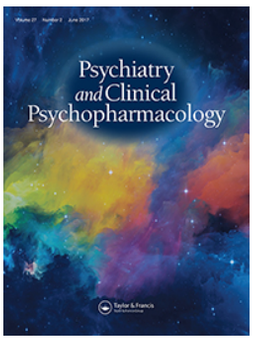

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Samet Kose & Mesut Cetin

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EDITORIAL

Ketamine and electroconvulsive therapy pairing in depression and mood disorders

Although a number of medications are available for treatment of depressive disorders, one of the major limitations of all present antidepressants is delayed onset of action [1]. In addition, despite recent advances in the pharmacological and non-pharmacological treatment of major depressive disorder, almost one third of patients fail to respond to any treatments [2]. In recent years, one of the efforts to overcome the current limitations in treatment of depression has been to administer intravenous ketamine. Studies showing a rapid-onset antidepressant effect for the anesthetic agent ketamine, N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, in patients with treatment-resistant depression (TRD), have stimulated a new wave of pre-clinical and clinical research focused on the glutamate system and the NMDA receptor complex in mechanisms in major depressive disorder. A series of studies showed that chronic- but not acute, administration of several antidepressants, including imipramine, the serotonin-selective reuptake inhibitor citalopram and electroconvulsive therapy (ECT) in rats produced dose-dependent and persistent changes in the binding profile of NMDA receptors [2]. These findings suggested that adaptive changes in NMDA receptors might be a final common pathway for antidepressant action [2].

Studies in mice has linked enhanced AMPA signaling with increased synaptic plasticity [3]. Previously, Li et al. reported that ketamine rapidly activates the mammalian target of rapamycin (mTOR) intracellular signaling pathway, resulting in increased amounts of synapse-related proteins as well as an increased number and function of new spine synapses in the prefrontal cortex of rats [4]. Blockade of mTOR signaling in rats prevented the ketamine-induced synaptogenesis and antidepressant behavioral responses. These findings provided a key link between neurotrophic- and plasticity-related theories of depression and the mechanism of action in NMDA receptor antagonists, suggesting that compounds that enhance neurotrophic support or activate the mTOR pathway directly may have had antidepressant activity. Li et al. [4] also showed that the synaptic and antidepressant effects of ketamine in animals were blocked by administration of an antagonist of the glutamate α-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid (AMPA) receptor. Taken together, these findings supported a model where ketamine may have decreased NMDA receptor signaling and enhance AMPA receptor signaling, with a net effect of increased synaptic plasticity and neuronal growth, which was postulated as the basis for the observed antidepressant effects.

Relapse prevention strategies in depression regarding ketamine use are worth noting. Encouraging results showed how repeated administration of low-dose ketamine three days a week for two weeks in patients with TRD, similar to an ECT, produced a sustained antidepressant response up to 3 months [5]. In an effort to reduce cognitive side effects related to NMDA receptor antagonists, compounds selective for the NR2B subunit of the NMDA receptor were investigated. An initial study of an NR2B-selective NMDA receptor antagonist showed acute antidepressant effects in 30 patients with TRD as adjunctive treatment to a stable dose of paroxetine [6]. Concerns regarding unique dissociative and other neurocognitive effects of ketamine, abuse potential, and neurotoxic effects of NMDA receptor antagonists shown in rats [7] require a cautious approach to the use of ketamine treatment for treatment-resistant depressed patients. Nonetheless, more than almost 60 years of clinical experience with ketamine use suggested that ketamine had been overall very safe and well-tolerated medication [8]. While the transient cognitiveand dissociative effects of ketamine might limit its widespread use in depression treatment, it certainly represents a crucial addition to the armamentarium of therapeutic interventions for TRD cases, similar to ECT.

Recently, Singh et al., in a multicenter, double-blind study, reported that ketamine, when administered intravenously at 0.5 mg/kg of body weight either two or three times weekly, appeared comparably effective in both achieving rapid onset and maintaining antidepressant efficacy in patients with TRD across the 15-day period of assessment [9]. The improvement was similar in the two frequency groups. As less frequent treatment administration is usually preferred in order to reduce the patient and clinic burden and costs, this result, taken together with other data acquired during the double-blind and open-label phases, suggests that the twice weekly treatment regimen administered for 4–6 weeks could induce and maintain a robust antidepressant effect in thetreatment-resistant depressed patients. Furthermore, both treatment regimens were found generally tolerable, with significant attenuation of dissociative adverse events across repeated infusions.

The use of ECT in depression is limited by concerns about its cognitive adverse effects. The neurotransmitter glutamate has a central role in cognition, especially in learning and memory, through its effects on synaptic plasticity and the signaling pathway involved in long-term potentiation in the hippocampus [10]. Memory

impairment after ECT could be a consequence of indiscriminate activation or saturation of glutamate receptors during the treatment, disrupting hippocampal plasticity involved in memory [11]. Ketamine, a dissociative anaesthetic, analgesic, and psychotomimetic, inhibits NMDA receptors, while stimulating glutamate release and potentiating glutamate function through non-NMDA receptors such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [12]. Animal and preliminary human trials suggested that the glutamate antagonist ketamine might improve reorientation and word recall after ECT and accelerate symptomatic improvement. In a recent multicentre, randomized, parallel-group study in 11 ECT suites serving inpatient and outpatient care settings in seven National Health Service trusts in the North of England published at Lancet Psychiatry; Anderson et al. [13] recruited severely depressed patients, aged 18 years and older who experienced moderate or severe unipolar or bipolar depressive episodes. Patients were randomly assigned to receive ketamine (0.5 mg/kg intravenous bolus) or saline adjunctive to the anesthetic (propofol or thiopental) for the duration of their ECT course. There were 33 patients in the ketamine treatment arm and 37 in the saline arm. Patients and the ECT treatment teams were masked to treatment allocation, although anesthetists administering the study medication were not. Ketamine, when compared with saline, had no benefit on the primary outcome of the Hopkins Verbal Learning Test-Revised delayed verbal recall component (HVLT-R-DR), as determined through analysis after four ECT treatments (difference in means, −0.43 [95% confidence interval (CI), −1.73 to 0.87), the researchers reported. For the primary outcome measure (anterograde verbal memory), an effect size benefit for ketamine of 0.3 or greater has been excluded with 95% confidence, and an effect size of 0.4 or greater excluded for other key outcomes (MADRS, CGI, and so forth) ; this is less than the moderate effect size originally proposed as clinically important. In this study, administering adjunctive ketamine with a course of bilateral brief-pulse ECT did not improve neuropsychological or clinical outcomes in patients with severe depression and the results did not support the use of adjunctive low-dose ketamine in routine ECT treatment. Although some studies suggested that ketamine could accelerate the clinical response to ECT, no evidence of that was found in this study. On average, although not statistically significant, patients who received ketamine achieved remission later than those who received saline treatment. This finding was in sharp contrast to the rapid antidepressant effect within hours or days reported when ketamine was administered alone. Anderson et al. [13] also reported that two patients in the ketamine group had transient psychological effects following ECT treatments, but no evidence of serious tolerability or safety problems with ketamine given at the dose provided in the study were found. The smaller-than-planned sample size is the most important limitation of the study. Therefore we cannot exclude either a small to moderate sized benefit or moderate harm from treatment with adjunctive ketamine.

At the level of clinical symptoms, ECT has been already rapidly acting and effective, such that any added speed or magnitude of antidepressant effects would be hard to detect without sufficiently large sample sizes (exceeding 200 patients per treatment arm). Notably, the results of this most recent trial were included in an updated systematic review and meta-analysis of adjunctive ketamine in ECT [14]. In that analysis researchers also found no evidence to support the use of ketamine over other induction agents used in ECT. Furthermore, the results of the KANECT trial (The use of ketamine as an anaesthetic during ECT for depression: does it improve treatment outcome?) [15] on the use of intravenous ketamine (up to 2 mg/kg) with ECT were also negative. No significant differences were found on any outcome measures during, at the end of or 1 month following the ECT course. The question at this stage is how ketamine exerts such substantial and rapid antidepressant effects when given at a subanesthetic dose in the absence of ECT, while it seems to confer little added benefit when combined with ECT. Additional research aimed at this important question would have the potential to understand the mechanism of action of this prototype rapidly acting antidepressant and possibly optimize augmentation strategies in ECT. We should also highlight that ketamine was not merely an adjunct to ECT, but also to other anesthetic agents (propofol or thiopental combined with the muscle relaxant suxamethonium) utilized in the ECT setting. Unfortunately, no differential efficacy analysis in terms of anesthetic agents was reported.

While caution in the area of ketamine research in depression is clearly warranted, the risks involved must be weighed against the tremendous illness burden resulting from TRD and the urgent public health need to identify new and more effective treatment targets. Since the patterns of recurrences and increasing severity of TRD are key reasons for its high illness burden, reducing the burden requires an entire paradigm shift, including emphasis on the prevention of recurrences. Considerable practical difficulties in doing multicenter ECT research and the uncertainty about the optimum dose and method for administering ketamine with ECT were important challenges for the design of conclusive research studies. Future research using sufficiently large sample size would be able to address these methodological problems. We would like to highlight that there is considerable promise in glutamatergic modulation in depression and mood disorders to overcome the limitations of current medications in terms of efficacy and speed of action, and meticulous clinical translational work has been of paramount importance.

Declaration of interest

S.K., M.C.: The authors reported no conflicts of interest related to this article.

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Samet Kose

Assoc. Prof. of Psychiatry, Franklin, TN, USA

sametkose@gmail.com

Mesut Cetin

Prof. of Psychiatry, Editor-in-Chief, Psychiatry &Clinical Psychopharmacology and Journal of Mood Disorders, Istanbul, Turkey

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