The Antisuicidal Effect of Esketamine Should Be Further Investigated

To the Editor: In a recent *Journal* article, Fu et al[1] reported no greater improvement in suicidal ideation (SI) at 24 hours with esketamine versus placebo (both in addition to standard of care) in severely depressed adults with active SI despite greater improvement in depressive symptomatology. Yet, this negative result should be interpreted cautiously.

First, we may point out that a greater reduction in SI was reported with esketamine versus placebo in patients with more severe depressive symptoms. Change in SI while taking into account the change in depressive symptoms is deserving of study. Indeed, evidence has shown that SI course was related to but separated from depression course.[2]

Second, the use of the Clinical Global Impression of Severity of Suicidality Revised version to assess SI is questionable. This clinician-rated module is part of the Suicide Ideation and Behavior Assessment Tool, specifically designed for studies testing esketamine.[3] However, according to the Montgomery-Asberg Depression Rating Scale suicidal thoughts measure, SI was significantly reduced at 4 hours post first dose and at day 25 in the esketamine group. In addition, previous studies have reported a discrepancy between patient and clinician ratings of SI.[4] Self-rating of SI could be more predictive of a future suicide attempt than clinician rating.[5] It is thus crucial to measure patients' ratings of change in SI with esketamine versus placebo.

Third, the high placebo effect could be partly explained by the innovative type of treatment administration (intranasal spray), the short duration of the trial, and the high number of visits during the trial (more frequent interactions between practitioners and patients than in usual care).[6]

Fourth, during the visits, the patients had close contacts with at least 3 health care workers (site staff member, safety rater, efficacy rater) for at least 90 minutes (minimum duration of the safety monitoring). Care, attention, and enhanced social support are beneficial to reduce SI.[7] This also raises the question of the organization of care, ie, the need to develop intensive care units providing specific therapeutic strategies in well-defined conditions for the management of suicidal depression (severely depressed patients with active SI).

Fifth, the effectiveness of treatments for SI is only partially explained by changes in depression symptoms.[8] It would thus be interesting to investigate whether esketamine, similarly to ketamine, may impact other suicide-related features such as pain or anhedonia.[9]

Come what may, this study shows a rapid impact of esketamine on depression in the context of suicidal crisis, which may reduce the probability of suicide attempt. SI and prior suicide attempts are among the most potent predictors of future death by suicide.[10] The significant reduction of SI in those who previously attempted suicide highlights that esketamine treatment must be proposed to patients who are at highest risk of suicide. Indeed, a history of suicidal behaviors has been associated with poor response to antidepressant treatment.[11] Individuals who attempt suicide may thus benefit from add-on esketamine treatment.

Dr Fu was shown this letter and declined to reply.

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