Published in final edited form as:

Am J Geriatr Psychiatry. 2017 November ; 25(11): 1210–1212. doi:10.1016/j.jagp.2017.08.009.

What Should be Done When Elderly Patients with Major Depression Have Failed to Respond to All Treatments?

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I read with interest the article by George et al.¹ in this issue of the *American Journal of Geriatric Psychiatry*. Although major depressive disorder (MDD) in older adults is common and can be effectively treated with antidepressants or electroconvulsive therapy (ECT), few treatment options exist for those who have not responded to established treatments. As with younger adults, only roughly one-third of older patients with MDD typically achieve remission with an antidepressant trial.² However, and in contrast to younger adults, the options for older MDD patients have not been as well researched, making informed, evidence-based treatment decisions difficult. Furthermore, use of existing treatment options is often limited in this population for reasons that can include age-related frailty or the presence of comorbid medical conditions. These can limit a clinician's ability to combine antidepressants or administer other augmentation therapies because of the risk of intolerable pharmacodynamic effects, drug–drug interactions, and noncompliance with treatment.

Currently available antidepressant treatment options for geriatric depression include both pharmacologic and nonpharmacologic therapies (including cognitive and behavioral therapies) that can be administered as monotherapy or in combination; these are typically administered in an orderly fashion by progressing through the decision tree of therapeutic options.³ A recent article explored the effectiveness of antidepressant switching versus augmentation in achieving remission for MDD patients who had not responded to traditional antidepressant therapies and found a statistically significant, although modest, increase in the likelihood of remission rates after 12 weeks of augmentation with aripiprazole compared with switching to bupropion monotherapy.⁴ Adverse effects more frequent in the group augmented with aripiprazole included somnolence, weight gain, and akathisia.⁴ In general, studies have found that ECT is highly effective in treating geriatric MDD patients who do not respond to other treatments, particularly elderly subjects who are frail or have complicated comorbid medical conditions.⁵ An issue of continuing concern, however, is the treatment of older MDD patients who have failed to respond to most treatment options, *including* ECT. When reaching this stage, almost no evidence exists to guide clinicians regarding the most appropriate next step for treating this vulnerable population.

Considerable evidence demonstrates that ketamine, a glutamatergic modulator, has rapid antidepressant, antisuicidal, anxiolytic, and antianhedonic effects in nonelderly individuals

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with treatment-resistant MDD.⁶⁻⁹ Furthermore, preliminary evidence suggests that acute ketamine administration has salutary effects on a number of immune and inflammatory biologic indices associated with heart disease and osteopenia, which are potentially modifiable risk factors and often found to be altered in depression.^{10,11} Whether acutely rectifying these indices in addition to improving depressive symptoms could have long-term effects on brain and body health, particularly as one ages, remains unknown. However, it is quite clear that treatments capable of producing a rapid (within hours), robust, and sustained antidepressant effect would be of major importance to individuals with geriatric depression. Such an intervention could also potentially minimize the cumulative morbid effects of depression and altered immune and inflammatory states that place MDD patients at increased risk of premature death from either medical conditions or suicide.^{12,13}

This is where the study by George et al.¹ becomes highly relevant. The study was designed to address a serious problem in this special population: how to treat MDD in patients who have failed to respond to existing standard treatments, particularly those who may be frail and are at considerable risk for suicide. George et al. conducted a double-blind, randomized, multiple-crossover, controlled trial of different subcutaneous doses of ketamine in individuals over age 60 years with MDD. An ascending dose schedule was used, and subcutaneous injections were administered 1 week apart. A single dose of midazolam was used as an active control. In this study subjects were quite severely treatment-resistant. Their average current major depressive episode had lasted 9 years, they had failed to respond to a mean of four antidepressant trials over the course of their current major depressive episode, and they had an average of eight lifetime antidepressant trials; 12% had failed ECT administered in the current episode. Notably, the authors found that single doses of subcutaneously administered ketamine in older patients were effective, safe, and well tolerated. Across all dose levels and time points, 11 participants (69%) met criteria for both response and remission after ketamine administration during at least one of the trial's timepoints. Furthermore, the proportion of the entire sample who met remission criteria improved as the ketamine dose was increased from 0.1 mg/kg to 0.5 mg/kg. In addition, repeated treatments resulted in a higher chance of remission or a longer time to relapse. The investigators also found that five patients remitted at doses below 0.5 mg/kg and that doses of at least 0.2 mg/kg were significantly more effective than midazolam.¹ Although this was a pilot study whose results cannot yet be generalized to "real-world" patients, it does offer exciting insights into how ketamine might enter existing treatment algorithms and how it might be placed in a hierarchy compared with other treatments.

Although these results are very promising, several cautionary issues bear mention. First, the findings of George et al.¹ are preliminary and need to be replicated in a much larger sample before any firm conclusions can be made. Second, even if replicable, these findings may not necessarily generalize to other populations, such as those who are acutely suicidal, inpatients, or particularly frail individuals. Until such studies are conducted, concerted efforts to gather systematic data on the use of ketamine across all ages¹⁴ should continue, as should efforts to translate such information for practical clinical use. Relatedly, ongoing, well-controlled, long-term trials are needed to address questions of efficacy, tolerability, safety, and effectiveness across patient populations.

In short, it is important to underscore that as with nonelderly individuals with treatment-resistant MDD, ketamine continues to be associated with considerable unknowns that will only be clarified with more extensive research. Indeed, we cannot assume that results found in younger adults will necessarily apply to geriatric individuals with MDD. Furthermore, because ketamine has been associated with dose-related side effects, including psychotomimetic and dissociative effects, transient elevations in blood pressure and heart rate, cognitive impairment, hepatotoxicity, and inflammation of the bladder endothelium,¹⁵ it remains imperative to conduct additional short- and long-term ketamine studies in elderly individuals with MDD to tease out issues related to optimal dosing, appropriate duration of continuation and maintenance treatments, and long-term safety indices in terms of cognition, neurotoxicity, and effects on other bodily functions. It should also be noted that most ketamine studies conducted to date have administered intravenous ketamine, which is not practical for several reasons, particularly with regard to the number of additional resources needed, cost, and other considerations. Thus, having options in terms of alternative forms of administration, particularly if well tolerated, would be a significant public health advantage; in this regard, the positive results observed by George et al. after subcutaneous administration of ketamine to elderly subjects with treatment-resistant MDD are particularly germane.

Despite the cautionary notes sounded above, it is clear that patients with MDD—including elderly patients whose treatment options are more limited—suffer enormously from this disorder, which places them at risk for early death if their depressive symptoms are not well controlled from the outset. As clinicians, it is obviously important to make sure that our patients receive the best and most appropriate care available at each step of the way. Presently, the evidence still strongly suggests that ECT should be administered before ketamine in the treatment algorithm because of its robust efficacy and well-known adverse event profile in the elderly. However, if existing proven antidepressant treatment options have been exhausted in this vulnerable elderly population, the results obtained by George et al.¹ suggest that ketamine may be considered a viable—and perhaps valuable—treatment option.

Acknowledgments

The author thanks the 7SE research unit and staff for their support. Ioline Henter (National Institute of Mental Health) provided invaluable editorial assistance.

Supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; ZIA MH002857). Dr. Zarate is listed as a co-inventor on a patent for the use of ketamine and its metabolites in major depression and suicidal ideation; as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (5*S*)-dehydronorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of (2*R*,6*R*)-ketamine metabolites in the treatment of depression and neuropathic pain; and as co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders. Dr. Zarate has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government.

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