Ketamine in the treatment of depression: opportunities and risks

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Abstract

There has been considerable interest in the potential of ketamine as a novel antidepressant with a unique mechanism of action. In a number of small trials, ketamine has been shown to lead to reductions in depressive symptoms within hours of administration in patients with symptoms that are otherwise refractory to treatment, with the antidepressant response lasting for days. Although the mechanism of action, as well as the efficacy and safety data, remain to be fully characterised, a number of centres have started to offer ketamine as an off-label treatment for depression. In tandem, a number of larger scale clinical trials are currently underway. At present, it is only advisable to consider the use of ketamine as an off-label treatment for depression in cases where all other treatments have failed, where access to a specialist centre with expertise in the use of ketamine as an antidepressant is available, and where the individual is not suitable to take part in a clinical trial of ketamine.

Treatment-resistant depression

Major depressive disorder is one of the largest single leading causes of health-related disability and the largest, and most costly of all mental health disorders (1), with estimated yearly costs in Europe of 113.4 billion euros (2). Only one-third of patients will achieve remission with initial antidepressant treatment; with prolonged and extensive treatment, this proportion eventually increases to approximately 60% (3), leaving one-third of patients with persistent, treatment-resistant depression.

The management of treatment-resistant depression is particularly difficult, often requiring the combination of different antidepressant agents and other medications in tandem with psychological treatments and occupational therapy. However, the discovery that ketamine, a dissociative anaesthetic with a relatively rich pharmacology, including N-methyl-D-aspartate (NMDA) receptor antagonism, has effects in individuals with treatment-resistant depression has been hailed as "the biggest breakthrough in depression research in half a century" (4).

Ketamine

Ketamine was developed in the 1960s as a dissociative anaesthetic agent with lower propensity to emergence reactions (agitation, dreams, hallucinations and dissociative effects - feeling unreal or that the environment is unreal - when emerging from the anaesthetised state) compared to phencyclidine. Following its licensing in 1970, ketamine was first used as a battlefield anaesthetic agent in the Vietnam War. Since that time, it remains a useful anaesthetic agent - particularly in situations where an anaesthetist is not available - because of its low propensity to cause respiratory depression (5, 6).

Although ketamine has a lower incidence of emergence reactions than phencyclidine, it nonetheless does lead to marked psychological experiences, including the sensation of body and time distortion at sub-anaesthetic doses or during the post-anaesthetic period, which many patients find unpleasant, and which has reduced its use in a hospital setting. Perhaps because of these effects, ketamine is used as a recreational drug and, by a small number of users, is taken regularly at high doses (5). Chronic ketamine use in recreational users has been associated with a number of serious adverse effects, including bladder damage, cognitive impairment, psychotic symptoms and, ironically, depression (6). Ketamine administration has also been associated with toxic brain changes in rodent models (7), and in chronic ketamine users brain volumes have been found to be reduced (8), although the clinical significance of these findings in humans is not currently known.

Ketamine as an antidepressant

The antidepressant effects of ketamine were first reported in 2000 by Berman and colleagues (9). This initial pilot study was followed up by a trial in treatment-resistant depression by Zarate and colleagues in 2006 (10). They showed that, in patients otherwise resistant to antidepressants, there was a significant reduction in depressive symptoms within two hours following an infusion of a subanaesthetic dose. The finding was doubly surprising in that these were people with exceptionally hard to treat symptoms, but also that the effect was so rapid (the consensus at the time was that depressive symptoms were slow to respond to treatment and required at least 2 - 4 weeks of treatment before any response would be expected). There have now been several studies of ketamine in patients with treatment-resistant depression, which have been summarised in recent meta-analyses confirming the initial finding of the rapid antidepressant effect, which is maintained after a single dose for an average of seven days (11). Subsequent research has revealed that ketamine may also reduce suicidal ideation (12), and that it may have an effect in patients with depression in the setting of bipolar affective disorder (11).

Mechanisms

Although theories abound, the mechanisms underlying the antidepressant effects of ketamine are currently unknown. It has been assumed, as ketamine is a potent NMDA receptor antagonist, that its main antidepressant effects are through this mechanism. However, it has been suggested that this may not be the case as ketamine has actions at a large number of other brain receptors that have also been implicated in antidepressant effects (13). A recent paper reported that one of its metabolites (2R, 6R hydroxynorketamine) that does not have any action at NMDA receptors was associated with antidepressant effects in a rodent model (14), although other authors have suggested that this finding does not invalidate the NMDA receptor hypothesis (15). Downstream effects of ketamine assumed to be related to its antidepressant action include increase in dendritic spine formation (16). Work is ongoing, but the discovery of the underlying mechanism is of particular importance as it may lead to the development of other treatments that may not have the same dissociative effects or abuse potential.

Off-label use

In the UK, ketamine has been used as an antidepressant for people otherwise unresponsive to treatments in a small number of centres, usually as an alternative to electroconvulsive therapy (ECT). The most established of these is the service in Oxford headed by Rupert McShane, as reported in a recent study of safety (17). Results when ketamine is used as an add-on treatment in this manner suggest a response rate (defined as a 50% reduction in Beck Depression Inventory scores) of around 30% (17). Building on the success of this model for treating otherwise resistant depression, there has recently been a case made that the use of ketamine as an off-label treatment is ethical and should be more widely available as a treatment for particularly hard-to-treat cases (18).

In contrast, there have been calls for restraint in the use of ketamine off-label for the treatment of depression (19). There remains a paucity of understanding about the long-term risks, optimal method and dose of administration for maximal effect, and the maintenance of response, questions that will only be addressed through large-scale, well-designed clinical trials, several of which are already underway, including a number of long-term safety studies of intranasal ketamine sponsored by Janssen (clinicaltrials.gov identifiers = NCT02782104, NCT02497287). If off-label use of ketamine became common, it might become more difficult to conduct these trials, as patients and clinicians may be less likely to engage with a trial because of the additional procedures involved and because of the chance that they might receive placebo.

In individuals who respond to ketamine, repeated (weekly to fortnightly) dosing is usually required in order to maintain the antidepressant response, and in most cases the depression will return after discontinuation of the ketamine infusion although, in a small minority of cases, maintenance of response can last for several months or more (17). When ketamine is given intravenously, weekly or fortnightly dosing leads to problems in terms of provision, as the service will quickly become filled with patients returning for repeated dosing, and taking on more patients to the service will become impossible. Furthermore, the long-term risks of ketamine as an antidepressant are unknown. It is not clear whether use of ketamine in a

controlled clinical setting for the treatment of depression is associated with the same health risks as seen in chronic recreational use.

Thus, at present, it is only advisable to use ketamine as an off-label treatment for depression in cases where all other treatments have failed, and where the individual is not suitable to take part in a clinical trial of ketamine. Where the decision to use ketamine off-label is taken, this should only be in a specialist setting, ideally with previous experience in the use of ketamine, and with adequate safety provision. However, there are considerable risks associated with this approach, and until the potential adverse effects of long-term ketamine treatment are known, it is premature to recommend ketamine as an antidepressant treatment for widespread use.

Conclusion

In summary, ketamine is a novel antidepressant that has effects in patients otherwise resistant to antidepressants, and with a remarkably rapid speed of onset. It works via a novel, but as yet not fully characterised, mechanism. The long-term risks are unknown and maintenance of response remains problematic. Larger clinical trials are currently underway, but until these have been completed it remains an off-label treatment for depression that should only be considered where all other avenues for treatment have been exhausted.

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