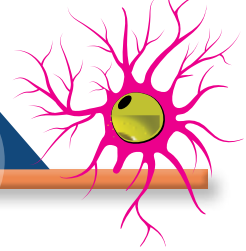

Ketamine and the glutamate hypothesis of depression

Ketamine is a promising but controversial drug that has gained attention in the past decade for the treatment of depression and suicidality. Ketamine is known to enhance the activity of glutamate, the main excitatory neurotransmitter in the brain. Increasing glutamate can result in enhanced neurotransmission and subsequent synaptogenesis (the creation of new synaptic connections), resulting in long-term potentiation.

Glutamate works through several receptors, including NMDA, AMPA and kainite, alongside the metabotropic receptors. Ketamine is an N-methyl-D-aspartate receptor (NMDA-R) antagonist (a substance that attaches to NMDA-R and blocks its effects) that enhances the activity of glutamate. This mechanism of action is different than for most other currently existing antidepressants, which primarily target the neurotransmitters serotonin and norepinephrine.

Ketamine is well-known in the medical community and is already on the World Health Organization's list of essential drugs for its use as a preoperative surgical anesthetic for both humans and animals. It was first used medically in 1965 as a successor to phencyclidine (PCP) in anesthesia. The incidental observation that patients receiving ketamine appeared to experience rapid improvements in their mood led to the first trial of ketamine for depression in 2000.

Ketamine offers the promise of robust antidepressant effects within a short period of time relative to other psychopharmacological agents (days rather than weeks or months) and generally limited, well-tolerated side effects. In at least four blind randomized controlled trials, ketamine was found to reduce depression rapidly (within 24 hours), with effects lasting for several days and as long as a week for some patients. In a study conducted in 2006 by Carlos Zarate and colleagues in the Mood and Anxiety Disorders Program at the National Institute of Mental Health, ketamine reduced depression within two hours of administration, with sustained effects for seven days for 35 percent of participants. There is also preliminary evidence to suggest possible anti-suicidal effects for ketamine, independent of its effect on depression, although larger studies are needed.

The typical dosing for ketamine is 0.5 milligrams/kilograms, administered as a slow IV over 40 minutes. It has also been used intranasally, although it is unclear whether intranasal administration is as effective as IV. Rapid IV ketamine infusion has also been tested, although a highly cited 2011 trial using this method by Gregory Larkin (then at the Yale School of Medicine) and colleagues recently was retracted for "misrepresenting both the protocol-specified doses and the actual delivered doses of ketamine." Subsequent research by Colleen Loo (University of New South Wales, Australia) and colleagues, published in 2014 and 2016, attempted to replicate Larkin's study unsuccessfully. Loo reported that research participants experienced substantial side effects, including dissociation and disorientation, from such a rapid dose of ketamine. The duration of administration had to be increased from two minutes to five minutes. They also found no benefit to rapid administration of ketamine compared with slower administration.

Modifying the functioning of glutamate

The observation for a possible rapid antidepressant effect may be understood by examining how ketamine impacts neural functioning. A 2010 study by Nanxin Li (Yale School of Medicine) and colleagues that was published in *Science* suggests that ketamine rapidly activates the mammalian target of rapamycin (mTOR) pathway in rats. The mTOR pathway increases synaptic signaling proteins and is responsible for long-term synaptic plasticity (i.e., changes to the release of neurotransmitters and whether synapses are inhibitory or excitatory neurotransmissions). The mTOR pathway thus plays a role in higher order brain functioning, such as learning and long-term memory. Chronic stress can result in the inhibition of glutamate production, and the 2010 study found that activation of the mTOR pathway may also counter this effect.

In effect, ketamine appears to modify the functioning of glutamate, resulting in more synaptic connections between neurons and enhanced neurotransmission. A recent study demonstrated that a single injection of ketamine caused increased production of new neurons and decreased depressive behavior for mature adult rats.

It is believed that NMDA-R antagonists enhance glutamate by increasing production of brain-derived neurotropic factor (BDNF). BDNF is considered "miracle grow" for the brain because it stimulates neurogenesis (the

birth of new neurons) and provides an ideal environment for the survival of those neurons. This may help mitigate the effect of conditions such as stress and depression, which weaken synaptic connections between cells, caused by reduced production of glutamate.

Subsequent studies have investigated whether currently existing antidepressants affect glutamate. Rat studies have found that many selective serotonin reuptake inhibitors (SSRIs) limit the effects of stress on overproduction of glutamate when taken consistently for two weeks or more, and researchers believe this helps to balance dysregulated brain states and alleviate anxiety. Even if SSRIs and other antidepressants modulate glutamate, they have less of an impact on glutamate than do NMDA-R antagonists such as ketamine.

Effects of ketamine

Given the mixed results, the question remains: How effective is ketamine, especially in comparison with other currently available options? Ketamine appears to be effective for approximately 60 percent of patients with depression, with the same rate found in cases of treatment-resistant depression. This is important, given the challenges in finding safe, effective and convenient treatments for treatment-refractory depression (i.e., depression that fails to respond to two or more adequate trials of antidepressants).

A systematic review of medications that influence the production of glutamate by Caroline Caddy (King's College London) suggests that of the 11 existing NMDA-R antagonists, only ketamine was consistently more effective than placebo for reduction of depression. The review also found, however, that antidepressant effects lasted no longer than a week and disappeared entirely in two weeks, indicating that the effects of ketamine may not be durable after discontinuation for most patients. The need for repeated dosing is a concern because ketamine has habit-forming properties, and users can develop tolerance with repeated use.

Ketamine is generally well-tolerated at the doses administered for depression. Lower doses of ketamine appear to mitigate ketamine's most prominent side effects of dissociative symptoms, elevations in blood pressure and hallucinations. Although most side effects resolve in 24 hours, people receiving ketamine are cautioned not to drive or use machinery until side effects abate.

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It is worth mentioning that NMDA-R antagonists can cause neurotoxicity in rodents and primates when used consistently at high levels. Higher doses can cause an altered state of consciousness sometimes referred to as the "k-hole" effect. This altered state is marked by euphoria, extreme dissociation, derealization (feeling as if one is in a dream), depersonalization (out-of-body experiences, sense of floating or falling), hallucinations, difficulty moving, disorientation and temporary memory loss.

At this time, ketamine is not approved by the Food and Drug Administration (FDA) for use for depression or other mental health disorders, although it is being used increasingly off-label in both hospital and outpatient specialty clinics. A 2017 survey of North American providers by Samuel Wilkinson at the Yale School of Medicine indicated that at least 3,670 patients have received ketamine for depression thus far.

Because of its history as an anesthetic, many operators of ketamine clinics are anesthesiologists rather than psychiatrists. It may be appropriate for anesthesiologists to treat depression with ketamine when practicing within the context of a multidisciplinary mental health treatment team. There is a concern, however, that anesthesiologists acting in isolation lack the training or expertise to correctly identify patients who may benefit from ketamine treatment for mental health indications.

Currently, the intervention remains relegated to specialty clinics with high out-of-pocket charges that are typically not reimbursed by insurance. As of July 2017, treatments cost $400 to $800 per infusion and may cost upward of $15,000 per year. Much like with electroconvulsive therapy, it is possible that "maintenance" treatments for ketamine may be a viable strategy if the antidepressant effects are nondurable. In 2017, Wilkinson surveyed practitioners who provided ketamine treatment. Notably, close to 90 percent of respondents administered ongoing maintenance treatments lasting beyond one month, with 30 percent administering monthly treatments.

Because glutamate appears to be important in the development of depression, pharmacologists are searching for other glutamate modulators that may be efficacious and more easily administered than ketamine. Agents such as riluzole and scopolamine are being trialed, with only anecdotal evidence available thus far.

Perhaps the most promising glutamatergic agent being trialed for depression is a relative of ketamine, known as esketamine. A double-blind randomized controlled trial conducted by Jaskaran Singh (Janssen Research and Development) and colleagues in 2016 found that intravenous administration of esketamine reduced treatment-resistant depression in approximately 60 percent of clients within three days of administration and was well-tolerated. Side effects were experienced by less than 20 percent of those who received the treatment and mostly consisted of headache, dizziness and nausea, which are common side effects even with SSRI treatments. Some participants did experience transient dissociation, which resolved within four hours of administration and occurred less frequently with repeated doses. This drug is currently in the final phases of clinical trials before being evaluated by the FDA.

Implications for counselors

Counselors are often the first professionals that individuals encounter when seeking mental health services, so it

is imperative for counselors to be aware of emerging treatments that could be of benefit. This is particularly true when psychotropic medications are added to existing treatment plans for individuals experiencing chronic treatment-resistant depression. Because clients may routinely be in concurrent treatment with both counselors and psychopharmacologists (i.e., psychiatrists, nurse practitioners), it is also important for counselors to have an appreciation for emerging treatments to which their clients may be exposed.

Although a course of counseling is often sufficient to treat mild or moderate depressive episodes, more severe cases usually require concurrent treatment with medications such as ketamine. Because drugs such as ketamine are controversial and often arise in public discourse, counselors are likely to receive inquiries from clients about these drugs. Furthermore, many clients are bombarded with advertisements regarding psychotropic medication and may be exposed to misinformation via the internet.

Drug-specific inquiries regarding use ultimately should be directed to a psychopharmacologist, although counselors can certainly explore the nature of clients' inquiries and provide needed psychoeducation within counselors' scope of practice. For example, counselors might explain that although ketamine has potential benefits for depression and suicidality, with rapid onset of effect, its benefits may be short-lived in the absence of repeated treatments, and it carries associated risks that should be carefully explored with an expert. Counselors should possess the base knowledge required to discuss these issues with psychopharmacologists on multidisciplinary treatment teams and to advocate for their clients when and where needed.

Ethical considerations

As ketamine and similar drugs become more widely available and utilized, they may also present some unique ethical concerns. For example, one can imagine a scenario in which a client is admitted to an inpatient psychiatric facility for complaints of suicidality, is given ketamine (which rapidly reduces the client's suicidality) and is discharged shortly thereafter.

We know from initial studies that ketamine's effects will diminish rapidly for most patients, at which time their suicidality may return. Therefore, further study and judicious planning are needed regarding the management of patients after their initial ketamine treatment.

Furthermore, the use of ketamine may establish a behavioral trap whereby the client may want to receive further treatment of ketamine to ward off his or her suicidality. If the drug is given repeatedly over a prolonged period, there is an increased likelihood that the individual may develop dependence on the drug, with all the associated risks, such as increased tolerance and maladaptive medication-seeking behaviors. Counselors are well-positioned as behavioral health care providers to discuss such ethical concerns with the psychopharmacologists on their multidisciplinary treatment teams.

Summary

Ketamine and related NMDA-R antagonists such as esketamine show promise to rapidly reduce major depression and suicidality within hours of administration, even for treatment-resistant forms of depression. Ketamine appears to have a different primary mechanism of action than currently existing antidepressant agents have. Although SSRIs such as fluoxetine also appear to have glutamatergic properties, these properties are likely less potent than drugs such as ketamine.

Increases in glutamate, the major excitatory neurotransmitter, have been found to enhance neural plasticity via the birth of new neurons, influenced by alterations to the production of BDNF and AMPA. Although ketamine's benefits appear to be substantial, they do not last long. Ketamine is generally well-tolerated at the subanesthetic doses used for depression and suicidality, but it does have the potential to be habit-forming. This requires a thoughtful risk-benefit discussion with the patient before considering longer-term maintenance treatment.

Driven by reports in the media, demand seems to be increasing for ketamine, leading to a growing number of specialty clinics providing ketamine treatment at high cost. In the future, counselors are likely to work with clients receiving ketamine treatment. Thus, it would be wise for counselors to become familiar with the pharmacological properties of the drug. Because ketamine's effects are not durable and longer-term maintenance treatment is poorly studied, counselors should also be aware of the potential for relapse of symptoms following short-term administration of the drug. This is particularly important to inpatient psychiatry units considering use of ketamine for their patients, given the high risk of relapse following discharge. ❖

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