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Treatment Resistant Depression, Ketamine versus ECT

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Abstract

Recent studies have highlighted the increase in treatment resistant depression. Of particular concern is the rising trend of depression and suicide rates among Young Adults. Ketamine was approved for treatment resistant depression in 2019 by the US Food and Drug Administration. It received an additional indication for treatment of suicidality. While intranasal Ketamine is approved for depression, recent data about intravenous infusion of Ketamine in controlled inpatient settings has been promising. ECT has a long-standing trend for being used for resistant depression and recent comparison trials have revealed positive results when head-to-head comparisons are made with Ketamine. Future studies need to focus on patient selection and wherein treatment algorithm should Ketamine be selected as treatment modality.

Keywords

Treatment Resistant Depression, Ketamine, ECT

1. Introduction

Treatment resistant depression continues to remain a challenge as remission rates remain as low as 15% among patients who have failed conventional treatments or augmentation strategies. Selective Serotonin Reupdate inhibitors and Serotonin Norepinephrine Reuptake inhibitors are often used as the first line of treatment [1]. In the Sequence Treatment Alternatives to Relieve Depression, STAR D study about 30% of patients did not achieve remission despite four sequential treatments [2]. In a recent decade, several advances in pharmacotherapy have shifted focus from monoamine neurotransmitters to drugs modulating glutaminergic, opiate and other neurotransmitter systems. Augmentation strategies

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with Lithium, Thyroxine and Second-Generation antipsychotic have limited efficacy. Olanzapine and Fluoxetine combination has risks of weight gain and metabolic syndrome.

There has been a rapid and notable increase in depression rates among young adults aged 18 - 25 years from 2015 to 2019 [3]. The highest prevalence across times was 17% among adolescents (aged 12 - 17 years) and young adults (aged 18 - 25 years). These trends remain unchanged when adjusted for socioeconomic differences. With the increase in proportion of young adults with depression, the need to increase options with different modalities of treatment for young adults is even greater given the implications on work force and economy.

ECT remains the gold standard for MDD with catatonia and suicidal features. Despite advances in Electroconvulsive therapy techniques and administration, it remains underutilized due to social stigma and limited availability. Significant concerns about cognitive issues remain a concern for most of the general population.

2. Overview

In March 2019, intranasal esketamine, co-initiated with a conventional antidepressant, was approved by the U.S. Food and Drug Administration (FDA) for adults with Treatment Resistant Depression. The European Medicines Agency granted regulatory approval for intranasal esketamine for TRD in December 2019. In August 2020, the FDA updated the approval of intranasal esketamine to include adults with major depression and suicidal ideation and behavior.

Ketamine, like many drug products, is a mixture of two mirror-image molecules, R-ketamine, and S-ketamine (arketamine and esketamine, respectively). Spravato (includes only esketamine molecule), is approved as a nasal spray for treatment-resistant depression in adults and for depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior (in conjunction with an oral antidepressant).

Ketamine's most potent pharmacodynamic targets include synaptogenesis and synaptic potentiation. It has high affinity for phencyclidine site of NMDA receptor, which in turn leads to glutamate surge and activation of AMP receptor resulting in increase in BDNF (Brain derived neurotropic factor) [4]. Animal studies report Ketamine's antidepressant effects may be evident by its suppressant effects on subgenual anterior cingulate gyrus [4]. Rapid reduction in suicidal thoughts after intravenous infusion of racemic Ketamine (0.5 mg/kg) have lasted for 7 days after single dosing and up to 6 weeks after repeat dosing. Some argue that antidepressant effects of Ketamine may be independent of its antisuicidal properties.

The global suicide mortality rate is over 800,000 per year while the estimated suicide attempts (SA) are around 16 million per year (WHO, 2014). Suicide has been identified as the second leading cause of death amongst individuals between the ages of 15 - 29, and high-income countries have the highest rates of suicide.

Systemic review of nine randomized controlled trials with 197 Ketamine

treated patients alluded to the efficacy of antisuicidal properties of a single dose IV Racemic Ketamine and Intranasal Ketamine [5]. Moderate and significant reductions in suicidal ideation scores were noted at 4 hours, between 12 hour and 24 hours, and between 24 hour and 72-hour post-ketamine. The pooled effect size for anti-suicidal effects at the 24-h time point was 1.035 (N = 6, CI: 0.793 to 1.277, $p < 0.001$) for intravenous (IV) racemic ketamine and 1.309 (N = 1, CI: 0.857 to 1.761, $p < 0.001$) for intranasal (IN) esketamine. This systematic review further establishes the potential for anti-suicidal properties of Ketamine. Further research is needed into the need for RCTs with use of standardized inventories for suicidal assessments.

In a retrospective analysis in patients who receive intravenous Ketamine infusions from 2017 to 2019, there was mixed response to treatment. While there was statistically significant improvement in Beck's Depression Inventory, the CGI (Clinical Global Impressions) and QIDS (Quick Inventory of Depressive Symptomatology) did not reveal any changes [6].

Rapid response to intravenous infusion was the highlight of a most recent study [7]. There was a significant reduction in depressive symptoms for over half of 50 inpatients treated with Intravenous infusion of Ketamine. Out of 41 inpatients who received treatment 19 (46.5%) met criteria for response and 15 of the 19 responders met criteria for remission (as defined by a MADRAS < 10) within five infusions. One of the key findings of the study was rapid response to intravenous infusion in 12 (80%) out of 15 patients with less than 4 sessions (10 days of treatment). More than 50% of patients did not respond to Ketamine and had to be switched to ECT or continue with psychopharmacological management. However, one third of patients achieved remission after five treatments.

In the last decade, several studies with head-to-head comparisons between Ketamine and ECT have been performed. Comparisons between Ketamine and ECT have led to mixed responses.

In an open labeled randomized controlled trial, Ketamine was compared with ECT. While 195 patients received Ketamine (0.5 mg/kg over 40 minutes infusion), 170 patients received ECT [8]. Patients with treatment resistant depression were given ECT treatments three times a week or Ketamine treatment twice a week. The primary outcome measure was a response rate defined by greater than 50% decrease from baseline on a 16 item Quick Inventory of Depressive Symptomatology—self report questionnaire. Secondary outcome measures included MADRAS, CGI-I, PGI-I, and other memory tests. The response rate in QIDS in the Ketamine group was 55.4% as opposed to the 41.2% in the ECT group. Changes in MADRAS scores were significant—50.8% in Ketamine group and 41.4% in the ECT group. Authors argue that somewhat lower response to ECT in the study could be attributed to the RUL ECT treatment, as the switch to Bilateral treatment was only made after six treatments and that the patient were evaluated after a fixed dose of six Ketamine and six to nine ECT treatments and perhaps a longer period of ECT would improve outcomes.

Response to single dose of intravenous infusion of racemic ketamine (0.5

mg/kg) was similar in patients who failed to respond to ECT or were ECT naïve [9]. In this small study there were 17 patients with treatment resistant depression who did not respond to ECT and 23 patients with treatment resistant depression who were ECT naïve. Depressive symptoms were significantly improved in the ECT-resistant group at 230 minutes with a moderate effect size ($p < 0.001$, $d = 0.50$, 95% C.I.: 0.21 - 0.80). At 230 minutes, the non-ECT exposed group showed significant improvement with a large effect size ($p < 0.001$, $d = 1.00$, 95% C.I.: 0.71 - 1.29). The sample size in this study was small and it is unknown if the patients who do not respond to ECT will continue to respond to Ketamine.

3. Discussion

When the FDA approved Esketamine treatment for depression, it also required that treatments be monitored in a structured, clinical environment due to its potential for psychomimetic and cardio stimulating effect. Acute side-effects following subanesthetic intravenous infusion of ketamine treatment are mild and transient. Most common side effects noticed are elevated blood pressure (asymptomatic), nausea, headache, blurred vision, perceptual disturbance, drowsiness, dizziness, dissociation, and anxiety [10]. Most of the side effects are noticed during the period of infusion and resolve soon after treatment is completed. Reports of initial response to Ketamine are favorable for inpatient settings where if patients who do not respond to Ketamine can be referred for ECT. When the patient voices an informed preference, clinicians should take this preference into account when choosing between ECT and Ketamine alongside other factors that warrant an individual benefit-risk assessment. Adequate placement of Ketamine and Esketamine in treatment algorithms, patient selection criteria, evaluating the efficacy on long term effects and monitoring of safety and tolerability of these agents remains to be seen.

While indications for ECT can expand to Treatment Resistant Depression with psychosis, catatonia, and Bipolar depression [11], concerns for cognitive side effects, risk of anesthesia and social stigma, lack of infrastructure for ECT treatment plague its consistent use. Literature remains sparse on using Ketamine as an alternative to ECT for effective treatment for depression. However, the benign cognitive profile of Ketamine makes it a favorable choice for patients. Relapse rates were compared with different doses after a single administration of Intravenous Ketamine. A linear dose response relationship was observed in both responders and remitters with the lowest relapse with 1 mg/kg followed by 0.5 mg/kg and 0.1 mg/kg [12].

4. Conclusion

Research in the use of Ketamine has the most robust literature for its use in TRD. Ketamine (intranasal and IV infusion) is a promising trend with its rapid onset of action and ease of administration. It will be the next frontier in the management of treatment resistant depression. More prospective trials examin-

ing the efficacy of Ketamine in Depression and suicidality are warranted.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Lochmann, D. and Richardson, T. (2018) Selective Serotonin Reuptake Inhibitors. M. InMacaluso, & S. Preskorn (Eds.), *Antidepressants*, Springer International Publishing, 135-144. https://doi.org/10.1007/164_2018_172

[2] Gaynes, B.N., Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Spencer, D. and Fava, M. (2008) The STAR*D Study: Treating Depression in the Real World. *Cleveland Clinic Journal of Medicine*, **75**, 57-66. https://doi.org/10.3949/ccjm.75.1.57

[3] Goodwin, R.D., Dierker, L.C., Wu, M., Galea, S., Hoven, C.W. and Weinberger, A.H. (2022) Trends in U.S. Depression Prevalence from 2015 to 2020: The Widening Treatment Gap. *American Journal of Preventive Medicine*, **63**, 726-733. https://doi.org/10.1016/j.amepre.2022.05.014

[4] McIntyre, R.S., Rosenblat, J.D., Nemeroff, C.B., Sanacora, G., Murrough, J.W., Berk, M., *et al.* (2021) Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. *American Journal of Psychiatry*, **178**, 383-399. https://doi.org/10.1176/appi.ajp.2020.20081251

[5] Xiong, J., Lipsitz, O., Chen-Li, D., Rosenblat, J.D., Rodrigues, N.B., Carvalho, I., *et al.* (2021) The Acute Antisuicidal Effects of Single-Dose Intravenous Ketamine and Intranasal Esketamine in Individuals with Major Depression and Bipolar Disorders: A Systematic Review and Meta-Analysis. *Journal of Psychiatric Research*, **134**, 57-68. https://doi.org/10.1016/j.jpsychires.2020.12.038

[6] Griffiths, C., O'Neill-Kerr, A., De-Vai, R., Sore, T. and Silva, K.D. (2019) Ketamine Infusion (KI) in Treatment Resistant Depression (TRD): Retrospective Clinical Data Analysis. *Open Journal of Depression*, **8**, 59-70. https://doi.org/10.4236/ojd.2019.83007

[7] Brody, B.D., Park, N., Christian, A., Shaffer, C.W., Smetana, R., Kotbi, N., *et al.* (2024) Ketamine for Major Depressive Disorder during an Inpatient Psychiatric Admission: Effectiveness, Adverse Events, and Lessons Learned. *Journal of Affective Disorders*, **351**, 293-298. https://doi.org/10.1016/j.jad.2024.01.207

[8] Anand, A., Mathew, S.J., Sanacora, G., Murrough, J.W., Goes, F.S., Altinay, M., *et al.* (2023) Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. *New England Journal of Medicine*, **388**, 2315-2325. https://doi.org/10.1056/nejmoa2302399

[9] Ibrahim, L., Diazgranados, N., Luckenbaugh, D.A., Machado-Vieira, R., Baumann, J., Mallinger, A.G., *et al.* (2011) Rapid Decrease in Depressive Symptoms with an N-Methyl-D-Aspartate Antagonist in ECT-Resistant Major Depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **35**, 1155-1159. https://doi.org/10.1016/j.pnpbp.2011.03.019

[10] Acevedo-Diaz, E.E., Cavanaugh, G.W., Greenstein, D., Kraus, C., Kadriu, B., Zarate, C.A., *et al.* (2020) Comprehensive Assessment of Side Effects Associated with a Single Dose of Ketamine in Treatment-Resistant Depression. *Journal of Affective Disorders*, **263**, 568-575. https://doi.org/10.1016/j.jad.2019.11.028

[11] Agarkar, S., Hurt, S., Lisanby, S. and Young, R.C. (2012) ECT Use in Unipolar and

Bipolar Depression. *The Journal of ECT*, **28**, e39-e40. https://doi.org/10.1097/yct.0b013e318255a552

[12] Salloum, N.C., Fava, M., Hock, R.S., Freeman, M.P., Flynn, M., Hoeppner, B., *et al.* (2020) Time to Relapse after a Single Administration of Intravenous Ketamine Augmentation in Unipolar Treatment-Resistant Depression. *Journal of Affective Disorders*, **260**, 131-139. https://doi.org/10.1016/j.jad.2019.09.017