Ketamine for Treatment-Resistant Depression and Related Conditions:

A Review of a Novel and Needed Treatment Option

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September 2018

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Introduction

The old is new again, and ketamine, a 50+ year-old anesthetic for humans and animals, is now under active consideration for patients with treatment-resistant depression (TRD) and post-traumatic stress disorder (PTSD). Modern life has become decentralized, digitized, and depressed, phenomena that collectively contribute to the growing prevalence of psychiatric conditions. Major Depressive Disorder (MDD) affects nearly 7% of the American population per year and is the leading cause of disability worldwide.[1] TRD is a common subtype of the condition in which the patient has gained little or no relief from depressive symptoms after two or more trials of traditional antidepressant medications. It is estimated that one-third of depressed individuals experience treatment resistance.[2] These patients endure recurrent episodes of depression, poor quality of life, and functional impairment.[3] PTSD is a psychological disorder that can develop in any person who has experienced a life-threatening event. Those affected have severe anxiety, flashbacks, insomnia, intrusive thoughts, and tend to avoid triggering stimuli.[4] Woven within this constellation of symptoms is an epidemic of opiate abuse and high rates of suicide. Outpatient clinics and emergency rooms are saturated with patients requiring immediate relief from their symptoms. Although psychiatric conditions have traditionally been stigmatized, American society is finally recognizing the public health impact of mood disorders. Initiatives like the Mental Health Parity Act and the Affordable Health Care Act were designed to and are succeeding at improving access to care.

Innovation is the human response to need. Interest has peaked in the ketamine molecule, an antagonist of the *N*-methyl-D-aspartate receptor (NMDAR), after reports of its rapid-onset antidepressant properties. Original basic science and clinical research of the topic has been prodigious with scores of articles emerging in the past few years. This attention has been spurred

by the growing realization that currently available antidepressant medications and somatic treatment modalities have limited efficacy in vast segments of the psychiatric population.

The purpose of my paper is to explore the current landscape of therapeutic ketamine in light of an evolving understanding of TRD and PTSD. I will offer some background on the limitations of current antidepressant treatments and why ketamine is now entering the conversation. The history of ketamine, from synthesis to animal studies to recently published human trials, will be examined, and the proposed mechanism of action will be elucidated. I argue that the bulk of available data suggests that clinical administration of ketamine is safe and worthwhile, particularly for imminently suicidal patients. Its presence on formularies will offer clinicians a sharp contrast to familiar medications, and in some circumstances, ketamine will outperform mainstream treatments. Yet resistance against the rapid adoption of ketamine is necessary to ground both practitioners and mental health consumers. This check is particularly needed in light of the commercial interests propelling the development of a potential blockbuster.[5] Caution is amplified by recent reports that ketamine exerts its therapeutic benefits via the endogenous opioid system. While this might account for its analgesic effect and rapid mood improvement, chronic administration may promote dependency and prove deleterious.[6] For these reasons, the pending adoption of esketamine by the FDA should be met with healthy skepticism. Until more is known, ketamine should be approved only for short-term use in acute TRD. Clinicians who specialize in the diagnosis and long-term management of depression and related conditions should play a central role in ketamine's emerging application.

Search Methods

Using Google Scholar and Pubmed, literature searches were conducted for the years 2000-2018. Keywords entered were "ketamine for depression," "esketamine," "treatment-resistant depression," "PTSD," "ECT" and "opioids/opiates." These words were combined with "selective serotonin reuptake inhibitors," "glutamate and depression," and "new antidepressant medications." In addition to scholarly sources, searches of the popular press such as The Washington Post and certain trade periodicals were included. These articles often served to explain the larger context of more focused scientific findings.

Background on Existing Treatment for Depression: Medications

The principles behind the treatment of depression are changing. Since the 1960s, the monoamine hypothesis has been dominant. This theory maintains that symptoms of depression are caused by a deficiency of the neurotransmitters serotonin, dopamine, and norepinephrine.[7] To correct this "chemical imbalance," monoamine oxidase inhibitors (MAOs) and tricyclics (TCAs) emerged during the mid-20th century. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitor (SNRIs) were famously introduced two decades later. Lacasse and Leo argued that Pfizer's brilliant marketing strategy for Zoloft (sertraline) misled the public into believing that a serotonin deficiency is the root cause of depression.[8] Indeed, the monoamine hypothesis provides a simplified explanation of the actual biochemical mechanisms which drive affective disorders in the central nervous system.[9] Furthermore, the clinical success rates of these ubiquitous medications are underwhelming. Many patients with complicated depression undergo sequential courses of medication from different antidepressant classes in an effort to augment efficacy and minimize side effects. Monoamine antidepressants, prototypically the SSRIs, fluoxetine and sertraline, and the SNRIs, venlafaxine and duloxetine,

diminish libido and cause weight gain. They have a long latency of onset and often fail to address the full range of depressive symptomology. With the exception of vortioxetine in 2013, there has been minimal development of novel antidepressants in the new millennium.[10] Pharmaceutical companies have shifted research and development to other pressing and more lucrative opportunities in oncology and diabetes. Before the recent ground swell of interest in ketamine, few "new" antidepressants were on the horizon.[11]

Background on Existing Treatments for Depression: Somatic Therapies

Somatic treatments are chosen when medication trials have been exhausted. Electroconvulsive therapy (ECT) has been a mainstay for more than 60 years. Vagus nerve stimulation (VNS) and repeated transcranial magnetic stimulation (rTMS) have been introduced in the last 15 years.[12] Historically, the most rapid means for mitigating severe depression has been electroconvulsive therapy. ECT was first implemented in 1940s to treat schizophrenia, later gaining adoption for mood disorders. Immortalized by dramatic depictions in films such as *One Flew Over the Cuckoo's Nest (1975)* and *Requiem for a Dream (2000)*, ECT remains a controversial and stigmatized practice. ECT machinery is considered a "high-risk medical device" by the FDA and the procedure is generally used as a last resort for treatment-resistant depression.[13] ECT involves unilateral or bilateral placement of electrodes onto the skull. A series of electrical pulses is administered, putting the brain into a controlled seizure. It is proposed that ECT alters the pattern of blood flow and stimulates the production of neurotrophic factors in the medial temporal lobe, resulting in the changes to the hippocampus.[14] General anesthetics are required, usually short-acting barbiturates, Propofol, or at times ketamine. Major side effects include retrograde amnesia and cognitive impairment. These

cognitive consequences may be due to widespread saturation of the glutamate receptors, which play a role in learning and memory.[15]

Efforts have been made to develop better-tolerated somatic treatments for mood disorders. Transcranial magnetic stimulation (TMS) is a non-invasive procedure which uses repeated electromagnetic induction to stimulate a targeted region of the prefrontal cortex. Despite early high hopes, the clinical utility in mild to moderately depressed patients is equivocal, with little confidence that the treatment is appropriate for TRD. Vagal Nerve Stimulation (VMS) sends electrical signals to the vagus nerve, the tenth cranial nerve. This procedure requires surgical intervention and demands that the patient adapt to an implanted nerve stimulator. Patients must tolerate periodic hoarseness when the modulation is active. Insurance coverage has been spotty for this elaborate program and uptake by the psychiatric community has been minimal.[16]

Patient Non-Responsiveness to Treatment: The STAR*D Study

Although fluoxetine and its successor analogues proved helpful in treating uncomplicated depression, clinical concerns have shifted toward SRI non-responders. In 2006, the National Institute of Mental Health completed a large-scale study that examined how patients responded to subsequent treatment after the first round of antidepressant medications had failed. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study involved over 4,000 subjects and was conducted across 41 clinical sites in the United States. The objective of this seven-year study was to determine the efficacy of available medications.[17]

The elaborate study design involved four different treatment levels. At level one, subjects were given the SSRI, citalopram for up to 14 weeks. Responders (50% reduction in depressive symptoms) were diverted into a naturalistic study, but non-responders were encouraged to enter

level two. In level two, patients were randomized to several different medications (sertraline, bupropion-SR, or venlafaxine-XR) and given the option to participate in concurrent cognitive behavioral therapy (CBT). Subjects who did not respond entered level three, where their antidepressants were augmented by either lithium or triiodothyronine. Those who were still symptomatic proceeded to level four and were given either tranylcypromine, a MAO inhibitor antidepressant, or a combination of venlafaxine-XR and mirtazapine. Only 142 subjects remained in the study to level four.

The STAR*D study revealed that the response rate to antidepressants was much lower than anticipated. Remission rates were only 33% for level one. Level two revealed that combinations of antidepressants acted more rapidly than adding CBT to one antidepressant. Remission rates in levels three and four were 12.3% and 13% respectively. The authors glumly conclude that "patients with difficult-to-treat depression can get well after trying several treatment strategies, but the odds of beating the depression diminish with every additional treatment strategy needed."[18]

The STAR*D study had limitations. The protocol did not include any somatic treatment such as ECT or rTMS. The study was conducted over such a long period that less than a tenth of the participants survived to the end. Notably, STAR*D muted the enthusiasm for existing therapies and spurred interest in alternative avenues. Next-generation treatments needed to be more rapidly-acting, better tolerated, and exert improved remission rates for treatment-resistant patients.[19]

A Brief History of Ketamine

The ketamine molecule was synthesized in the early 1960s by Wayne State University professor Calvin Lee Stevens.[20] Prior to this development, phencyclidine

(PCP) saw widespread use as a surgical anesthetic and experimental psychoactive medication. PCP had serious postoperative effects, such as paranoia, convulsions, agitation, and disorientation upon emerging from induction. Initial tests of ketamine as an anesthetic began in 1964, when University of Michigan researchers Edward Domino and Guenter Corssen examined the clinical effects on 130 surgical patients ranging in age from 6 weeks to 86 years.[21] They discovered that subjects experienced greater tolerability with ketamine compared to its sister NMDAR antagonist, PCP. The most notable adverse effects associated with ketamine – elevated heart rate, nausea, a feeling of unreality, and disorientation – were transient.[22] The new drug received the green light as an anesthetic from the FDA in 1970.

Deemed a "dissociative anesthetic," ketamine proliferated worldwide. It was adopted as a quick-acting and easily-administered analgesic during the Vietnam War, where it was favored over morphine due to its limited effect on respiratory depression. In 1985, the World Health Organization (WHO) included ketamine in the Model List of Essential Medicines. Veterinary clinics incorporated the anesthetic into daily practice. Ketamine is still used and researched in animal medicine.[23]

Ketamine's descent into controversy began when New Age practitioners became intrigued with ketamine's euphorigenic and dissociative properties for use in psychotherapy.[24] Owing to its "essential medicine" status and stockpiling at veterinary clinics, the drug was exploited for recreational purposes. The array of psychedelic symptoms – detachment, disorientation, loss of inhibition, word slurring, and a floating sensation – is colloquially known as a "K-hole." Ketamine became a notorious club drug and "date-rape" agent.[25] Skepticism delayed clinical explorations in psychiatry and it was not until the turn of the 20th century that serious research began on ketamine's antidepressant effects.

Glutaminergic Transmission

Ketamine targets the glutaminergic system, and it is important to understand how it affects the glutamate receptors in depression and other mood disorders. Glutamate is the most abundant neurotransmitter and is considered the "master switch" of the CNS.[26] It enhances synaptic connections in the brain and plays a fundamental role in learning, memory and neuroplasticity. Glutamate is highly concentrated in the synaptic terminals, where its two most significant ionotropic receptors reside: the NMDA receptor is more slowly activated and is permeable to calcium, while AMPA is impermeable and quick-acting. Under normal circumstances, the binding of glutamate (and glycine) to the NMDAR permits calcium influx via allosteric dissociation of the gatekeeping Mg+ plug.[27] Depressed patients have lower mitochondrial energy production in their glutamatergic neurons, which results in dysfunctional clearance and metabolism of glutamate.

Ketamine Pharmacology

Ketamine ((R,S)-2-(2-Chlorophenyl)-2-methylaminoclyclo-hexanone) is a noncompetitive NMDA receptor antagonist. It is both water and lipid soluble and can be absorbed through all standard routes of administration. It selectively binds to the PCP-binding site on the NMDAR with a tenfold lower potency than PCP itself. Ketamine modulates pain through complex interactions with numerous classes of receptors, including opioid receptors, nicotinic/muscarinic receptors, the monoaminergic system, and the GABAergic system. Ketamine preferentially blockades the NMDAR, and consequent disinhibition of pyramidal GABAergic neurons permits AMPA receptor upregulation and increased downstream glutamatergic signal transmission.[28] The synaptic

cleft experiences an increase in glutamate that heretofore would have been directed toward the NMDAR. Instead, a concurrent increase in post-synaptic AMPA density allows for an signaling cascade that activates mammalian target of rapamycin (mTOR) and neurotrophins such as brain-derived neural growth factor (BDNF) (see Fig. 1). The proliferation of these downstream pathways increases synaptogenesis, amplifies translation of neurotrophic proteins, and ultimately reduces depressive symptoms.[29] Through calcium channel inhibition, ketamine diminishes pain sensitivity.[30]

Ketamine's most important interactions are with the NMDAR, but it also has an affinity for the opioid receptors, binding to the μ, κ, σ receptors. This relationship may provide clues about ketamine's strong analgesic effect. However, relatively high binding to the μ receptor raises the question as to whether the clinical benefit is from the glutaminergic or opioidergic pathways. This is an important distinction that will be discussed later.

Animal Models Lead to Initial Human Subject Studies

It is proposed that when organisms face chronic stress, repeated depolarization of NMDAR unleashes a flood of post-synaptic glutamate. This phenomenon is called "excitotoxicity." Too much glutamate in these permeable receptors causes excessive calcium influx, which damages cell structures and precipitates neuronal apoptosis. Over time, excitotoxicity lead to a number of central nervous system diseases.

Whereas "escapable stress" is acute and prompts the fight-or flight response, "inescapable stress" is chronic and leads to behavioral depression. In 1990, Trullas and Skolnick posited that overstimulation of the NMDA receptor could contribute to depressive symptoms of inescapable stress. To simulate this, rodent subjects were placed in a series of unfamiliar and crowded cages. They later administered either a competitive antagonist, a noncompetitive

antagonist, or a partial agonist to decrease NMDA neurotransmission in their rodent models. They found that the resultant synaptic connections in the CA1 region in the hippocampus could transform from a state of Long-Term Depression (LTD) to one of Long-Term Potentiation (LTP). They proposed that drugs that inhibit the NMDAR could parallel the effects of established antidepressants.[31]

Studies in rodents allow insight into the behavioral effects of ketamine administration. Ketamine-dosed rats subjected to the Forced Swim Test (FST) were more likely to try to escape than controls. Compared to TCAs, SSRIs, or MAOs, ketamine demonstrated the most rapid-onset reduction in learned helplessness behaviors. In one study, it was shown that rats were less likely to choose a sugary drink over plain water when placed under conditions of chronic stress. This behavior is consistent with the loss of pleasure frequently exhibited by depressed patients. When injected with ketamine, previously anhedonic rats had renewed interest in sucrose consumption. Taken together, these rodent studies give credence to ketamine's effect of ameliorating anxiety, depression, and anhedonia.[32]

Bench research and animal models are essential steps in the identifying potentially useful therapeutic agents in humans. Still, certain limitations exist; the animal model relies on primarily on assessing locomotion, and unlike humans, rodents cannot express the emotional symptoms of depression. We should proceed cautiously with the model that "chronic stress" in the rodent translates clinically to the human condition of TRD or PTSD.

First Ketamine Study in Depression

While ketamine had been used as a surgical anesthetic and recreational drug for decades, serious research into its efficacy as a treatment for severe depression is more recent. In 2000, Berman and colleagues organized the first double-blind trial to examine the effects of subanesthetic ketamine hydrochloride on seven depressed human subjects. The ketamine group received intravenous 0.5 mg/kg doses and the control group received saline solution over 48 hours. The ketamine group demonstrated statistically significant improvement on the Hamilton Depression Rating Scale within 72 hours of infusion, a finding not shared by the placebo group. This small but positive study affirmed NMDAR antagonism as a valid therapeutic approach and spurred other larger and more sophisticated trials.[33]

Epidemiology and Morphology in Treatment-Resistant Depression

The Berman study focused on patients with major depression. A more perplexing issue facing psychiatry is the nature of treatment-resistant depression. TRD is characterized by extended duration and severity of the depressive episode. The designation is given after an inadequate response to at least two courses of two different classes of antidepressants.[34] In a large meta-analysis, nearly 60,000 patients were studied comparing treatment-resistant to treatment-responsive depression. Resistant patients had greater number of prior depressive episodes and lower scores on quality of life assessments (see Figure 2). Both variants of depression significantly reduce economic productivity, with a total estimate of societal cost as high as $118 billion per year.[35] Beyond the objective human suffering associated with chronic depression, TRD patients are at greater risk of suicide. Suicidal ideations tend to emerge episodically, even within the context of chronic low mood. For this reason, rapid-onset therapies to relieve suicidal ideations are of premium importance.

Morphological findings in TRD have been elucidated by neuroimaging. Changes to the caudate nucleus, the right superior and middle temporal gyri, and the subgenual anterior cingulate cortex (ACC) have been correlated with recurrent depression. Most significantly, hippocampal volume has been shown to shrink under these circumstances. It has been noted that patients with notable reduction in the hippocampus – a classic biomarker of severe depression indicative of glutamate dysfunction – respond poorly to treatment with traditional antidepressants.[36] Several studies suggest that modulators of the glutaminergic system such as ketamine are more therapeutic for patients with smaller hippocampal volume. Notably, Murrough and colleagues used fMRI to analyze emotion perception in subjects with TRD. In the control condition, subjects showed reduced neural activity in the right caudate when presented with photos of smiling faces. After being infused with ketamine, this same brain region showed greater activation.[37]

Ketamine Trials in TRD

Established depression rating scales are more practical than neuroimaging for ascertaining treatment response. In the last several years, ketamine has been subjected to numerous controlled trials. In a single site study, Zarate and colleagues recruited depressed adults who had failed two antidepressant trials and scored 18 or above on the 21-item Hamilton Depression Scale (HDS). Following a two-week washout period, 18 subjects received intravenous infusions of either saline solution or 0.5 mg/kg of ketamine hydrochloride. The infusions were administered one week apart using a randomized double-blind crossover design. Subjects were rated using the HDS and other secondary outcome measures one hour before infusion and again at specified time post dose. Results revealed statistically significant improvement of ketamine over placebo. The effect size

was large after 24 hours (d =1.46) and after 1 week (d = 0.68). Adverse events were more common in the ketamine-treated group and included perceptual disturbances, confusion, elevated blood pressure, euphoria, dizziness and increased libido. Still, the side effects were transient and well-tolerated.[38] These results fortified Berman's preliminary finding that hinted at ketamine's rapid antidepressant response.

Murrough sought to expand on this finding with a two-site study of 72 patients with TRD. In this trial ketamine was compared to midazolam. Midazolam, a sedative without mood-altering properties, was chosen as an active control because like ketamine it has obvious anxiolytic effects. Therefore, subjects were less likely to speculate into which group they were randomized; this ambiguity promoted the blind nature of the study and the quality of the findings. The trial revealed that the ketamine group had greater mood improvement than the midazolam group 24 hours after treatment.[39] Adverse events were similar to the Zarate study.

Ketamine and Suicidality

Given the rapid onset of ketamine's effects, it was logical to pursue studies in patients with suicidal thoughts. The WHO estimates that 800,000-1 million people take their own lives each year.[40] Cognizant of the predisposition to suicide of patients with major depression, Grunebaum and colleagues studied 80 adults with MDD and a score ≥ 4 on the Scale of Suicide Ideations (SSI), of whom 43 were on active antidepressant treatment. Subjects were randomized to intravenous ketamine or midazolam groups. One day after treatment the reduction in the SSI was 4.96 points greater for the ketamine group. (d = 0.75). Clinical response was defined as having a 50% reduction in the SSI score. Using this metric, the proportion of responders in the ketamine group was 55% compared to 30% for the midazolam group. The authors concluded that

ketamine adjunctive to existing antidepressant medications could lead to a clinically significant reduction in suicidal ideations when compared to midazolam.[41]

Ketamine as an Adjunct to ECT

As a group, TRD patients are clinically challenging and they typically require polypharmacy or other elaborate treatments. ECT has been considered the gold standard of last-ditch treatment and researchers speculated that ketamine added to ECT would augment response and mitigate the cognitive side effects of ECT.

Unfortunately, controlled trials did not prove any of these hypotheses. Anderson and colleagues conducted a three-year, 79-subject study of patients with severe unipolar depression. They found no conclusive evidence that the anti-depressive effects of ECT were enhanced by sub-anesthetic doses (0.5 mg/kg) of ketamine. They conceded that their sample size was smaller than expected, however, and they did not rule out a potential benefit.[42] McGirr et al reached similar negative findings in a larger meta-analysis that determined that ketamine did not have any pro-cognitive effects in patients undergoing ECT.[43] Perhaps the negative outcome was attributable to the fact that ketamine raised seizure threshold, which would have directly interfered with ECT's core objective of placing the depressed brain into controlled convulsion. Given the concurrent use of ketamine as an induction anesthetic, it is not surprising that ECT treatment-centers would assess the additive effects of the two anti-depressants modalities. Despite expectations, these two studies do not support ketamine added to ECT. The findings should guide future studies that examine which existing treatment pairs most favorably with ketamine.

Development of Esketamine

Ketamine in its traditional form is a racemic mixture consisting of equal parts R- and S-ketamine. This form of the drug has been long-approved by the FDA and is widely used via intravenous administration for surgical anesthesia and pain management. For surgical patients, ketamine infusion provides sympathetic stimulation necessary for keeping the cardiovascular system functioning. The latest development in the field is esketamine, the S-(+) enantiomer of the molecule. Both the racemic and enantiomeric formulations similarly affect the glutaminergic system, but S-ketamine inhibits the NMDAR with 400% greater effectiveness than R-ketamine.

Unlike ketamine, esketamine, does not interact with central sigma receptors. The enantiomer has greater affinity for the PCP binding site on the NMDA receptor than does the racemic mixture.[44] Clinically, S-ketamine has been shown to have less marked hallucinogenic and other disorienting psychomimetic effects.[45]

Another difference is that esketamine can be absorbed via internasal administration. Johnson & Johnson's subsidiary, Janssen, has been conducting ambitious multicentered clinical studies for several years. While ketamine is a viable molecule to develop for psychiatric indications, it is a generic and no company will invest hundreds of millions into a product they do not have exclusive rights to manufacture. The Janssen esketamine nasal spray is currently in Phase III and has received FDA fast-track status. It is on pace to receive full approval for a 2019 market release. The expected indications would be as an adjunct to antidepressant medication and for acute suicidal ideations associated with major depression.[46] Ketamine will remain a less expensive alternative to esketamine, albeit without formal FDA indication. Patients are expected to embrace the intranasal method of drug delivery.[47]

First Clinical Trial of Esketamine in TRD

The first randomized clinical trial of intranasal esketamine adjunctive for TRD was published in 2018. Daly et al screened 67 subjects in a three-period study. In the first period, participants were randomized into a 3:1:1:1 format; 33 participants received placebo, 11 received 28 mg of ketamine, 11 received 56 mg and 12 received 84 mg. Nasal inhalations were administered twice weekly. In the second period, participants who received placebo during the first period were given active agent, although a small number of the placebo patients with mild symptoms remained on placebo. All other participants continued to receive treatment. In the third and final period all participants were given esketamine in an open label. Dosing frequency in the open label phase decreased from bi-weekly to weekly.

The results were robust and positive. In all three dosing strategies, depression scores in the esketamine treated groups improved to a statistically significant extent. These improvements were dose-dependent. Onset was rapid, and scores did not fall when the dosing frequency decreased during period three. Three out of the 56 completers dropped out due to adverse events.[48]

Ketamine in PTSD

Posttraumatic stress disorder (PTSD) is a psychological disorder that occurs after trauma. It is typically associated with combat veterans who have witnessed death and destruction but can develop in any person who has experienced a life-threatening event. Exposure to natural disaster and chronic sexual and emotional abuse also constitute provocative factors. Women suffer at higher rates than men. Those affected have severe anxiety, flashbacks, insomnia, intrusive thoughts, and tend to avoid triggering stimuli.[49]

PTSD is notoriously difficult to treat and substantial investment by the Department of Veterans Affairs since the Vietnam War have not yielded anticipated results. Most regimens consist of a combination of individual cognitive behavioral therapy, group therapy, Eye Movement Desensitization and Reprocessing (EMDR) and SRI medication.[50] The high rates of psychiatric disability that persist testify to the limitations of available therapies, and the epidemic of veteran suicide amplifies this complicated story.

Intravenous ketamine, however, may provide a therapeutic option. Feder et. al organized a trial in which forty-one subjects with PTSD were recruited. Subjects were infused with 0.5 kg/kg of ketamine or 0.045 mg/kg of midazolam as a control. Results concluded that ketamine infusion provided a more rapid and marked decrease in PTSD symptoms. Comorbid symptoms of depression also abated.[51] Albott et. al examined the efficacy of ketamine infusions for combat veterans with comorbid TRD and PTSD. As expected, repeated ketamine injections briefly increased feelings of dissociation, although none of the subjects reported a worsening of their PTSD symptoms. The authors concluded that sustained ketamine administration could be improve quality of life for patients suffering from both TRD and PTSD.[52]

A recent study at Columbia University Medical Center hints at creative potential for ketamine in clinical practice. Mice were injected one week prior to a traumatic event and demonstrated a diminished condition fear response afterward. While this is an animal study, the heuristic implications of "inoculating" soldiers or others certain to experience psychological trauma is intriguing.[53] Other researchers rooted in an interest in the psychedelic experience are investigating the dissociative properties of ketamine infusion during exploratory psychotherapy.[54]

The March to FDA Approval

The sheer number of positive safety and efficacy trials involving esketamine have paved the path for imminent FDA approval. The fast-track trajectory allows a quicker entrance into the marketplace for drugs that can treat serious or life-threatening conditions. The anti-regulatory philosophy of the current executive administration has guided the approval of a record number of new drug and generic applications over the past 18 months.[55] Fueled by online publications and social media, the interest in ketamine in the lay community has surged and scores of ketamine clinics have popped up throughout the country. Marketing their services to depressed patients, the clinics are typically run by anesthesiologists or pain medicine specialists with experience administering IV ketamine, but with little experience treating TRD patients at high suicide risk. The American Psychiatric Association recently issued a non-binding consensus statement ahead of the medication's formal approval. The APA guidelines conclude that the bulk of available research supports the efficacy of ketamine for short-term use. Ketamine should be administered in a medical setting under the auspices of trained physicians. Because of the dissociative side effects, it should not be self-administered at home.[56] The cautionary language appears appropriate for a number of reasons.

Safety Concerns

There have been questions raised about ketamine's safety, tolerability, and abuse potential. Both ketamine and esketamine cause transient dissociative symptoms and for this reason, ketamine will need to be administered in a supervised outpatient setting. This represents a significant departure from self-administered oral antidepressants. The need

for monitoring will increase costs and tangle logistics. Other glutaminergic agents do not share this undesirable side effect.[57]

On the other hand, evidence supports that beyond the transient psychedelic effects of ketamine, the drug is well-tolerated. A 2015 study by Wan (n = 97) found that a single low dose of ketamine (0.1-1.0 mg/kg) resulted in a 50-70% improvement in TRD symptoms. A total of 205 intravenous subanesthetic doses infusions were conducted to assess the various dissociative and psychotomimetic effects. The most common short-term side effects included drowsiness, dizziness, loss of coordination, blurred vision, and feelings of unreality. After the trial, study participants were interviewed on their reactions to ketamine treatment.[58] Only one of the them claimed that the treatment increased their level of anxiety and dysphoria. No participant reported increased cravings for the drug after treatment. This encouraging finding dampened the claim that therapeutic ketamine will have high rates of abuse.

Is the Antidepressant Effect Mediated by the Opioid System?

The reassurances derived from Wan's post-trial interviews were challenged by an August 2018 report from Stanford University. Dr. Alan Schatzberg, former president of the APA, understood ketamine to have dual properties of an NMDAR antagonist and an activator of opioid receptors. His team conducted a double-blind crossover of 30 adults with TRD using standard ketamine dosing. Half the subjects were pretreated with the opioid receptor antagonist naltrexone. In an interim analysis, subjects given naltrexone plus ketamine had significantly better reductions in their HAM-D scores than the ketamine plus placebo group. Naltrexone did not impact the dissociative effect seen in either group.[59]

In an interview, Schatzberg speculated that ketamine activates the opioid system, and this explains its rapid antidepressant effect. The glutamate system may be responsible for the psychomimetic effects and sustaining the clinical benefits once the ketamine is metabolized. “Before we did the study, I wasn’t sure that ketamine really worked to treat depression. Now I know the drug works, but it doesn’t work like everyone thought it was working.” He cautions that the activation of the endogenous opioid system by ketamine might create dependency and that the FDA would be wise to limit the use of ketamine to acute rather than chronic depressive symptoms.[60]

Summary and Conclusions

Depression and other mental health conditions are on the rise. Uncomplicated cases respond to available antidepressant treatment, but the monoamine hypothesis of depression has proven inadequate and simplistic. Existing antidepressant medications take too long to start working and cause undesirable side effects. The STAR*D study revealed that significant percentages of depressed patients have treatment-resistant conditions that were unresponsive to available drugs on the market. Appropriate attention has shifted to the role of glutamate modulation in depression. Ketamine exerts its effects both on the NMDAR and the opioid receptor system, which in this addiction-averse climate muddies enthusiasm for its widespread use in the near future.

Solid research supports ketamine as treatment for treatment-resistant depression. The initial studies by Berman in 2000 identified a new mechanism for depression and catapulted a movement dedicated to uncovering the mysteries of TRD. Murrough isolated morphological changes using fMRI and Zarate extended these findings in larger studies. Grunebaum demonstrated improvement in suicidality. Trials of esketamine have been

resoundingly positive and its introduction to the marketplace will likely occur in the next year.

Still, caution should be exercised. Several studies reveal that ketamine does not improve depression when used as an adjunct to ECT. Ketamine causes dissociative effects which will raise cost and lower access to the drug. Concerns have been raised about its interaction with the opioid receptors, and much more research is required to unravel the long-term abuse potential. Ketamine has had a winding journey from the Detroit laboratory bench to branded intranasal formulation. It will undoubtedly become a vital asset in the antidepressant arsenal desperately in need of innovation.

Figures

Figure 1

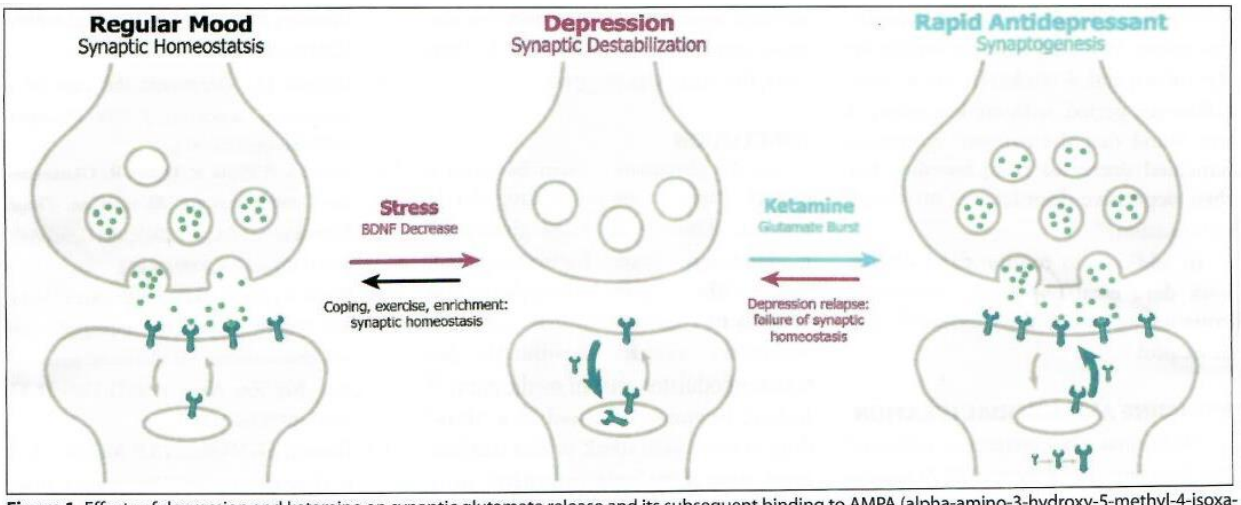

Figure 1. Effects of depression and ketamine on synaptic glutamate release and its subsequent binding to AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic) receptors leading to synaptogenesis in the prefrontal cortex. BDNF, brain-derived neurotrophic factor. Adapted from Abdallah et al.[30]

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Biographical Sketch

I graduated from the University of Michigan in 2013 with a degree in history. I then pursued my premedical studies at Oakland University while working in psychometric testing, a role which has given me the privilege of caring for thousands of patients. I enrolled in Wayne State's MS in Basic Medical Sciences in 2016. I am currently applying to medical school. I have learned so much in the BMS program and feel well-prepared for the journey ahead. In my free time, I enjoy reading, technology, running, sports, and playing with my two golden retrievers.