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In their article on the ESCAPE-TRD trial, Reif et al. (Oct. 5 issue)¹ report on the efficacy and safety of esketamine nasal spray in comparison with extended-release quetiapine therapy in patients with treatment-resistant depression. The between-group differences in the change from baseline in the score on the Montgomery–Åsberg Depression Rating Scale (MADRS; scores range from 0 to 60, with higher scores indicating more severe depression) at 8 weeks (–2.8 points, favoring esketamine) and 32 weeks (–2.2 points, also favoring esketamine) were significant but were less than the minimum clinically important difference.² The data on remission that were provided are unreliable because small differences between treatments can be inflated in dichotomized data.³

Patients in whom treatment was discontinued were classified as having had an unfavorable outcome, which might have artificially improved the outcome in the esketamine group (in which fewer patients had discontinued treatment than in the quetiapine group). Data from a “retrieved dropout analysis” are presented only at 8 weeks and lack transparency. The esketamine group also had more hours of contact with staff (for safety monitoring) than the quetiapine group, a factor that may reduce depression scores and affect attrition.⁴

Esketamine may induce short-term euphoria that reduces depression scores but may not modify the condition in the long term.⁵ The difficulties that patients may have in stopping esketamine because of its withdrawal effects, which have been highlighted in a recent study,⁶ as well as its diminishing effects over time (i.e., tolerance effects), were not examined. Adverse events occurred in almost all the patients in the esketamine group (91.9%), with serious adverse events, mostly psychiatric, occurring in a similar number of patients in the esketamine group (in 19 patients) and the quetiapine group (in 17).

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