

The Promise of Rapidly Acting Antidepressants: Challenges and Opportunities

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Despite availability of a variety of new monoaminergic reuptake blockers in the 50 years since imipramine, a meta-analysis of 28 trials found that full clinical response typically requires 6 weeks on average (1). This length of suffering is not only unacceptable but is also linked to an increased risk of suicide. Despite suicide prevention programs, better recognition of depression, and the availability of antidepressants and hospitalization, the overall rate of suicide has not improved over the last several decades. All this causes untold suffering to the victims, friends, and family.

But there is hope for more effective and faster-acting antidepressants. Much of the excitement stems from the serendipitous finding that the *N*-methyl-D-aspartate (NMDA) antagonist ketamine rapidly and robustly elevated mood in depressed patients (2). In addition to the discovery that a nonmonoaminergic mechanism had antidepressant effects, the study was most remarkable for the fact that mood elevation occurred within hours after the infusion and persisted for about a week in some individuals. Subsequently Zarate *et al.* (3) replicated this finding in double-blind, placebo-controlled, crossover studies in unipolar and bipolar depression. A body of evidence is now accumulating to indicate that the antidepressant effects of ketamine occur rapidly (within hours) and persist for days to weeks, depending on the individual patient (4). Of particular interest, there seems to be a rapid effect on suicidal ideation (5).

The ketamine findings add to the well-known effects of sleep deprivation to prove that the state of depression is indeed rapidly reversible. (Here we will define rapid response as a clinically meaningful and statistically significant treatment effect vs. placebo that is apparent within 24–72 hours after initiation of the therapy.) The sceptics are quick to note that ketamine infusions cause transient psychotomimetic side effects that effectively unblind the treatment to both patients and investigators. Clearly there is a need for a study directly comparing ketamine with another drug that has obvious behavioral side effects but is known to be devoid of antidepressant effects. Such a trial using midazolam is underway (ClinicalTrials.gov identifier: NCT00768430).

Regardless of whether one is testing a glutamatergic agent, sleep deprivation, a device such as transcranial magnetic stimulation, or other potential drugs such as scopolamine, several caveats should be kept in mind when trying to document rapid antidepressant effects such as the following:

1. There is no consensus as to the best approach for documenting the onset of treatment benefit. However, there is agreement that equating the time at which a drug's therapeutic effect begins with the first time the mean difference between drug and placebo is statistically significant is not a valid approach (6). Statistical significance can be bought with a larger sample size.

2. Based on our experience, there will be great expectancy on the part of patients and investigators in any trial of a potential rapid antidepressant. Treatment-resistant depression patients may derive little benefit from current antidepressants, but they have not lost hope. The fact that placebo responders often improve within the first week of a trial will be particularly problematic for proving that a drug is a rapid-acting antidepressant. Unless one has the luxury of establishing a patient's baseline level of depression by weeks of observation, then novel trial designs such as the sequential parallel comparison design and those using placebo run-in, staggered starts, etc. may be necessary.
3. Another important caveat in determining the veracity of rapid antidepressant effects is whether they quickly have an impact on the core depression items contained within the multifactorial depression scales. For example, sedating antidepressants obviously improve sleep rapidly, but the onset of an antidepressant effect is better judged by when the core items of sadness, etc. begin to improve. Indeed, the time scale may be so short that sleep and appetite cannot be accurately assessed, and new depression scales for use over hours and days may need to be developed and validated.
4. Achievement of a rapid antidepressant response will inevitably be followed by the question of what to do next. Unfortunately, response to a single infusion of ketamine lasts only about 2 weeks on average, and attempts to sustain the response with glutamatergic agents such as riluzole have so far been unsuccessful (7). Transcranial magnetic stimulation and electroconvulsive therapy are faced with similar challenges in establishing appropriate strategies to sustain their early antidepressant responses and often resort to maintenance schedules of reduced frequency. Although repeated infusions of ketamine appear to be relatively well tolerated, there have been no double-blind, placebo-controlled, parallel-design studies examining the long-term efficacy of repeated ketamine infusions. Sustaining the effect of a rapid antidepressant appears to be the biggest challenge currently.

Regardless of these factors, a rapid-acting antidepressant such as ketamine is an invaluable tool for compressing the timeframe of response, remission, and relapse of a depressive episode into a week or so. This makes it easier for the scientist to study the phenomenon in the clinical laboratory. For instance, it will now be much easier to monitor changes in circuit connectivity with the use of imaging, electroencephalograms, etc. and correlate these physiologic changes with mood scores over a reasonable amount of time (days) without having to require patients to come back months later when they may finally be in remission. These translational studies should facilitate our understanding of the cascade of events triggered by drugs such as ketamine that quickly lead to a lifting of depressive symptoms. Perhaps even more interesting will be any insights gained by monitoring patients who unfortunately return to baseline a week or so after a ketamine infusion. Single administration of rapid-acting antidepressants such as ketamine and sleep deprivation appear to relieve depressive symptomatology acutely but not in a sustained fashion. This implies they are

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effectively counteracting the depressive process, whatever it is, but not fundamentally abolishing it (i.e., not terminating the current depressive episode and causing recovery). Conducting intensive biomarker studies during the response, remission, and relapse after administering a rapid-acting antidepressant could tell us something fundamental about the pathophysiology of depression.

So how can we expand on ketamine to discover novel, effective, and perhaps better tolerated, rapid-acting antidepressants that can be used long term to sustain the effects? The glutamate system complexity affords drug developers a variety of new targets including glycine antagonists, ampakines and metabotropic glutamate modulators etc. that might prove to have rapid antidepressant properties and yet have a different side effect profile to ketamine. Several opportunities present themselves with nonketamine NMDA antagonists such as the following:

1. Ketamine has several active and inactive metabolites that may have specific efficacy and side effect profiles that could be further characterized.
2. A NR2B-selective NMDA antagonist (CP-101,606) was shown to have relatively rapid antidepressant effects (5 days) in patients who had an inadequate response to paroxetine (8). The dose of CP-101,606 was lowered to avoid the typical phencyclidine-like side effects of NMDA antagonists and still had considerable efficacy. However, the therapeutic margin appeared narrow.
3. Will other NMDA antagonists with low affinity and better tolerability prove to be effective antidepressants? So far, the results for drugs like memantine have been disappointing in unipolar and bipolar depression. Although both ketamine and memantine are noncompetitive NMDA antagonists, they differ in several important regards including route of administration, half-life (memantine is ~ 60 hours), binding to NMDA subtypes, and off rate from the closed receptor (partial trapping). These differences need to be understood to engineer an NMDA antagonist with a better risk/benefit profile than ketamine.

The need for a rapid antidepressant response is most compelling in patients with major depression experiencing suicidal ideation and/or behavior. This is a medical emergency. Studies of risk factors for suicide consistently show that suicidal ideation is among the most salient risk factors for suicide and appears to be a precondition for suicide attempts among patients with depression. Hospitalization in a locked, restrictive psychiatric unit is usually the standard of care. In a sense, hospitalization is what passes for rapid antidepressant treatment for the very sick, depressed, suicidal patient. However, there is a risk of suicide attempts and suicides in the

hospitalized patient population as well as a concerning rate of suicide soon after discharge (9,10). With average length of stays on the order of 1 week in the United States, there is a large unmet medical need to develop rapidly acting agents that could supplement the current treatments for the very sick, depressed, hospitalized patient. There are no approved drugs effective in managing this emergency. On the contrary, the time after starting an antidepressant may be a period of increased vulnerability for suicidal ideation and behavior. Preliminary evidence of the efficacy of ketamine in the rapid reduction of suicidal ideation offers real hope to the field of psychiatry that is craving better treatments for this medical emergency.

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