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Eunsaem Lee
MD, Department of Psychiatry, Hangil Hospital, Jeonju, South Korea

Rithika Narravula BS
University of Pittsburgh, Pennsylvania, USA

Namitha Maria Mathew
MD, Amala Institute of Medical Sciences, Thrissur, Kerala, India

Eric Wang
Edgemont Junior Senior High School, New York, USA

Yasmine Busaibe
College of Medicine and Health Sciences, Khalifa University, Abu Dhabi, UAE

Sagar Sanjeev Dua
MD, West Delhi Psychiatry Centre, Delhi, New Delhi, India

Tornike Phagava
MD, Center for Mental Health and Prevention of Addiction, Tbilisi, Georgia

Mina Oza
MD, 2nd ARC Associates, White Plains, USA

Dr. Parinda Parikh
MD, Department of Psychiatry, Weill Cornell Medical College, White Plains, USA

Corresponding Author:
Dr. Parinda Parikh
MD, Department of Psychiatry, Weill Cornell Medical College, White Plains, USA

A stepwise strategy on treatment-resistant depression: Rapid ketamine induction, followed by Auvelity (Dextromethorphan-Bupropion) maintenance

Eunsaem Lee, Rithika Narravula BS, Namitha Maria Mathew, Eric Wang, Yasmine Busaibe, Sagar Sanjeev Dua MD, Tornike Phagava, Mina Oza and Parinda Parikh

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Abstract
Background: Treatment-resistant depression (TRD) remains a topic that warrants investigation in both preclinical and clinical settings. Emerging hypotheses involving the glutamatergic and GAB Aergic pathways have opened up a gateway to new treatment plans aside from traditional antidepressants. Ketamine's function as a prototypical N-methyl-d-aspartate (NMDA) receptor antagonist that exerts rapid antidepressant and antisuicidal effects overlaps with the functions of Auvelity. This overlapping mechanism demonstrates a compounding efficacy comparable to other emerging agents. However, their inherent limitations restrict widespread use, leading to the proposal of an adjusted approach.
Case presentation: A 34-year-old woman showed partial response to multiple antidepressants (desvenlafaxine, bupropion) while experiencing persistent depressive symptoms. She then received weekly ketamine infusions for two years with adjusted previous oral medications. Then she started to take Auvelity every day. Her depressive symptoms markedly improved, allowing her to manage daily life and childcare.
Conclusion: This case report underscores a novel therapeutic approach in TRD by introducing a sequential strategy of ketamine induction followed by Auvelity maintenance. While ketamine provides rapid antidepressant and antisuicidal effects, Auvelity may extend these benefits by sustaining glutamatergic modulation. To our knowledge, this appears to be the first report to apply such a strategy, offering important clinical insight and opening new avenues for developing durable treatment options in TRD.

Keywords: Auvelity, Esketamine, Glutaminergic antidepressant, treatment-resistant depression, rapid-acting antidepressant, ketamine, dextromethorphan, dextromethorphan-bupropion

Introduction
Major depressive disorder (MDD) affects approximately 5% of the global population [1], making it one of the most prevalent and disabling psychiatric conditions worldwide. Because depression impairs nearly all domains of functioning, timely and effective management is of critical importance. However, a substantial proportion of patients, about one-third, fail to achieve remission [3]. Conventionally, most antidepressant strategies have been based on the monoamine hypothesis [6], which proposes that depressive states arise from reduced activity or availability of serotonin, norepinephrine, and dopamine within synapses [6]. However, the modest effect of traditional medications draws attention toward other potential mechanisms.
Among the numerous proposed hypotheses, the glutamatergic pathway has emerged as a promising candidate for depression treatment [7]. Glutamate is widely recognized as an excitatory neurotransmitter, involved in memory, mood regulation, and modulation of synaptic plasticity [8]. Accumulating evidence indicates that disruptions in glutamatergic transmission contribute to the pathomechanism of depression [8]. In this context, NMDA receptor antagonists, which act on receptors requiring glutamate and glycine [9], have emerged as a putative therapeutic target. These medications can disinhibit GABAergic interneurons, inducing a glutamate surge [16]. This effect facilitates synaptic remodeling, though the precise mechanism is not yet fully elucidated [16].

Among them, ketamine is the well-studied NMDA receptor modulator and has been demonstrated to produce immediate antidepressant and antisuicidal effects [10]. Ketamine has intravenous and intranasal forms, which can limit accessibility [10]. On the other hand, Auvelity, an oral NMDA receptor antagonist, has shown therapeutic benefit in treating TRD while offering the advantage of convenient administration [23]. We propose a stepwise treatment strategy in which ketamine infusion serves as an induction phase, followed by Auvelity to sustain therapeutic effects. Such an approach may optimize glutamatergic modulation, increase treatment accessibility, and ultimately improve both effectiveness and adherence.

Case presentation

A 34-year-old female presented to the clinic with a six-month history of depressed mood, fatigue, anhedonia, psychomotor slowing, poor appetite, and concentration. She had a history of recurrent severe depressive episodes, previously treated with desvenlafaxine 125 mg, bupropion 450 mg, cariprazine 1.5 mg, and aripiprazole 5 mg, with partial response.

At the time of her presentation, her regimen was adjusted. She was initiated on intravenous ketamine at a dose of 80 mg weekly, which she continued for two years. Concomitantly, she was maintained on desvenlafaxine 100 mg, bupropion 450 mg, and aripiprazole 5 mg, while cariprazine was discontinued. Over this period, her depressive symptoms significantly improved.

Following ketamine therapy, the patient was transitioned to Auvelity (dextromethorphan 45 mg/bupropion 105 mg) twice daily. Gradually, other medications were tapered off; she stayed on desvenlafaxine 100 mg. She reported marked sustained improvement in mood, functional recovery, and restored capacity to care for her children. She continues under close monitoring and follow-up to ensure treatment adherence and stability.

Discussion

TRD is commonly defined in clinical practice as an inadequate response to two or more antidepressant trials of sufficient dose and duration. However, only a minority of studies, approximately 17%, apply this definition consistently [4]. Empirical evidence has added to the clinical definition as a depressive illness unresponsive to conventional treatments, often characterized by persistent symptoms, recurrent episodes, comorbidities, increased healthcare utilization, and heightened suicide risk [5]. To date, no universally accepted guideline exists. However, Noah *et al*. have suggested that management should begin with careful optimization of the current regimen and, if unsuccessful, proceed to strategies such as within-class or cross-class switching, or augmentation with an additional agent [11]. More recently, consensus statements have endorsed a stepwise treatment procedure utilizing glutamatergic modulators under specific indications, alongside cautious monitoring [12].

Glutamatergic and GABAergic pathways have garnered particular attention as therapeutic targets in a wide range of psychiatric disorders, including depression, stress-related conditions, and dementia. Glutamate accounts for more than 90% of synaptic connections and is the most widespread excitatory neurotransmitter in the central nervous system [8]. Glutamate plays a pivotal role in cell migration, neural signaling, and synaptic plasticity, as well as facilitating the migration of pyramidal neurons from the cortex and striatum to their designated locations during neuronal development [15]. However, when glutamate activity surges beyond normal levels,

It can disrupt this process, resulting in structural and functional impairments [15]. In the context of depression, dysregulation of glutamatergic and GABAergic neurons in the prefrontal cortex and anterior cingulate cortex plays an integral role in its pathophysiology [13]. Moreover, impairment can disrupt synaptic plasticity, a process essential for learning and emotional regulation [15]. According to these findings, several studies have reported that individuals with depression exhibit reduced glial cell density and decreased expression of the glutamate reuptake transporters excitatory amino acid transporter 1 (EAAT1) and excitatory amino acid transporter 2 (EAAT2) [14].

Ketamine is the most extensively investigated among rapid-acting antidepressants, exerting its primary effect through modulation of glutamatergic neurotransmission [17]. Besides its established role as an NMDA receptor antagonist, mounting evidence has suggested that ketamine enhances alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic

acid (AMPA) receptor activity and activates downstream signaling cascades, including brain-derived neurotrophic factor (BDNF) and mechanistic target of rapamycin complex 1 (mTORC1), which contribute to synaptic plasticity and dendritic growth [17]. Preclinical and clinical findings further support the 'disinhibition hypothesis,' which proposes that ketamine temporally suppresses GABAergic inhibition, triggering a glutamate surge that facilitates synaptic remodeling [16].

At the clinical level, subanesthetic doses of ketamine have demonstrated rapid and robust antidepressant and anti-suicidal effects in patients with treatment-resistant depression (TRD) [17]. A single infusion can alleviate depressive symptoms within 24 hours, with benefits often enduring for up to one week [19]. Furthermore, repeated administration of intravenous and oral regimens has been associated with extended efficacy, with randomized trials reporting sustained therapeutic effects lasting up to six weeks in TRD populations [20].

Although ketamine demonstrates therapeutic potential, its clinical application remains limited due to concerns regarding renal and bladder toxicity, dependence, and cognitive impairment [21]. Additionally, withdrawal from ketamine has been reported to produce significant symptoms and can exacerbate suicide risk [21]. Because of these safety concerns, esketamine was developed. As the S-enantiomer of ketamine, it exhibits more than fourfold greater affinity for the NMDA receptor while producing fewer adverse effects, including dissociation and dependence [22]. However, esketamine is still limited by concerns about accessibility and safety. It requires careful monitoring and can only be given under strict protocols.

Dextromethorphan, a non-selective and non-competitive NMDA receptor antagonist long used as an antitussive, has more recently attracted attention as a putative rapid-acting antidepressant. In addition to NMDA, it also has sigma-1 receptor agonism, serotonin-norepinephrine reuptake inhibition (SNRI), and nicotinic acetylcholine (nACh) receptor antagonism, collectively enhancing both glutamatergic and monoaminergic neurotransmission [16]. Vecera *et al*. (2023) showed that despite hopeful preclinical

results, phase III trials failed to confirm efficacy for depression [5]. To overcome extensive first-pass metabolism and limited bioavailability, dextromethorphan was used in combination with quinidine (Nuedexta), Auvelity, and other agents [5]. Auvelity was the only one to be FDA approved for major depression in adults (2022) [23], which worked by increasing the dextromethorphan concentration in the plasma by CYP2D6 inhibition [5]. Its Phase II and Phase III trials have shown rapid and early responses, good tolerability, but not regularly observed [23].

Glutamatergic modulation offers clinicians a new therapeutic opportunity in depression, but maintaining its benefits remains a key challenge in TRD, prompting trials of combination strategies with other agents [2, 6]. For example, Chen *et al*. evaluated a protocol in which intravenous ketamine was followed by agents such as D-cycloserine or riluzole. Although overall efficacy did not significantly exceed the placebo, the intervention was associated with a meaningful reduction in suicidal ideation [6]. Another investigation found that administering oral dextromethorphan or memantine after ketamine infusion extended its analgesic benefit [2]. In that trial, additional measures such as quality of life and symptom scales suggested improved general health and reduced anxiety in the combination group [2].

In this case, ketamine acted as a rapid-acting agent while Auvelity followed to maintain these levels in a person with depression and suicidality. To date, clinical literature on this strategy remains limited. In the present case, the patient achieved meaningful symptomatic relief with long-term ketamine infusion after years of partial response to conventional antidepressants. Auvelity helped her to sustain this improvement and elevate her functional capabilities. This outcome supports the feasibility of a stepwise induction-maintenance strategy in real-world TRD management and highlights the potential role of Auvelity in sustaining remission once stability is achieved with ketamine.

Conclusion

Even as remarkable advances in available treatments for depression come to light, large numbers of patients with depression remain unresponsive or only partially responsive. The treatment of Individuals with TRD continues to encapsulate an eminent field in depression research. The development of antidepressants that act on glutamatergic neurotransmission has created new pathways and possibilities for treating TRD. Among these, ketamine has garnered attention for its ability to act rapidly. This rapid-acting property seems promising in treatment options for patients in an acute crisis. Despite the promising usages of ketamine, several concerns regarding the accessibility, durability of effect, and safety weigh down attitudes towards its implementation. Particularly in patients who demonstrate responsiveness to glutamatergic agents, long-term management has been displayed as an effective strategy for treatment. The overlapping effects of ketamine and Auvelity indicate a compounding effect and may be regarded as a viable maintenance method for TRD patients.

Declarations

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