

Ketamine and the potential role for rapid-acting antidepressant medications

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Ketamine appears to be the first medication to produce a rapid, although short-lasting, antidepressant response. This finding emerges from two studies: the first was a pilot study published in 2000 by a group of investigators at Yale University [1], and the second was a larger study published last year by an investigative team based at the U.S. National Institute of Mental Health Intramural Research Program [2]. Both studies make the same essential points: 1) depressed patients who had not responded to other antidepressant treatments began to show an antidepressant response within hours of ketamine administration that was significantly better than placebo, 2) for a subgroup of patients (it is difficult to estimate the true size of this group given the small sample sizes for the two studies) this response constituted a remission of their depressive symptoms, 3) that the antidepressant response to a single dose of ketamine persisted for a week or more in some patients, 4) that ketamine administration in these patients was associated with transient cognitive impairments and perceptual changes consistent with psychotogenic effects of ketamine reported in healthy individuals, and 5) overall, ketamine was safe and well-tolerated by the depressed patients studied to date. It is important to note that ketamine is not the first rapid-acting antidepressant treatment identified. That distinction probably belongs to sleep deprivation, whose transient antidepressant effects have been known for over 35 years [3], but whose underlying mechanisms still remain unclear.

One can imagine many uses for a rapid-acting antidepressant medication. For example, it might be used to prevent suicide, to reduce the need for hospitalisation for psychiatric patients, to minimise depression-related disability or social disruption, and to simply reduce the distress associated with an episode of depression. However, a medication that induces a transient remission of depression is not, by itself, a treatment for depression. A critical question is whether a rapid-acting antidepressant can play a role within “real world” treatment planning. To this end, we need to know the answers to many questions including:

1) can ketamine be administered repeatedly or combined with another treatment to sustain improvement in depression;

- 2) does ketamine produce any adverse effects with regard to subsequent antidepressant response;
- 3) is there any risk of long-lasting psychoses after ketamine administration;
- 4) may ketamine be administered safely to bipolar depressed patients as well as unipolar depressed patients;
- 5) are there ways to predict who will respond favourably to ketamine?

The question of how ketamine works to produce antidepressant effects is critical to the effort to devise better treatments that retain the therapeutic effects of ketamine while avoiding its cognitive and perceptual effects [4]. It will be important to determine, for example, whether ketamine doses that are sufficiently low to avoid altering perception reduce depression symptoms. Ketamine is an antagonist of NMDA glutamate receptors. Unfortunately, it is also not clear whether NMDA receptor antagonists with greater tolerability will have antidepressant efficacy. There were some preliminary studies suggesting that the low potency NMDA receptor antagonist, amantadine, might reduce depression symptoms [5]. However, a recent study found that low doses of a related NMDA receptor antagonist, memantine, lacked antidepressant efficacy [6].

There are four main subtypes of NMDA receptors. It will be important to know whether drugs that selectively block subtypes of NMDA receptors are effective and better-tolerated antidepressants than ketamine.

One reason that ketamine may act more rapidly than typical antidepressant medications is that it may more directly produce some effects that emerge as gradual adaptations to these other antidepressant medications, including reductions in NMDA glutamate receptor function; induction of the transcription factor, CREB, and brain-derived neurotrophic factor (BDNF); and enhancement of AMPA glutamate receptor function [4]. It is possible that drugs that directly target CREB, BDNF, and AMPA receptors might have rapid-onset antidepressant effects.

Glutamate neurotransmission is an important focus in mood disorders research. Although keta-

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mine may be the first rapid-acting antidepressant to emerge from this area of study, other medications are found that target other components of glutamatergic neurotransmission [7, 8]. With several potential emerging treatment approaches, glutamate psychopharmacology research appears to be poised to have an important impact on the treatment of depressed patients.

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