

Managing Treatment Resistant Depression and Molecular Mechanism of Ketamine- An Update

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Abstract

Treatment resistant depression (TRD) is refractory in nature and patients do not respond to conventional treatment for depression. It affects approximately 25-30% of depressive patients and causes severe humanistic and financial burden. This review highlights strategies such as Switching therapies, Augmentation, Combination, and Optimization put forth by researchers to achieve better health outcomes in TRD patients. Further this review summarizes the possible modulation of glutamate transmission by ketamine which is emerging as a new lead for the development of novel antidepressants.

Keywords: Ketamine; Antidepressant; Molecular Mechanism; Glutamate Transmission

Abbreviations

TRD: Treatment Resistant Depression; MDE: Major Depressive Episode; HRQoL: Health Related Quality of Life; SACO: Switching Therapies, Augmentation, Combination, and Optimization; SSRIs: Selective Serotonin Reuptake Inhibitors; SNRI: Serotonin-Nor: Epinephrine Reuptake Inhibitors; US-FDA: United States: Food and Drug Administration; NMDA: N-Methyl-D-Aspartate; BDNF: Brain Derived Neurotropic Factor; AMPA: α -Amino-3-Hydroxy-5-Methyl-4-Isioxazolepropionic Acid; ERK: Extracellular-Signal-Regulated Kinase; mToR: Mammalian Target of Rapamycin

Introduction

One third of the patient population with depression is treatment resistant despite the presence of multitude of drugs available for treating depression [1]. Treatment resistant Depression (TRD) is an inconsistently defined term and a widely accepted definition being a major depressive episode (MDE) that is non-responsive to two or more conventional antidepressants [2,3]. One of the latest systemic review on analysis of economic and quality of life reported that TRD imparts both monetary and humanistic burden to patients, caregivers, and their families with prolonged hospital stay being the main contributor to economic burden and magnitude of depression contributing to the Health Related Quality of Life (HRQoL) of the patients [4]. The purpose of this mini review is to highlight treatment options for TRD and a recently reported mechanistic pathway of ketamine's antidepressant action.

Treatment strategies for TRD

In the absence of any straightforward algorithms, Dawn F Ionescu, *et al.* summarized the psychopharmacological strategies to treat TRD using 'SACO' meaning 'bag' in Spanish [5]. The acronym SACO stands for Switching therapies, Augmentation, Combination, and Opti-

mization, which can be used in any order tailored to the needs of patients. The SACO strategy put forth by Dawn., *et al.* is described briefly in this section.

Switching and augmentation are the two available options for the psychiatrists when the patient is non-responsive to single antidepressant [6]. Switching is preferred when the patient shows intolerance to the agent administered initially. Switching can be done within the same class of antidepressants or with different class of antidepressants. More evidence is needed to ascertain the superiority of aforementioned options to guide the clinicians during treatment of TRD. Further, it is important to check the potential Drug-Drug interactions and co-morbidities to avoid any clinical mishaps.

Augmentation refers to the addition of a non-antidepressant medication to an antidepressant which is in use and can be employed when the patient shows partial response. The antidepressant actions of Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) are enhanced by atypical antipsychotics [3]. Patients using atypical antipsychotics showed better remission compared to placebo [7].

Lithium and Thyroid hormone (T3) are also reported beneficial as augmenting agents for antidepressants during the treatment of TRD [8,9]. However, careful risk-benefit analysis should be done before employing these agents, especially atypical antipsychotics for augmentation.

Combination is different from augmentation and it refers to the addition of another anti-depressant to an existing antidepressant. Generally, two or more antidepressants having different mechanism of action act synergistically and reduces discontinuation symptoms compared to switching [10]. As evident from the published literature, combination therapy is not generally preferred for treating depression and hence should be employed only after careful consideration of Drug-Drug interaction and disease status of the patients [11-13].

Optimization is the primary strategy in managing TRD and should be considered before trying other strategies. Optimization refers to perfecting the dose of antidepressant to suit the patient's need. Optimization strategy is beneficial to patients who are tolerant and at least partially responsive as the dose may be increased to standard maximal dose for up to twelve weeks [14,15].

Ketamine as an antidepressant

Ketamine, a popular dissociative anesthetic was approved by US-FDA in 1970. Due to its abuse potential its use is restricted in clinical setting. Ketamine was tested beneficial for its quick acting anti-depressant effect since early 2000 and on March 2019, FDA has approved Spravato (esketamine), a ketamine based nasal spray for TRD [16]. Esketamine works similar to Ketamine but its structure makes it bind more tightly to NMDA glutamate receptors and makes them more potent [17].

There are at least seven ways through which Ketamine may exert its antidepressant effect [18]. The most rational and convincing postulation was given by Duman., *et al* [19]. According to them, when given in low doses, ketamine increases glutamate neurotransmission by increasing the release of glutamate and by increasing AMPA receptor expression. The increase in the glutamate levels increases Brain Derived Neurotrophic Factor (BDNF) which in turn activates extracellular-signal-regulated kinase (ERK) signaling. The ERK activation stimulates the all important mammalian target of rapamycin (mTOR) that controls the translation of proteins. The stimulation of mTOR results in increased structural connectivity in the prefrontal cortex. The increased global connectivity achieved by the stimulation of mTOR may be the result of its ability to increase synaptic expression of GluR1 proteins [20].

Conclusion

Though ketamine is portrayed as a magic bullet for the treatment of TRD, its long term effect needs to be elucidated. The ketamine should be indicated only as a last resort in the treatment of TRD when all other options are not effective in the patient. The abuse potential of

ketamine and the expensive nature of (esketamine) are the major limiting factors to extensive use of ketamine in patients with treatment resistant depression.

Conflict of Interest

None.

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