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ROUND THE CORNER

Ketamine: a novel antidepressant with a fast onset of action?†

COMMENTARY ON… COCHRANE CORNER

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†See pp. 214–215. For a discussion of the controversy surrounding ketamine as a rapid antidepressant, see Ho & Zhang, pp. 223–233, this issue.

SUMMARY

Glutamate receptor modulators, including ketamine, are possible candidates for new antidepressants with a novel mode of action. The pair of reviews discussed in this month's Round the Corner considered their use in treating unipolar major depression and bipolar depression. Promising results were seen for ketamine, but further studies are needed, in particular to investigate whether the benefits are sustained or can be extended by repeated or adjunctive treatment, whether ketamine is effective in treatment resistance, whether other modes of administration are as effective as the intravenous route and the long-term adverse effects of use.

DECLARATION OF INTEREST

None

Clinical setting

Major depressive disorder and bipolar disorder often take a chronic course and are associated with significant disability (World Health Organization 2008). They generally have a relapsing and remitting pattern, with significant impairment even during periods of remission (Conradi 2011). Pharmacological and psychological treatments are available but are not always effective, even when given adequate trials (Malhi 2015; Goodwin 2016).

Pharmacological treatments for unipolar depression focus on antidepressants (National Institute for Health and Care Excellence 2009). Their effects and side-effects vary, but the beneficial mood-elevating effects are thought to be mediated through increasing intra-synaptic levels of monoamines, including noradrenaline and serotonin. However, in the clinical setting, one-third of patients remain unwell even after several trials of antidepressants. These patients can be described as having 'treatment-resistant depression' and, although the exact definition of this term remains a matter of some debate (Malhi 2016), patients with this chronic and unremitting illness experience high levels of disability and mortality.

For bipolar depression, the treatment challenge is even greater. There is scarce evidence that antidepressants are effective as a first-line treatment (Sidor 2012), and mood instability is an additional challenge. Current recommendations (Kendall 2014) focus on the use of quetiapine; lamotrigine, fluoxetine plus olanzapine and lithium are also recommended. A recent trial (CEQUEL) demonstrated that there may be benefit in the combination of lamotrigine with quetiapine (Geddes 2016).

Although the differences in treatment response between unipolar and bipolar depression suggest underlying mechanistic differences, they nevertheless share common clinical features, including the central features of low mood and lack of interest and enjoyment. Feelings of guilt, lack of motivation, and anxiety and suicidal thoughts are also common to both. Both unipolar (Hawton 2009) and bipolar (Merikangas 2011) depression have an increased risk of suicide.

There is a clear need to investigate novel approaches to treatment for both unipolar and bipolar depression that might either enhance remission rates, or shorten the speed of therapeutic action or both. The shared symptom profiles across bipolar and unipolar depression suggest that there may be a common underlying pathway that could be the focus of new approaches.

Ketamine and other glutamate receptor modulators

In the search for novel targets in treating depression, investigation has turned to the glutamatergic system, as glutamate is involved in memory, learning and cognition. There is substantial evidence of abnormal glutamate conduction in depression (Altamura 1995). In addition, there is some evidence for the effectiveness of drugs that target the glutamate system, including lamotrigine in bipolar depression (Geddes 2009) and ketamine in major depression (McGirr 2014).

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist, as well as having effects on the cholinergic, opioid and monoamine transmitter

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systems. Animal data suggest that antagonism of NMDA receptors (a subpopulation of glutamate receptors) is associated with antidepressant effects (McGirr 2014). Ketamine was originally developed for the induction of anaesthesia. It has a low bioavailability orally, so the usual routes of administration are intravenous or intranasal. Following the initial report of a rapid but short-lived antidepressant effect of ketamine (Berman 2000), there have been further studies, but these have tended to be small with methodological variations. There has also been concern about potential adverse events (Caddy 2014); short-term side-effects include hallucinations, trance-like states and intoxication. In addition, longer-term use as a street drug is associated with cognitive side-effects and symptoms indicating damage to the bladder and lower urinary tract (including dysuria, increased urinary frequency and urgency, and haematuria) (Tsai 2009).

Methods

The two reviews considered in this commentary were published separately in the Cochrane Library, one investigating unipolar depression (Caddy 2015) and the other bipolar depression (McCloud 2015), but they used very similar methods. The reviewers searched (last update: January 2015) for double- or single-blind randomised controlled trials (RCTs) investigating the efficacy and acceptability of ketamine or other glutamate receptor modulators when compared to placebo, or to other pharmacological agents or electroconvulsive therapy (ECT) in adult patients (aged over 18). The reviewers decided not to include lamotrigine, as this had been assessed in other reviews (Thomas 2010; Zavodnick 2012). Comorbidity was allowed, as long as the primary disorder was depression. In mixed populations, studies were included in the unipolar analysis if 20% or less of the patients had bipolar depression, and *vice versa*.

The primary outcomes assessed were efficacy and adverse events. Efficacy was assessed as a 'dichotomous outcome' (Box 1),[a] by standard measures of either 'response' (such as a 50% reduction in Hamilton Rating Scale for Depression (HRSD) score) or 'remission' (such as a score of <17 on the HRSD-17), and as a 'continuous outcome' (Box 1), by assessing depression scores. The reviewers also examined suicidality, cognition, healthcare costs and acceptability (from the drop-out rate).

Results

The searches identified 25 studies of unipolar depression and 5 of bipolar depression. Of the 30 studies, 11 examined ketamine and 5 memantine. Ketamine was administered intravenously in all studies except one (Lapidus 2014), in which the drug was administered intranasally, and the majority of the remaining glutamate receptor modulators were administered orally. In the bipolar studies, participants continued on mood stabilisers, and some took concomitant antidepressants. In approximately half of the unipolar studies, patients received concomitant medication for their depression alongside the experimental intervention. Of interest, the unipolar review identified 41 ongoing trials and the bipolar review identified 3.

The quality of evidence from both reviews according to GRADE criteria (Box 2) was rated low to very low. In addition, comparisons between ketamine and placebo are limited by difficulty in maintaining the masking ('blinding') of

BOX 1 Dichotomous *v.* continuous data

Dichotomous data can only take one of two possible values. Examples include present/not present or smoker/non-smoker. In these reviews, dichotomous data were presented for response/non-response.

Continuous data have a potentially infinite number of possible values within a given range. Examples include height, weight and blood pressure. In these reviews, individual depression scores were used as continuous data.

Sometimes, continuous data are simplified into dichotomous data (e.g. age in years could become <65 years or ≥65 years). In these reviews, the continuous data of HRSD scores were simplified into the dichotomous outcome of remission/no remission, using a cut-off score of 17 on the HRSD-17. This simplifies the data, but means that results refer to only two groups, and there may be significant variation within each group. Thus, in this example, results relate to all patients who achieved remission (whatever their HRSD-17 score within that group) and all those who did not.

BOX 2 GRADE quality assessment

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (www.gradeworkinggroup.org), used by the Cochrane collaboration, NICE and publications such as the *BMJ*, assesses the quality of evidence according to the type and quality of the included trials. 'Low quality' indicates that further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate. 'Very low quality' indicates that reviewers are very uncertain about the estimate.

a. For Boxes 1, 2, 3 and 4, please see the Cochrane glossary (https://community.cochrane.org/glossary) and Cochrane handbook (http://handbook.cochrane.org) for more details.

TABLE 1 Summary statistics for significant results found in the two Cochrane reviews[a]

Comparison	Depressive disorder	Time of assessment	*N*	Statistics
Ketamine v. placebo	*Unipolar*			
Response		24 h	56	OR 10.77, 95% CI 2.00 to 58.00; *P*=0.006; NNTB=3
		72 h	56	OR 12.59, 95%CI 2.38 to 66.73; *P*=0.003; NNTB=3
		1 week	131	OR 2.58, 95% CI 1.08 to 6.16; *P*=0.03; NNTB=6; n=76
Confusion			76	OR 3.76, 95% CI 1.13 to 12.47; *P*=0.03; NNTH=4
Emotional blunting			30	OR 23.40, 95% CI 1.12 to 489.52; *P*=0.04; NNTH=3
Ketamine v. placebo	*Bipolar*			
Response		24 h	33	95% CI 2 to 10; NNTB=3
Depression scores		24 h	32	m.d. –11.81, 95% CI –20.01 to –3.61; *P*=0.005
		72 h	31	m.d. – 9.10, 95% CI –16.00 to –2.21; *P*=0.010
Ketamine v. midazolam	*Unipolar*			
Response		24 h	72	OR 0.36, 95% CI 0.14 to 0.58; *P*=0.002; NNTB=3
		72 h	72	OR 0.37, 95% CI 0.16 to 0.59; *P*=0.0005; NNTB=3
		1 week	72	OR 0.29, 95% CI 0.08 to 0.49; *P*=0.005; NNTB=3
Suicidal ideation score		Composite score	57	m.d. –1.32, 95% CI –2.52 to –0.12; *P*= 0.03
Ketamine v. thiopental	*Unipolar*			
Depression scores		72 h	29	m.d. –3.87, 95% CI –6.08 to –1.66; *P*=0.0006
Memantine v. placebo	*Bipolar*			
Response		4 weeks	29	OR 5.33, 95% CI 1.02 to 27.76; *P*=0.05; NNTB=3
Sarcosine v. citalopram	*Unipolar*	4 weeks	40	OR 6.93, 95% CI 1.53 to 31.38; *P*=0.01
Ketamine v. ECT	*Unipolar*	24 h	18	OR 28.00, 95% CI 2.07 to 379.25
		72 h	18	OR 12.25, 95% CI 1.33 to 113.06

CI, confidence interval; ECT, electroconvulsive therapy; m.d., mean difference; *N*, total number of participants; NNTB, number needed to benefit; NNTH, number needed to harm; OR, odds ratio.
a. Caddy *et al* (2015); McCloud *et al* (2015).

BOX 3 Number needed to benefit or harm

Number needed to treat to benefit (NNTB)

The NNTB is an estimate of how many people need to receive a treatment before one person would experience a beneficial outcome. For example, when comparing ketamine *v.* placebo for unipolar depression (Table 1), the data from 56 individuals suggest that you would need to give ketamine to 3 people before one person would experience response (a 50% reduction in their HRSD score) at 24 h. Thus, the NNTB at 24 h for response is 3.

Number needed to treat to harm (NNTH)

NNTH is an estimate of how many people need to receive a treatment before one more person would experience a harmful outcome or one fewer person would experience a beneficial outcome. For example, Table 1 shows that placebo caused less confusion than ketamine (OR 3.76, 95% CI 1.13 to 12.47; *P*=0.03; NNTH=4; *n*=76). Given NNTH=4, then after treating 4 patients with ketamine, one will experience confusion compared with 4 people on placebo.

Important notes

NNTs are always expressed as positive whole numbers, all decimals being rounded up (you cannot treat a fraction of a patient).

Each NNT is a comparative measure of effect (e.g. the effect of taking ketamine compared with the effect of taking placebo) and not a general property of a single intervention (e.g. ketamine).

The NNT gives an 'expected value'. For example, NNT=3 does not imply that one additional event will occur in each and every group of 3 people; it is that we expect this to occur.

NNTs are used for dichotomous outcomes (Box 1) as they refer to events (e.g. remission *v.* non-remission).

allocation. There are well documented short-term side-effects of intravenous ketamine that are not seen with intravenous saline, making it possible for the investigator and participant to guess the allocation. However, none of the ketamine studies assessed whether measures to ensure masking were effective.

Ketamine v. placebo

Unipolar studies

Compared with placebo, there was a significant difference in response in favour of intravenous ketamine (administered as a single infusion in 4 out of the 5 studies) at 24 h, at 72 h and at 1 week, but not at 2 weeks (Table 1). This finding was supported by similar findings for remission and change in depression scores. There were no data for suicidality, cognition or healthcare costs, and there were no differences in drop-out rates. There were significant differences in favour of placebo over ketamine in terms of confusion and emotional blunting, but no significant difference in terms of other adverse events.

Bipolar studies

The results were similar, in that ketamine was more effective than placebo, but the effects appeared to be shorter-lasting (Table 1 and Box 3). There was a significant difference in

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response in favour of a single intravenous dose of ketamine over placebo at 24 h, but this was no longer significant at 72 h or at 1 or 2 weeks. There was no evidence that ketamine was more effective than placebo in remission at any time point, but it was more effective than placebo on depression scores at 24 h and 72 h, but not at 1 or 2 weeks. Again, there were no significant differences between ketamine and placebo in acceptability, in terms of drop-out rates.

Ketamine v. active agents

For unipolar depression, numbers for comparisons of ketamine *v.* active agents were small. The results of one RCT ($n = 72$) suggested a favourable effect of ketamine over midazolam, with significant differences in response at 24 h, 72 h and 1 week (Table 1). Similar results were found for remission and depression scores. Interestingly, ketamine also had a beneficial effect on a composite score of suicidal ideation. There were no differences in drop-out rates, but ketamine showed an increase in side-effects of blurred vision, dizziness, general malaise and nausea/vomiting at 24 h post-infusion. In one small study of ketamine *v.* thiopental ($n = 29$), no participant met criteria for response or remission in either group, although ketamine was more efficient at changing depression scores at 72 h.

No data were available for bipolar depression.

Memantine v. placebo

Memantine was given orally in all studies, titrating from 5 mg/day in weekly increments as tolerated up to 20 mg/day, and compared with placebo. In studies of unipolar depression, there was no difference in response or depression scores at 1 or 2 weeks. Studies of bipolar depression found no difference in response or depression scores at 1 or 2 weeks. There was a marginally significant effect in favour of memantine at 4 weeks (Table 1), but no significant effect at 3 months. There was no significant difference in remission rates, depression scores or drop-out rates at any time point.

Other glutamate receptors

Single studies in unipolar depression of the following drugs *v.* placebo found no significant effect on response, remission or mean depression scores at various time points: atomoxetine, AZD6765 (lanicemine), CP-101,606 (traxoprodil), D-cycloserine, MK-0657, *N*-acetylcysteine, Org 26576, and riluzole. One trial of sarcosine ($n = 40$) showed a benefit in response at 4 weeks *v.* citalopram (Table 1), with similar effects in remission and depression scores.

A single study of cytidine *v.* placebo in bipolar depression found no significant effect on response to treatment.

Comparisons with ECT

One small study of unipolar depression ($n = 18$, rated as low quality) compared ketamine with ECT. Superior efficacy in response at 24 h and 72 h (Table 1) was found for ketamine as well as superior remission and depression scores at 24 h, 72 h, 1 week and 2 weeks. There was no difference in adverse events. There were no studies in bipolar depression.

Conclusions

Overall, the results were positive for ketamine, with evidence of efficacy over placebo. In unipolar depression, this effect was seen at time points up to 1 week in response, remission rate and end-point depression scores. The response rate and depression severity score effect reduced over time, but remission rate remained consistent up to 1 week. This suggests that ketamine has a rapid antidepressant effect (patients can be in remission within 24 h) and that those patients who remit early continue in remission up to 1 week. The results for bipolar depression were similar, but with a shorter effect. There has been clinical interest in whether ketamine could provide a safe and effective alternative to ECT, replicating the fast onset of therapeutic action. For unipolar depression, ketamine was more efficacious than ECT (up to 72 h) and no difference was found between ketamine and ECT in adverse events, but this was a very small sample size in a single study.

Findings from these reviews were limited by small sample sizes, low to very-low quality of evidence, and a lack of complete data on important outcomes, including response rates and side-effects. Studies varied in treatment-administration duration and route, and at what time points outcomes were assessed. In addition, although all participants met standard diagnostic criteria for a depressive episode, they varied in severity and degree of treatment resistance. Only five studies investigated bipolar depression.

The results for ketamine confirm previous reviews (McGirr 2014; Naughton 2014) in showing a rapid onset of antidepressant effect lasting up to 1 week. However, the previous reviews also included data from non-randomised studies and from both phases of cross-over trials, which may have overestimated the efficacy of ketamine owing to selection bias and carry-over treatment effect (Box 4). The current reviews reduced the potential for overestimation of effects by using only randomised evidence and evidence from the first phase of cross-over trials.

BOX 4 Cross-over trials and carry-over treatment effects

Cross-over trials compare two or more interventions, but each participant completes both courses of treatment, switching from one to the other half-way through the trial. For example, in a cross-over trial of ketamine and placebo, participants would be randomly allocated to groups receiving either first ketamine then placebo or first placebo then ketamine.

However, cross-over trials are at risk from carry-over treatment effects. These occur when treatment effects persist from one period into a later period of treatment.

For example, the effects of ketamine given in the first half of the trial might persist during the second half of the trial when placebo is being given. This affects the data recorded from the placebo arm, but only in those participants who received ketamine first.

One way to exclude this problem (as demonstrated by the analysis used in these reviews) is to use only the data from the first period of cross-over trials. This reduces the data available, but ensures that no carry-over effects are present.

Implications

For both unipolar and bipolar depression, these preliminary results suggest a rapid antidepressant effect of ketamine. An important clinical indication for ketamine in depression might therefore be where a rapid response is crucial, for example to reduce the risk of suicide or severe self-neglect, or in those with treatment resistance. However, given the variable reporting of the study details and outcome measures, it was not possible to separate out the results for those with severe depression and/or treatment resistance in order to investigate the comparative efficacy of ketamine in these high-risk groups. Reduction in suicidal ideation after ketamine was assessed and found in only one RCT in this review (ketamine *v.* midazolam; Price 2014), and so further data are required. However, open-label studies investigating suicidal ideation and anhedonia suggest that both are reduced after acute intravenous ketamine (Schwartz 2016). Further studies are needed to assess whether this effect is related to the antidepressant effect or is independent of it.

It is unclear whether the antidepressant effect of ketamine is sustained beyond 1 week. As depression is a recurrent illness, longer follow-up RCTs are needed to assess the duration of ketamine's efficacy and to assess possible relapse that may occur following ketamine administration. There may also be potential for sustaining ketamine's beneficial effects, either through repeated administration or by using adjunctive psychotherapy or medication, which would enhance the clinical application of the drug. To date, the only studies that have examined repeated doses of ketamine are open-label trials. For example, Murrough *et al* (2013) administered up to 6 doses of ketamine over 2 weeks, and 70.8% of patients responded to treatment. However, 76% of these relapsed within a median of 18 days after the final dose. The studies included in the Cochrane reviews varied in their use of concomitant medication, but the numbers were too small to consider subgroup analysis.

Of the 11 studies investigating ketamine, all but one used intravenous administration. This poses obvious practical problems. However, there may be potential for other methods of administration, such as intranasal (Lapidus 2014) and intramuscular (Cusin 2012), but again more data are needed to explore whether these routes are equally effective.

Adverse events, particularly those of longer-term use (such as possible cognitive impairment and bladder dysfunction), need to be assessed. For example, some observational studies report persistant decrements in spatial working memory, pattern recognition memory and verbal recognition memory (Morgan 2010) in long-term ketamine misuse, but these were not seen in healthy volunteers following an acute dose of ketamine (Honey 2003). In addition, ketamine's psychotomimetic effects raise the potential for addiction and misuse, which might constrain clinical prescribing. Only one study compared a psychoactive drug (midazolam) with ketamine. Further trials are needed, as comparison with placebo is limited by the difficulties of maintaining the masking of participants and researchers.

Overall, the results for ketamine as a fast-acting antidepressant are promising but require further study. The literature search in January 2015 for these reviews identified a large number of ongoing studies. This indicates the level of interest in glutamatergic receptor modulators in general, and ketamine in particular, as potential new therapeutic agents for depression. The new data will be included in further updates of the two Cochrane reviews and will help to clarify the efficacy, practicality and side-effect profile of ketamine as an antidepressant agent.

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