

## Editorial

## Ketamine: stimulating antidepressant treatment?

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## Summary

The appeal of ketamine – in promptly ameliorating depressive symptoms even in those with non-response – has led to a dramatic increase in its off-label use. Initial promising results await robust corroboration and key questions remain, particularly concerning its long-term administration. It is, therefore, timely to review the opinions of mood disorder experts worldwide pertaining to ketamine's potential as an option for treating depression and provide a synthesis of perspectives – derived from evidence and clinical experience – and to consider strategies for future investigations.

## Declaration of interests

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Professor Gin S. Malhi (pictured) is a mood disorders specialist and clinical academic with expertise in diagnosis, psychopharmacology, neurocognition and neuroimaging. Dr Yulisha Byrow is an expert in social anxiety disorder and mood disorders. Professor Frederick Cassidy is a mood disorders specialist with expertise in diagnosis, psychopharmacology, and electroconvulsive therapy. Professor Andrea Cipriani is a clinical academic with expertise in mood disorders and a specific interest in evidence synthesis. Professor Koen Demyttenaere is a mood disorders expert. Professor Mark A. Frye is an educator, clinician, and researcher with expertise in depression, bipolar, and addiction. Professor Michael Gitlin specializes in mood disorders and psychopharmacology. Professor Sidney Kennedy is a specialist in mood disorders and their treatment. He conducts integrated biomarker research on treatment outcome. Professor Terence A. Ketter is a bipolar disorder specialist and expert

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clinical academic with expertise in etiology, phenomenology, and treatment. Professor Raymond W. Lam is a psychiatrist and clinical researcher with expertise in clinical trials, workplace depression, and e-mental health. Dr Rupert McShane leads a service which provides ECT and ketamine treatments. Dr Alex J Mitchell is a consultant in liaison psychiatry and psycho-oncology with a long standing interest in mood disorders. Professor Michael J. Ostacher is a psychiatrist whose expertise is in clinical trials and evidence-based practices in mood disorders. Dr Sakina Rizvi is a researcher in mood disorders with a focus on reward mechanisms, neuroimaging and neuropsychopharmacology. Professor Michael E. Thase is an academic psychiatrist with expertise in mood disorders; his research focuses primarily on differential therapeutics. Professor Mauricio Tohen is a mood disorders expert

Major depressive disorder (MDD) is a leading cause of disability worldwide,<sup>1</sup> and its treatment includes both psychological and pharmacological strategies, as well as social and lifestyle interventions. The same approaches can be used to maintain remission and achieve recovery<sup>2</sup> but, in practice, approximately two-thirds of depressed patients fail to achieve an adequate response to first-line pharmacotherapy, and ultimately as many as one-third of patients remain unwell even after several adequate trials of antidepressants.<sup>3</sup> These patients are regarded as having treatment-resistant depression – the definition of which remains contentious.<sup>4</sup>

Even so, the impact of treatment-resistant depression on personal, social and economic variables is substantial, and these individuals are generally more prone to attempt suicide than those who respond to treatment.<sup>5</sup> Thus, there is an ever-present need for the development of novel antidepressant treatments that are effective and act rapidly, and this partly accounts for the resurgence of interest in ketamine.

### Ketamine

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist, introduced in the 1960s as an anaesthetic alternative to the drug phencyclidine (PCP).<sup>6</sup> Commercially known as Ketalar®, Ketaject®, Ketaset® and Vetalar®, it was approved by the US Food and Drug Administration in 1970 for use in humans as a prescription anaesthetic. The precise mechanisms that underpin its purported antidepressant effects are still unknown, but NMDA antagonism is unlikely its sole mechanism of action given that: (i) its mood-altering effects outlast its bioavailability (potentially pointing to ongoing downstream effects beyond NMDA receptor blockade), and (ii) many alternative NMDA antagonists fail to ameliorate depressive symptoms satisfactorily.<sup>7</sup>

Like many serendipitous discoveries in the first generation of psychopharmacology, the antidepressant effects of ketamine were initially met with scepticism and lack of interest. This is because it has been known for centuries that ‘depression’ can be countered using intoxicating substances to transiently lift one’s spirits and/or numb psychic pain. Hence individuals who use drugs for recreational purposes are already familiar with the psychotomimetic and dissociative effects of ketamine; properties that in these circles accord ketamine a unique status reflected in its alternative name – ‘Special K’. Ketamine’s potential for misuse may stem from its agonist effects on mu-opioid receptors<sup>7</sup> among other actions, and in some countries, most notably those in Asia, ketamine misuse is prolific.<sup>8</sup> However, thus far, in the USA and the UK, concern regarding the potential for misuse of ketamine – classified as a Schedule III compound by the Drug Enforcement Agency (USA) and Class B under the Misuse of Drugs Act (1971) (UK) – is much lower than, say, for heroin or cocaine. Hence, as attempts to develop truly novel antidepressants have repeatedly met with failure in the early part of the 21st century, interest in the putative antidepressant properties of ketamine and related drugs has steadily grown.

It is now more than 15 years since the initial discovery that intravenous delivery of sub-anaesthetic doses (i.e. 0.4–0.5 mg/kg) of ketamine could produce rapid, antidepressant-like effects.<sup>9</sup> The positive findings of several small but well-controlled studies<sup>10</sup> at the National Institute of Mental Health (NIMH) coupled with exciting findings from preclinical work on the potential role of glutamatergic neurotransmission in adaptation to chronic stress<sup>11</sup> fuelled interest further and prompted speculation that ketamine’s ‘antidepressant’ effects are, at least in part, mediated by NMDA receptors, and that perhaps the first truly novel mechanism of antidepressant response in more than 30 years has been identified.<sup>7</sup>

### Rationale and approach

Opinions regarding the use of ketamine to treat depression were canvassed from mood disorder experts (e.g. clinicians, academics and researchers) worldwide. Each expert was invited to address the following question: ‘Based on the current evidence available, is the use of ketamine justified in the treatment of depression? If no, then what further evidence is needed to establish its efficacy? If yes, then in what context (e.g. how, for whom) would you advocate its use?’

When answering this question, respondents considered the available evidence and drew on their personal clinical and research experience and expertise. All those who agreed to participate are acknowledged as co-authors and their respective responses and views have been synthesised according to several common themes that emerged: efficacy, tolerability and potential for misuse, administration (route and setting), and recommendations for future research.

### Aim

To provide a considered perspective on the current status of ketamine with regard to its potential use in the treatment of depression.

### Synthesis of responses

#### Efficacy

Randomised evidence supporting a short-term antidepressant effect of ketamine in adults with severe depression is quite limited, but exists, and points to a modest effect that is sustained for up to 1 week.<sup>12</sup> However, confidence in these findings is limited by the risk of performance bias and a lack of robust trials corroborating these findings thus far. Furthermore, although findings from several meta-analyses, for example,<sup>13,14</sup> demonstrate the efficacy of intravenous ketamine for treatment-resistant depression, the studies included in these analyses involve mainly single-dose infusions, and the necessary studies of repeated infusions or longer term use needed to assess more sustained improvement remain sparse. Indeed to date, the only studies that have examined repeated doses of ketamine are open-label trials; for example, Murrrough *et al*<sup>15</sup> administered up to six doses of ketamine over 2 weeks to patients with MDD and found that 70.8% of patients responded to treatment. However, notably more than three quarters (76% of patients) relapsed within 18 days (median time) after the last intravenously administered dose. A separate study examining treatment-resistant depression in unipolar and bipolar depressed patients found that the efficacy of repeated doses of ketamine was much less, with fewer than a third (29%) of patients achieving an adequate response and a duration of response lasting between 25 and 168 days (median 70 days).<sup>16</sup> In a similar vein, ketamine’s rapid onset of action has led a number of researchers and practitioners to explore its suitability for diminishing suicidal ideation in the context of depression, and preliminary evidence suggests that it may indeed reduce suicidal thoughts.<sup>17,18</sup> However, long-term effects on suicidal behaviour are unknown and await investigation.<sup>19</sup>

Likewise in acute bipolar depression, a handful of studies suggests that ketamine may have rapid antidepressant effects.<sup>20</sup> In particular, in two NIMH-funded crossover studies, with 18<sup>21</sup> and 15<sup>22</sup> non-psychotic bipolar I or II depressed and treatment-resistant patients, adjunctive intravenous infusions of ketamine hydrochloride (0.5 mg/kg) versus placebo yielded improvements in MADRS scores at 40 min that persisted through day 3, and resulted in marked differences in rates of response.

The putative mechanism of action of ketamine is intriguing, and its seeming near-instantaneous benefit is something that

is painfully lacking in other existing treatments. However, the question whether ketamine has a brief euphoriant effect instead of a genuine antidepressant response remains open.<sup>23</sup> Critical of current findings some researchers have suggested that adequate blinding to treatment assignment (neither saline nor midazolam are convincing placebos),<sup>12</sup> appropriate sample sizes, and robust replication are necessary before ketamine can be regarded as an effective antidepressant treatment for depression. Furthermore, much more needs to be learnt about the maintenance of response and long-term outcome before using ketamine more widely in clinical practice. Hence, though phase III trials of intranasal esketamine are underway, much needed clinical trials studying the repeated administration of intravenous and subcutaneous ketamine are urgently needed, and hopefully these studies will provide the necessary evidence to support or refute its clinical use in the treatment of depression.

### Tolerability and potential for misuse

Ketamine's side-effects include transient hypertension, psychotomimetic or dissociative effects, and the potential for drug misuse and psychosis.<sup>24,25</sup> Therefore, it is important that both short- and long-term side-effects are fully understood before considering widespread clinical use. Wan *et al*<sup>26</sup> pooled data from trials investigating ketamine in treatment-resistant depression and reported short-term dizziness, drowsiness, poor coordination, dissociative symptoms, psychotomimetic effects and haemodynamic changes. Interestingly, during long-term follow-up, none of these side-effects persisted and no patients experienced increased substance misuse. Indeed in most cases, side-effects and behavioural changes dissipated within 4 h after administration. However, it is important to note that in these studies ketamine was administered either as a single dose or in a series of up to six doses over a 2-week period. Therefore, whilst this pattern of side-effects reflects the consequences of short-term treatment, it may not reflect the sequelae of longer term administration. For instance, it is possible that long-term use of ketamine in the treatment of depression will be associated with significant adverse events, as is evident to some extent from parallel literature and in pain studies.<sup>8,27</sup> Furthermore, although most of the side-effects observed in studies examining ketamine treatment for depression thus far have been mild and transient, the reports of neurotoxicity in animals<sup>28</sup> are sufficient to prompt caution when considering ketamine's long-term safety. Similar concerns apply to the use of ketamine in the treatment of bipolar depression, and additional research, with larger more representative groups of bipolar depressed patients, is needed to establish its efficacy and assess risks such as triggering and/or exacerbating psychotic/manic symptoms.<sup>29,30</sup>

In summary, the concerns regarding the use of ketamine, though well formulated, are not immediately evident in the short term; but before endorsing widespread use, future research should focus on longer term use for the treatment of both unipolar and bipolar depression.

### Administration

#### Route

Almost all studies published to date have administered ketamine intravenously. But if ketamine is to be a viable clinical treatment, it needs to be both simple and cost-effective to administer. Intravenous infusion is possible in specialist units, but in routine clinical practice it may pose significant problems that will impact uptake and adherence. Alternative modes of ketamine administration, that are currently available, include parenteral, intranasal and oral. Intranasal delivery of ketamine has been examined in one controlled study in which depressive symptoms improved

24 h after administration, compared to saline placebo.<sup>31</sup> However, given the small sample size in this study ( $n=20$ ), these findings require replication before intranasal delivery of ketamine can be regarded as effective. Daily oral ketamine, over months or years, is used by some pain physicians at daily divided doses of 20–200 mg/day. However, oral ketamine generally has lower bioavailability and, as of yet, there is no evidence that it is as efficacious in the treatment of depression as intravenous ketamine.<sup>32</sup> Therefore, intravenous delivery remains impractical for current routine psychiatric care (though slower infusion is an alternative possibility, which is being investigated),<sup>33</sup> whereas oral and nasal ketamine need further thorough evaluation.

Another interesting and clinically relevant question worth considering is whether intravenous infusions could be used to establish responsiveness and act as a gate-keeping mechanism for longer term treatment via other routes. This practical 'assessment' may have greater specificity and prove to be more useful than current predictive clinical markers. Hence, further research with respect to dosing strategies (e.g. dose–response, infusion rate and frequency of treatments) and the relative benefits of different modes of delivery (intranasal, oral) is essential to make ketamine a viable antidepressant treatment option.

#### Setting (clinics)

Initially ketamine was used in limited academic research settings, but recently independent outpatient clinics have emerged for the treatment of depression, as well as other conditions such as pain. Increasingly, ketamine infusion is conducted by physicians other than psychiatrists, such as anaesthesiologists, neurologists, internists, and family practitioners, who, whilst qualified to administer ketamine, often have limited experience of treating depression *per se*. To standardise the use of ketamine and ensure that it is safe and effective, and to facilitate research, there may be merit in developing highly specialised ketamine clinics that can also address the unmet need of treatment-resistant depression. However, in order to minimise any ethical issues associated with such an environment, off-label prescription would need to be tightly regulated with appropriate support from administrative policies on practice standards, informed consent and regulations regarding clinical criteria for treatment, and outcome measures,<sup>34,35</sup> along with sufficient safeguards to prevent drug diversion or misuse.<sup>36</sup> Such proposals have prompted broader questions such as, 'How far should experimentation with antidepressants in clinical practice be regulated?' The off-label use of licensed drugs already has clear legal standing and therefore perhaps a related question should be, 'Is there something about ketamine that makes it so different from other off-label use of controlled drugs that it should be a legal special case?'

Growing, but limited, clinical experience with short-term ketamine for treatment-resistant depression suggests that its safety is at least comparable to other widely used drugs. For example, in one centre in Oxford with experience of treating over 70 patients with ketamine infusions, only one case of possible ketamine-related cystitis has occurred and this resolved with the cessation of ketamine and treatment with antibiotics. It is also notable that in this same UK centre, which conducts daily mood monitoring, there have been no reports of tolerance or tachyphylaxis. Albeit uncontrolled, such clinical knowledge is invaluable and may usefully inform future research and studies.

Another difficulty in implementing a treatment such as ketamine is that clinical governance surrounding medical interventions varies considerably from country to country. For example, in some countries it is possible to walk into a ketamine clinic and receive ketamine infusion treatment administered by medical professionals other than psychiatrists; this clinic's fee results in

personal remuneration for the clinician. In the UK, referral by and correspondence with GPs and psychiatrists who know the patient, review of previous psychiatric treatments, an hour-long assessment interview to manage expectations, completion of consent forms, physical examination and blood tests may be required, and the clinicians involved may have no personal remuneration. In part this not only reflects the prevailing norms of medical practice in various countries but also highlights the range of possible practices and potential associated problems.

### Recommendations for future research

Our understanding of ketamine as an antidepressant currently approximates to the ‘concept-proved’ level of drug development, and hence further steps are clearly warranted. The priority for the next stage of development is to determine the optimal course and duration of acute ketamine therapy for those who show a robust response to initial therapy. As durations of therapeutic exposure increase, it will be possible to collect further data to ensure that ongoing therapy is safe and that neither tolerance nor neurotoxicity (nor other rarer, unexpected toxicities) develops across months of therapy. Furthermore, the highest level of quality data being garnered from academically driven centres should not preclude systematic collection of data, regarding both efficacy and adverse effects, from the numerous non-academic ketamine programmes. In fact, trying to create data registries may help improve quality of care in all ketamine clinics.

Of course, there are many important topics for ongoing research including, for instance, studying differences in biosignatures of ketamine response and non-response and, if possible, identifying in advance patients who might be outstanding candidates, as well as those who might have little prospect of benefitting. Another intriguing question is whether a short course of intravenous ketamine therapy can restore, or induce, responsiveness to conventional antidepressants. This may also provide a means for minimising ketamine exposure and concerns about later emerging toxicity.

Studies involving neuroimaging<sup>37</sup> and animal studies<sup>38</sup> are likely to assist in elucidating the precise mechanism of action associated with ketamine treatment. Research along these lines may facilitate development of the next generation of glutamatergic antidepressants, in which ketamine data channels research towards more rapid acting agents with mechanisms of action that differ from the usual manipulations of monoamine neurotransmitters. One example is the recent development of the glutamatergic agent rapastinel (GLYX-13).<sup>39,40</sup>

### Discussion

Research to date shows that ketamine has a transient antidepressant-like effect, and in short term it is well tolerated, though the optimal and most acceptable mode of delivery is yet to be determined. Longer term use of ketamine for the treatment of depression needs evidence from randomised controlled trials that critically evaluate its efficacy and tolerability. At the same time, it is important to decide to what extent the use of ketamine needs to be ‘policed’ with respect to its prescription by psychiatrists and GPs when treating non-treatment-resistant depression in the community.

Perhaps, as with any novel treatment for depression, it is useful to review some of the key features of an ‘ideal antidepressant’ (Box 1) – the standard to which ketamine should perhaps be held. Currently, ketamine does not fulfil a number of these criteria and in fact falls far short of the ideal. But this is also true of all other antidepressants. Thus, whilst ketamine cannot yet be endorsed as an antidepressant for general use on the basis of current evidence, it

#### Box 1 Features of an ideal antidepressant

- Sustained efficacy that minimises frequency of dosing and enhances compliance
- Well tolerated with minimal short-term and longer term side-effects
- Safe at clinical doses and ideally safe during overdose
- Simple for clinicians to administer and for patients to take, maximising compliance
- Minimal discontinuation symptoms, low-misuse potential and non-addictive
- Widely available and accessible, with good cost-effectiveness
- Effective at population level: community and/or primary care

should not be dismissed completely. Further study may reveal that ketamine is useful in the management of treatment-resistant depression and that it provides a stepping stone to the development of new and more effective medications – especially those with similar glutamatergic actions that potentially activate a broader set of neurotransmitters and neural networks than conventional antidepressants. Similarly, research into ketamine’s short-term effects has opened up interesting possibilities – for example, a potential ‘facilitatory role’ in which short acting agents, such as ketamine, may be able to initiate a response that can then be sustained by conventional antidepressants.

### Stimulating times ahead

The use of ketamine to treat depression is a contentious issue that will continue to polarise views until more is learnt about the effects of this molecule. In the meantime it is imperative that high-quality clinical evidence is garnered, and that as more evidence comes to light the issues outlined in this article are systematically and critically appraised. Given the poor state of new drug development in mood disorders,<sup>41</sup> it is important that a potential opportunity to better understand depression and possibly develop new medications for its treatment is not squandered. However, it is also important that the benefits and risks of ketamine therapy are firmly established prior to making any clinical recommendations and encouraging widespread administration.

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