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Ketamine for Treatment-Resistant Depression in Adolescents: Hope or Risk?

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Abstract: Treatment-resistant depression (TRD) in adolescents remains a major clinical challenge because of the limited efficacy of conventional antidepressants and the high risk of suicidal behavior. Ketamine has emerged as a rapidly acting antidepressant with a unique glutamatergic mechanism, promoting neuroplasticity and reducing neuroinflammation. Clinical studies demonstrate significant symptom improvement, often within 24 hours, although the effects are generally short-lived. Concerns remain regarding dissociative and cardiovascular adverse effects, abuse potential, and the uncertain long-term impact on the developing brain.

Key words: ketamine; depression; adolescents; psychiatry; antidepressant

Background: Adolescent TRD is associated with severe functional impairment and poor response to standard treatments, highlighting the need for faster-acting therapeutic options.

Aim: To review the efficacy, mechanisms of action, and safety of ketamine in adolescents with TRD.

Materials and methods: A narrative review of the literature on ketamine pharmacology, clinical efficacy, and safety in adolescent TRD was conducted.

Summary: Ketamine produces rapid antidepressant effects through modulation of glutamatergic neurotransmission and enhancement of neuroplasticity. Current evidence supports short-term efficacy, while long-term outcomes remain uncertain.

Conclusions: Ketamine is a promising option for selected adolescents with TRD requiring rapid symptom relief, but its use should remain limited to specialized clinical settings until further evidence confirms its long-term safety and efficacy.

Introduction

Ketamine, originally used as a dissociative anesthetic agent, particularly in the pediatric population, has in recent years gained increasing recognition as a rapidly acting antidepressant. In this paper, the term "ketamine" refers in particular to esketamine, the active S-enantiomer of racemic ketamine [1]. Its unique pharmacological profile enables the onset of therapeutic effects significantly faster than that of classical monoaminergic antidepressants. This property is of particular importance in conditions requiring urgent intervention, which has led to growing interest in the potential application of ketamine in acute psychiatric states in children and adolescents [2]. This issue is embedded in the context of adolescent depression, which represents a major public health concern, with a prevalence estimated at approximately 2-5% among individuals aged 13 to 18 years. Moreover, data indicate that nearly 20% of adolescents experience at least one episode of major depression before reaching adulthood [3]. A particular clinical challenge is treatment-resistant depression (TRD), defined according to American criteria as the lack of improvement following at least a two-month course of antidepressant pharmacotherapy at a dose equivalent to 40 mg of fluoxetine daily or 8-16 sessions of psychotherapy (cognitive-behavioral therapy - CBT or interpersonal therapy - IPT) [4]. Its significance is further amplified by a markedly increased risk of suicidal behavior in this patient population, underscoring the need for therapeutic strategies with a rapid onset of action [5].

The aim of this study is to analyze the efficacy and safety of ketamine use in adolescents, with particular consideration of the specific nature of treatment-resistant depression (TRD) as a condition requiring intensive and modern intervention capable of interrupting the destructive course of the illness at a critical stage of a young person's development.

Neurobiology of treatment-resistant depression

Treatment-resistant depression (TRD) currently represents a significant clinical problem among adolescents, implying the need for modifications in therapeutic approaches. An increasing body of evidence suggests that the neurobiological basis of this disorder differs substantially from that of episodic depression, indicating that it is not merely a more severe form of the disorder but rather a distinct depressive subtype [6]. The lack of response to standard pharmacological treatment may result from the fact that traditional antidepressants target the monoaminergic system, whereas in patients with TRD the pathophysiology is considerably more complex [7]. It involves significant impairments in signaling pathways responsible for the formation and reorganization of synaptic connections as well as neuronal survival, a phenomenon referred to

as neuroplastic dysfunction. This is associated with molecular and structural barriers that prevent adaptive reorganization of neural circuits in response to treatment, which is essential for achieving a therapeutic effect. [6,7,8] Genetic and pharmacological factors also play an important role in determining treatment resistance. The heritability of TRD has been estimated at 8% based on known genetic variants; however, family-based data suggest a heritability of the phenotype of up to 60%, which may indicate a complex genetic architecture of treatment resistance. [9] Polymorphisms in neurotransmitter-related genes play a key role. One of the best-documented markers is the polymorphism of the SLC6A4 gene (serotonin transporter), where the presence of the short (s) allele is associated with a significantly poorer response to SSRIs and reduced hippocampal volume. [8,10] Equally important is the Val66Met polymorphism in the BDNF gene, in which the Met variant reduces the secretion of brain-derived neurotrophic factor, thereby impairing neuroplasticity mechanisms and potentially diminishing the effects of newer-generation antidepressant therapies [7,8].

In some patients, treatment failure may be related to pharmacogenetics of drug metabolism. Of particular importance are variants of cytochrome P450 enzymes, which lead to altered drug kinetics and, consequently, failure to achieve therapeutic concentrations. In differential diagnosis, the presence of pseudoresistance should be considered, resulting from inappropriate medication use or suboptimal dosing [11,12].

In recent years, the neuroinflammatory hypothesis has played an increasingly important role in explaining the mechanisms of treatment resistance, highlighting the systemic nature of TRD. It proposes that TRD is not only a disorder of neurotransmitter imbalance, but also a state of chronic, low-grade systemic inflammation that impairs neuronal function and limits the effectiveness of standard pharmacological treatments [13]. Patients with TRD exhibit persistently elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which activate the kynurenine pathway, considered a key mediator linking monoaminergic systems and inflammation [14,15].

Mechanism of action of ketamine

Ketamine is an anesthetic agent belonging to the chemical class of arylcyclohexylamines, whose primary mechanism of action is the blockade of N-methyl-D-aspartate (NMDA) receptors [16]. Due to its rapid onset of action, it is considered particularly useful in acute psychiatric conditions requiring urgent intervention [17]. Its pharmacological profile differs substantially from that of conventional antidepressants targeting the monoaminergic system

[17,18]. Its mechanism of action is multifactorial and includes modulation of glutamatergic transmission, effects on neuroplasticity, and regulation of the immune response [19,20,27].

NMDA receptors, as part of the excitatory glutamatergic system involved in synaptic plasticity, learning, memory, and mood regulation, constitute the primary target of ketamine's action. Through preferential blockade of these receptors located on GABAergic interneurons, a reduction in their inhibitory activity occurs [18]. Consequently, there is decreased release of the inhibitory neurotransmitter GABA, leading to disinhibition of pyramidal neurons and a subsequent rapid increase in synaptic glutamate release, a phenomenon referred to as the "glutamate surge" [17]. This transient event initiates downstream processes that ultimately result in long-lasting changes in brain plasticity, contributing to the therapeutic effect. The increased glutamate concentration in the synaptic cleft leads to activation of AMPA receptors, which in turn triggers a signaling cascade involving the mTOR pathway, responsible for regulating synaptic protein synthesis and synaptogenesis [17]. In animal models, it has been shown that local administration of mTOR inhibitors such as rapamycin abolishes the neuroplastic and antidepressant effects of ketamine, suggesting a key role of mTOR pathway activation; however, clinical data do not unequivocally confirm this effect, indicating a more complex involvement of mTOR in ketamine's mechanism of action [21]. It should be noted that these changes are not uniform across all brain regions, but are primarily observed in the prefrontal cortex, hippocampus, and anterior cingulate cortex - areas involved in cognitive function and emotional regulation [22]. In these structures, alterations in neurotrophic factors are also observed, particularly in the expression of brain-derived neurotrophic factor (BDNF), which plays a central role in neuroplasticity processes [23,24]. Released glutamate binding to postsynaptic AMPA receptors leads to the activation of voltage-dependent calcium channels, and the resulting increase in intracellular calcium acts as a signal that enhances BDNF release from postsynaptic terminals [25]. In the next step, BDNF binds to its receptor, tropomyosin receptor kinase B (TrkB), on the same postsynaptic neuron, further stimulating mTOR activation via a positive feedback loop [22,17]. Additionally, BDNF, through TrkB activation, inhibits glycogen synthase kinase-3β (GSK-3β), a kinase involved in regulating the insertion of glutamatergic receptors into neuronal membranes, synaptogenesis, and restoration of dendritic spine density in regions affected by atrophy, such as the prefrontal cortex and hippocampus [17,25].

Ketamine's effects are not limited to modulation of the GABAergic and glutamatergic systems. They also involve other neurotransmitter systems, including dopaminergic, serotonergic, adrenergic, and cholinergic pathways, which play an important role in the pathophysiology of depression [16]. Moreover, ketamine's antidepressant effects may depend on the pharmacological activity of its metabolites, such as hydroxynorketamine, which may exert antidepressant effects independent of direct NMDA receptor antagonism [26,27].

An additional component of ketamine's antidepressant action may involve its anti-inflammatory properties. This is of particular relevance in TRD, in which increased inflammatory activity and elevated cytokine levels are implicated in disease pathogenesis. By modulating the immune response, ketamine may lead to a reduction in inflammatory mediators [27]. The drug is able to inhibit the synthesis and release of TNF-α, IL-1β, and IL-6 in macrophages, microglia, and astrocytes, which represents a key component of its direct anti-inflammatory effect [27]. Furthermore, ketamine also modulates the activity of glial cells, which constitute a major source of inflammatory mediators in the brain [28].

Concurrently, ketamine has been shown to modulate the kynurenine pathway, the excessive activation of which has been observed in TRD. It may reduce the activity of indoleamine 2,3-dioxygenase (IDO), thereby limiting the production of neurotoxic metabolites such as quinolinic acid (QUIN) - an NMDA receptor agonist that, under inflammatory conditions, enhances excitotoxicity and neurodegenerative processes [28].

Additionally, ketamine increases the concentration of kynurenic acid (KYNA), an endogenous NMDA receptor antagonist with neuroprotective properties. It is noteworthy that an early increase in the KYNA/KYN ratio following drug administration is currently being considered as a potential biomarker of treatment efficacy [27,28].

An important aspect is also ketamine's effect on the transcription factor NF-κB, which acts as a link between the resolution of inflammation and neuroplasticity, modulating CREB/BDNF signaling required for the restoration of damaged synaptic connections [27].

In summary, the anti-inflammatory effects of ketamine may constitute one component of its therapeutic mechanism in TRD. They may potentially contribute to disrupting the relationship between chronic inflammation, glutamatergic dysregulation, and impaired neuroplasticity, which may mutually exacerbate depressive symptoms [28].

Comparison with other treatment modalities for treatment-resistant depression

The treatment of TRD in adolescents requires a multi-stage and individualized approach based on current treatment algorithms [11]. In clinical practice, various therapeutic strategies are employed, including pharmacotherapy, psychotherapy, and neuromodulatory interventions [29]. The cornerstone of treatment is pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs), most commonly fluoxetine or escitalopram, which are combined with cognitive-behavioral therapy (CBT) [30]. The importance of combined treatment has been demonstrated in the TORDIA study, in which adolescents who did not respond to first-line therapy achieved better outcomes with a medication switch combined with CBT than with medication switching alone [31].

Unfortunately, despite the use of the aforementioned strategies, a substantial proportion of patients fail to achieve remission. Before initiating more complex treatment procedures, it is necessary to exclude pseudoresistance, which may result from incorrect diagnosis, inadequate dosing, insufficient treatment duration, or poor medication adherence [11]. In such cases, therapeutic drug monitoring (TDM) is a useful tool, as it allows assessment of whether the patient metabolizes the drug appropriately and whether plasma drug concentrations fall within the therapeutic range [30].

After confirmed treatment-resistant depression (TRD), treatment optimization strategies are implemented, including dose escalation of antidepressant medications (e.g., increasing fluoxetine to 40-60 mg), switching to another SSRI or to venlafaxine. In addition, augmentation strategies are used, involving the addition of another agent, such as lithium - particularly in cases of high suicide risk - or antipsychotic medications, although in the pediatric population their efficacy and safety are less clearly established. [9,30] Among further therapeutic options, increasing interest has been directed toward transcranial magnetic stimulation (TMS), a non-invasive adjunctive method aimed at accelerating remission in patients who do not fully respond to pharmacological treatment [32]. However, it should be emphasized that despite growing evidence, data on TMS are based on studies with limited methodological robustness due to small sample sizes, heterogeneity, and short-term follow-up [32]. In the most severe forms of depression and TRD, one of the most effective treatment modalities is electroconvulsive therapy (ECT). It is associated with high remission rates of up to 50-70% and durable treatment effects, and is often described by clinicians as a life-saving intervention, particularly in situations where rapid control of high suicide risk is essential [33,34].

Limitations of ECT are mainly related to its availability, the need for anesthetic procedures, potential transient adverse effects, and social factors such as stigma. In the United States, this therapy is referred to as a "last resort treatment" and may be used in children over 13 years of age; however, its use in the pediatric population raises significant ethical concerns [33,35].

Against this background, ketamine represents one of the newer treatment options for TRD in adolescents, differing substantially from classical therapeutic approaches. Most importantly, it demonstrates a very rapid antidepressant effect, with clinical improvement occurring within as little as 24 hours after administration, which constitutes a clear advantage over SSRIs, which typically require 4-6 weeks to achieve full therapeutic efficacy [32,33,36]. However, it should be emphasized that its effects are predominantly short-term, with response rates of approximately 50-71%, indicating only moderate long-term efficacy [36]. Thus, in contrast to more traditional approaches such as SSRI pharmacotherapy, ketamine produces a rapid onset of action, but its effects are not always sustained, which limits its use as a standalone treatment strategy.

Differences between ketamine and classical treatment methods for TRD concern not only the onset and duration of action, but also distinct neurobiological mechanisms. Ketamine's direct effect on the glutamatergic system, and consequently rapid activation of AMPA receptors together with stimulation of BDNF- and mTOR-related pathways, enables rapid synaptogenesis and remodeling of neuronal networks, in contrast to the secondary and slower neuroplastic changes achieved through modulation of the monoaminergic system by classical antidepressants such as SSRIs [37]. More direct and rapid neurobiological changes further distinguish ketamine from methods such as TMS, whose effects on cortical excitability and functional network connectivity, although non-invasive, require repeated sessions to achieve a therapeutic response [38,39]. Ketamine is also characterized by a more selective pattern of action, inducing changes primarily within neural circuits involved in mood regulation, which represents an important difference compared with the more global neuronal activation observed during ECT [22,40]. Additionally, in depression with an inflammatory component, ketamine may more prominently modulate the immune response, which is associated with its effects on the kynurenine pathway and its potential to reduce pro-inflammatory cytokine levels and attenuate kynurenine pathway activation; however, for other treatment modalities this effect is less well documented [41].

In one of the first systematic reviews and meta-analyses conducted by Faries et al., the efficacy of three treatment modalities for TRD in children and adolescents was comprehensively

compared, and the following conclusions were drawn. It was demonstrated that each intervention (ECT, rTMS, and ketamine) led to a statistically significant reduction in depressive symptoms compared with baseline. In addition, the meta-analysis showed that rTMS produced the greatest reduction in depression scale scores (SMD = 2.79). Accordingly, the authors suggested that rTMS should be considered as a first-line therapy for TRD in young individuals due to its more favorable safety profile [42].

Table 1. Efficacy and characteristics of interventional treatments for depression in children and adolescents (SMD) [9,42]

Intervention method	Symptom reduction (SDM*)	Evidence status and clinical conclusions	Advantages and challenges
Repetitive transcranial magnetic stimulation (rTMS)	2,79	Shows the greatest symptom reduction in meta-analyses. Considered a potential first-line treatment method for TRD in children.	**Advantages:** Non-invasive, no anesthesia required. **Challenges:** One RCT did not show a statistically significant difference compared to the "sham" group, suggesting the need for further research.
ECT (Electroconvulsive therapy)	1,99	Effective in symptom reduction ($p < 0.001$). Traditionally used in severe cases, although there is a lack of RCT studies for children.	**Advantages:** High efficacy in severe depression and suicidality. **Challenges:** Requirement of

			general anesthesia, risk of side effects (cognitive functions), stigmatization.
Ketamine	1,58	Rapid antidepressant effect. In an RCT, 76% of adolescents responded to ketamine treatment compared to 35% in the control group.	**Advantages:** Very rapid onset of action (as early as 24h). **Challenges:** Need for studies on long-term safety and repeated dosing.

**SMD - Standardized Mean Difference; higher values indicate a greater reduction in depressive symptoms.*

Although the results are promising, the authors emphasize the need for further head-to-head studies (direct comparisons within a single clinical trial) to confirm these findings [42].

Safety and Risk: Discussion

Safety and risk associated with ketamine use in adolescents with TRD remain subjects of intensive investigation [29]. Adolescence represents a dynamic period of brain development, rendering the brain particularly vulnerable to external influences; therefore, the assessment of both short- and long-term adverse effects of ketamine treatment is of critical importance [43]. Although existing evidence suggests that ketamine may be relatively well tolerated under controlled clinical conditions, data regarding its safety remain limited, and its risk profile in the pediatric population has not yet been clearly established. Most available evidence is derived from small-scale, short-term studies, and there is a lack of longitudinal research enabling the evaluation of long-term treatment outcomes and potential delayed adverse effects. [18, 29, 44]

One of the most frequently reported adverse effects of ketamine administration in the pediatric population is dissociation, including depersonalization and derealization [45]. These symptoms typically return to baseline within 1-2 hours after completion of the infusion, and no significant correlation has been observed between the severity of depressive symptoms and the

antidepressant efficacy of the drug [46]. This phenomenon is also relatively often accompanied by transient autonomic symptoms, including increased blood pressure and heart rate, as well as nausea, dizziness, and vomiting, highlighting the need for continuous monitoring of patients' vital signs by medical staff during drug administration [46, 47]. With regard to long-term ketamine use, its safety profile remains poorly understood. The majority of available data come mainly from small short-term clinical studies and extrapolation of findings from adult studies, whereas data on structural risk are derived from animal models [48, 49, 50]. In the context of long-term adverse effects, attention is primarily focused on the protection of the developing brain, particularly the adolescent prefrontal cortex, as well as the risk of addiction and the neurobiological consequences of drug action [43]. In clinical settings, the risk of addiction appears to be low due to the use of significantly lower doses than in recreational use [50]. Nevertheless, ketamine acts on the reward system and therefore has abuse potential, and its therapeutic use should be approached with caution [51]. Particular caution should be exercised in patients with current or past substance use disorders, as well as in individuals undergoing withdrawal from psychoactive substances [52]. The frequent co-occurrence of substance use disorders and adolescent depression is also important [53]. Patients requiring careful selection also include those with psychotic disorders, bipolar disorder, other severe neuropsychiatric disorders, movement disorders, cardiovascular diseases, and conditions associated with a risk of respiratory depression. In these groups, the potential benefits of treatment should always be weighed against the possible risk of adverse effects [52].

Regardless of its addictive potential, a significant concern remains the impact of ketamine on the central nervous system, particularly in the context of the intensive neurodevelopmental processes occurring during adolescence. Potential excitotoxic neuronal damage induced by ketamine has been demonstrated in animal models [54]. Preclinical studies suggest that exposure to this drug may lead to disturbances in synaptogenesis and structural alterations in neurons, resulting in long-term impairment of the morphology and function of inhibitory neurons [43]. At the same time, it should be emphasized that the available data are not conclusive; both neurotoxic and potentially neuroprotective effects of ketamine have been reported, the latter associated with enhanced synaptic plasticity, highlighting the need for further research [55]. In this context, the effects of ketamine on cognitive functions are also important. While chronic misuse of the drug is associated with their impairment, primarily resulting in memory deficits, short-term clinical studies in adolescents with depression have

shown improvements in processing speed of memory, with no negative impact on working memory or verbal learning [43, 56, 57].

Studies in animal models suggest that ketamine administration during adolescence may lead to persistent impairment in the development of excitatory synapses on GABAergic interneurons, resulting in functional deficits in adulthood. For this reason, the current recommendation is to use short treatment courses (approximately 1-2 months), together with ongoing monitoring of patient development [43].

In summary, ketamine may represent a promising therapeutic option in selected patients with treatment-resistant depression, particularly in situations requiring rapid clinical improvement. At the same time, it cannot currently be considered a treatment associated with a low risk of adverse effects. Its use in adolescents should be limited to monitored clinical settings, exclusively in specialized centers, under strict medical supervision, and with consideration of the limited evidence regarding the long-term safety of ketamine use in children and adolescents.

Conclusions

Ketamine represents a potential therapeutic option in the treatment of treatment-resistant depression (TRD) in adolescents; however, its place in clinical practice remains under investigation and has not been definitively established. Current evidence indicates that its mechanism of action, involving modulation of the glutamatergic system and effects on neuroplasticity processes, is associated with a rapid onset of antidepressant effects, which may be particularly relevant in situations involving a high risk of suicidality. Clinical trial data primarily confirm the short-term efficacy of ketamine, whereas evidence regarding long-term effects, particularly in the adolescent population, remains limited. At present, there is insufficient evidence to conclusively demonstrate its superiority over standard TRD treatment strategies, which include pharmacotherapy, psychotherapy, and neuromodulation techniques. Furthermore, ketamine use is associated with important limitations, such as transient psychotomimetic effects, potential for misuse and dependence, effects on the autonomic nervous system, and uncertainty regarding long-term safety, including potential impacts on the developing brain. Its use is additionally constrained by systemic factors, such as availability and high treatment costs.

For these reasons, ketamine should currently be regarded as an intervention with a promising but still insufficiently established role in the treatment of TRD in adolescents, warranting further prospective clinical studies to optimize its safety and efficacy.

Disclosure

Authors do not report any disclosures.

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