

Novel Combination Therapy For Improved Management of Depression

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Overview

Psychiatric disorders, especially major depressive disorder (MDD), are leading causes of disability and premature death across the globe, with patients showing a heightened risk of self-harm and suicidal ideation. Prof. Alon Chen and his team found that the sustained antidepressant effects of Ketamine, an approved drug indicated for treatment-resistant depression, are mediated by the upregulation of the *Kcnq2* gene. The team found that combination therapy comprised of Ketamine and retigabine, an approved KCNQ agonist, boosted the anti-depressive effects of Ketamine in mice. Therefore, the novel combination treatment of two approved drugs, Ketamine and retigabine, may improve current treatment protocols for psychiatric disorders, including depressive disorders MDD.

Background and Unmet Need

Major depressive disorder (MDD) is the third-leading cause of disease burden and the most common cause of disability and premature death in the general population. While clearly effective, available anti-depressive drugs are significantly limited by time-to-response of up to 8 weeks, a latency period that increases the risk of suicide and self-harm. In parallel, 30-50% of patients display inadequate responses or suffer from remission. Moreover, their long-term use is often associated with side effects that further increase the risk profile of this fragile patient population. In particular, a one-time intravenous dose of Ketamine, a potent glutamate N-methyl-D-aspartate (NMDA) receptor blocker, elicits a rapid and sustained antidepressant response, even among treatment-resistant patients, and effectively manages suicidal ideation. Spravato, an intranasal formulation of esketamine, was recently approved by the FDA for treatment-resistant depression. Yet, its chronic use is associated with hallucination, impaired sensory perception, and risk of addiction, raising concerns regarding its extensive use, particularly in unsupervised outpatient settings. Overall, these limitations increase the risk of self-harm and suicide in MDD patients, highlighting the dire need for fast-acting agents with an acceptable safety profile.

The Solution

Ketamine-based combination treatment to amplify the anti-depressive effect of Ketamine while minimizing side effects

Technology Essence

In their pursuit of the molecular basis of the anti-depressive effect of Ketamine, the team led by Prof. Alon Chen conducted a single-cell RNA sequencing of ventral hippocampus cells of mice treated with Ketamine. The team found that in response to Ketamine, the *Kcnq2* gene is upregulated in glutamatergic neurons, generating a response that is characteristic of resilience to stress. The team found that *Kcnq2* knockdown in the ventral hippocampus of mice eliminated the antidepressant effects of Ketamine, as measured by immobile time in a forced swim test. Similarly, its pharmacological inhibition with a selective and potent channel antagonist abolished the anti-

depressive effect of Ketamine. In contrast, the coadministration of Ketamine and retigabine, a selective KCNQ-activator, augmented the anti-depressive effect of Ketamine in mice, as demonstrated by significantly less immobile time in a forced swim test as compared to untreated mice and mice treated with Ketamine only.¹ Importantly, the combined treatment of Ketamine and retigabine can induce a potent antidepressant effect with relatively low doses of Ketamine, which would have otherwise been sub-efficacious. Therefore, the combination therapy could potentially reduce the current undesired side effects of Ketamine, at least partially.

Applications and Advantages

- Combination therapy for ketamine-based antidepressants
- Improved efficacy of ketamine-based antidepressant regimes, especially for treatment-resistant depression
- Improved safety profile of ketamine-based antidepressant regimes

Development Status

The enhanced effectiveness of Ketamine in combination with KCNQ-agonists has been demonstrated ex-vivo in extracted glutamatergic neurons and validated in ex-vivo electrophysiological recording analyses, as well as in vivo by monitoring animal behavior following combination treatment with pharmacological agonists and antagonists.

References

Lopez JP, Läckén MD, Brivio E, et al. Ketamine exerts its sustained antidepressant effects via cell-type-specific regulation of *Kcnq2*. *Neuron*. Published online May 2022:S0896627322004093. [doi:10.1016/j.neuron.2022.05.001](https://doi.org/10.1016/j.neuron.2022.05.001) [1]

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