DRUG REVIEW

Ketamine for Adolescent Depression: An Overview and Considerations for Future Directions

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Major depressive disorder in adolescence is associated with suicide attempts, substance use, and poor psychosocial functioning (1). In clinical trials, around 30%–40% of adolescents with depression remain depressed despite treatment with evidence-based interventions, which include selective serotonin reuptake inhibitors and psychotherapy (2, 3). With longer-term follow-up periods of up to 1 year after acute treatment, approximately 60% of adolescents eventually achieve sustained remission (3, 4). However, 40% continue to remain depressed despite ongoing treatment and are considered to have treatment-resistant depression. Thus there is a need for exploration of additional interventions for these treatment-refractory cases.

Ketamine has emerged as an increasingly utilized treatment option as augmentation for refractory depression for adults and is noted for its rapid antidepressant and antisuicidality effects, with a large effect size of 0.9, compared with placebo (5). Several international task forces have reviewed the evidence for efficacy and safety of ketamine and have provided recommendations for its use in clinical practice for adults (6, 7) but not for adolescents. Here we review the current literature on use of ketamine for adolescent depression.

PHARMACOLOGY OF KETAMINE

Ketamine is a dissociative anesthetic that was originally approved for anesthesia by the Food and Drug Administration (FDA) in 1970. Ketamine has several features that promote safe use, compared with other dissociative anesthetic medications. It does not suppress circulation or depress respiratory drive, unless at very high doses, and it has a relatively short onset and quick elimination half-life (8). The doses used for antidepressant effects are subanesthetic.

Ketamine is an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, which is an ionotropic glutamate receptor. Ketamine also binds to other neurotransmitter receptors, including opioid, dopamine, and sigma receptors. The mechanism alleviating depressive symptoms is not known.

Systematic research on the side effects of ketamine use in adolescent depression has been limited. In adults, side effects include dissociation, anxiety, headache, dizziness, increased blood pressure, increased heart rate, and cognitive side effects (9). Ketamine is mostly metabolized by cytochrome P450 (CYP)2B6 and CYP3A4. Therefore, substances that induce or inhibit these enzymes will decrease or increase exposure to ketamine. In addition, important pharmacodynamic considerations with regard to ketamine include the diminishment of its antidepressant effects by concurrent opioid antagonist therapy (e.g., naltrexone) or benzodiazepine therapy (10, 11). Most antidepressants are likely to be safe to administer alongside ketamine (12).

CURRENT AVAILABILITY AND USE OF KETAMINE

In the United States, ketamine is placed as a schedule III drug in the United States Controlled Substances Act. It is available in oral/sublingual, intranasal, intravenous (IV), and intramuscular (IM) formulations. Although ketamine is not formally approved by the FDA as a treatment for depression, intranasal esketamine, the (S)-enantiomer of the racemic ketamine, was FDA approved in 2019 for treatment-resistant depression, with a unique specifier to include suicidality in adults 18 and older, but not currently approved for individuals under 18. Use of esketamine in clinical settings requires providers and patients to be registered in a Risk Evaluation and Mitigation Strategy database to help ensure that the benefits of the medication outweigh its risk.

Ketamine is offered off label to treat psychiatric symptoms, including depression. Although ketamine is typically offered as an IV infusion, some providers pair psychotherapy during or after ketamine administration. The dissociation experienced on ketamine is seen as a potentially important therapeutic component rather than as a side effect (8).

KETAMINE AND ADOLESCENT DEPRESSION

Compared with the available literature on ketamine use for depression in adults, literature on ketamine for adolescent depression is limited. In a 2017 case report, a 16-year-old boy with a history of major depressive disorder, attention-deficit hyperactivity disorder (ADHD), Crohn's disease, gender dysphoria, and five psychiatric hospitalizations for depression in about 1 year was admitted for treatment of acute suicidal ideation with past suicide attempts (13). He had trials of escitalopram, aripiprazole, and lithium, and his family consented to ketamine treatment over electroconvulsive therapy because of concerns about possible cognitive side effects. The patient received repeated IV ketamine infusions dosed at 0.5 mg/kg over 40 minutes (three infusions during the first week and weekly infusion thereafter, for a total of seven infusions over an 8-week hospitalization). After the first infusion, the patient had a rapid reduction in his depressive symp-

toms and suicidal ideation, which further improved and persisted throughout his hospital stay. Side effects included mild nausea and dissociative symptoms during infusion that self-resolved.

In another case report, a 15-year-old adolescent with major depressive disorder, generalized anxiety disorder, and posttraumatic stress disorder, who did not improve on multiple medication trials, was hospitalized on the inpatient psychiatric unit after a suicide attempt of ingestion of sertraline (14). The adolescent was considered to have severe treatment-resistant depression with psychotic features and received repeated ketamine infusions dosed at 0.5 mg/kg for 3 weeks, starting with three infusions in the first week, then one infusion per week for the remaining 2 weeks, for a total of six infusions. Across the 3 weeks, the authors noted gradual decreases in depressive symptoms and suicidality on clinician-administered rating scales for depression although the patient subjectively denied improvement until 2 weeks after the final infusion. The only side effects experienced by the patient were dissociation and nausea, which was managed with chlorpromazine.

Cullen et al. (15) published an open-label study of repeated ketamine infusion as an acute intervention for adolescent participants ages 12–18 with treatment-resistant depression. Thirteen participants received six infusions over 2 weeks, dosed at 0.5 mg/kg. Five participants (38%) responded to ketamine. Three maintained remission at 6 weeks, and the other two relapsed within 2 weeks. Side effects included transient dissociative symptoms, infusion-related dysphoria, nausea that was treated with ondansetron, and hand pain related to intravenous catheter placements; the only hemodynamic effect was minor blood pressure changes (15).

In a randomized, double-blind clinical trial, 17 adolescents ages 13–17 with severe major depressive disorder but without active suicidal ideation or comorbid substance use disorders were randomly assigned to receive a single IV infusion of either ketamine or midazolam (16). An inclusion criterion was nonresponse to an antidepressant for 8 weeks; however, on average, subjects had not responded to three antidepressant medications and six total psychotropic medications, not including ADHD medications. Ketamine was dosed at 0.5 mg/kg over 40 minutes, and midazolam, which served as a placebo-control, was dosed at 0.045 mg/kg over 40 minutes. The primary endpoint was score on the Montgomery-Åsberg Depression Rating Scale (MADRS) 24 hours after treatment, which is the same measurement tool used in adult trials. A single infusion of ketamine significantly reduced depressive symptoms at 24 hours after infusion, from a mean baseline MADRS score of 33.1 to a mean of 15.4, compared with midazolam (score of 24.1 at 24 hours), with a strong effect size of 0.78 (p=0.036). (Possible scores on the MADRS range from 0 to 52, with higher scores indicating more severe depressive symptoms.) Overall, 76% of participants responded to ketamine, compared with 35% of midazolam participants (p=0.046). Adverse effects included transient dissociative symptoms and mild increase in blood pressure and heart rate, but none of the participants experienced dysphoria, panic, or emergent diazepam use.

The findings of these studies are limited because of small sample sizes and short study durations, but together they show promising results in the reduction of depressive symptoms in adolescents. All available studies utilized the IV formulation of ketamine. Parents have reported high acceptability of ketamine for adolescent depression and expressed preferences for short-term applications and intranasal and oral/sublingual IV/IM routes (17).

Regarding the safety of ketamine for adolescents, a systematic review of the safety profile from available research suggested that ketamine appears to be safe and well tolerated in adolescents, although these effects were assessed studies with small samples and of low quality (18). However, in adolescents with increased genetic risk factors for schizophrenia, ketamine treatment for depression warrants increased caution and further research (19). Acute bolus administration of ketamine has been shown in animal models and healthy adult subjects to be associated with schizophrenia-like symptoms, with large effect sizes (20). This highlights the importance of using slower infusions rather than boluses. However, the risk of developing a schizophrenia spectrum disorder with repeated use of ketamine is not currently known, particularly during a developmental age when adolescents can be at clinically high risk of first-episode psychosis. Research is needed to explore this relationship to prevent harm.

DISCUSSION

Given the potential of ketamine for treating depression in adolescents, particularly those with treatment-resistant depression, further research is needed before its use in clinical practice becomes standard. In addition to establishing safety data, further research should also be conducted and replicated to determine efficacy, comparing with placebo as well as with other standard treatments for depression. Another area needing further exploration is the method of delivery. A study showed parents' strong preference for intranasal and oral/sublingual routes (17), but the studies examined here used only intra-

KEY POINTS/CLINICAL PEARLS

- Ketamine is an NMDA receptor antagonist used in treatment-resistant depression as an augmentation in adults, and its use in adolescents has been reported in two case reports, one open label study, and one randomized double-blind clinical trial.
- Most conventional antidepressants are likely safe to administer alongside ketamine, and concurrent use of benzodiazepines and opioid antagonists may diminish ketamine's antidepressant activity.
- Data regarding efficacy and safety of ketamine for adolescents are limited, and further studies are required to develop practice parameters at point of care for implementation in clinical practice.

venous administration. Finally, more research is needed to explore the role of psychotherapy during ketamine treatment for depression.

CONCLUSIONS

Ketamine has a potential for treating treatment-resistant depression among adolescents. Further research is needed to determine best practices for prescribing ketamine in adolescent populations to prevent harm and ensure benefit, particularly with regard to safety and method of delivery.

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