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COMMENTARY

Cautious optimism and a call for additional studies

Depression is a highly prevalent mental health disorder with a wide range of consequences at the individual and collective scale. The World Health Organization (WHO) ranks depression as the leading contributor to number of years lost due to disability, and the seventh leading overall cause of global disease burden (World Health Organization, 2017). In the elderly population, depression is the second most common psychiatric disorder and is strongly associated with an increased risk of cardiovascular disease, cognitive decline, institutionalization, and overall mortality (Hajek *et al.*, 2015; Zhang *et al.*, 2018). The biological, social, and psychological complexity of older adults contributes to the widely heterogenous presentation of late-life depression and therefore poses challenges with treatment resistance. While antidepressants are superior to placebo, initial treatment leads to remission in less than 50% of patients, with roughly one-third having no response to pharmacotherapy (Mrazek *et al.*, 2014). Neuromodulation interventions like electroconvulsive therapy (ECT) offer an effective alternative for treatment-resistant depression, but there are also barriers related to a patient's ability to participate in and tolerate these treatments (Knöchel *et al.*, 2015). As a result, there is a strong demand for novel treatment strategies. In this commentary, we will briefly outline the history of research of ketamine's benefits in late-life depression and highlight the current gaps in our knowledge of its use in the geriatric population that may direct future areas of research.

Over the last 20 years, the steady rise in evidence showing the promise and efficacy of ketamine in managing treatment-resistant depression was primarily based upon studies that examined patients of the younger adult age range. By the year 2017, only five case reports examined intravenous (IV) ketamine treating depression in adults older than the age of 60 years (Bryant *et al.*, 2019; Ribeiro and Riva-Posse, 2017; Srivastava *et al.*, 2015; Szymkowicz *et al.*, 2014). Of these initial reports, more than half of the patients older than the age of 60 years did not respond to IV ketamine. In the 2014 study by Szymkowicz *et al.*, one patient from a total of four had partial response after the first infusion, but this improvement was not sustained after repeated administration. According to Srivastava *et al.* in 2015, the sole patient in the study achieved sustained yearlong remission after four infusions of IV ketamine over the course of 2 weeks. The patients from both studies varied in the time course of their depressive episode, the frequency and number of IV ketamine infusions received, and their treatment history profile. Of note, every patient in the 2014 study had failed courses of ECT, whereas the patient in the 2015 study had no reported history of an ECT trial. The heterogeneity of patient profiles highlights the importance of identifying predictors of future response to treatment, which are not well known at this time. This gap in our understanding, along with the increased risk of side effects from ketamine in the elderly (e.g. dissociation, dizziness), may all have contributed to the current scarcity of placebo-controlled studies and thus limited the data's applicability to the rest of the geriatric population.

The studies by George *et al.* and Ochs-Ross *et al.* are the only two placebo-controlled, double-blinded, randomized controlled trials (RCTs) of using ketamine for treatment-resistant depression in the geriatric population (George *et al.*, 2017; Ochs-Ross *et al.*, 2020; Gupta *et al.*, 2020). Unlike the case reports that preceded them, these studies assessed the benefits of a dose titration strategy rather than a fixed dose, shared a more homogenous patient profile, and standardized the timing of the intervention in relation to the patient's course of illness. In addition to tracking patient response to the acute phase of ketamine delivery, both studies assessed how the frequency and duration of treatment affected a patient's time to relapse and tolerability to treatment, which may offer clues for developing future maintenance protocols. The RCTs demonstrated an attenuation of symptom improvement with an overall sustained reduction of Montgomery–Asberg Depression Rating Scale scores with repeated ketamine dosing that were not seen in the earlier case reports. Key differences in subject profile (e.g. prior response to ECT, history of suicide) were noted between the case reports and RCTs and therefore may have contributed to the variance of these results.

One notable study design feature of both RCTs was the exclusion of acute suicidal ideation in subjects. Therefore, the question of ketamine's touted benefits in the acute reduction of suicidality, which have been observed in studies of younger adults, remains unanswered for the geriatric population (Berman *et al.*, 2000). This limitation, as well as

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the known increased lethality of suicide in older adults, certainly demands the future investigation of ketamine's benefits in this population subset (Conwell *et al.*, 2011).

Clinical trials comparing the efficacy and adverse effects of ketamine with other pharmacologic treatments in older adults remain scarce. It is encouraging that the studies by George *et al.* and Ochs-Ross *et al.* had an extended follow-up period to assess for long-term adverse effects. However, there is no data on patient morbidity and mortality due to chronic treatment with ketamine beyond 12 months. While there is mixed evidence that chronic use of antidepressants can both increase and decrease risks of mortality in older adults, a 5-year prospective study of antidepressant use determined that cognitive impairment, cardiovascular health, and activities of daily living function were significant confounding factors of mortality rates that influenced these discrepant findings (Boström *et al.*, 2016). Future ketamine studies could stratify risks to treatment based on these factors.

Our understanding of ketamine's role of treating depression within the geriatric population remains at an early stage. Prior studies have been limited by sample size, diversity of patient characteristics, and risk of intolerable side effects. The two RCTs examined in this systematic review mark important first steps forward to answering questions that can shape practice guidelines in both the acute and maintenance phase of treatment. Despite these advancements, more clinical trials are needed to replicate and validate the evidence. Identifying predictors of response to treatment and clarifying long-term exposure safety risks will be key areas of future research.

Michael G. Li, MD and
Erica Garcia-Pittman, MD

Dell Medical School, The University of Texas at Austin, Austin, TX, USA

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