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EDITORIAL COMMENT
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Ketamine and Electroconvulsive Therapy for Treatment-Refractory Depression

Major depressive disorder (MDD) is a highly incapacitating condition that has a significant impact on a large number of individuals worldwide, representing the greatest burden of disease among mental and neurological disorders.[1] In China, MDD has been projected to be the second leading cause of years lived with disability.[2] Regrettably, over 30% of those who undergo major depressive episodes fail to attain antidepressant remission even after undergoing multiple attempts with antidepressants.[3] This form of depression, known as treatment-resistant depression (TRD), is linked to premature mortality, including suicide.[4] In psychiatry, TRD represents a major challenge.

Electroconvulsive therapy (ECT) has a longstanding history of over 80 years as a highly effective and expeditious approach for treating TRD. Due to its well-established and demonstrably superior effectiveness, ECT is widely regarded as the gold standard treatment for TRD.[5] However, the utilization of ECT remains insufficient in many Western countries due to constraints such as restricted accessibility, social stigma, and apprehensions regarding impermanent cognitive impairment as a potential adverse effect.[6] Notably, China is estimated to possess the highest number of ECT recipients globally.[7] The Brain Hospital of Guangzhou Medical University conducts an average of 1500 ECT sessions per month, with an annual total reaching up to 18000 sessions. Following a successful acute treatment for TRD, maintenance ECT was used to prevent relapse.[8]

Ketamine, a receptor antagonist of the *N*-methyl-$_D$-aspartate (NMDA) receptor, has received approval from the Food and Drug Administration for its use as a sedative, analgesic, and general anesthetic. Over the past 2 decades, numerous meta-analyses have revealed that ketamine, when administered intravenously at a subanesthetic dose of 0.5 mg/kg of body weight, exhibits rapid antidepressant and antisuicidal effects.[9,10] Consequently, ketamine, whether administered in a single or multiple doses, is increasingly being utilized in patients suffering from TRD.[9,10] Notably, ketamine's appeal lies in its ability to circumvent the need for general anesthesia, making it an attractive alternative for patients. Contrary to expectations, it has been observed that the administration of either a single ketamine infusion or multiple ketamine infusions does not result in noteworthy neurocognitive impairments.[11] This is exemplified by a recent investigation that revealed enhancements in speed of processing and verbal learning among individuals diagnosed with MDD who underwent a course of 6 ketamine infusions.[11] The cumulative and long-term risks associated with ketamine should be investigated.[9]

Prior to ECT, intravenous anesthetic medications, including propofol, ketamine, methohexital, thiopental, and the combination of ketamine and propofol (ketofol), are administered to mitigate the occurrence of adverse events and subjective discomfort associated with tonic–clonic seizures.[12] A meta-analysis found that the utilization of ketamine as a sole anesthetic agent does not demonstrate enhanced effectiveness in comparison to other anesthetic agents in ECT.[5] However, the combination of ketamine with other anesthetic agents may provide a temporary advantage in alleviating depressive symptoms during the initial stages of ECT.[5] Importantly, Wang et al's[13] study found that anesthesia with ketofol should be preferred for MDD patients undergoing ECT.

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The comparative evaluation of the efficacy and safety of ketamine at a subanesthetic dosage in relation to ECT continues to be a significant inquiry within the clinical field.[14] A recent meta-analysis of 6 controlled trials involving 340 individuals afflicted with major depressive episodes indicates that ECT may exhibit greater effectiveness in ameliorating the severity of depression when compared to ketamine intravenous injection (0.5 mg/kg).[14] However, it is crucial to tailor treatment choices to the specific needs and preferences of each patient, taking into account the distinct adverse effects associated with each intervention.[14] This meta-analysis[14] did not incorporate a recent randomized controlled study,[6] which had the largest sample size (n = 403) and demonstrated that the administration of ketamine at a subanesthetic dose (0.5 mg/kg over 40 minutes) was comparable to ECT in treating TRD without psychosis. It is important to note that this particular RCT[6] focused exclusively on patients suffering from TRD without psychosis, distinguishing it from a recent European trial[15] and the previous meta-analysis.[14] Electroconvulsive therapy is widely recommended for its high efficacy in rapidly treating late-life depression, catatonic depression, and suicidal depression.[16] Consequently, further investigations are warranted to evaluate the comparative effectiveness of ketamine and ECT, specifically in older patients and those with bipolar depression.[6]

New antidepressants with robust effects for TRD are potentially beneficial. In addition to ECT and ketamine, TRD has been treated with novel pharmacological interventions, including esketamine nasal spray[17] and psilocybin.[18] Esketamine, the S-enantiomer of ketamine racemate, has been recently sanctioned by the US Food and Drug Administration for the management of TRD in adult individuals. This compound exhibits a greater affinity for the NMDA receptor compared to its R-enantiomer counterpart. Notably, esketamine nasal spray has exhibited prompt onset and sustained effectiveness in patients with TRD as well as in depressed individuals who are at a high risk of imminent suicide.[17] Furthermore, psilocybin is a tryptamine alkaloid found in several species of psilocybe mushrooms. A 25-mg dose of psilocybin, but not a 10-mg dose, significantly improved depressive symptoms over a 1-mg dose at 3 weeks in patients with TRD.[18] To date, there have been no head-to-head studies published that compared ECT either with esketamine nasal spray or psilocybin for TRD. In summary, both ECT and ketamine have demonstrated efficacy and safety in the treatment of TRD. The provision of ketamine solely entails the delivery of a minimal dosage of anesthesia medication, whereas the administration of ECT encompasses the delivery of a complete dosage of anesthesia along with an electrical stimulus that triggers a seizure. Therefore, it is anticipated that ketamine will exhibit greater tolerability and safety in comparison to ECT. In certain instances, ketamine infusion may be considered as a viable alternative therapeutic approach, particularly for younger individuals or those who have encountered pronounced adverse reactions stemming from ECT.

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