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EDITORIAL

Ketamine: a new chapter in antidepressant development

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From the beginning of the neuropsychiatric drug era, the development of antidepressants has been mostly based on serendipity. One of the first examples, iproniazid, was an antitubercular drug observed to induce euphoric effects in individuals with tuberculosis. Investigators who pursued this intriguing finding argued that similar compounds might have antidepressant properties, ultimately paving the way to developing monoamine oxidase inhibitors (MAOIs) for treating depression. This discovery ushered in the era of monoaminergic-based antidepressants, and the next 50-60 years consisted mainly of developing "me too" drugs that were largely monoaminergically-based. These medications typically yielded only minor refinements – for instance, improved side-effect profiles – to existing antidepressants without offering significant advantages in terms of efficacy or remission and recovery rates.[1] While it is certainly true that these "conventional antidepressants" did help many, it is equally true that not all were helped. Furthermore, these agents are associated with notable limitations, including low remission rates, slow onset of therapeutic effects, and lower efficacy in comorbid psychiatric conditions and syndromes. In addition, many of the patients who did respond – or partially responded – to these treatments continued to relapse despite ongoing treatment, developed treatment resistance, attempted suicide, or had impaired functioning. Given the urgent need for better treatments, several targets for new, non-monoaminergic-based antidepressants have been pursued over the decades; few, if any, novel ones reached the clinic.

In this context, one of many targets of interest is the glutamatergic system.[2] Trullas & Skolnick were among the first to examine the possible link between depression and glutamatergic system dysfunction[3] and, building on their preclinical work, Berman et al. discovered that ketamine exerted rapid, robust, and relatively sustained antidepressant effects in depressed patients.[4] Despite the pioneering nature of the results, the paper did not have an immediate dramatic impact on the field. Researchers might have viewed the reported rapid and robust antidepressant effects as a "fluke" or perhaps did not want to test a drug that possessed abuse potential and psychotomimetic effects.

Nevertheless, since then, numerous placebo-controlled studies have shown that subanesthetic-dose ketamine has rapid, robust, and relatively sustained antidepressant effects in individuals with treatment-resistant major depressive disorder and bipolar depression. Building on this growing evidence, investigators wondered whether other N-methyl-D-aspartate receptor (NMDAR) antagonists might exert antidepressant effects similar to those of ketamine. Unfortunately, NMDAR antagonists or modulators of the NMDAR complex (e.g., GLYX-13, CERC-301) have failed in the clinic. Generally speaking, no other tested NMDAR antagonists have shown the same rapid, robust, and sustained antidepressant effects as ketamine; in other words, they are simply not ketamine.[2]

Despite these setbacks, ketamine itself has led to much more focused research seeking to identify promising characteristics of next-generation treatments. In particular, because ketamine's antidepressant effects are so rapid, and because the onset and offset of its therapeutic effects are fairly predictable, investigators began using ketamine as a tool – both clinically and preclinically – to decipher its mechanistic effects and identify biomarkers of treatment response. For instance, one series of studies implicated glutamate and gamma aminobutyric acid (GABA) signaling dysfunction in depression; similarly, convergent evidence from behavioral, cellular, and molecular ketamine studies supported the theory that enhanced α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activity – with a concomitant increase in synaptic plasticity – is critical to ketamine's mechanism of action and may be the key to developing similarly rapid-acting antidepressants.[2] On the clinical front, investigating ketamine's mechanistic properties has led to the exploration of a variety of human biomarkers, as well as treatment options such as scopolamine and electroconvulsive therapy.

Ketamine clinics – which typically administer racemic ketamine intravenously – have proliferated globally. As a whole, the field has urged caution regarding the need for more research, and several meetings have been conducted to share clinical experience and standardize ketamine use. Perhaps the most salient recent development is the March 2019 FDA approval of esketamine (Spravato; the *S*-isomer of ketamine). Spravato can only be dispensed and administered to patients in medically-supervised healthcare settings that provide monitoring (Risk Evaluation and Mitigation Strategies). This is

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particularly important given that ketamine has abuse liability and possesses clinical side effects – including blood pressure changes, dissociation, psychotomimetic effects, cognitive effects, risk of cystitis, and hepatotoxicity (though the latter two are less common). These issues remain a concern despite Risk Evaluation and Mitigation Strategies, especially with long-term use of ketamine or Spravato. Thus, while many safety concerns can certainly be addressed, ketamine's side effect, safety, and addiction profile suggests that larger and longer-term studies are needed to better characterize the limitations associated with ketamine and ketamine-related treatments. Research is ongoing to examine these concerns as well as separate them from ketamine's efficacy profile.

Despite these concerns, the research surrounding ketamine has ushered in a new era of considerable hope regarding our ability to develop better treatments for patients with depression. It bears repeating that ketamine is the first antidepressant with a completely new mechanism of action. In contrast to conventional repurposed antidepressants, ketamine's effects are robust, occur rapidly, and effectively treat not only depressive symptoms but also suicidal ideation, anxiety, anhedonia, and comorbid conditions.[5] Studying the precise mechanisms implicated in its unique therapeutic profile has opened the door to the possibility of developing novel and improved versions of ketamine – medicines that retain its unique, broad therapeutic profile without its troublesome side effects and risk of addiction. In many ways, the field's current focus on ketamine signals the end to the long and often frustrating chapter on conventional antidepressants and the beginning of a new era. This new chapter is likely to be one of many and, although it will not be the end of the story until a cure is found, it promises to be a heartening chapter nonetheless.

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Disclosure

CAZ is listed as a co-inventor on a patent for ketamine use in major depression and suicidal ideation; as a co-inventor on a patent for using (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydroxylated and hydroxylated (*R,S*)-ketamine metabolites for treating depression and neuropathic pain; and as a co-inventor on a patent application for using (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders. He has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government.

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