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Column

# Biological Perspectives

## Ketamine as an Alternative Treatment for Treatment-Resistant Depression

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> Studies have shown that a single infusion of the NMDA receptor antagonist ketamine produces a very robust response, including full remission, in treatment-resistant unipolar or bipolar depression within 1 to 2 hours.
> Dr. Henry Nasrallah (2012)

Major depressive disorder (MDD) is a significant healthcare issue, with approximately 10% of Americans suffering from it in any given year (Anand & Mathew, 2011). Anand and Mathew (2011) succinctly capture the enormity of the problem, indicating it is second only to ischemic heart disease as a health burden on the economy. When considered with less-debilitating variants of this apathy-inducing condition, the total worldwide expenditure for depression-fighting medicines amounts to a staggering $20.4 billion/year. Not surprisingly, antidepressants rank #9 in top global therapeutic classes of drugs (IMS Health Midas, 2011) and they are among the top three medications prescribed for on-therapy patients who received dispensed prescriptions in prior months (IMS Institute for Healthcare Informatics, 2012). These "lost" monies, when added to diminished productivity, failed relationships, and other downstream consequences, deliver a devastating blow to our national fabric.

Beyond these potentially fixable problems is the irreversibility of suicide. Suicidal ideation is a cardinal symptom of depression, with completed suicide being the third highest cause of death among young people aged 15–24 (Murrough, 2012). This statistic perhaps partially explains why antidepressants in the United States were the second highest ranked medications for having largest changes in usage by patients, ages 19–25 years of age (IMS Institute for Healthcare Informatics, 2012).

MDD, as a leading cause of psychiatric morbidity, becomes a particular scourge when it does not respond to typical psychotherapeutic and psychopharmacologic treatment interventions. One would think financial resources poured into the treatment of depression would keep it somewhat in check—not so, however! The Sequenced Treatment Alternatives to Relieve Depression study found that only 37% of patients who received optimized antidepressant treatment (i.e., an adequate dosage of antidepressant for an adequate length of time) achieved remission (Rush et al., 2006). The Combining Medications to Enhance Depression Outcomes trial reported similar modest results (Rush et al., 2011). Thus, a term that has crept into the literature is treatment-resistant depression (TRD). TRD is an increasingly well-recognized phenomenon and is defined as continued, severe depression after an optimized trial of antidepressants. It is thought that up to 15% of patients diagnosed with MDD do not respond to traditional treatments and are consequently classified as TRD (Messer & Haller, 2010). These individuals tend to be more depressed, more disabled, and more likely to experience relapses than non-TRD individuals (Murrough et al., 2012). When coupled with the statistics noted above, the burden of this mental disorder on society can be rightly judged as a national concern if not a national emergency.

One view of depression proposes to link it to neuronal atrophy and death (Duman, Li, Liu, Duric, & Aghajanian, 2012). Imaging techniques have revealed a reduction in limbic volume, especially in the hippocampi and in the prefrontal cortex (Duman & Li, 2012). Neurons appear to fall prey to high extrasynaptic levels of glutamate, leading to neuronal death via excitotoxic-driven over-firing (aan het Rot, Charney, & Mathew, 2008). Glutamate overactivity is related to chronic stress and neurons are thought to atrophy, shrink, and die when consistently exposed to these high stress levels (aan het Rot, Zarate, Charney, & Mathew, 2012). A popular view is that depression-caused reductions in brain-derived neurotrophic factor (BDNF) remove a protective barrier to neurodegenerative forces.

Standard antidepressant medications modulate the monoamine system, principally serotonin, norepinephrine, and/or dopamine (aan het Rot et al., 2012). Augmenting agents, including second-generation antipsychotic and thyroid medications (T3 and T4), are commonly employed when a patient does not obtain adequate symptom relief from treatment with one or more antidepressants. However, even with this level of prescriptive complexity, some patients

continue experiencing significant depressive symptoms, thus the hunt for yet other therapeutic approaches. Nonpharmacologic approaches have gained appeal. For example, repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), deep brain stimulation (DBS), and electroconvulsive therapy (ECT) have all been found effective for some people. It should be noted that, save for rTMS, all of these somatic treatments are invasive—VNS requires surgical implantation, electrodes are embedded in the brain for DBS, and ECT requires general anesthesia (Anand & Mathew, 2011). Particularly with ECT, but with VNS and DBS as well, there is a general reluctance to undergo these procedures. This is especially unfortunate with ECT because it has remarkable success in TRD, although not infrequently associated with memory loss as an adverse side effect. Thus, the search for yet another treatment for depression continues.

Current pharmacologic efforts include manipulating mechanisms beyond the three monoamines mentioned. In particular, the N-methyl-D-aspartate (NMDA) receptor has drawn much attention. Drugs capable of modulating this receptor have been the focus of recent clinical research. Ketamine is such an agent. Ketamine is composed of a stereoisomer with the S enantiomer having a four to five times greater affinity for the NMDA receptor (aan het Rot et al., 2008). It selectively binds to the NMDA receptor site and only minimally to the other glutamate receptors (i.e., alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid [AMPA] and kainite receptors), although it does increase glutamate availability at AMPA receptor sites. It is classified as a noncompetitive glutamate NMDA receptor antagonist. It has a half-life of about two hours and is metabolized by the cytochrome 2B6, 3A4, and 2C9 enzymes (Anand & Mathew, 2011). Bioavailability drops significantly when the oral form is used. Beyond the glutamate receptors mentioned, ketamine interacts with muscarinic receptors, voltage-gated calcium channels, and inhibits serotonin and norepinephrine reuptake.

Ketamine, which is primarily used as an anesthetic agent in human and veterinary medicine, has shown great promise as an alternative medication for treatment-resistant MDD. It has the advantage of a rapid onset of action, often after just one dose of medication, in terms of promoting relief from significant symptoms of depression (including suicidal ideation) and feelings of hopelessness and helplessness. These sought-after outcomes occur within hours in most patients, rather than days, weeks, or even months that may elapse before the standard antidepressant medications and/or other treatments mentioned above show effect (Duman et al., 2012). So far, studies that have been performed indicate that patients who receive benefit from ketamine do best when they are given a course of medication, as its antidepressant effect often appears to be relatively short lived. Ketamine may be given intravenously, intramuscularly, intranasally, and orally.

As noted, ketamine acts quickly. Although a number of routes are available, it appears to be given intravenously most often at a dosage of about 0.5 mg/kg over 40 min or so (aan het Rot et al., 2008). Its antidepressant action develops within 2 hr, with an effect lasting for 3–7 days (aan het Rot et al., 2012; Duman & Li, 2012). Ketamine's antidepressant response is accompanied by increase in synaptic activity (i.e., synaptogenesis) which allows for more efficient neurotransmission and intracellular signaling mechanisms (Duman et al., 2012). Ketamine also increases glutamate transmission and the release of BDNF, thus restoring depression-linked BDNF reductions. Of course, these ketamine-driven events plus even more complex processes belie its simplistic designation as an NMDA receptor blocker.

While ketamine with its rapid and beneficial effect suggests an optimism missing from traditional treatment of TRD, it is not without failings. For example, ketamine's therapeutic effect is time limited, hence the recommendation for continuous treatment. Also, ketamine produces a number of potential side effects, of which the most concerning from a psychiatric perspective is the induction of psychotic, manic, or dissociative symptoms. The dissociative state can be described as dreamlike, with depersonalization and a sense of unrealness being consistent themes. While these serious effects are typically mild and transient, they nonetheless discourage its use (Murrough, 2012). Alarmingly, these same potential side effects have also caused ketamine to be a substance which is sometimes abused. Several studies have also shown that ketamine has been beneficial in terms of treating depressive symptoms in individuals with bipolar disorder without a significant induction of manic symptoms in most individuals. Further, some patients have experienced brief changes in their vital signs (aan het Rot et al., 2012) as well as blurred vision and feeling drowsy or sleepy (Murrough et al., 2012).

While side effects are typically mild and transient, nursing implications include monitoring patients who receive ketamine for these psychotic, manic, or dissociative symptoms. Maintaining safety of the patient receiving ketamine as well as others in the patient's environment is essential. Further, stability of vital signs should be assessed before and after administration. Of course, these patients also should be instructed to sit up slowly, and initial walking should be done with assistance until the nurse concludes their alertness, gait, and vision have returned to normal or that it is safe to ambulate.

## Summary

Since Dr. Roland Kuhn's (1958) discovery of imipramine in the late 1950s, a deluge of "newer and better" antidepressants has been presented to clinicians and to sufferers of depression. The motivation for this continuous search is 2-fold.

First, this is a highly lucrative business. Second, as noted above, a significant subpopulation of individuals with depression is not helped with the drugs now available. These individuals are said to be treatment resistant. Further, current treatments can take weeks to months to achieve their antidepressant effect (Machado-Vieira, Salvadore, DiazGranados, & Zarate, 2009). Ketamine appears to be different from standard medications in at least three ways: (a) its primary effect is not on the monoaminergic systems, (b) complete relief from depression can occur within 2 hr or so, and (c) its therapeutic effect appears to be quite transient when given by infusion. Nevertheless, ketamine looks to be a potentially valuable tool for the treatment of depression resistant to existing remedies. Time will tell.

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