterised by a chronic pattern of relapse into mania and depression. In addition to the effects of symptoms (both syndromal and subsyndromal) on functioning and quality of life, the depressive phase of the illness is associated with a greatly increased risk of self harm and suicide. Current treatments for depressive symptoms are of limited efficacy and onset of action is generally slow (Kendall 2014). As for unipolar depression, there is some evidence that ketamine and other glutamate receptor modulators might provide rapid relief of severe depression (McGirr 2015), but also concerns about potential adverse events (Caddy 2014). There are also concerns about the short-term effects of ketamine, which induces trance-like or hallucination states during which patients report feeling "out of it," intoxicated, and disconnected in general (Rasmussen 2014). Ketamine is also associated with cognitive side effects, and there are reports that when used longer-term as a 'street drug' it can cause urological damage (CADTH 2014). Furthermore, the evidence for the effects of ketamine and other glutamate receptor modulators is accumulating and, whereas early studies involved use of intravenous infusion, later studies have considered other, easier-to-administer routes (which, if effective, might negate the need for hospital admission and the involvement of anaesthetists) (Dutta 2014). It is therefore important to review the available literature for studies not included in earlier reviews, both to inform current use of these medications and to identify areas where more research is required. Since the publication of the Aan Het Rot 2012 review, further research into the effects of ketamine and other glutamate receptor modulators has been published (Naughton 2014), but has not been systematically searched and analysed.

This review is one of a pair, the other of which focused on ketamine and other glutamate receptor modulators for unipolar depression in adults (Caddy 2015).

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 comparison with placebo or other antidepressant agents in people with bipolar disorder who are experiencing acute depression symptoms.

METHODS

Criteria for considering studies for this review

Types of studies

We included only double-blind or single-blind RCTs (either published or unpublished) comparing ketamine, memantine, or other glutamate receptor modulators with other active psychotropic drugs or saline placebo in people with bipolar depression.

For trials that have a cross-over design, we only considered results from the first period prior to cross-over.

We included cluster randomised trials (CRTs) if the effect of clustering could be accounted for in the statistical analysis.

We excluded quasi-randomised trials, such as those allocating by using alternate days of the week, as well as trials that did not explicitly describe the method of allocation as randomised.

Types of participants

Participant characteristics

We considered for inclusion, people of both sexes aged 18 years or older with a primary diagnosis of bipolar disorder (currently experiencing a depressive episode) according to any of the following standard operational criteria: Feighner criteria (Feighner 1972), Research Diagnostic Criteria (Spitzer 1978), DSM-III (APA 1980), DSM-III-R (APA 1987), DSM-IV (APA 1994), DSM-IV-TR (APA 2000), DSM-5 (APA 2013), or ICD-10 (WHO 1992). We included studies using operational diagnostic criteria essentially similar to the above.

We excluded studies using ICD-9, as it has only disease names and no diagnostic criteria. We also excluded studies that defined depression as scoring above a certain cut-off on a screening questionnaire.

We would have included studies recruiting participants with treatment-resistant bipolar depression, and had planned to examine these in a sensitivity analysis.

Comorbidities

We would have included studies in which less than 20% of participants were suffering from unipolar depression, and planned to examine the validity of this decision in a sensitivity analysis. We did not consider concurrent secondary diagnosis of another psychiatric disorder an exclusion criterion. However, we excluded studies in which all participants had a concurrent primary diagnosis of another Axis I or II disorder. We also excluded participants with a serious concomitant medical illness or with postpartum depression.

Setting

We applied no restriction on setting.

Subset data

We also included studies with a subset of participants that met the review inclusion criteria in the analysis, provided we could extract data for this subset from the study report.

Types of interventions

Experimental Interventions

1. Ketamine: any dose and pattern of administration
2. Riluzole: any dose and pattern of administration
3. Amantadine: any dose and pattern of administration
4. Dextromethorphan (alone or in combination with quinidine)
5. Quinolinic acid: any dose and pattern of administration
6. Memantine: any dose and pattern of administration
7. Atomoxetine: any dose and pattern of administration
8. Tramadol: any dose and pattern of administration
9. Lanicemine: any dose and pattern of administration
10. MK-0657: any dose and pattern of administration
11. Any other glutamate receptor modulators (for example, D-cycloserine, GLYX-13)

Comparator interventions

1. Placebo (or saline placebo)
2. Any pharmacologically active agent (either conventional, e.g. midazolam, or nonconventional, e.g. scopolamine or *Hypericum*) or agent included to mimic the psychotropic side effects of the glutamate agent.

All interventions could be either as monotherapy or as combined with other treatments. We applied no restrictions on dose, frequency, intensity, route, or duration. We included trials that allow rescue medications (as required, short-term, infrequent use of medications aimed at emergent symptom relief only, for example short-term use of hypnotics) as long as these medications were equally distributed among the randomised arms.

We did not include lamotrigine among the list of comparisons because the randomised evidence about this drug has been synthesised recently elsewhere (Thomas 2010; Zavodnick 2012).

Types of outcome measures

We included studies that met the above inclusion criteria regardless of whether they reported on the following outcomes.

Primary outcomes

1. Efficacy outcome (dichotomous): number of participants who respond to treatment, where treatment response is defined as (1) a reduction of at least 50% compared to baseline on the Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960), Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery 1979), or any other depression scale, depending on the study authors' definition or (2) 'much or very much improved' (score 1 or 2) on the Clinical Global Impression-Improvement scale (Guy 1976). Where both scales are provided, we preferred the former criteria for judging response. We used the response rate instead of a continuous symptom score for the primary efficacy analysis to make the interpretation of results easier for clinicians (Guyatt 1998). To avoid possible outcome reporting bias, we did not use the original authors' definitions of response or remission, if different from above, in this review (Furukawa 2007a).
2. Adverse events outcome (dichotomous): We evaluated adverse events using the following outcome measures.
   i) Total number of participants experiencing at least one side effect.
   ii) Total number of participants experiencing the following specific side effects:
      a) agitation/anxiety
      b) constipation
      c) delusions
      d) diarrhoea
      e) dissociative symptoms
      f) dizziness
      g) dry mouth
      h) hallucinations
      i) headache
      j) hypo/hypertension
      k) insomnia
      l) mania/hypomania
      m) nausea
      n) seizure
      o) sleepiness/drowsiness
      p) urination problems
      q) vomiting
      r) tremor

In order to avoid missing any relatively rare or unexpected, yet important side effects (for instance sexual side effects), in the data

extraction phase we collected information on all side effects data reported in the studies and discussed ways to summarise them post hoc. We extracted descriptive data regarding adverse effect profiles from all available studies. Due to a lack of consistent reporting of adverse effects, which came primarily from the study authors' descriptions, we combined terms describing similar side effects. For example, we combined 'dry mouth', 'reduced salivation', and 'thirst' into 'dry mouth'. We then grouped all adverse effect categories by organ system, such as neuropsychiatric, gastrointestinal, respiratory, sensory, genitourinary, dermatological, and cardiovascular.

Secondary outcomes

1. Efficacy outcome (dichotomous): Number of participants who achieve remission. Remission is defined as (1) a score of less than 7 on the HRSD-17 (Furukawa 2007b), or less than 8 for all the other longer versions of the HRSD, or less than 11 on the MADRS (Bandelow 2006), or less than 6 on the Quick Inventory of Depressive Symptomatology (16-Item) (QIDS) (http://www.ids-qids.org/); or (2) participants who were 'not ill or borderline mentally ill' (score 1 or 2) on the Clinical Global Impression-Severity score out of the total number of randomised participants. Where both are provided, we used the former criterion for judging remission.
2. Efficacy outcome (continuous): Mean endpoint scores or mean change scores in depression severity (on HRSD, MADRS, Clinical Global Impression-Severity or Inventory of Depressive Symptomatology (IDS)) from baseline to the time point in question (we allowed a looser form of intention-to-treat (ITT) analysis, whereby all the participants with at least one post-baseline measurement were represented by their last observations carried forward (LOCF), but in any pooled analysis we examined the impact of the LOCF in a sensitivity analysis).
3. Suicidality, including suicidal ideation, suicide attempts (nonfatal self harm), and deaths by suicide. We examined suicidality and suicide ideation according to the outcome measures reported in the original studies (either as spontaneously reported or as a score on a standardised rating scale).
4. Cognition. We examined this according to the outcome measures reported in the original studies.
5. Loss of hope and other health-related quality of life measures. We included data on the following validated quality of life instruments: SF-12 (Ware 1998), SF-36 (Ware 1992), Health of the Nation Outcome Scales (Wing 1998), and the WHO-QOL (WHOQOL Group 1998).
6. Costs to healthcare services. We collected data according to what was reported in the original studies.
7. Acceptability (dichotomous), evaluated using the following outcome measures.

i) Overall number of participants who dropped out during the trial as a proportion of the total number of randomised participants.

ii) Number of participants who dropped out due to lack of efficacy during the trial as a proportion of the total number of randomised participants.

iii) Number of participants who dropped out due to side effects during the trial as a proportion of the total number of randomised participants.

Timing of outcome assessment

As study authors report response rates at various time points of trials, we decided a priori to subdivide the treatment indices as follows.

1. Ultra-rapid response: at 24 hours, ranging between 12 and 36 hours (primary efficacy outcome).
2. Rapid response: at 72 hours, ranging between 37 and less than 96 hours.
3. Early response: at one week, ranging between four and 10 days.
4. Acute response: at two weeks, ranging between 11 days and less than three weeks.
5. Medium response: at four weeks, ranging between three and six weeks.
6. Long-term response: at three months, ranging between seven weeks and six months.

Hierarchy of outcome measures

When several possible outcome measures are reported for the same outcome, we used the primary outcome according to the original study.

Search methods for identification of studies

The Cochrane Depression, Anxiety and Neurosis Review Group's Specialised Register (CCDANCTR)

The Cochrane Depression, Anxiety and Neurosis Group (CCDAN) maintains two clinical-trials registers at their editorial base in Bristol, UK: a references register and a studies-based register. The CCDANCTR-References Register contains more than 37,500 reports of RCTs in depression, anxiety, and neurosis. Approximately 60% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register, and records are linked between the two registers through the use of unique study ID tags. Coding of trials is based on the EU-Psi coding manual, using a controlled vocabulary; please contact the CCDAN Trials Search Co-ordinator for further details. Reports of trials for inclusion in the CCDAN's registers are collated from routine (quarterly) searches of the Cochrane Central Register of Controlled Trials (CENTRAL); weekly generic searches of MEDLINE (1950-), EMBASE (1974-), and PsycINFO (1967-); and review-specific searches of additional

databases. Reports of trials are also sourced from international trials registers c/o the World Health Organization's trials portal (the International Clinical Trials Registry Platform (ICTRP)), pharmaceutical companies, the handsearching of key journals, conference proceedings, and other (non-Cochrane) systematic reviews and meta-analyses.

Details of CCDAN's generic search strategies (used to identify RCTs) can be found on the CCDAN's website.

Electronic searches

1. CCDANCTR (Studies and References Register)

We searched CCDAN's specialised register (to 9 Jan 2015) using the following terms.

#1. (depress* or dysthymi* or "affective disorder*" or "affective spectrum disorder*" or "affective state*" or "affective symptom*" or "mixed state*" or "mood disorder*" or MDD or unipolar or bipolar):ti,ab,kw,ky,emt,mh,mc

#2. (amantadin* or atomoxetin* or *cycloserin* or dextromethorphan or "GLYX 13" or "MK 0657" or (ketamin* or Ketalar or Ketaject or Ketanest) or (lanicemin* or AZD6765) or memantin* or quinolin* or rellidep or riluzol* or (tramadol* or ETS6103 or viotra) or ampa or "cerc 301" or "d serin*" or glun2b or glutamate or glutamin* or glutamatergic or glutathione* or glycin* or mglu* or "N acetyl cysteine*" or "N methyl D aspartate" or nmda or "nrx 1074" or kainite or nr2b or sarcosin* or NAC): ti,ab,kw,ky,emt,mh,mc

#3. (#1 and #2)

[Key to field codes: ti:title; ab:abstract; kw:keywords: ky:additional keywords; emt:EMTREE headings; mh:MeSH headings; mc:MeSH checkwords]

2. International trial registries

We searched international trial registries via the World Health Organization's trials portal (ICTRP) and ClinicalTrials.gov to identify unpublished or ongoing studies (to 9 Jan 2015).

Where appropriate, we searched pharmaceutical trial registers and repositories of results (http://www.gsk-clinicalstudyregister.com// ; http://www.lillytrials.com/).

3. Adverse events search

We also conducted a companion search for adverse events data (11 Nov 2014) on OVID MEDLINE, EMBASE and PsycINFO (Appendix 1), although we have not incorporated this data into this version of the review.

We applied no restrictions on date, language, or publication status to the searches.

Searching other resources

Grey literature

We conducted complementary searches on the websites of the following drug regulatory authorities for additional unpublished data: the US Food and Drug Administration, the Medicines and Healthcare products Regulatory Agency in the UK, the European Medicines Agency in the EU, the Pharmaceuticals and Medical Devices Agency in Japan, and the Therapeutic Goods Administration in Australia (Jan 2015).

Handsearching

We had already handsearched and incorporated into the CCDANCTR appropriate journals and conference proceedings relating to the treatment of depression with ketamine and other glutamate receptor modulators.

Reference lists

We checked the reference lists of all included studies and relevant systematic reviews and major textbooks of affective disorder written in English to identify additional studies missed from the original electronic searches (for example unpublished or in-press citations).

Correspondence

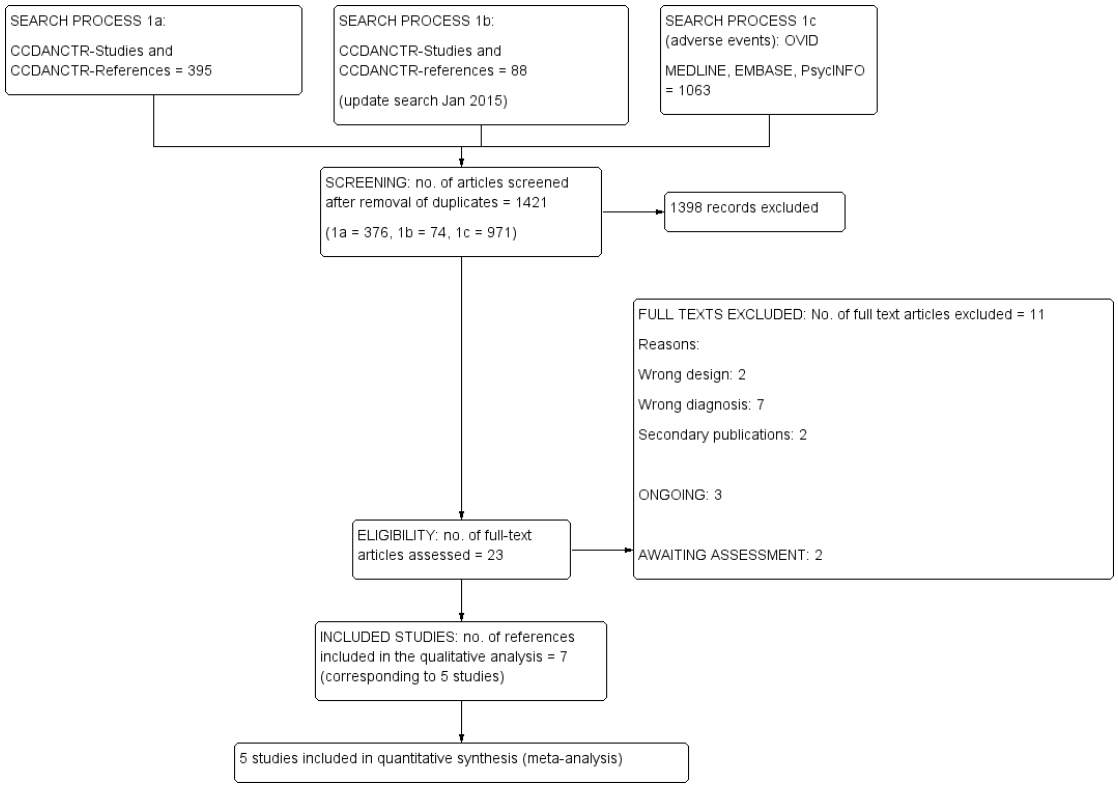
We contacted trialists and subject experts for information on unpublished or ongoing studies or to request additional trial data.

Data collection and analysis

Selection of studies

Six review authors (JR, BHA, CS, JJ, PD, DB) independently screened titles and abstracts for inclusion of all the potential studies we identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publication, and six review authors (JR, BHA, CS, JJ, PD, DB) independently screened the full-text and identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. Any disagreement was resolved through discussion or, if required, by consulting a third person (AC). We identified and removed duplicate records and collated multiple reports that related to the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA (Moher 2009) flow diagram (Figure 1) and Characteristics of excluded studies table.

Figure 1. Study flow diagram.



Data extraction and management

We used a data collection form to extract study characteristics and outcome data that had been piloted on at least one study in the review. Five review authors (CS, JJ, DB, PD, JR) extracted study characteristics and outcome data from included studies, with at least two of the five authors independently extracting data from each study. We extracted the following study characteristics.

1. Participant characteristics (age, sex, depression diagnosis, comorbidity, depression severity, antidepressant treatment history for the index episode, study setting).
2. Intervention details (intended dosage range, mean daily dosage actually prescribed, cointervention if any, ketamine as investigational drug or as comparator drug, sponsorship).
3. Outcome measures of interest from the included studies.

We noted in the Characteristics of included studies table if outcome data were not reported in a usable way. We resolved disagreements by consensus or by involving a third person (AC). Two review authors (TMC, JJ) transferred data into the Review Manager 5 (RevMan 2014) file. We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. Two review authors (TMC, JJ) spot-checked study characteristics for accuracy against the trial report.

Main comparisons

1. Ketamine versus placebo
2. Ketamine versus other glutamate moderators
3. Ketamine versus other pharmacologically active agents (either conventional, e.g. midazolam, or nonconventional, e.g. scopolamine or *Hypericum*)
4. Other glutamate receptor modulators versus placebo
5. Other glutamate receptor modulators versus other pharmacologically active agents (either conventional, e.g. midazolam, or nonconventional, e.g. scopolamine or *Hypericum*)

All interventions could be either as monotherapy or combined with other treatments. We applied no restrictions on dose, frequency, intensity, route, or duration.

Assessment of risk of bias in included studies

Five review authors (TMC, JJ, JR, PD, DB) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins

2011b). Any disagreements were resolved by discussion or by involving another review author (AC). We assessed the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

We judged each potential source of bias as high, low, or unclear and provided a supporting quotation from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (for example, for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a participant-reported mood scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Measures of treatment effect

Dichotomous data

We calculated the odds ratio (OR) with corresponding 95% confidence interval (95% CI) for dichotomous or event-like outcomes. We calculated response rates out of the total number of randomised participants. We applied ITT analysis whereby all dropouts not included in the analysis were considered nonresponders. For statistically significant results, we calculated the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH).

Continuous data

We calculated the mean difference (MD) or standardised mean difference (SMD) along with corresponding 95% CI for continuous outcomes. We used the MD where the same scale was used to measure an outcome. We employed the SMD where different scales were used to measure the same underlying construct.

For both continuous and dichotomous data, we undertook meta-analyses only where this was meaningful, that is if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense. We narratively described skewed data reported as medians and interquartile ranges.

Where multiple trial arms are reported in a single trial, we planned to include only the relevant arms. However, this did not apply to any of the included studies.

Unit of analysis issues

Cluster randomised trials

We planned to include CRTs if either of the two methods below were possible.

1. When the CRT was correctly analysed in the original report, we entered the effect estimate and standard error using the generic inverse variance method in RevMan 2014.
2. If the original report failed to adjust for cluster effects, we could still include such a trial in the meta-analysis if we could extract the following information.

i) Number of clusters randomised to each intervention or the average size of each cluster.

ii) Outcome data ignoring the cluster design for the total number of participants.

iii) Estimate of the intracluster correlation coefficient (ICC).

The ICC may be borrowed from similarly designed studies when such are available. We planned to then conduct the approximately correct analysis following the procedures described in section 16.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). However, no CRTs met the inclusion criteria.

Cross-over trials

A major concern of cross-over trials is the potential of carry-over effects, which occur if an effect (for example, pharmacological, physiological, or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase, the participants can differ systematically from their initial state, despite a washout phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in bipolar depression, we only used data from the first phase of cross-over studies. However, we are aware that cross-over trials for which only first period data are available should be considered to be at risk of bias (Higgins 2011c).

Studies with multiple treatment groups

Where a study involved more than two treatment arms, we planned to include all relevant treatment arms in comparisons. If data were binary, we would have simply combined them into one group or divided the comparison arm into two (or more) groups as appropriate. If data were continuous, we planned to combine data following the formula in section 7.7.3.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d). However, this was not the case for any of the included studies.

Dealing with missing data

Dichotomous data

We calculated treatment responders and treatment remitters on a strict ITT basis; we included dropouts in the analysis. Where participants were excluded from the trial before the endpoint, we assumed that they experienced a negative outcome (for example, failure to respond to treatment). We planned to examine the validity of this decision in sensitivity analyses by applying worst- and best-case scenarios (that is, we assumed missing data to be responders or nonresponders in the corresponding sensitivity analyses). When dichotomous outcomes were not reported but baseline mean, endpoint mean, and corresponding standard deviations (SDs) of the HRSD (or other depression scale) were reported, we converted continuous outcome data expressed as mean and SD into the number of responding and remitted participants, based on a validated imputation method (Furukawa 2005). When the more sophisticated and arguably more valid imputation method (for example, mixed-effects model, multiple imputation) was reported in the original study, we used these numbers to impute the number of responders. We planned to examine the validity of this imputation in sensitivity analyses.

Continuous data

When there were missing continuous data and the method of LOCF was used to perform an ITT analysis, we used the LOCF data.

Missing data

We contacted the original study authors for missing data.

Missing statistics

When only the standard error or t-test or P values were reported, we calculated SDs as suggested by Altman 1996. Where SDs were not reported, we contacted trial authors and asked them to supply the data. In the absence of a response from the trial authors, we borrowed SDs from other studies in the review (Furukawa 2006). We planned to examine the validity of this imputation in sensitivity analyses.

Assessment of heterogeneity

We first investigated heterogeneity between studies by visual inspection of the forest plots. If the 95% CIs of the ORs for each study in the pooled analysis did not include means of other studies, we investigated potential sources of heterogeneity. We also calculated the I^2 statistic (Higgins 2003). We used the *Cochrane Handbook for Systematic Reviews of Interventions*' rough guide to its interpretation as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity. We also kept in mind that the importance of the observed value of I^2 depends on (i) the magnitude and direction of effects and (ii) the strength of evidence for heterogeneity (for example P value from the Chi^2 test, or a CI for I^2). If the I^2 value is below 50% but the direction and magnitude of treatment effects were suggestive of important heterogeneity, we investigated the potential sources of heterogeneity. Finally, we performed subgroup analyses to investigate heterogeneity.

Assessment of reporting biases

We planned to enter data from included studies into a funnel plot (trial effect against trial variance) to investigate small-study effects (Sterne 2000), but none of our analyses contained sufficient studies to allow this. In future updates of this review, we plan to use the test for funnel plot asymmetry only when at least 10 studies are included in the meta-analysis, as per protocol. In the event of using a funnel plot, we will interpret results cautiously, with visual inspection of the funnel plots (Higgins 2011b). If we identify evidence of small-study effects, we will investigate possible reasons for funnel plot asymmetry, including publication bias (Egger 1997).

Data synthesis

For the primary analysis, we calculated the pooled OR with corresponding 95% CI for dichotomous outcomes. We calculated the pooled MD or SMD as appropriate with corresponding 95% CI for continuous outcomes. We presented any skewed data and non-quantitative data descriptively. An outcome that has a minimum score of zero could be considered skewed when the mean is smaller than twice the SD. However, the skewness of change scores is difficult to depict as the possibility of negative values exists. We therefore used change scores for meta-analysis of MDs. We considered a P value of less than 0.05 and a 95% CI that does not cross the line of no effect statistically significant. In forest plots with two or more studies we used a random-effects model for both dichotomous and continuous variables. We adopted the random-effects model under these circumstances because it has the highest generalisability for empirical examination of summary effect measures in meta-analyses (Furukawa 2002). However, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (10.4.4.1), when concerned about the influence of small-study effects on the results of a meta-analysis with between-study heterogeneity, we routinely examined the robustness by comparing the fixed-effect model and the random-effects model. We reported any material differences between the models.

Subgroup analysis and investigation of heterogeneity

As multiple analyses lead to false-positive and false-negative conclusions, subgroup analyses should be performed and interpreted with caution (Brookes 2001; Brookes 2004). We planned to perform the following subgroup analyses where possible for the following variables, however this was not necessary.

1. Depression severity (severe major depression, moderate or mild major depression): 'Severe major depression' was defined by a threshold baseline severity score for entry of 25 or more for the 17-item HRSD (Dozois 2004) and 31 or more for MADRS (Muller 2003).
2. Treatment settings (psychiatric inpatients, psychiatric outpatients, primary care): As bipolar depressive episodes in primary care may have a different profile than that of psychiatric inpatients or outpatients (Suh 1997), it is possible that results obtained from either of these settings may not be applicable to the other settings (Arroll 2009).
3. Older people (greater than 65 years of age), separately from other adult participants: Older people may be more vulnerable to adverse effects associated with antidepressants, and a decreased dosage is often recommended. We pooled groups whose mean age was more than 65 years.

Sensitivity analysis

We planned the following sensitivity analyses for primary outcomes a priori.

1. Excluding trials with unclear allocation concealment or unclear double-blinding.
2. Excluding studies that included participants with unipolar depression or psychotic features.
3. Excluding studies that recruited participants with treatment-resistant bipolar depression.
4. Excluding studies with unfair dose comparisons (Cipriani 2009).
5. Excluding trials with a dropout rate greater than 20%.
6. Excluding trials for which the response rates had to be calculated based on an imputation method (Furukawa 2005), and for which the SD had to be borrowed from other trials (Furukawa 2006).

Our routine comparisons of random-effects and fixed-effect models, as well as our secondary outcomes of remission rates and continuous severity measures, may be considered additional forms of sensitivity analyses.

'Summary of findings' table

We constructed a 'Summary of findings' table for each head-to-head comparison, with regard to the following five outcomes. Where possible, we presented data at all four prespecified time points for the primary outcomes. For secondary outcomes, we selected a primary time point of one week, as this was considered the most clinically relevant, and presented the data closest to this time point only.

1. Response.
2. Total dropouts.
3. Remission.
4. Severity of depression at end of trial.
5. Dropouts due to adverse effects.

In the 'Summary of findings' tables we used GRADEproGDT software (GRADEproGDT 2015) and the principles of the GRADE approach (Atkins 2004), which assess the quality of a body of evidence based on the extent to which there can be confidence that the obtained effect estimate reflects the true underlying effect. The quality of a body of evidence is judged on the basis of the included studies' risks of bias, the directness of the evidence, unexplained heterogeneity, imprecision, and the risk of publication bias. We used the average rate in all the arms of the included trials as the 'assumed risk' for each outcome because we did not expect salient differences in such risks among different agents. We therefore did not target any particularly high- or low-risk populations; all the tables were for medium-risk populations.

RESULTS

Description of studies

Results of the search

CCDAN's Trials Search Co-ordinator initially ran searches in 2014 using two separate strategies: one for RCTs (CCDANCTR all years to 1 Oct 2014) (n = 395 refs); and one for adverse effects data (OVID MEDLINE, EMBASE, PsycINFO, all years to 11 Nov 2014) (n = 1063). An update search was performed on 9 Jan 2015, (CCDANCTR only, n = 88). Relevant trial protocols from ClinicalTrials.gov and the WHO Trials Portal (ICTRP) had already been incorporated into the CCDANCTR so have not been counted separately for the purposes of the PRISMA diagram.

From a total of 1546 records retrieved from the searches, we removed 125 duplicate records and excluded a further 1398 on the basis of the title and abstract. We retrieved full-text articles for 23 records, yielding seven primary references to five studies.

Included studies

See: Characteristics of included studies; Figure 1.

We identified five studies from the search which met the inclusion criteria for this review (Anand 2012; Diazgranados 2010; Lee 2014; Yoon 2009; Zarate 2012). Two of these studies assessed the efficacy of ketamine (Diazgranados 2010; Zarate 2012); two assessed the efficacy of memantine (Anand 2012; Lee 2014); and one assessed the efficacy of cytidine (Yoon 2009). All of the included

studies were two-arm, placebo-controlled trials. We did not find any head-to-head trials (i.e. active drug versus active drug).

Design

All included studies were double-blind, randomised, placebo-controlled trials. Three out of the five studies had a parallel design (Anand 2012 and Lee 2014, investigating memantine; Yoon 2009, investigating cytidine), whilst the remaining two studies, both of which investigated ketamine, used a cross-over design. The treatment period ranged from a single administration for ketamine (Diazgranados 2010; Zarate 2012) to eight to 12 weeks for memantine (Anand 2012; Lee 2014) and 12 weeks for cytidine (Yoon 2009). Ketamine was administered intravenously in both of the included studies, whilst the remaining interventions were administered orally. In all cases, the glutamate receptor modulators were given as an add-on to mood stabilisers (valproate, lithium, or lamotrigine). In three studies, participants were required to have been taking these previously (either continuously or in another trial), and have shown "inadequate response"; either valproate or lithium in Diazgranados 2010 and Zarate 2012, and lamotrigine in the case of Anand 2012. In one case (Lee 2014), participants started taking valproate at the beginning of the study, and in the final case it is unclear whether patients were selected based on mood stabiliser status (though they were required to take valproate throughout; Yoon 2009).

Sample sizes

The total number of participants from the five included studies was 329, with a minimum sample size of 15 (Zarate 2012) and a maximum sample size of 232 (Lee 2014).

Setting

Two of the trials treated patients on an inpatient basis (Diazgranados 2010; Zarate 2012), and one on an outpatient basis (Anand 2012). In the remaining two studies the setting was unclear. The majority of trials took place in the USA (Anand 2012; Diazgranados 2010; Zarate 2012) and one took place in Taiwan (Lee 2014); the location of Yoon 2009 was unknown. Two of the studies (Diazgranados 2010; Zarate 2012) were conducted by the same research team at the National institute for mental health (NIMH) Mood Disorders Research Unit, in Bethesda, Maryland and followed the same protocol (NCT00088699). However, it is worth noting that the majority of patients included in the present review were from Taiwan (70.5%). Three of the five trials were single-centre studies (Anand 2012; Diazgranados 2010; Zarate 2012), and in the remaining two it was unclear whether the trials were single-centred or multi-centred.

Participants

All studies reported demographic and/or clinical characteristics of participants. The proportion of women randomised ranged from 49% (Yoon 2009) to 67% (Diazgranados 2010). No studies recruited participants under 18 years or over 65 years, and mean ages ranged from 31.8 years to 47.9 years.

In all the included studies, all patients had a primary diagnosis of bipolar disorder, according to the DSM-IV or DSM-IV-TR (and confirmed through clinical interview), and defined an inclusion criteria of a current depressive phase, specifying the severity of the depression as at least moderate, with the exception of one study (Anand 2012), which had a HRSD score more than or equal to 15 as an inclusion criteria. One trial recruited only patients with bipolar II depression (Lee 2014), whilst all of the remaining trials recruited both types of the disorder. Three studies included only participants who had had an 'inadequate response so far' to an open-label mood stabiliser, with no further definition provided (Anand 2012; Diazgranados 2010; Zarate 2012), and no studies defined 'treatment-resistant' patients as an inclusion criteria.

Interventions

Of the two which compared ketamine to placebo, both used ketamine as the experimental intervention and administered it intravenously; one with a single dose (Zarate 2012), and the other with two doses (Diazgranados 2010), two weeks apart. Of the two studies which used memantine as the experimental intervention, one administered a fixed dose of 5 mg orally per day (Lee 2014), while the other titrated the dose weekly from 5 mg to 20 mg according to tolerability (Anand 2012).

All of the trials required participants to receive concomitant mood stabiliser medication as an add-on. In two of the studies, participants were required to have been taking either valproate or lithium for at least four weeks with inadequate response, and then continued doing so throughout the trial (Diazgranados 2010; Zarate 2012). Anand 2012 used the same criteria, with the drug lamotrigine. The remaining two studies (Lee 2014; Yoon 2009) treated all participants with open-label valproate throughout the trial. Two studies allowed patients to receive other concomitant medication for their depression (Anand 2012; Lee 2014), whilst the remaining three studies specified washout periods.

Outcomes

We managed to include dichotomous efficacy outcomes (response and remission rates) for at least one time point in every included study. In one case, we imputed these from the available continuous data (Lee 2014). In another case, we calculated data for missing time points using the graph provided (Anand 2012). The continuous efficacy outcome in all included studies was measured on the MADRS or HRSD. There was no usable information on adverse events in the comparison ketamine versus placebo, so we included

data from across both phases of these cross-over trials. All studies reported data on total dropout rates for the main acceptability outcome.

Excluded studies

See: Characteristics of excluded studies; Figure 1
We excluded 11 studies. The main reason for exclusion was wrong diagnosis (seven studies).

Ongoing studies

See: Characteristics of ongoing studies
We identified three ongoing studies, through screening retrieved records and online database information (Figure 1).

Studies awaiting classification

See: Characteristics of studies awaiting classification.
There were two studies which were awaiting classification, largely owing to a lack of available information and/or contact authors.

Risk of bias in included studies

For details of the risk of bias judgements for each study, see Characteristics of included studies. A graphical representation of the overall risk of bias in included studies can be seen in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

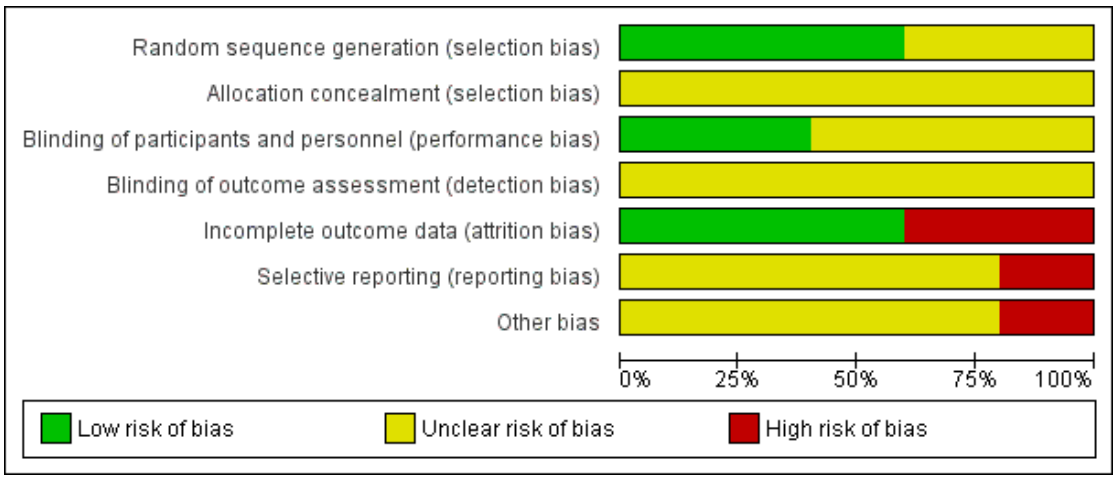
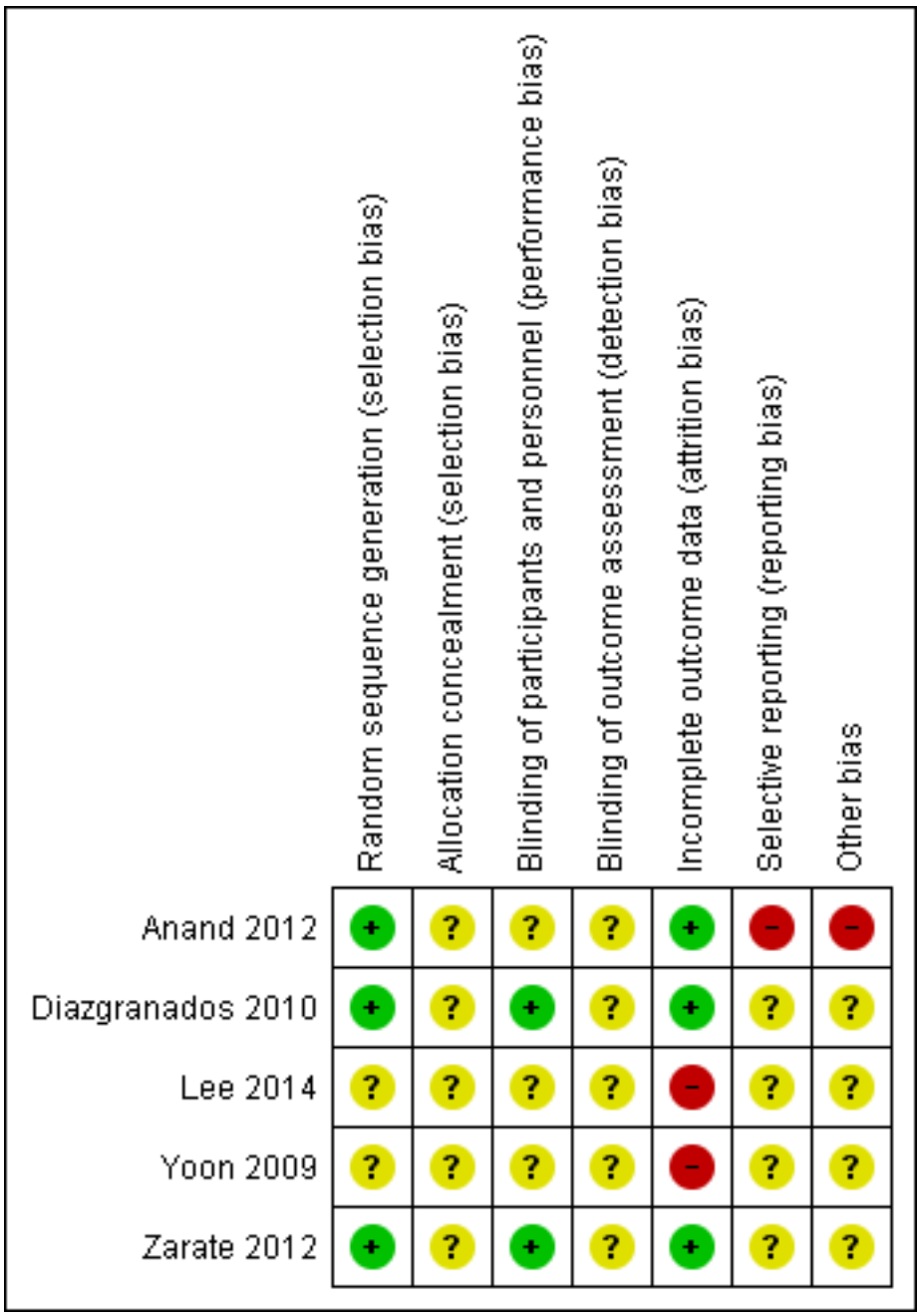


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



We cannot rule out the potential bias introduced by inadequate blinding procedures. For instance, saline infusion does not necessarily provide adequate blinding for ketamine, as both patients and personnel could possibly guess which treatment a patient has received based on differences during the infusion, for example psychotomimetic side effects. The assessment of bias reported below is based on the adequacy of blinding attempts as described in each papers' methods, not on the actual degree of blinding achieved. We rated studies as 'low risk' when all measures used to blind study participants and personnel from knowledge of which intervention a participant received was described. Studies were rated as 'unclear risk' when there was a lack of information on blinding procedures. Neither of the two included studies assessing the efficacy of ketamine tested the blind or provided any information relating to whether the intended blinding was effective.

Allocation

Random sequence generation

We classified three of the five studies (Anand 2012; Diazgranados 2010; Zarate 2012) as 'low risk' for selection bias, having described the method of random sequence generation in details. The remaining two studies (Lee 2014; Yoon 2009) reported only that the trials were "randomised", with no information on the method used, and so we classified them as 'unclear risk'.

Allocation concealment

Of the five included studies, none reported details on allocation concealment, and so we classified them all as 'unclear risk'.

Blinding

Blinding of participants and personnel

We rated two studies as 'low risk' with reference to blinding of participants and personnel (Diazgranados 2010; Zarate 2012). We classified the remaining three studies as 'unclear risk', having not reported sufficient detail on the blinding of participants and personnel.

Blinding of outcome assessment

None of the five included studies, provided details of the methods used in blinding of outcome assessment, and so we classified them all as 'unclear risk'.

Incomplete outcome data

We classified two studies as being at 'high risk' with regards to attrition bias (Lee 2014; Yoon 2009), owing to a lack of information on dropout rates. We considered the remaining three studies to be of 'low risk' as sufficient dropout detail was provided (Anand 2012; Diazgranados 2010; Zarate 2012).

Selective reporting

We considered one of the included studies to be at 'high risk' of reporting bias (Anand 2012), as a result of missing primary outcome data and a lack of supplemental information. We classified all other studies as 'unclear risk', having reported data graphically but not in tables.

Other potential sources of bias

We identified one other potential source of bias, relating to one of the included studies (Anand 2012). The authors stated that "blind was opened after ten subjects completed the study to examine the side-effect and tolerability profile of active memantine". We rated all the remaining studies as 'unclear'.

Effects of interventions

See: **Summary of findings for the main comparison** Ketamine compared to placebo for depression in bipolar disorder in adults; **Summary of findings 2** Memantine compared to placebo for depression in bipolar disorder in adults; **Summary of findings 3** Cytidine compared to placebo for depression in bipolar disorder in adults

We contacted all study authors for missing and unpublished data. We were able to obtain supplementary information for two of the five studies (Diazgranados 2010; Zarate 2012), from one author (see Acknowledgements).

All studies reported response rate data for at least one time point. However, adverse events data were unavailable for phase 1 (before cross-over) in the two ketamine studies (Diazgranados 2010; Zarate 2012), so we have included adverse events data from across both phases for completeness. All other data were from either phase 1 of cross-over trials or from parallel design trials. We found no data for three of the prespecified secondary outcomes: cognition, quality of life, and cost to healthcare services. Included below are all available data, as set out in the methodology.

In terms of interventions, our included studies evaluated only ketamine and two drugs classified in the prespecified category 'other glutamate receptor modulators', memantine and cytidine. These drugs were all compared to placebo; none of the studies which met criteria for inclusion used a pharmacologically active agent as a comparator.

In terms of the different time points specified in the protocol for the efficacy outcome, for ketamine we found data were available for all time points up until two weeks (Diazgranados 2010; Zarate 2012), whilst for memantine, data were only available for time points from one week onwards (Anand 2012; Yoon 2009). For cytidine, data were only available at the three-month time point (Lee 2014). For adverse events, we reported all findings in the tables and forest plots, but in the text below we only mentioned results that were statistically significant (all analyses here below used a fixed-effect model, unless otherwise specified).

1. Ketamine versus placebo

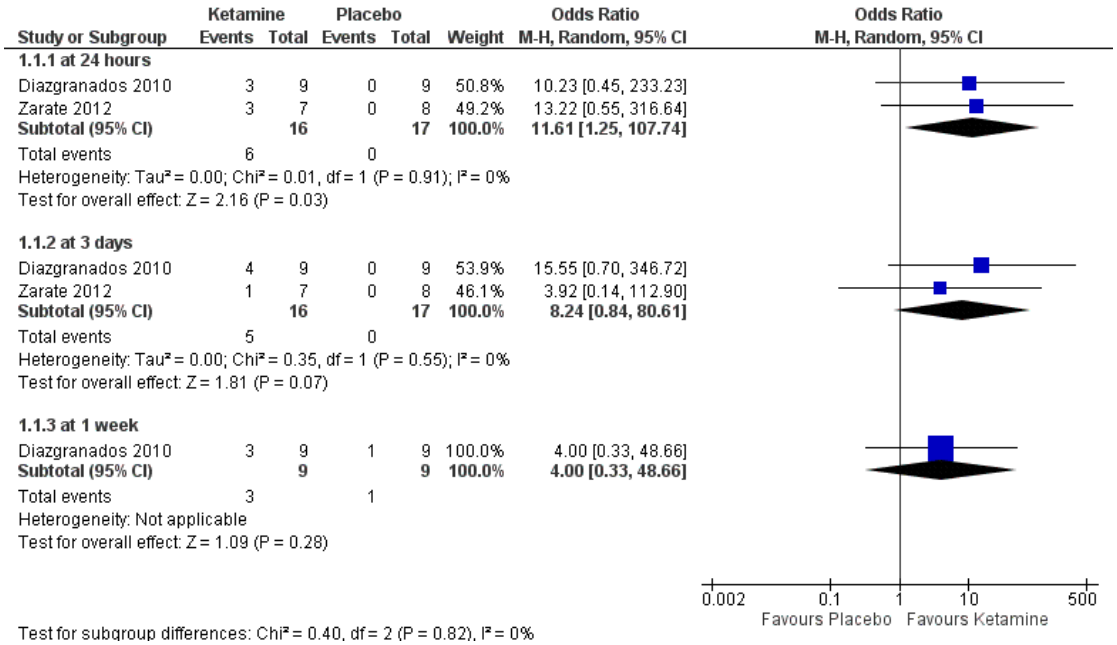
Two studies contributed to this comparison, providing outcome data on 33 participants (Diazgranados 2010; Zarate 2012). We obtained data at 24 hours, three days, one week and two weeks, for the outcome measures: response, remission, and change scores from baseline. We also obtained data on adverse events and acceptability, but no data were available on other prespecified outcomes. In both of the included studies, ketamine was given as an add-on to valproate or lithium (depending on what the participant had taken previously). See also Summary of findings for the main comparison.

Primary outcomes

1.1 Response

We found a significant difference in response in favour of a single intravenous dose of ketamine over placebo at 24 hours (OR 11.61, 95% CI 1.25 to 107.74; P = 0.03, I^2 = 0%, 2 studies, 33 participants, NNTB = 3, 95% CI 2 to 10 - Analysis 1.1, Figure 4). At 72 hours, effect sizes still favoured ketamine over placebo, but this difference was no longer statistically significant (OR 8.24, 95% CI 0.84 to 80.61; P = 0.07, I^2 = 0%, 2 studies, 33 participants). We found no significant 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). We note that no responders were found in either group by Zarate 2012 at the one-week time point, or by either of the included studies after two weeks.

Figure 4. Forest plot of comparison: 1 Ketamine versus placebo, outcome: 1.1 Response rate.



1.2 Adverse events

We found no significant differences in any adverse events between ketamine and placebo (Table 1).

Secondary outcomes

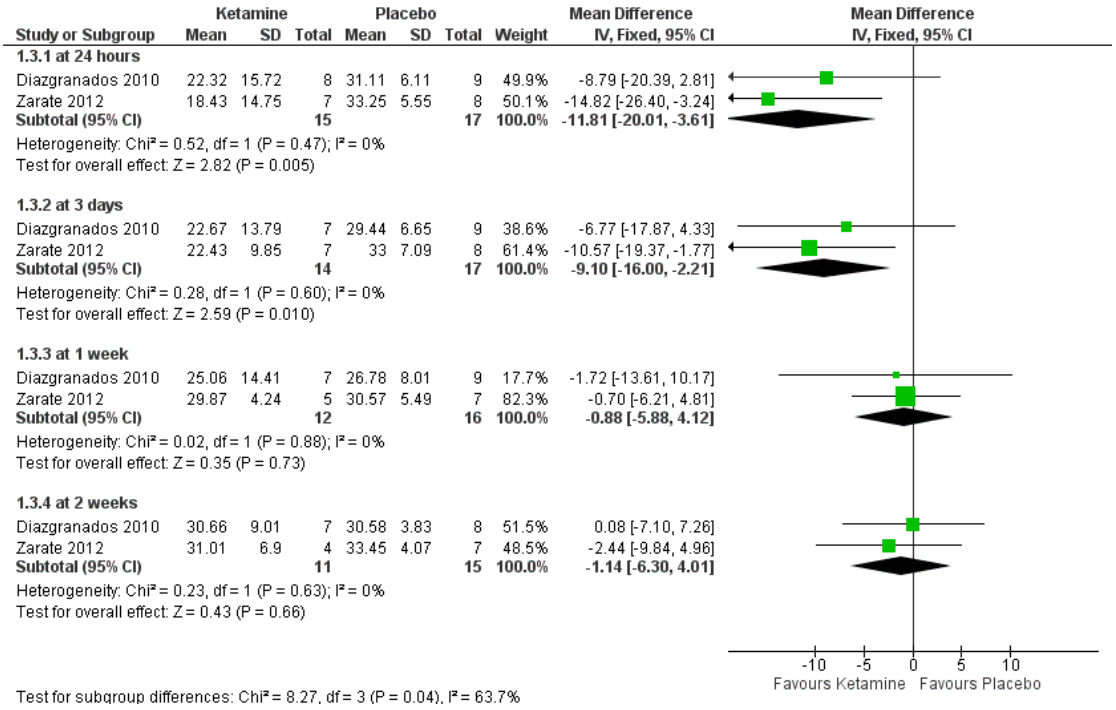
1.3 Remission

There was no evidence that ketamine was more effective than placebo in remission at any time point (Analysis 1.2). We note that there were no remitters in either group, in either study at the two-week time point.

1.4 Change scores on depression scale from baseline

Ketamine was more effective than placebo at 24 hours (MD -11.81, 95% CI -20.01 to -3.61; P = 0.005, I^2 = 0%, 2 studies, 32 participants; Analysis 1.3, Figure 5), and at 72 hours (MD -9.10, 95% CI -16.00 to -2.21; P = 0.010, I^2 = 0%, 2 studies, 31 participants). However, this effect disappeared after one week (MD -0.88, 95% CI -5.88 to 4.12; P = 0.73, I^2 = 0%, 2 studies, 28 participants). No significant difference between ketamine and placebo was observed at two weeks (MD -1.14, 95% CI -6.30 to 4.01; P = 0.66, I^2 = 0%, 2 studies, 26 participants).

Figure 5. Forest plot of comparison: 1 Ketamine versus placebo, outcome: 1.3 Depression rating scale score.



1.5 Suicidality

No data were available for this outcome.

1.6 Cognition

No data were available for this outcome.

1.7 Loss of hope or other health-related quality of life measures

No data were available for this outcome.

1.8 Costs to healthcare services

No data were available for this outcome.

1.9 Acceptability

We found no significant difference between ketamine and placebo in acceptability, either in terms of total dropouts (Analysis 1.4), or in relation to lack of efficacy (Analysis 1.5).

2. Memantine versus placebo

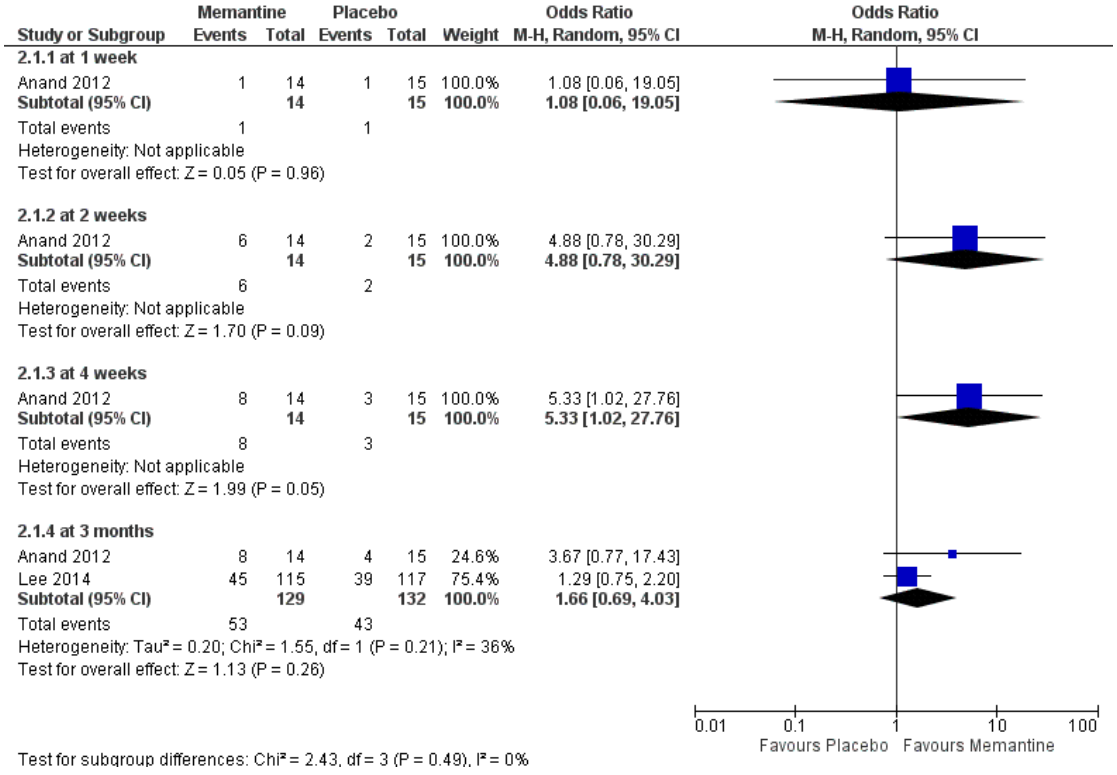
Two studies contributed to this comparison, providing outcome data on 261 participants (Anand 2012; Lee 2014). We obtained outcome data at one week, two weeks, four weeks and three months for the measures response and remission rate. For change scores from baseline, we obtained data for the three-month time point only. We also obtained information on adverse events, suicidality and acceptability, but no data were available on the other outcomes we prespecified in the review protocol (Amit 2014). In the Anand 2012 study, both arms received lamotrigine throughout (and had already been taking it), whilst in the Lee Lee 2014 study all participants began taking valproate for the study.

Primary outcomes

2.1 Response

There was no significant difference between memantine and placebo in response at one week (OR 1.08, 95% CI 0.06 to 19.05; P = 0.96, 1 study, 29 participants; Analysis 2.1, Figure 6). At two weeks, the effect size favoured memantine, but was not significant (OR 4.88, 95% CI 0.78 to 30.29; P = 0.09, 1 study, 29 participants), and became only marginally significant in favour of memantine at four weeks (OR 5.33, 95% CI 1.02 to 27.76; P = 0.05; 1 study, 29 participants, NNTB = 3, 95% CI 2 to 25). Importantly, no significant effect was present at the three-month time point (OR 1.66, 95% CI 0.69 to 4.03; P = 0.26, I^2 = 36%, 2 studies, 26 participants).

Figure 6. Forest plot of comparison: 2 Memantine versus placebo, outcome: 2.1 Response rate.



2.2 Adverse events

We found no significant difference between memantine and placebo in any adverse events (Analysis 2.2; Table 1).

Secondary outcomes

2.3 Remission

There was no significant difference observed between memantine and placebo in remission rate at any time point (Analysis 2.3).

2.4 Change scores on depression scale from baseline

Change scores on depression scale from baseline did not differ significantly between ketamine and placebo groups (Analysis 2.4).

2.5 Suicidality

A suicidality measure showed no significant difference between memantine and placebo (OR 0.34, 95% CI 0.01 to 8.34; P = 0.51, 1 study, 232 participants; Analysis 2.5). This was defined by the authors as number of participants who dropped out of the study as a result of attempted suicide within the duration of the trial.

2.6 Cognition

No data were available for this outcome.

2.7 Loss of hope or other health-related quality of life measures

No data were available for this outcome.

2.8 Costs to healthcare services

No data were available for this outcome.

2.9 Acceptability

We found no difference in dropout rate between the memantine and placebo groups, either as overall dropout rate (Analysis 2.6), due to lack of efficacy (Analysis 2.7), or due to adverse effects (Analysis 2.8).

3. Cytidine versus placebo

One study contributed to this comparison, providing outcome data on 35 participants (Yoon 2009). Data were available on response rate at the three-month time point only, and on the outcome measures: adverse events and acceptability. No other prespecified outcome data were available. Both arms of the study also took valproate throughout, though it is unclear whether participants had been taking this previously or not.

Primary outcomes

3.1 Response

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; Analysis 3.1).

3.2 Adverse events

We found no significant difference between the cytidine and placebo groups in adverse events experienced (Table 1).

Secondary outcomes

3.3 Acceptability

No significant difference in overall acceptability (total dropouts) between cytidine and placebo was identified (OR 0.94, 95% CI 0.12 to 7.52; P = 0.95, 1 study, 35 participants; Analysis 3.2).

Subgroup analyses

Due to the small number of included studies per comparison, we could not perform any of the pre-planned subgroup analyses.

Sensitivity analyses

Due to the small number of included studies per comparison, we could not perform any of the pre-planned sensitivity analyses.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Memantine compared to placebo for depression in bipolar disorder in adults

Patient or population: adults with bipolar disorder (currently experiencing a depressive episode)
Setting: outpatient (1 study) and unclear (1 study)
Intervention: memantine
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with memantine				
Response rate - at 1 week	Study population		OR 1.08 (0.06 to 19.05)	29 (1 RCT)	⊕◯◯◯ VERY LOW[1,2]	
	67 per 1000	72 per 1000 (4 to 576)				
	Moderate					
	67 per 1000	72 per 1000 (4 to 577)				
Response rate - at 2 weeks	Study population		OR 4.88 (0.78 to 30.29)	29 (1 RCT)	⊕◯◯◯ VERY LOW[1,2]	
	133 per 1000	429 per 1000 (107 to 823)				
	Moderate					
	133 per 1000	429 per 1000 (107 to 823)				
Response rate - at 4 weeks	Study population		OR 5.33 (1.02 to 27.76)	29 (1 RCT)	⊕◯◯◯ VERY LOW[1,2]	

	200 per 1000	571 per 1000 (203 to 874)			
	Moderate				
	200 per 1000	571 per 1000 (203 to 874)			
Response rate - at 3 months	Study population		OR 1.66 (0.69 to 4.03)	261 (2 RCTs)	⊕⊕◯◯ LOW[1,3]
	326 per 1000	445 per 1000 (250 to 661)			
	Moderate				
	300 per 1000	416 per 1000 (228 to 633)			
Remission rate - at 1 week	Study population		OR 1.08 (0.06 to 19.05)	29 (1 RCT)	⊕◯◯◯ VERY LOW[1,2]
	67 per 1000	72 per 1000 (4 to 576)			
	Moderate				
	67 per 1000	72 per 1000 (4 to 577)			
Depression rating scale score at 3 months	The mean depression rating scale score at 3 months was 0	The mean depression rating scale score at 3 months in the intervention group was 0.6 undefined fewer (2.63 fewer to 1.43 more)	-	157 (1 RCT)	⊕⊕◯◯ LOW[1,3]
Acceptability - total dropouts	Study population		OR 0.77 (0.45 to 1.31)	261 (2 RCTs)	⊕⊕◯◯ LOW[1,3]

	333 per 1000	278 per 1000 (184 to 396)			
	Moderate				
	275 per 1000	226 per 1000 (146 to 332)			
Acceptability - dropouts due to adverse events	Study population		OR 0.34 (0.01 to 8.34)	232 (1 RCT)	⊕⊕◯◯ LOW[1,3]
	9 per 1000	3 per 1000 (0 to 67)			
	Moderate				
	9 per 1000	3 per 1000 (0 to 67)			

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __OR:__ odds ratio; __RCT__: randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one point because no studies described the outcome assessment as masked.
[2] Downgraded by two points because of the very small sample size and the wide confidence interval.
[3] Downgraded by one point because of wide confidence intervals.

Cytidine compared to placebo for depression in bipolar disorder in adults

Patient or population: adults with bipolar disorder (currently experiencing a depressive episode)
Setting: unclear
Intervention: cytidine
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with cytidine				
Response rate - at 3 months	Study population		OR 1.13 (0.30 to 4.24)	35 (1 RCT)	⊕◯◯◯ VERY LOW[1,2]	
	471 per 1000	501 per 1000 (211 to 790)				
	Moderate					
	471 per 1000	501 per 1000 (211 to 790)				
Acceptability - total dropouts	Study population		OR 0.94 (0.12 to 7.52)	35 (1 RCT)	⊕◯◯◯ VERY LOW[1,2]	
	118 per 1000	111 per 1000 (16 to 501)				
	Moderate					
	118 per 1000	111 per 1000 (16 to 501)				
Remission	No data available	No data available	-	-	-	
Depression rating scale score	No data available	No data available	-	-	-	

Acceptability - dropouts due to adverse events	No data available	No data available	-	-	-

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __OR:__ odds ratio; __RCT__: randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded by one point because no studies described the outcome assessment as masked.
[2] Downgraded by two points because of the very small sample size and the wide confidence interval.

DISCUSSION

Summary of main results

In this systematic review, we sought to appraise both the efficacy and acceptability of ketamine and other glutamate receptor modulators for the treatment of depressive symptoms in bipolar disorder. We identified five randomised controlled trials (RCTs), totaling 329 participants and assessing three different interventions in comparison with placebo, all as an add-on to mood stabilisers. We did not find any active drug versus active drug trials.

While the quality of evidence ranged between low and very low, we found evidence of the efficacy of ketamine over placebo in terms of the primary outcome (response rate) at time points up to 24 hours. There was evidence that ketamine was more effective than placebo in terms of the continuous efficacy outcome (mean change or endpoint severity score) at time points up to three days, with this effect disappearing at one week. However, these results indicate that any rapid antidepressant effects of ketamine are not long-lasting. For the secondary efficacy outcome of remission rate, there was no significant difference between ketamine and placebo at any time point, with no patients remitting after two weeks. Finally, we did not find any significant differences between ketamine and placebo in terms of adverse effects, but this was likely due to the small amount of data available for this outcome. These findings, demonstrating a rapid antidepressant effect of ketamine are quite similar to what we found in another Cochrane review on unipolar depression (Caddy 2015). However, the present review suggests that the antidepressant effect is shorter in bipolar depression. Owing to the delayed onset of many other antidepressants (Berton 2006), these preliminary results of ketamine (among all other glutamate receptor modulators) may provide proof of principle for a new class of antidepressants with more rapid efficacy than currently achieved using monoaminergic modulators (Wang 2015).

There was not enough evidence available to draw any reliable conclusions regarding the efficacy of memantine or cytidine.

Overall completeness and applicability of evidence

Although we carried out a thorough search, the overall completeness of evidence is limited. We obtained data on only five studies which met our inclusion criteria, and these investigated only three glutamate receptor modulators. We did not obtain data for eight of the prespecified interventions, and none of the included studies involved an active placebo as comparator. For the main intervention (ketamine versus placebo) data were only available on five of nine predefined outcomes, on a total of 33 participants. This review is therefore limited by the very preliminary evidence in this area, although what is available suggests that further research is warranted to better inform clinical practice. It must be noted, however, that our literature search identified a number of ongoing trials which could provide valuable data in addition to that presented in this review; we will include these in future updates.

Several factors restrict the applicability of the evidence presently reviewed. Although all participants had received a DSM-IV or DSM-IV-TR diagnosis of bipolar disorder, the baseline level of depression varied across participants, with one study including some patients within the 'mild' range according to the Hamilton Rating Scale for Depression (HRSD). Some studies attempted to define a 'treatment-resistant' population for recruitment (only as having had an 'inadequate response so far' to open-label mood stabilisers), whilst others treated patients who had not been prescribed psychotropic drugs before. One study included only those with a bipolar II diagnosis, whilst the remaining studies recruited a mixture. This heterogeneity did not translate into significant heterogeneity in the statistical analyses, however the differences among the samples of patients studied in this review limited the applicability of this evidence to the wider population of patients with bipolar disorder. Moving towards a universally agreed upon definition of 'treatment-resistant' depressive episodes in bipolar disorder would also be beneficial, in line with the focus on this in the unipolar literature (Kubitz 2013). Two of the studies did not mention the efficacy of previous treatments in the inclusion criteria, and the remaining three stated that participants were required to have had an 'inadequate response so far' to open-label mood stabilisers.

It should also be noted that the included ketamine studies both administered the drug as a single intravenous dose; adverse effects may differ with intranasal administration or multiple doses.

Quality of the evidence

The quality of the included studies was difficult to ascertain, owing to the fact that the majority of the risk of bias judgements were deemed 'unclear'. This is a result of problems in study reporting, but introduces the potential for bias within this review. In particular, 'selection bias' and 'performance bias' were deemed unclear for all of the included studies.

Although we attempted to reduce the risk of reporting bias by contacting all authors of included trials, many studies are also missing data for key time points. For example, the cytidine versus placebo comparison contains efficacy data at three months only, despite the tendency for other glutamate receptor modulators to have a rapid, short-lived effect.

Overall, sample sizes were on average very small (more than one study had less than 10 participants per arm), which makes it difficult to draw meaningful conclusions. This resulted in wide confidence intervals, which lowered our confidence in the results for many of our outcomes by two levels according to GRADE. The lower limit for the confidence interval of the effect of ketamine on response at 24 hours when compared with placebo was compatible with a reasonably beneficial effect, so we considered this to

warrant downgrading by one level rather than two in view of the small sample size (Summary of findings for the main comparison). It is also problematic to make comparisons between ketamine and the two other drugs, owing to the indirectness of this evidence.

An important factor to take into consideration is the bias that may have occurred in blinding procedures. Given the profile of ketamine and its psychotomimetic side effects, participants and personnel may not have remained blinded to treatment arm allocation, despite attempts to blind them. Neither of the two included studies assessing the efficacy of ketamine tested the blind or provided any information relating to whether the intended blinding was effective, but Diazgranados 2010 recognised the potential of the dissociative effects to compromise study blinding. This should be considered a major limitation for all ketamine studies, which is likely to result in a biased assessment of the intervention effect.

The retrieved data were also limited in their scope owing to study limitations. Substantial variation among the included studies was seen regarding concomitant medications. One study allowed other psychotropic medications to be taken throughout the trial (Anand 2012), whilst others had strict washout periods (excepting relevant mood stabilisers) which varied in length. All studies required participants to receive mood stabilisers alongside the glutamate receptor modulator, but some participants were already taking these (and showing 'inadequate response'), whilst others began doing so after screening. This is a particular problem when it is considered that several studies only assessed participants against inclusion criteria at screening, rather than before the start of treatment. This could mean that an observed response for some participants was a result of the new mood stabiliser rather than the experimental drug. Dosages and titration schedules also differed, an issue which may have caused some conflicting results in the memantine studies.

The quality of the evidence in the present review ranged from low to very low according to the GRADE approach and this information should be taken into account when interpreting results from this study.

Potential biases in the review process

We contacted the original study authors and were able to obtain supplemental data for the majority of included studies with unpublished information. Notwithstanding this, there are still outcome data missing from several of the preplanned analyses, which could have made an important contribution to this review with an impact on the final results. In order to include as much data as possible, we also imputed some dichotomous efficacy outcomes, using a validated method which has been employed in previous Cochrane reviews (Cipriani 2010; Cipriani 2012; Cipriani 2013b; Guaiana 2010; Magni 2013; Purgato 2014). All imputed data were sent to the study authors for confirmation before we entered them into Review Manager 5 (RevMan 2014) for the statistical analyses. In the two ketamine studies (Diazgranados 2010; Zarate 2012) there were no data for adverse events from before cross-over, so we included data from across both phases in order to include as much information as possible when assessing the tolerability of ketamine. The small number of included studies made it impossible to formally evaluate the potential for publication bias (i.e. with funnel plots). Whilst every effort was made to identify all relevant trials, we cannot rule out the possibility that unpublished trials remain unknown to us.

Agreements and disagreements with other studies or reviews

Other recently published reviews in the field have found that ketamine exerts a rapid effect that diminishes in efficacy around one to two weeks after infusion (Caddy 2014; Coyle 2015; Naughton 2014; Niciu 2014). These reviews, though, have generally collated findings from both major depressive disorder and bipolar disorder, which is problematic owing to their differences in both biological basis and symptom presentation. Moreover, all previous reviews considered cumulative data from cross-over studies. To overcome these limitations, in our review we tried to be as rigorous as possible, including only double-blind or single-blind randomised studies in bipolar depression and considering only data before crossing over in cross-over trials (we did this according to Higgins 2011a, in order to reduce the risk of a 'carry over' treatment effect). Other reviews have found differing effect sizes for unipolar depression and bipolar disorder, where the effect at 24 hours was significantly larger for the former and at 7 days was significantly larger for the latter (Coyle 2015). Our findings were different and, according to our results, ketamine could represent a treatment which is efficacious only in a very short time window and probably for a selected sample of patients. To the best of our knowledge, this is the first systematic review and meta-analysis specific to bipolar disorder which assesses the efficacy of all glutamate receptor modulators with such a high methodological standard.

As reported in other recent reviews, in terms of adverse events we did not manage to find very informative data (Coyle 2015; Naughton 2014; Niciu 2014). This is a relevant issue most of all for long-term treatment. Some observational studies reported persisting decrements in frequent ketamine users compared to other groups in spatial working memory and pattern recognition memory, a trend for poorer performance in verbal recognition memory and a reduction in the percentage correct on the pattern recognition memory task, with a greater number of errors on the spatial working memory task (Morgan 2010). Cognitive impairment is particularly important in patients with bipolar disorder (Bauer 2014). It is important to highlight, however, that the same tasks did not show an impairment in healthy volunteers following an acute dose of ketamine (Honey 2003), so it is likely that these adverse events may be a purely chronic effect.

AUTHORS' CONCLUSIONS

Implications for practice

Overall, this review provides very limited evidence for an antidepressant effect of acute administration of ketamine (as an add-on therapy to mood stabilisers) compared with placebo in bipolar depression. Our confidence in the findings of the review is limited by the low number of trials overall and contributing data to the meta-analysis for each comparison. The largest body of evidence included in a single forest plot was only two studies (see the ketamine versus placebo comparison). We found no evidence to support the use of other glutamate receptor modulators in bipolar depression.

The effect of ketamine was found to have a quick onset, which may be promising for clinical practice, but the effect was not long-lasting. An important clinical implication for ketamine in bipolar depression would be in cases where a rapid response is crucial, for instance in patients at high risk of deliberate self harm or suicide. However, the studies included in this review did not report adequate data about such important outcomes.

The two studies included in this review that compared ketamine to placebo administered ketamine intravenously, which poses problems in clinical application. The practicalities of the equipment, time and staff requirements limit the access and widespread clinical application. However, there may be potential for other methods of administration which would not pose as many challenges clinically, such as intranasal. A further important consideration is ketamine's psychotomimetic profile, which leads to question the abuse potential and liability in prescribing this drug to clinical populations.

In the present review, there was inconclusive information found on the side effect profile of ketamine, with the only available data being from both phases of cross-over trials. The adverse events documented from long-term ketamine abuse include cognitive impairment and bladder dysfunction. It is therefore important that both short- and long-term side effects are thoroughly evaluated in considering the clinical application of ketamine.

Implications for research

We assessed the quality of evidence in the present review as low to very low, according to GRADE. There were very few trials included overall and in each comparison, and sample sizes for each data point were usually very small. In order for robust conclusions to be drawn regarding the antidepressant effects of this drug in bipolar disorder, studies that are of a high methodological standard are required, with larger sample sizes and longer follow-up periods. In order to generate high quality trials, future research should also focus on adequate blinding methods by using an active comparator. Additionally, there is a need for bipolar disorder studies which compare glutamate receptor modulators (and most of all, ketamine) with other active interventions, or as a monotherapy, in order to draw reliable conclusions about comparative efficacy between treatments.

Long-term adverse effects, particularly of repeated exposure to ketamine, remain a major concern in this area. The present review did not find conclusive evidence on the primary outcome of adverse events in ketamine, and it is therefore difficult to draw conclusions of the risk:benefit profile of the drug. Furthermore, the included studies involved only a single intravenous infusion. Morgan 2010 noted that frequent recreational users of the drug are more likely to show some cognitive impairments (such as impaired spatial working memory), dissociative and delusional symptoms, and even, interestingly, elevated depression scores. Therefore, further research is needed in order to assess the short- and long-term side effect profile of ketamine.

In the present review the included ketamine studies both administered the drug as a single intravenous dose, of which the practical limitations are outlined above. Preliminary evidence has suggested potential efficacy of other methods of administration, such as intranasal and intramuscular. It is, however, clear that further high quality research is needed to explore the efficacy and side effect profile of other forms of administration.

The longest trial included in this review examining the efficacy of ketamine was two weeks, which emphasises the short-term nature of the trials to date. There may be potential to sustain ketamine's antidepressant effects through repeated administrations or combination treatment regimes, such as the delivery of psychotherapy or other medications following ketamine administration. Future research should therefore focus on conducting longer-term trials and study ways in sustaining ketamine's antidepressant effects.

It would be beneficial for future research to assess whether (and how) glutamate receptor modulator efficacy would differ between bipolar I and bipolar II patients, which is an important factor that has not yet been considered. More research addressing the factors which distinguish bipolar depression from unipolar depression is necessary. The difference between individual diagnoses is an area which still requires consideration, as it is as yet unclear the role that bipolar versus unipolar diagnosis can play in treatment response to ketamine. In fact, antidepressants are generally not very efficacious in the bipolar disorder population (Taylor 2014) and some studies have found more success in patients with a family and/or personal history of alcohol dependence (Phelps 2009), which is promising considering that this is commonly comorbid with bipolar disorder.

In the presently reviewed studies, there is inconsistency regarding the allowance of concomitant medication. This is something worth focusing on in future bipolar research, owing to the frequent use of mood stabilisers in clinical practice. In particular, researchers should ensure that any observed effects cannot be attributed to mood stabilisers by only recruiting patients who have failed to show an adequate response to their current mood stabiliser (as in

Zarate 2012 and Diazgranados 2010), and should move towards a strict definition for this.

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Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Servive (NHS), or the Department of Health.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anand 2012

Methods	Double-blind, randomised controlled trial
Participants	**Diagnosis:** DSM-IV bipolar disorder; HRSD score ≥ 15; current depressed episode **N:** 29 (outpatients) **Age:** Memantine group M = 38 (SD = 15); placebo group M = 41 (SD = 14) **Sex:** Memantine group 9 female + 5 male; placebo group 8 females + 7 males. **Baseline depression severity:** Memantine group HRSD = 19 (SD = 4); placebo group HRSD = 19 (SD = 4)
Interventions	8 weeks of treatment 100 mg/day lamotrigine in both arms, with either memantine or placebo as add-on Memantine + lamotrigine - week 1: 5 mg/day then increased weekly (depending on tolerability) to max 20 mg/day Placebo + lamotrigine - capsules (Concomitant medication not mentioned) No washout period
Outcomes	Change in HRSD score Change in YMRS score Response rate (> 50% decrease in HRSD scores) Remission rate (final HRSD score < 8) Acceptability Adverse events Clinical global impression scores
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number list generated by statistician sent to pharmacy
Allocation concealment (selection bias)	Unclear risk	Reported as double-blind managed by pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Matching active and placebo capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Anand 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals reported
Selective reporting (reporting bias)	High risk	Missing time points on HRSD. No continuous data available
Other bias	High risk	'Blind was opened after ten subjects completed the study to examine the side-effect and tolerability profile of active memantine'

Diazgranados 2010

Methods	Randomised, double-blind placebo-controlled trial (cross-over)
Participants	**Diagnosis:** DSM-IV bipolar I or II depression without psychotic features; MADRS score ≥ 20; current major depressed episode for at least 4 weeks. **N:** 18 randomised. **Age:** 47.9 years (SD = 13.1) **Sex:** 12 females, 6 males. **Baseline depression severity:** Phase 1: Placebo group MADRS = 33.889 (SD = 4.833) ; ketamine group MADRS = 31.222 (SD = 4.410)
Interventions	Ketamine (9 in phase 1) vs placebo (9 in phase 1) as add-on treatment to valproate or lithium, as mood stabilisers (continued taking as usual, but no other treatment allowed) 2 weeks (study duration) ketamine = 0.5 mg/kg single intravenous dose Intravenous saline solution as placebo 2-week washout period
Outcomes	Change in MADRS scale HRSD-17 score BDI Visual Analogue Scale Hamilton Anxiety Rating Scale BPRS Clinician Administered Dissociative Scale YMRS Response rate (50% improvement from BL in MADRS) Remission rate (MADRS score < 10) Dropout rate Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Diazgranados 2010 (*Continued*)

Random sequence generation (selection bias)	Low risk	'Patients were randomly assigned to the order in which they received the two infusions by a random number chart'
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All staff, including the anaesthesiologist, were blind to whether placebo or drug was being administered. Study solutions were supplied in identical 50 ml syringes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates reported and 'n' given for each time point
Selective reporting (reporting bias)	Unclear risk	No results tables available in original publication. All requested data received through correspondence
Other bias	Unclear risk	No other bias was identified in this study, but this possibility cannot be ruled out

Lee 2014

Methods	Double-blind randomised controlled trial
Participants	**Diagnosis:** DSM-IV Bipolar II diagnosis, all with HRSD > 17 **N:** Memantine group: 115 Placebo group: 117 **Age:** Memantine group: 32.9 (SD = 12.02) Placebo group: 30.66 (SD = 11) **Sex:** Memantine group: 53 males, 62 females Placebo group: 65 males, 52 females **Baseline depression severity:** Memantine group: 19.20 (SD = 5.60) Placebo group: 19.22 (SD = 5.39)
Interventions	13 weeks trial of memantine vs placebo as add-on treatment to open-label valproate continuation (500 mg and 1000 mg daily) Low dose memantine (5 mg/day) for 12 weeks Concomitant benzodiazepine medication (lorazepam < 8mg) was used for night-time sedation and to treat agitation and insomnia. Up to 20 mg daily fluoxetine was permitted for associated depressive symptoms Patients claimed to have never taken antidepressants/antipsychotics and had no history of taking memantine or mood stabilisers (no washout period)

Lee 2014 (*Continued*)

Outcomes	Changes in depressive and manic symptoms (HRSD and YMRS scales) Adverse events Acceptability Effect of memantine on cytokine levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	'We conducted a double-blind placebo-controlled study'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Does not specify when dropout occurred or whether LOCF is used
Selective reporting (reporting bias)	Unclear risk	Only baseline and endpoint continuous data reported in text (measured at weeks 1, 2, 4, 8 and 12), but all reported graphically
Other bias	Unclear risk	No other bias was identified in this study, but this possibility cannot be ruled out

Yoon 2009

Methods	Randomised, double-blind placebo-controlled trial
Participants	**Diagnosis:** DSM-IV Bipolar I or II diagnosis, all in depressed phase with HRSD > 18 **N:** Cytidine group: 18 Placebo group: 17 **Age:** Cytidine group: 33.5 (SD = 7.7) Placebo group: 36.8 (SD = 10.7) **Sex:** Cytidine group: 9 males, 9 females Placebo group: 9 males, 8 females **Baseline depression severity:** Cytidine group: 23.3 (SD = 2.3) Placebo group: 23.1 (SD = 2.0)

Yoon 2009 (*Continued*)

Interventions	12-week trial of cytidine vs placebo as add-on treatment to valproate 1 mg twice per day of cytidine in capsules Placebo formulated as an inert fructose pill Valproate dosage changed until target plasma concentration achieved (50-100 mg/ml) over a 5-day period Minimum 1 week washout period before randomisation (from all antimanic drugs or mood stabilisers other than valproate) Zolpidem (5-10 mg per day) for bedtime sedation and concomitant medications for stable medical conditions were permitted
Outcomes	Changes in HRSD scores from baseline Response rate (> 50% reduction in HRSD scores from baseline) Acceptability Adverse events Changes in cerebral glutamate/glutamine levels
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	'double-blind'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants in each condition dropped out, but no information available on whether LOCF was used, etc
Selective reporting (reporting bias)	Unclear risk	Measurements taken at weeks 1, 2, 3, 4 and 8 but only baseline reported in tables. All reported graphically
Other bias	Unclear risk	No other bias was identified in this study, but this possibility cannot be ruled out

Zarate 2012

Methods	Double-blind randomised placebo-controlled cross-over study
Participants	**Diagnosis:** DSM-IV bipolar I or II diagnosis without psychotic features, currently experiencing a major depressive episode of at least 4 weeks. MADRS > 19 at screening and at the start of each infusion **N:** 15 randomised. **Age:** 46.7 years (SD = 10.4) **Sex:** 8 females, 7 males. **Baseline depression severity:** Ketamine group = 34.143 (SD = 5.429); Placebo group = 35.625 (SD = 5.854)
Interventions	Ketamine (7 in phase 1) vs placebo (8 in phase 1) as add-on treatment to either lithium or valproate within the specified range during the entirety of the study (levels obtained weekly) 0.5 mg/kg single dose intravenous ketamine infusions Placebo saline solution (0.9%) No concomitant treatment with psychotropic medications in 2 weeks before randomisation (5 weeks for fluoxetine) other than lithium or valproate (2 week washout period)
Outcomes	MADRs scores HRSD scores BDI scores Visual Analogue Scale Hamilton Anxiety Rating Scale BPRS Clinician Administered Dissociative Scale YMRS Adverse events Response rates (50% improvement from baseline on MADRS) Remission rates (MADRS < 10) Effects on suicidal ideation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned using a random number chart
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All staff, including the anaesthesiologist, were blind to whether placebo or drug was being administered. Study solutions were supplied in identical 50 ml syringes

Zarate 2012 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates recorded and 'n' provided for each time point
Selective reporting (reporting bias)	Unclear risk	No results tables available in original publication. All requested data received through correspondence
Other bias	Unclear risk	No other bias was identified in this study, but this possibility cannot be ruled out

BDI: Beck Depression Inventory
BL: Baseline
BPRS: Brief Psychiatric Rating Scale
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
HRSD: Hamilton Rating Scale for Depression
MADRS: Montgomery-Asberg Depression Rating Scale
YMRS: Young Mania Rating Scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Berk 2008	Incorrect diagnosis
Chen 2014	Incorrect diagnosis (not all depressed)
Cocchi 1977	Incorrect diagnosis (not all depressed)
Crane 1961	Incorrect diagnosis
Dean 2011	Secondary data publication of Berk 2008
Ehrensing 1978	Incorrect diagnosis (mixed with unipolar)
Ellis 2014	Wrong design
Lee 2012	Incorrect diagnosis (not all depressed)
Luckenbaugh 2014	Incorrect diagnosis (mixed with unipolar); secondary data

(*Continued*)

Magalhaes 2012	Secondary data publication of Berk 2008
NCT01684163	Wrong design

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT01306760

Methods	Double-blind, parallel randomised controlled trial
Participants	18-65 years Depression diagnosis + ECT referral no psychiatric comorbidities or neurological disease/cognitive impairment
Interventions	Ketamine vs propofol, both as anaesthetic with ECT
Outcomes	MADRS HRSD CANTAB (cognitive side effects)
Notes	Unclear if 'depression' diagnosis includes bipolar disorder

Rasmussen 2014

Methods	Single-blind, parallel randomised controlled trial
Participants	Inclusion criteria consisted of presence of a non-psychotic major depressive episode, whether unipolar or bipolar. Only patients providing their own consent for ECT were approached for the study. Excluded were patients diagnosed with any psychotic or major neurological disorder
Interventions	Ketamine vs methohexital, both as anaesthetic with ECT
Outcomes	PHQ-9 HADS MMSE Baseline and after treatments 2, 4 and 6 Side effects Blood pressure and pulse
Notes	Unclear on proportion of participants with bipolar disorder

CANTAB: Cambridge Neuropsychological Test Automated Battery
ECT: Electroconvulsive Therapy
HADS: Hospital Anxiety and Depression Scale
HRSD: Hamilton Rating Scale for Depression

MADRS: Montgomery-Asberg Depression Rating Scale
MMSE: Mini Mental State Examination
PHQ-9: Patient health questionnaire 9

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12612000830897

Trial name or title	Mitochondrial agents in the treatment of bipolar disorder
Methods	Three-arm, parallel randomised controlled trial
Participants	DSM-IV bipolar disorder, current depressive phase (MADRS < 19), stable other therapy, 18+
Interventions	1. NAC capsules for 16 weeks (500 mg twice a day) 2. Acetyl L carnitine 500 mg + mitochondrial combination capsule + cardonutrient capsule for 16 weeks 3. Placebo treatment for 16 weeks
Outcomes	BL and every 4 weeks afterwards (6 visits) MADRS BDRS HAM-A YMRS Impairment Functioning Tool SOFAS QLES-Q CGI BP and CGI-I Patient global impressions scale Change in blood oxidative and inflammatory markers
Starting date	4/3/2013
Contact information	Professor Michael Berk Mental Health Swanston Centre PO BOX 281 GEELONG VIC 3220 mikebe@barwonhealth.org.au
Notes	Recruiting

ISRCTN14689382

Trial name or title	Ketamine augmentation of ECT to improve outcomes in depression
Methods	Parallel RCT
Participants	Current DHRSD: Hamilton Rating Scale for DepressionSM-IV diagnosis of a major depressive episode, moderate or severe as part of unipolar or bipolar disorder mood disorder 18+ years old Verbal IQ more than or equal to 85

ISRCTN14689382 (*Continued*)

Interventions	Ketamine hydrochloride injection vs saline solution
Outcomes	HVLT-R, AMI-SD, COWAT MVG complex figure, GSE-My MADRS more than or equal to 10 Number of ECT treatments to achieve response (50% MADRS decrease from baseline) CGI-S, CGI-I
Starting date	1/5/2012
Contact information	ian.anderson@manchester.ac.uk
Notes	Ongoing

NCT01881763

Trial name or title	Ketamine as an augmentation strategy for electroconvulsive therapy (ECT) in depression
Methods	Double-blind, parallel randomised controlled trial
Participants	DSM-IV unipolar or bipolar depression, 18-70 years HRSD > 21 pre-treatment MADRS > 19 at screening
Interventions	Ketamine vs methohexital (both IV)
Outcomes	Time to achieve remission (HRSD-24) Cognitive side effects
Starting date	June 2010
Contact information	Contact: Styliani Kaliora, M.D. skaliora@nshs.edu
Notes	Recruiting

BDI: Beck Depression Inventory
BDRS: Bipolar Depression Rating Scale
BL: Baseline
BPRS: Brief Psychiatric Rating Scale
CGI-I: Clinical Global Impression - Global Improvement
CGI-BP: Clinical Global Impression - Bipolar
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ECT: Electroconvulsive Therapy
HADS: Hospital Anxiety and Depression Scale
HAMA: Hamilton Anxiety Rating Scale
HRSD: Hamilton Rating Scale for Depression

MADRS: Montgomery-Asberg Depression Rating Scale
MMSE: Mini Mental State Examination
NAC: N-acetyl cysteine
PHQ-9: Patient health questionnaire 9
Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire
SOFAS: Social and Occupational Functioning Assessment Scale
YMRS: Young Mania Rating Scale

DATA AND ANALYSES

Comparison 1. Ketamine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response rate	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 at 24 hours	2	33	Odds Ratio (M-H, Random, 95% CI)	11.61 [1.25, 107.74]
1.2 at 3 days	2	33	Odds Ratio (M-H, Random, 95% CI)	8.24 [0.84, 80.61]
1.3 at 1 week	1	18	Odds Ratio (M-H, Random, 95% CI)	4.0 [0.33, 48.66]
2 Remission rate	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 at 24 hours	2	33	Odds Ratio (M-H, Random, 95% CI)	5.16 [0.51, 52.30]
2.2 at 3 days	2	33	Odds Ratio (M-H, Random, 95% CI)	3.62 [0.34, 38.60]
2.3 at 1 week	1	18	Odds Ratio (M-H, Random, 95% CI)	3.35 [0.12, 93.83]
3 Depression rating scale score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 at 24 hours	2	32	Mean Difference (IV, Fixed, 95% CI)	-11.81 [-20.01, -3.61]
3.2 at 3 days	2	31	Mean Difference (IV, Fixed, 95% CI)	-9.10 [-14.00, -2.21]
3.3 at 1 week	2	28	Mean Difference (IV, Fixed, 95% CI)	-0.88 [-5.88, 4.12]
3.4 at 2 weeks	2	26	Mean Difference (IV, Fixed, 95% CI)	-1.14 [-6.30, 4.01]
4 Acceptability - total dropouts	2	33	Odds Ratio (M-H, Random, 95% CI)	3.48 [0.56, 21.74]
5 Acceptability - lack of efficacy	2	33	Odds Ratio (M-H, Random, 95% CI)	5.65 [0.76, 41.87]

Comparison 2. Memantine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response rate	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 at 1 week	1	29	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.06, 19.05]
1.2 at 2 weeks	1	29	Odds Ratio (M-H, Random, 95% CI)	4.88 [0.78, 30.29]
1.3 at 4 weeks	1	29	Odds Ratio (M-H, Random, 95% CI)	5.33 [1.02, 27.76]
1.4 at 3 months	2	261	Odds Ratio (M-H, Random, 95% CI)	1.66 [0.69, 4.03]
2 Adverse events: Young Mania Rating Scale (12 weeks)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Remission rate	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 at 1 week	1	29	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.06, 19.05]
3.2 at 2 weeks	1	29	Odds Ratio (M-H, Random, 95% CI)	1.77 [0.25, 12.60]
3.3 at 4 weeks	1	29	Odds Ratio (M-H, Random, 95% CI)	3.67 [0.77, 17.43]
3.4 at 3 months	2	261	Odds Ratio (M-H, Random, 95% CI)	1.74 [0.68, 4.46]
4 Depression rating scale score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 at 3 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Suicidality: suicide attempts	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6 Acceptability - total dropouts	2	261	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.45, 1.31]
7 Acceptability - lack of efficacy	2	261	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.18, 2.02]
8 Acceptability - adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 3. Cytidine versus placebo

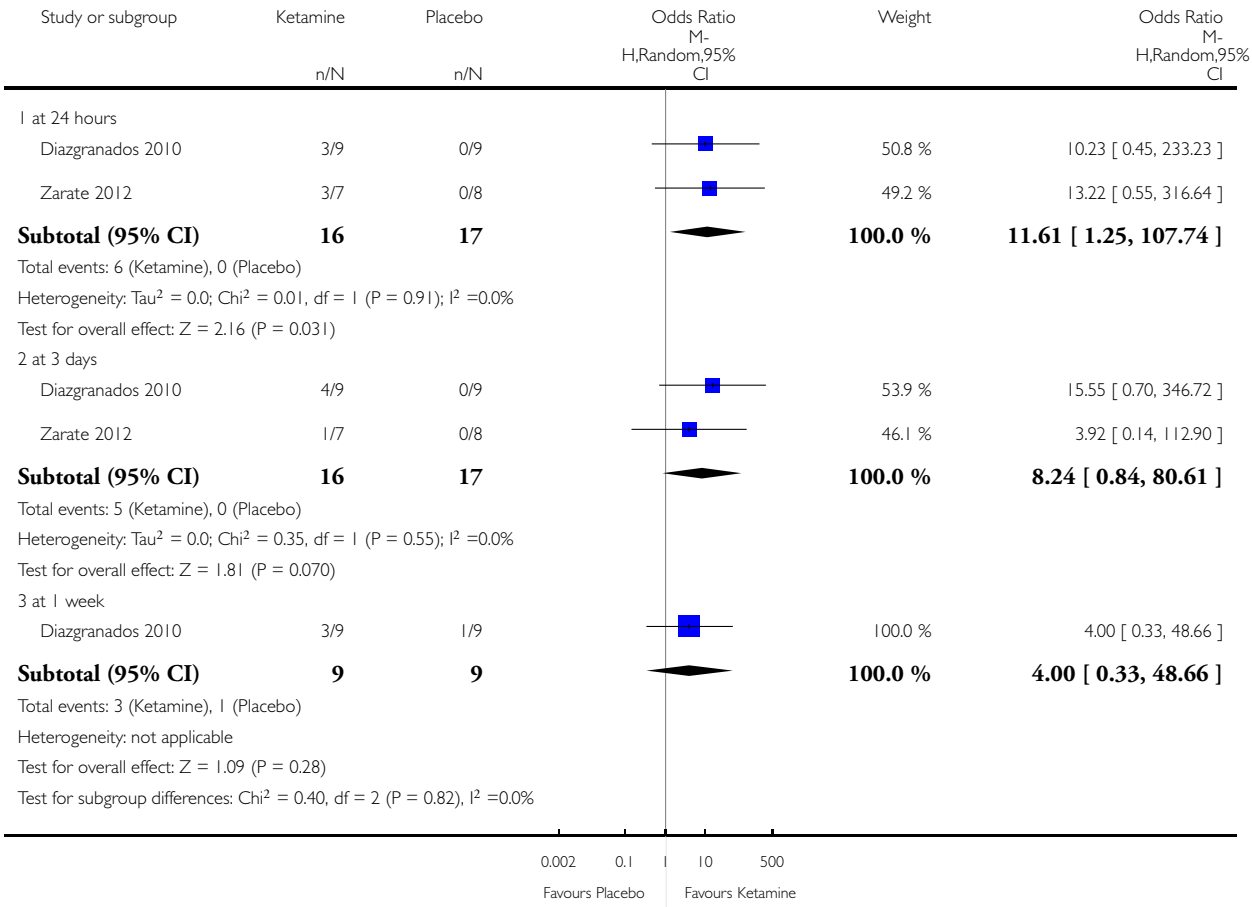
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 at 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Acceptability - total dropouts	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Ketamine versus placebo, Outcome 1 Response rate.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 1 Ketamine versus placebo

Outcome: 1 Response rate

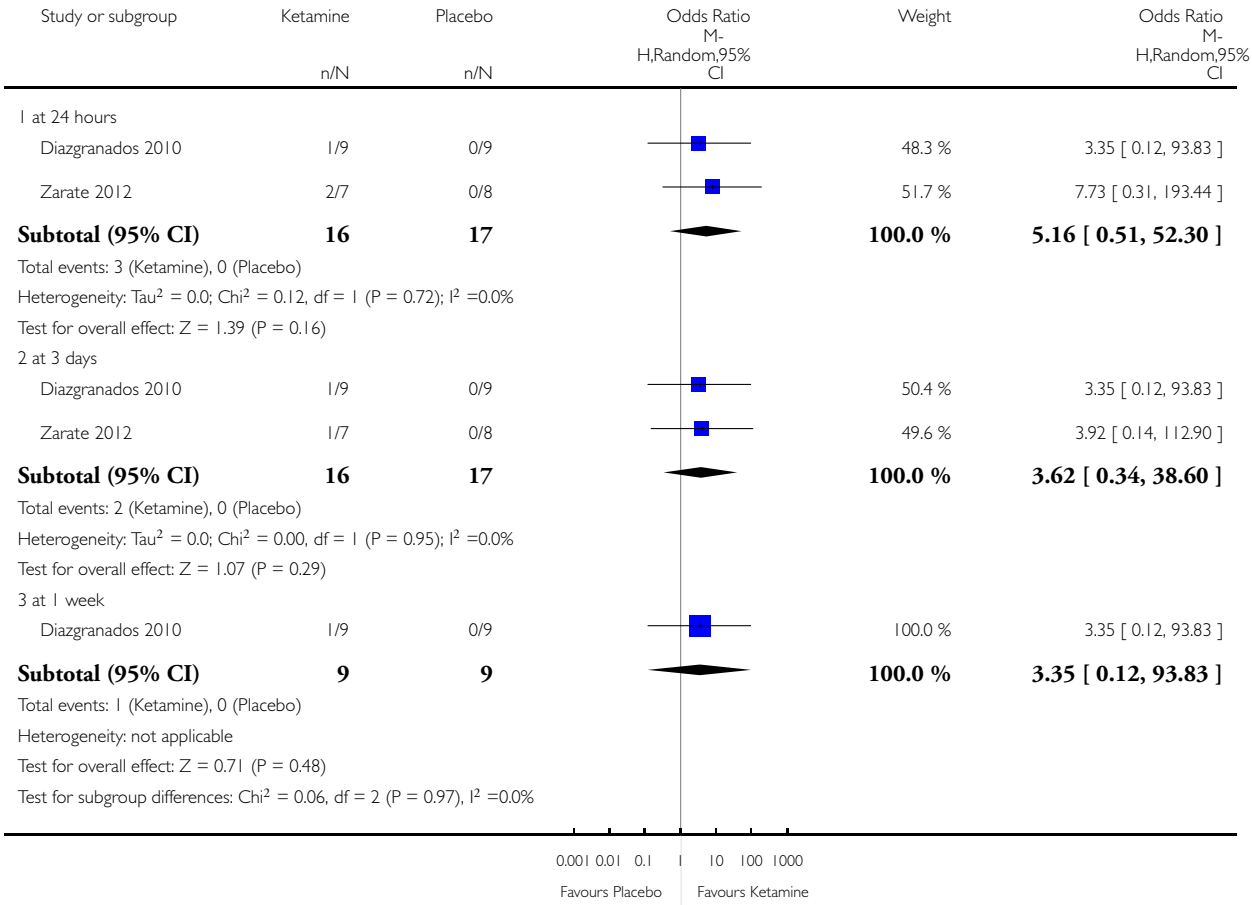


Analysis 1.2. Comparison 1 Ketamine versus placebo, Outcome 2 Remission rate.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 1 Ketamine versus placebo

Outcome: 2 Remission rate

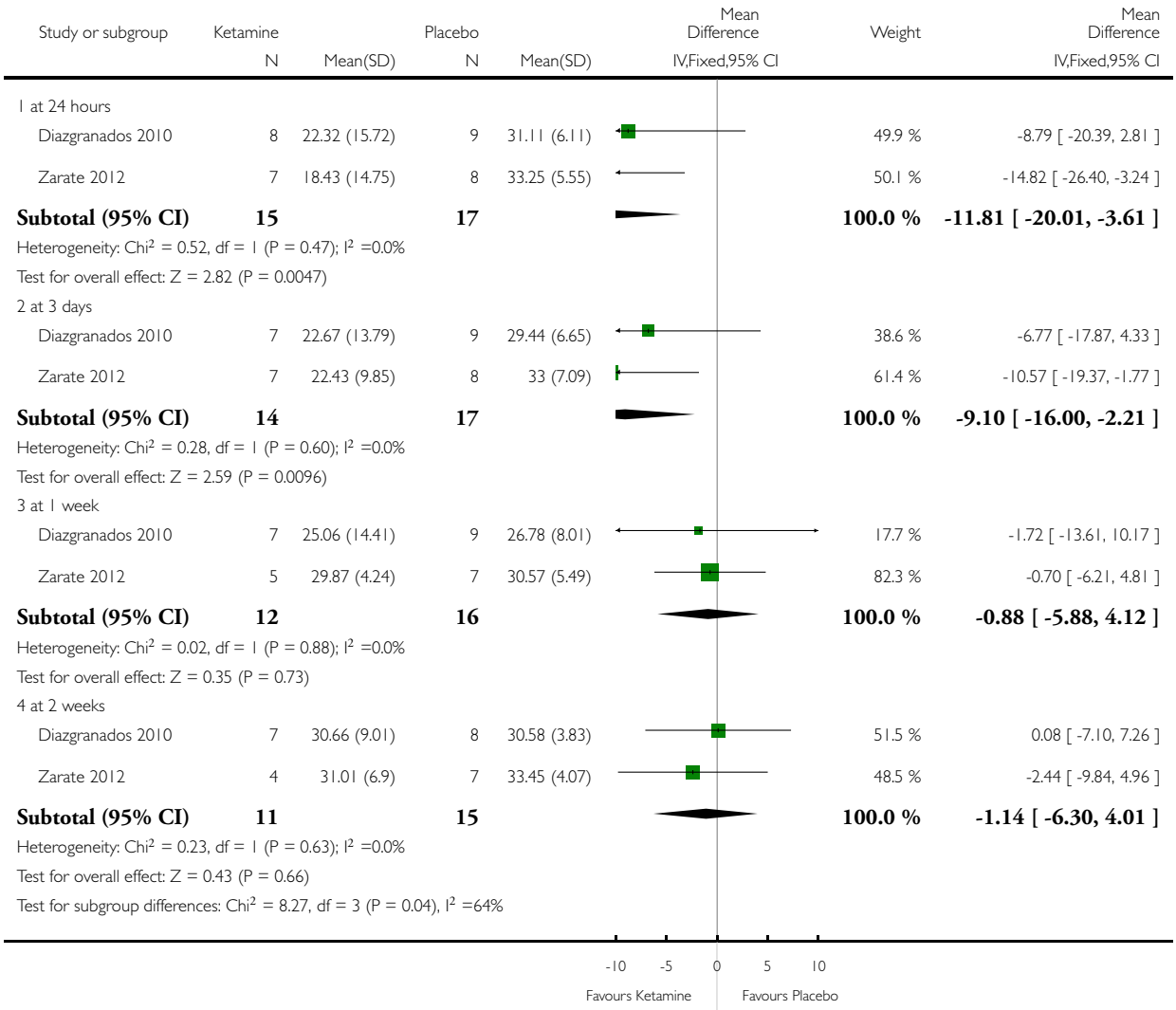


Analysis 1.3. Comparison 1 Ketamine versus placebo, Outcome 3 Depression rating scale score.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 1 Ketamine versus placebo

Outcome: 3 Depression rating scale score

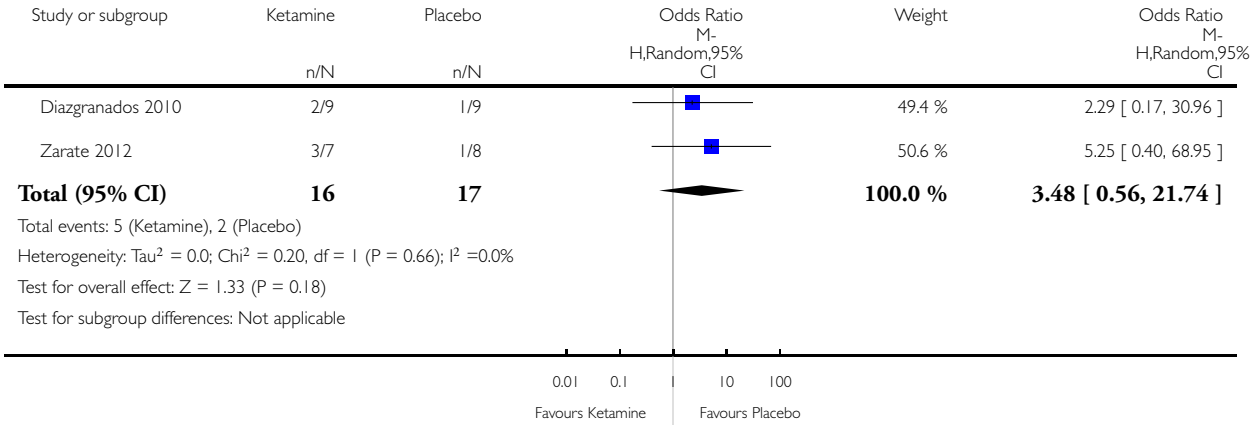


Analysis 1.4. Comparison 1 Ketamine versus placebo, Outcome 4 Acceptability - total dropouts.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 1 Ketamine versus placebo

Outcome: 4 Acceptability - total dropouts

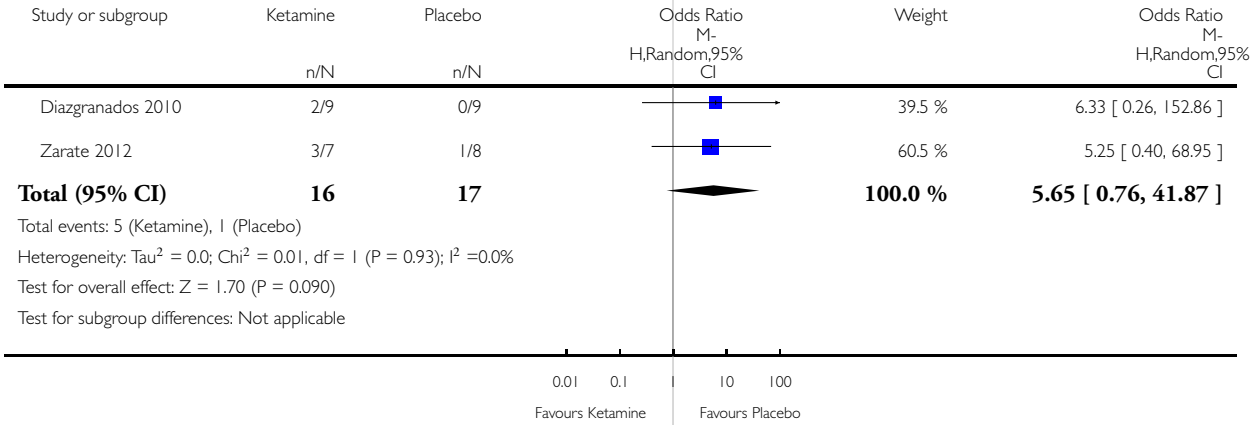


Analysis 1.5. Comparison 1 Ketamine versus placebo, Outcome 5 Acceptability - lack of efficacy.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 1 Ketamine versus placebo

Outcome: 5 Acceptability - lack of efficacy

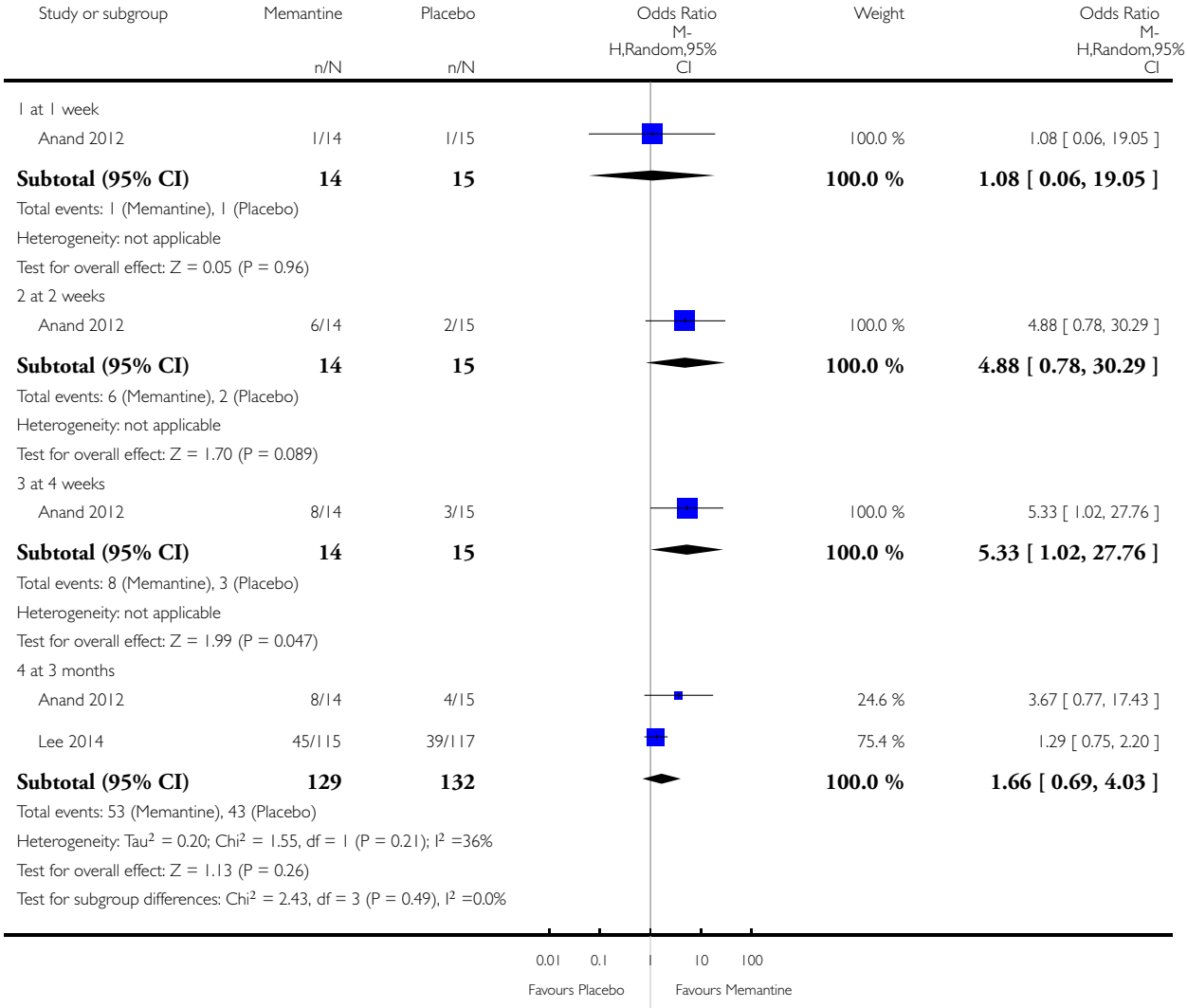


Analysis 2.1. Comparison 2 Memantine versus placebo, Outcome 1 Response rate.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 2 Memantine versus placebo

Outcome: 1 Response rate

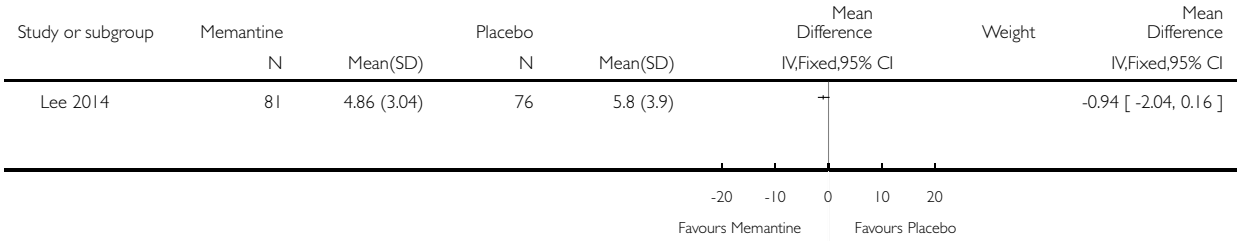


Analysis 2.2. Comparison 2 Memantine versus placebo, Outcome 2 Adverse events: Young Mania Rating Scale (12 weeks).

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 2 Memantine versus placebo

Outcome: 2 Adverse events: Young Mania Rating Scale (12 weeks)

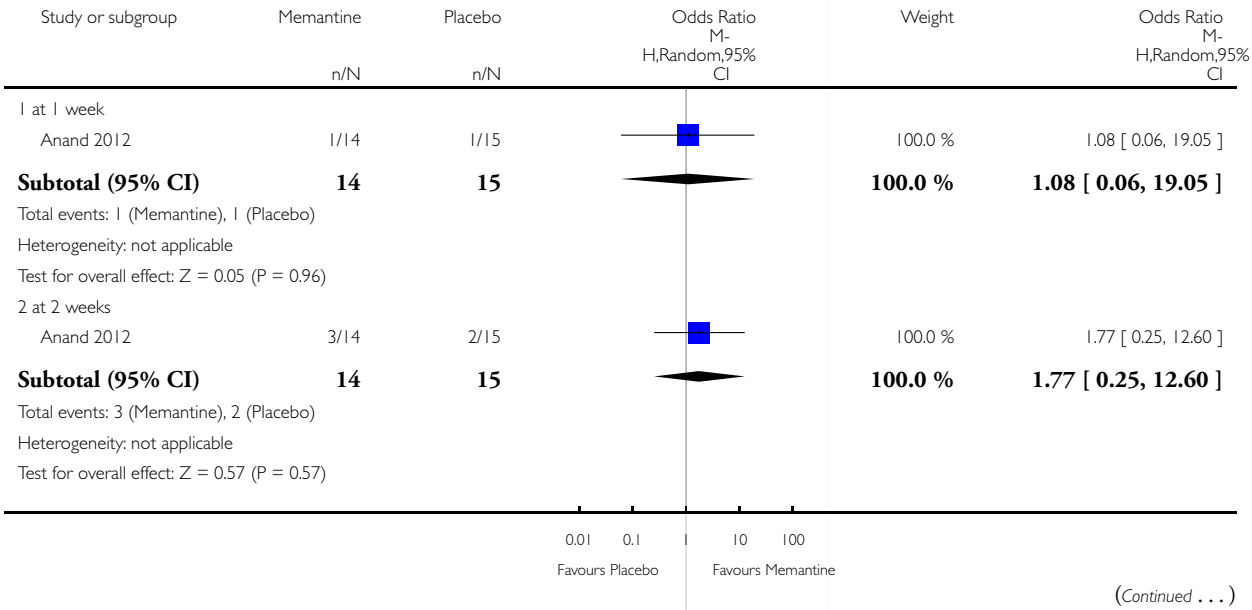


Analysis 2.3. Comparison 2 Memantine versus placebo, Outcome 3 Remission rate.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 2 Memantine versus placebo

Outcome: 3 Remission rate



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Study or subgroup	Memantine n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
3 at 4 weeks					
Anand 2012	8/14	4/15		100.0 %	3.67 [0.77, 17.43]
Subtotal (95% CI)	**14**	**15**		**100.0 %**	**3.67 [0.77, 17.43]**
Total events: 8 (Memantine), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.63 (P = 0.10)					
4 at 3 months					
Anand 2012	7/14	3/15		25.0 %	4.00 [0.77, 20.67]
Lee 2014	37/115	31/117		75.0 %	1.32 [0.75, 2.32]
Subtotal (95% CI)	**129**	**132**		**100.0 %**	**1.74 [0.68, 4.46]**
Total events: 44 (Memantine), 34 (Placebo)					
Heterogeneity: Tau^2 = 0.23; Chi^2 = 1.57, df = 1 (P = 0.21); I^2 =36%					
Test for overall effect: Z = 1.15 (P = 0.25)					
Test for subgroup differences: Chi^2 = 0.86, df = 3 (P = 0.84), I^2 =0.0%					

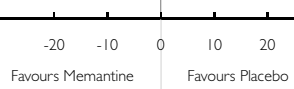
Analysis 2.4. Comparison 2 Memantine versus placebo, Outcome 4 Depression rating scale score.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 2 Memantine versus placebo

Outcome: 4 Depression rating scale score

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 at 3 months						
Lee 2014	81	8.84 (6.47)	76	9.44 (6.51)		-0.60 [-2.63, 1.43]

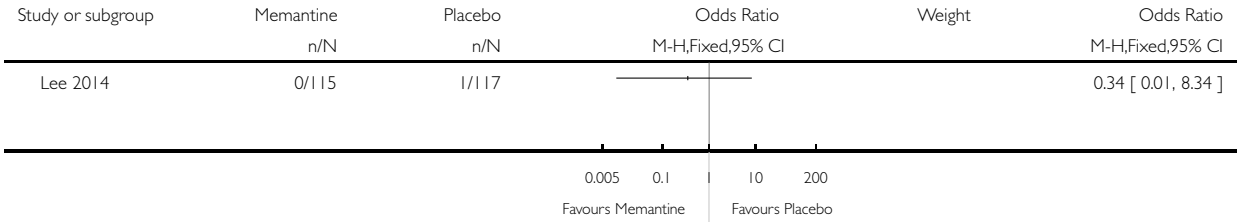


Analysis 2.5. Comparison 2 Memantine versus placebo, Outcome 5 Suicidality: suicide attempts.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 2 Memantine versus placebo

Outcome: 5 Suicidality: suicide attempts

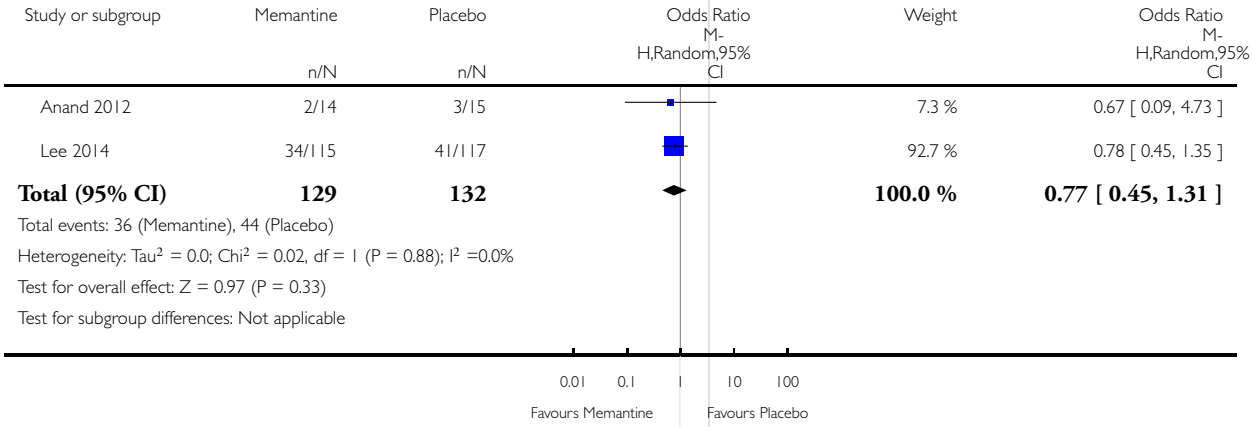


Analysis 2.6. Comparison 2 Memantine versus placebo, Outcome 6 Acceptability - total dropouts.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 2 Memantine versus placebo

Outcome: 6 Acceptability - total dropouts

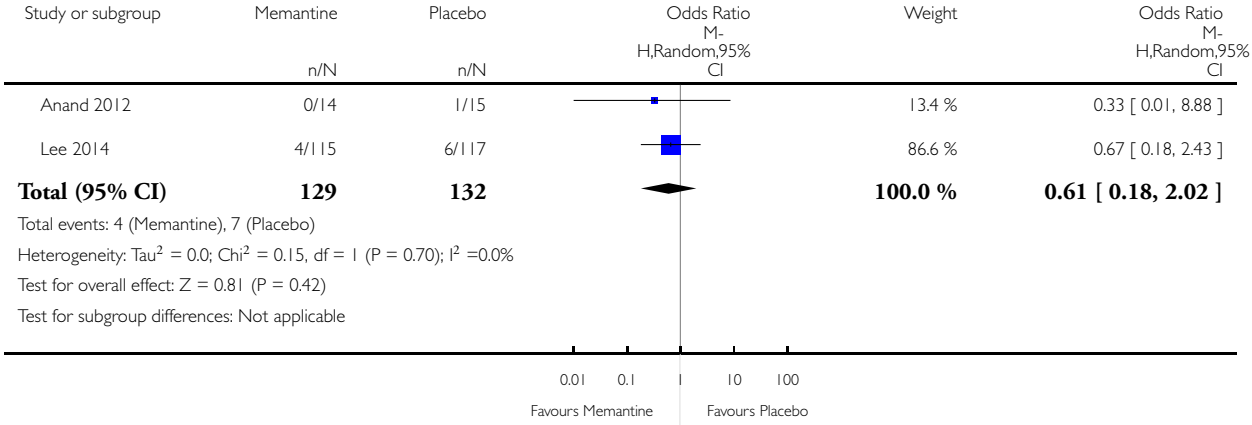


Analysis 2.7. Comparison 2 Memantine versus placebo, Outcome 7 Acceptability - lack of efficacy.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 2 Memantine versus placebo

Outcome: 7 Acceptability - lack of efficacy

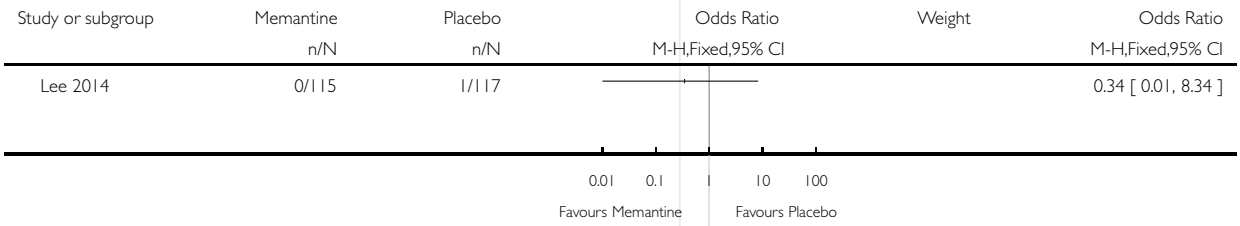


Analysis 2.8. Comparison 2 Memantine versus placebo, Outcome 8 Acceptability - adverse events.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 2 Memantine versus placebo

Outcome: 8 Acceptability - adverse events



Analysis 3.1. Comparison 3 Cytidine versus placebo, Outcome 1 Response rate.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 3 Cytidine versus placebo

Outcome: 1 Response rate

Study or subgroup	Cytidine n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 at 3 months				
Yoon 2009	9/18	8/17		1.13 [0.30, 4.24]

Analysis 3.2. Comparison 3 Cytidine versus placebo, Outcome 2 Acceptability - total dropouts.

Review: Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults

Comparison: 3 Cytidine versus placebo

Outcome: 2 Acceptability - total dropouts

Study or subgroup	Cytidine n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Yoon 2009	2/18	2/17			0.94 [0.12, 7.52]

ADDITIONAL TABLES

Table 1. Adverse events

Adverse event	Study	Glutamate receptor modulator		Comparator		Odds ratio, random-effects (95% CI)
		Events	Total	Events	Total	
Ketamine versus placebo						
Neuropsychiatric						
Agitation/ anxiety	Zarate 2012	1	14	2	12	0.38 [0.03 to 4.87]
Cognitive impairments	Diazgranados 2010	1	17	1	16	0.94 [0.05 to 16.37]
Concentration difficulties	Zarate 2012	1	14	1	12	0.85 [0.05 to 15.16]
Difficulty speaking	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Dissociative symptoms	Diazgranados 2010	1	17	0	16	3.00 [0.11 to 79.13]
Dizziness	Diazgranados 2010; Zarate 2012	4	31	3	28	1.22 [0.25 to 5.94]
Fearful	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Feeling spacey	Diazgranados 2010	1	17	2	16	0.44 [0.04 to 5.36]
Feeling strange/ weird/bizarre	Diazgranados 2010	0	17	1	16	0.30 [0.01 to 7.79]
Insomnia	Zarate 2012	9	14	5	12	2.52 [0.52 to 12.30]
Noise sensitivity	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Sleepiness/ drowsiness	Diazgranados 2010; Zarate 2012	7	31	5	28	1.33 [0.37 to 4.80]
Slowed	Zarate 2012	0	14	1	12	0.26 [0.01 to 7.12]

Table 1. Adverse events (*Continued*)

Vivid dreams	Diazgranados 2010; Zarate 2012	4	31	1	28	3.06 [0.44 to 21.01]
Gastrointestinal						
Appetite decrease	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Diarrhoea	Zarate 2012	1	14	0	12	2.78 [CI 0.10 to 74.70]
Dry mouth	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Flatulence	Zarate 2012	2	14	0	12	5.00 [0.22 to 115.05]
Nausea	Diazgranados 2010	1	17	0	16	3.00 [0.11 to 79.13]
Stomach/abdominal discomfort	Zarate 2012	1	14	1	12	0.85 [CI 0.05 to 15.16]
Stool discolouration	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Weight loss	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Respiratory						
Coughing	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Somatic						
Breast pain/swelling	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Decreased body temperature	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Flushed	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Increased body temperature	Zarate 2012	0	14	1	12	0.26 [0.01 to 7.12]
Leg cramping	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Muscle/bone/joint pain	Zarate 2012	0	14	4	12	0.07 [0.00 to 1.36]

Table 1. Adverse events (*Continued*)

Sweating	Zarate 2012	1	14	0	12	(OR 2.78, 95% CI 0.10 to 74.70)
Genitourinary						
Decreased libido	Zarate 2012	0	14	1	12	0.26 [0.01 to 7.12]
Increased libido	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Dermatological						
Dermatological/skin irritation/lesions	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Red blotching	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Cardiovascular						
Tachycardia	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Neurological						
Headache	Zarate 2012	3	14	3	12	0.82 [0.13 to 5.08]
Tremor	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Endocrine						
Menstrual irregulation	Zarate 2012	1	14	0	12	2.78 [0.10 to 74.70]
Memantine versus placebo						
Neuropsychiatric						
Dizziness	Lee 2014	0	115	1	117	0.34 [0.01 to 8.34]
Mania/ hypomania	Anand 2012	2	14	3	15	0.67 [0.09 to 4.73]
Gastrointestinal						
Gastrointestinal problems	Anand 2012	5	14	3	15	2.22 [0.42 to 11.83]
Respiratory						

Table 1. Adverse events (*Continued*)

Respiratory problems	Anand 2012	1	14	1	15	1.08 [CI 0.06 to 19.05]
Somatic						
Hair loss	Lee 2014	0	115	1	117	0.34 [0.01 to 8.34]
Genitourinary						
Sexual issues	Anand 2012	1	14	0	15	3.44 [0.13 to 91.79]
Urination problems	Anand 2012	0	14	1	15	0.33 [0.01 to 8.88]
Cardiovascular						
Cardiovascular problems	Anand 2012	1	14	3	15	0.31 [0.03 to 3.38]
Endocrine						
Endocrine problems	Anand 2012	1	14	0	15	3.44 [0.13 to 91.79]
Miscellaneous						
Central nervous system issues	Anand 2012	10	14	11	15	0.91 [0.18 to 4.64]
Immunological issues	Anand 2012	0	14	1	15	0.33, [0.01 to 8.88]
Cytidine versus placebo						
Neuropsychiatric						
Agitation/ anxiety	Yoon 2009	1	18	0	17	3.00 [CI 0.11 to 78.81]
Dizziness	Yoon 2009	0	18	1	17	0.30 [0.01 to 7.81]
Sleepiness/ drowsiness	Yoon 2009	2	18	1	17	2.00 [0.16 to 24.33]
Gastrointestinal						
Dry mouth	Yoon 2009	0	18	1	17	0.30 [0.01 to 7.81]

Table 1. Adverse events (*Continued*)

Gastrointestinal problems	Yoon 2009	2	18	2	17	0.94 [0.12 to 7.52]
Weight gain	Yoon 2009	1	18	0	17	3.00 [0.11 to 78.81]
Neurological						
Headache	Yoon 2009	3	18	2	17	1.50 [0.22 to 10.30]
Tremor	Yoon 2009	2	18	2	17	0.94 [0.12 to 7.52]

APPENDICES

Appendix 1. Adverse events search

Ketamine and other glutamate receptor modulators (OVID databases 11-Nov-2014)
OVID MEDLINE was searched using the following terms:
1. (adverse outcome* or complication* or drug fatalit* or drug hypersensitivity or drug reaction* or drug safety or drug tolerance or patient safety or safety or side effect* or contraindication*).ti,sh.
2. (safety or adverse or tolerability or tolerance or tolerat* or harm or harms or harmful or injur* or damage* or impair* complication* or risk or risks).ti,ab.
3. (side effect* or treatment emergent or undesirable effect*).ti,ab.
4. (suicid* or death*).mp.
5. (agitat* or constipat* or delusion* or diarrh* or dissociat* or dizz* or dry mouth or hallucinat* or headache* or hypoten* or hyperten* or insomni* or manic or mania or hypomani* or nause* or seizur* or sleep* or drows* or urin* or vomit* or temor*).ti,ab,sh.
6. ae.fs. *[Floating Subheading: Adverse Effects - MEDLINE]*
7. to.fs. *[Floating Subheading: Toxicity - MEDLINE]*
8. ct.fs. *[Floating Subheading: Contraindications - MEDLINE]*
9. or/1-8
10. (atomoxetine or "GLYX 13" or "MK 0657" or lanicemine or AZD6765 or rellidep).mp.
11. *Amantadine/ae,to
12. *Cycloserine/ae,to
13. *Dextromethorphan/ae,to
14. *Ketamine/ae,to
15. *Memantine/ae,to
16. *Quinidine/ae,to
17. Riluzole/ae,to
18. *Tramadol/ae,to
19. or/11-18
20. (amantadine or ketamine or dextromethorphan or memantine or riluzole or cycloserine or quinidine or tramadol).ti,sh.
21. (adverse outcome* or complication* or drug fatalit* or drug hypersensitivity* or drug reaction* or drug tolerance or safety or side effect* or contraindication* or tolerability or harm or harms or harmful or side effect* or treatment emergent or undesirable effect*).ti.
22. (depression or depressive or mood disorder* or affective disorder* or bipolar).ti,ab,sh.
23. exp animals/ not humans.sh.

24. exp *anesthesia
25. ((9 and 10 and 22) or ((19 or (20 and 21)) and 22)) not (23 or 24)

OVID EMBASE was searched using the following terms:

1. (adverse outcome* or complication* or drug fatalit* or drug hypersensitivity or drug reaction* or drug safety or drug tolerance or patient safety or safety or side effect* or contraindication*).ti,sh.
2. (safety or adverse or tolerability or tolerance or tolerat* or harm or harms or harmful or injur* or damage* or impair* complication* or risk or risks).ti,ab.
3. (side effect* or treatment emergent or undesirable effect*).ti,ab.
4. (suicid* or death*).mp.
5. (agitat* or constipat* or delusion* or diarrh* or dissociat* or dizz* or dry mouth or hallucinat* or headache* or hypoten* or hyperten* or insomni* or manic or mania or hypomani* or nause* or seizur* or sleep* or drows* or urin* or vomit* or temor*).ti,ab,sh.
6. ae.fs. *[Floating Subheading: Adverse Drug Reaction - EMBASE]*
7. to.fs. *[Floating Subheading: Drug Toxicity - EMBASE]*
8. or/1-7
9. ("GLYX 13" or "MK 0657" or lanicemine or AZD6765 or rellidep).mp.
10. *Amantadine/ae,to
11. *Atomoxetine/ae,to
12. *Cycloserine/ae,to
13. *Dextromethorphan/ae,to
14. *Ketamine/ae,to
15. *Memantine/ae,to
16. *Quinidine/ae,to
17. Riluzole/ae,to
18. *Tramadol/ae,to
19. or/10-18
20. (amantadine or atomoxetine or ketamine or dextromethorphan or memantine or riluzole or cycloserine or quinidine or tramadol).ti,sh.
21. (adverse outcome* or complication* or drug fatalit* or drug hypersensitivity* or drug reaction* or drug tolerance or safety or side effect* or contraindication* or tolerability or harm or harms or harmful or side effect* or treatment emergent or undesirable effect*).ti.
22. (depression or depressive or mood disorder* or affective disorder* or bipolar).ti,sh.
23. ((animal*1 or nonhuman) not (human*1 and (animal*1 or nonhuman))).sh.
24. exp *anesthesiological procedure/
25. ((8 and 9 and 22) or ((19 or (20 and 21)) and 22)) not (23 or 24)

OVID PsycINFO was searched using a more sensitive set of terms:

1. (adverse outcome* or complication* or drug fatalit* or drug hypersensitivity or drug reaction* or drug safety or drug tolerance or safety or side effect* or contraindication* or toxicity).ti,id,sh,tm.
2. (safety or adverse or tolerability or tolerance or tolerat* or harm or harms or harmful or injur* or damage* or impair* complication* or risk or risks or toxicity).ti,id,ab.
3. (side effect* or treatment emergent or undesirable effect*).ti,id,ab.
4. (suicid* or death*).ti,ab,id,sh,tm.
5. (agitat* or constipat* or delusion* or diarrh* or dissociat* or dizz* or dry mouth or hallucinat* or headache* or hypoten* or hyperten* or insomni* or manic or mania or hypomani* or nause* or seizur* or sleep* or drows* or urin* or vomit* or temor*).ti,ab,id,sh,tm.
6. or/1-5
7. (ketamin* or ketaject or ketalar or ketanest or ketaset or ketalean or vetalar or amantadin* or atomoxetine or "GLYX 13" or "MK 0657" or lanicemine or AZD6765 or rellidep or dextromethorphan or memantine or riluzole or cycloserine or quinidine or tramadol).ti,ab,id,sh.
8. N-Methyl-D-Aspartate/ or Tramadol/
9. or/7-8
10. (depression or depressive or mood disorder* or affective disorder* or bipolar).ti,ab,id,sh,tm.
11. (animal not ((human or inpatient or outpatient) and animal)).po.
12. (6 and 9 and 10) not 11

CONTRIBUTIONS OF AUTHORS

AC, RMcS, and KH conceived the review. AC, JR, CS, BHA, DB, JJ, CC, and PD selected the studies, appraised their quality, and extracted data. JJ, LH, and TMC entered the data into Review Manager 5 and AC carried out the analyses. TMC, CC, LH, and AC drafted the manuscript and all other authors critically reviewed the text.

DECLARATIONS OF INTEREST

AC, BHA, DB, JJ, CS, CC, TMC, JR, LH and KH report no competing interests.

Rupert McShane runs an NHS clinic using ketamine for treating resistant depression, is an investigator on trials of esketamine sponsored by Janssen, has led an NIHR-funded study of intravenous ketamine, is exploring alternative routes for ketamine and has received consultancy fees amounting to <£500 for advice concerning the care pathway for treatment resistant depression. He has no financial conflicts which directly relate to the production of this review.

PD worked as research assistant on a non-randomised study of ketamine for treatment-resistant depression.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In order to address the comments of the peer reviewers, we decided to use a different threshold for depression severity (25 rather than 27 on HRSD-17), and changed the references accordingly.

We removed the third objective, ('to investigate the adverse effects of ketamine and other glutamate receptor modulators in unipolar major depressive disorder, including general prevalence of adverse effects, compared with placebo or other antidepressant agents') in order to make it clearer that whilst we did the search for adverse events data, in the end we only included data from RCTs.

Extra detail was added about the implementation of the random-effects model in order to clarify methods used (see Data synthesis). The protocol stated: 'We will use a random-effects model because it has the highest generalisability for empirical examination of summary effect measures in meta-analyses (Furukawa 2002). We will routinely examine the robustness of this summary measure by calculating the fixed-effect model and random-effects model ORs. We will report material differences between the models. We will calculate the pooled MD or SMD as appropriate with corresponding 95% CI for continuous outcomes. We will also use the random-effects model for continuous outcomes. However, we will also routinely perform fixed-effect analyses to investigate the effect of the choice of method on the effect estimates. We will report material differences between the models.'

The following statement was added to the Types of interventions section: 'We did not include lamotrigine among the list of comparisons because the randomised evidence about this drug has been synthesised recently elsewhere (Thomas 2010; Zavodnick 2012)'.

We removed the statement: 'We will also conduct a cited reference search on the Web of Science'.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [*therapeutic use]; Bipolar Disorder [*drug therapy; psychology]; Cytidine [*therapeutic use]; Depression [*drug therapy; psychology]; Excitatory Amino Acid Antagonists [*therapeutic use]; Ketamine [*therapeutic use]; Memantine [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans