Ketamine and related drugs are arguably one of the most exciting developments in antidepressant pharmacology in more than half a century and are a potentially new mechanism capable of mediating antidepressant action. That mechanism is the antagonism of the N-methyl-D-aspartate (NMDA) receptor (NR) and possibly one or more subtypes of that receptor. By blocking NMDA receptors, ketamine and related drugs target glutamate, which is the major excitatory neurotransmitter in the brain and a transmitter not directly affected by any currently marketed antidepressant.

In their thought-provoking paper, aan het Rot and colleagues (1) review many of the studies that have been done with ketamine to date and suggest some necessary steps forward in its development.

Historical Perspective

To fully appreciate the import of the preliminary findings of antidepressant efficacy with ketamine and related drugs, one needs to take a historical perspective. For more than 60 years, prescribers and their patients have not had an antidepressant with a new mechanism of action. Arguably, all of our existing antidepressants have mechanisms of actions that are variations on the pharmacology of imipramine, iproniazid, and amphetamine (2). Although beyond the scope of this editorial, the same is true for all currently available antipsychotics, which are variations on the pharmacology of chlorpromazine.

The preceding statement should not be interpreted to mean that nothing has occurred over the last 60 years but instead that the advances made during this period were incremental rather than revolutionary.

From the 1970s to the present, the pharmacology of antidepressants and antipsychotics was refined to make them safer and better tolerated. For more than a quarter of a century, tricyclic antidepressants (TCAs) were the leading cause of drug overdose death in the United States because of their narrow therapeutic index. The introduction of the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors gave prescribers antidepressants that were generally safe in overdose and better tolerated compared with the TCAs. However, the efficacy of the SSRIs and serotonin-norepinephrine reuptake inhibitors was not better than TCAs because their apparent mechanism of action remained the same and may have even become a bit more constrained as a result of rational drug discovery.

So What Is Important About Having a New Mechanism of Action?

The answer to this question comes from a study funded by the National Institute of Mental Health, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (3), which to date is the largest and most complex antidepressant trial ever conducted. The goal of STAR*D was to provide prescribers with empirical evidence about what to do if the first antidepressant tried failed to produce an adequate response. The results underscored the substantial need for antidepressants with mechanisms beyond effects on biogenic amine neurotransmission. The study began with treatment with citalopram, one of the most widely used SSRIs today. Patients who did not benefit adequately from that treatment went on to receive up to three additional adequate trials of currently available biogenic amine-based antidepressants, alone or in combination with other augmenting agents (e.g., lithium) (3).

The results were sobering: 70% of depressed patients did not experience a full remission despite receiving an adequate trial (i.e., dose × duration) of citalopram plus good clinical management (GCM), and 40% did not respond after three more adequate trials of existing biogenic amine–based antidepressants. Even those who did remit had a high relapse rate despite continued treatment with the medication that produced that remission. The bottom-line from the STAR*D study is that almost half of patients with major depression are not fully treated with antidepressants that appear to work via biogenic amine mechanisms. This is a major public health concern, given that inadequately treated major depression kills patients (suicide being responsible for more deaths in the United States than leukemia), ruins families, and is a major cause of chronic disability worldwide.

The results of the STAR*D study suggest an analogy with antibiotics. Although penicillin was a miracle discovery, it does not treat all infections. As with the sequential trials of biogenic amine antidepressants in STAR*D, there is a similar diminishing return when one gives sequential trials of antibiotics that have the same mechanism of action to treat a resistant pathogen.

So What Is the Problem with Developing Ketamine?

The problems are legion. First, ketamine is an old drug that is off patent, meaning there is no opportunity to recoup development costs on ketamine, at least delivered in the currently available formulation. Recall that lithium was not available in the United States for 20 years after Cade discovered its antimanic properties in the late 1940s. The reason was the same: no patent protection. The federal government, through the National Institute of Mental Health, the Food and Drug Administration, and the Veterans Administration Healthcare System, had to do the necessary studies to obtain approval for the marketing of lithium. Perhaps the same will be true for ketamine.

Second, ketamine and most related drugs are generally administered intravenously, can cause dissociative reactions, and have abuse liability. Those features are significant concerns for pharmaceutical companies. The accepted model for current antidepressants is oral administration. Potential developers are concerned that intravenous administration will limit market size and hence the return on investment. However, ketamine and other potential related agents in the pipeline could revolutionize psychiatry from an outpatient, nonprocedural specialty to an ambulatory, procedural specialty. The conundrum for marketers is that novel treatments drive market changes because they highlight true unmet medical needs. Market surveys tell you what the market perceives as possible rather than what is possible. The studies with ketamine and

From the Department of Psychiatry and Behavioral Health, Kansas University School of Medicine-Wichita (KUSM-W) and the KUSM-W Clinical Trial Unit, Wichita, Kansas.

Address correspondence to Sheldon Preskorn, M.D., Kansas University School of Medicine-Wichita, Department of Psychiatry and Behavioral Sciences, 1010 N. Kansas, Wichita, Kansas 67214; E-mail: speskorn@cri-research.net.

Received and accepted Jul 20, 2012.

0006-3223/$36.00 http://dx.doi.org/10.1016/j.biopsych.2012.07.021

© 2012 Society of Biological Psychiatry
related drugs provide a glimpse into what is possible: rapid and robust antidepressant effect in a sizable portion of patients with a form of major depression that is not principally responsive to biogenic amine-based interventions.

The dissociative reactions associated with ketamine can be managed by a procedural (e.g., analogous to ambulatory surgery or dialysis)–based approach to medication administration and may also be reduced by drugs that work on NMDA receptor subtypes or affect NMDA receptors through a different mechanism than ketamine. Such developments would in turn reduce abuse potential by controlling access (the procedural approach) or by minimizing the effect (the refinement in mechanism of action approach). It could also be lessened by formulation approaches that could also either limit access (e.g., single dose administration formulations) or control delivery to minimize peak effects. These approaches have been successful with other drugs (e.g., analgesics) with abuse or adverse effect liabilities.

Notably, work with oral administration of ketamine dates back over 30 years (4), and there have been case reports of oral ketamine being effective as an antidepressant (5,6). Intranasal forms of ketamine have also been successfully used for sedative and analgesic indications (7,8). There have also been small studies of NR2B preferring NMDA antagonists showing antidepressant activity with reduced or absent perceptual changes: one orally and one intravenously administered (9,10). At least two other oral brain-penetrant, NR2B preferring NMDA receptor antagonists have also been tested (http://www.nature.com/nrd/journal/v8/n5/full/nrd2880.html).

The third barrier to the development of ketamine as an antidepressant is the malaise that has arisen in the pharmaceutical industry. Over the past 2 years, several large major companies have announced that they are getting out of the business of psychiatric drug development because of its costly and highly speculative nature.

However, that is in part because of a history of 60 years of “me too” drug development and an approach of “WalMarting” clinical trials, by which I mean large industrialized, primarily private, for-profit clinical sites, coupled with a belt-tightening mentality among sponsors and a layered superstructure of purveyors of various services to the pharmaceutical industry (i.e., contract research organizations).

Moreover, the psychiatric drug development has become somewhat ossified and dependent on syndromic diagnoses rather than pathophysiological or pathoetiological diagnoses. This problem is further complicated by rating scales (e.g., Hamilton Depression Rating Scale) that were developed based on the pharmacology of older agents such as TCAs as much as on any symptoms that are necessarily core to the pathophysiology of the illness.

The history of medicine shows that syndromes typically turn out to be several different disorders when understood from a pathophysiological and/or pathoetiological perspective. The same is likely true for major depression as witnessed by that fact that approximately 60% of patients with syndromic major depression respond to biogenic amine–based antidepressants plus GCM but 40% do not. Of the latter, 15–60% respond to drugs that block one or more NMDA receptors. These findings suggest that there are three or more biochemical forms of major depressive disorder.

Summary

Change is difficult. Practice patterns developed over more than 60 years are hard to break. However, the need is great and cannot be denied. Efforts to make ketamine and related drugs available to patients will require new thinking and possibly new approaches to drug development and to the practice of psychiatry. However, there are desperately and seriously ill patients who are not adequately treated by existing therapies. In addition to being potentially game-changing therapies, these drugs may also serve as probes into brain functions that mediate biochemically different subtypes of the same syndromic diagnosis of major depression. If so, they can drive the development of a better understanding of the fundamental nature of these illnesses, which will in turn increase the ability to develop novel, effective treatments. The path ahead is not easy because there are many practical questions to answer, as outlined by aan het Rot and colleagues (1). On the other hand, if the path ahead were easy, it would already have been transversed.

Dr. Preskorn reports no biomedical financial interests or potential conflicts of interest in relation to the topic of this paper. However, in the interest of full disclosure, he reports the following: Over his career, he has worked with more than 85 pharmaceutical companies. In the past one year, he has served as a consultant to Abbott, Biovail, Boehringer Ingelheim, Bristol-Myers Squibb, Dey Pharma, Eisai, Johnson & Johnson, Merck, Naurex, and Orexigen. He has been a speaker for Merck, Pierre Fabre, and Sunovion. He has received study contracts/grants (through Kansas University School of Medicine–Wichita) from Abbott, Cyberonics, Lundbeck, Naurex, the National Institute of Mental Health, Pfizer, and the Stanley Medical Research Institute. He also coauthored guidance with Food and Drug Administration staff on modified release formulations.