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Use of Ketamine in Elderly Patients with Treatment-Resistant Depression

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Abstract
Purpose of Review The purpose of this paper is to provide a review of the use of ketamine as an antidepressant for treatment-resistant depression (TRD) in the geriatric population. Available treatment options for late-life treatment-resistant depression are limited and include electroconvulsive therapy and transcranial magnetic stimulation as well as possible pharmacologic augmentation. Ketamine has been shown to be a promising treatment in TRD; however, data regarding the use of ketamine in the elderly includes only five case reports.
Recent Findings We discuss the use of ketamine for late-life TRD and present two cases where ketamine led to a significant and sustained improvement in depressive symptoms.
Summary Ketamine is a promising treatment for geriatric patients with TRD. Further studies in the elderly will provide valuable insights into the use of ketamine for a population much in need of safe and effective treatments for TRD.

Keywords Depression · Ketamine · Elderly · Antidepressants · Resistant · Geriatric

This article is part of the Topical Collection on *Geriatric Disorders*

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Introduction

Depression is one of the most significant causes of global disease burden and is associated with considerable disability. Lifetime prevalence of depression ranges from 2 to 15% [1], and according to the World Health Organization, depression is the seventh leading cause of global disease burden, the third cause in high-income countries, and the top leading cause of years of life lived with disability [2]. Despite this impact on world health, available pharmacologic treatments for major depression are many times suboptimal with a significant amount of patients being found to be resistant to current pharmacologic therapies.

Initial treatment with one antidepressant leads to remission in less than 50% of patients, and up to 30% have no response to pharmacotherapy [3]. In the elderly, about one third of depressed older patients is resistant to available treatments [4••].

Among older adults, the prevalence of depression ranges from 9 to 18% [5]. Older depressed individuals (late-life depression or LLD) have higher risk for comorbid chronic illness and functional impairment, and also an increased mortality risk from cardiovascular causes and suicide [5]. Late-life depression is also associated with impairments in cognition including executive function, memory, processing speed, attention, and visuospatial skills, which greatly affect functioning [6].

LLD treatment resistance rates to the first trial of antidepressants have been shown in randomized controlled trials to be as high as 77% with selective-serotonin reuptake inhibitors (SSRIs) [7]. Despite this fact, studies evaluating approaches to treatment-resistant depression (TRD) in the elderly population are scarce. There have been studies, mostly open-label, reporting strategies such as augmentation with lithium and second-generation antipsychotics such as aripiprazole. These strategies, while appealing, raise concerns due to the burden of side effects in elderly populations [8].

Other available approaches for LLD TRD include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS) [9], vagus nerve stimulation [10, 11], and experimental techniques such as deep brain stimulation. However, the response rates of rTMS are relatively low, and approximately 20% of patients do not respond to ECT [12]. In addition, older patients are more susceptible to the cognitive side effects (such as delirium) and cardiovascular complications of ECT [12]. Considering the high rates of treatment resistance, higher susceptibility to adverse effects of ECT, and few other strategies available seeking further treatment options for older depressed patients is extremely important.

The prevalence of treatment resistance in LLD and the difficulties in tolerability of therapies like ECT make the understanding and investigation of ketamine in this population even more important. Most studies report age ranges that include patients older than 60–65 years old without disclosing precise ages or differentiating responses between adults and elder patients. Other studies only report the mean age of the sample making it impossible to distinguish if older patients were even part of the sample [13]. Interestingly, the geriatric population is usually not distinguished from adults in ketamine studies despite significantly different causal factors and mechanisms reported in literature [14–17].

Since the first study showing the rapid and robust effect of ketamine as an antidepressant [18••], several studies and clinical trials have expanded on ketamine as a potential therapeutic option [13, 19–21]. Ketamine has been shown to be a promising treatment in TRD [22]; however, reports of the therapeutic effects of ketamine infusion therapy in older patients are limited to five case reports. In the first study, four patients with a mean age (± SD) of 72.25 (± 5.38) years with comorbid psychiatric and neurological disorders including generalize anxiety disorder (GAD), atypical major depressive disorder (MDD), and Parkinson's plus syndrome had insignificant changes in depression scores with the infusion. In addition, with the usual dose of 0.5 mg/kg over 40 min, patients experienced psychotomimetic effects without the benefit of response or an insufficient response (less than 50%) to the infusion [23•].

The second study is a single case report of a 65-year-old patient in which ketamine infusion therapy was administered in a patient during a fourth episode of depression after failure to respond to two antidepressants and antipsychotic augmentation. After four ketamine infusions of 0.5 mg/kg over 40 min in a 2-week period (biweekly), the patient achieved significant subjective improvement, and ketamine infusions were discontinued. The patient maintained a sustained remission from depression for the year following the infusions [24•].

The infusion-related side effects of ketamine warrant caution in the geriatric population. Short-term cognitive effects for ketamine are well known; however, long-term effects have been less studied in the depression literature. The available reports of repeated ketamine use in humans depend on the studies in chronic drug users. And, although these reports described cognitive deficits [25••], it is unclear how these reports apply to ketamine infusions in depressed patients. Studies evaluating the neurological effects of ketamine in patients who abuse the drug have shown cortical changes after years of use. Wang et al. evaluated 21 patients with up to 12 years of ketamine abuse with an average dose of 1 g daily through intranasal route and found a correlation between years of use and presence of white matter lesions or regional atrophies. After about 2–4 years of use, cortical atrophy was seen in frontal, parietal, and occipital regions of the cortex [26•]. Liao et al. also found reduction in frontal gray matter after chronic ketamine use that is likely related to decline in executive functioning. The authors suggested an association between the duration and cumulative doses of ketamine with these changes [27•].

In addition to cognitive/psychotomimetic side effects, ketamine use has been associated with urinary, cardiovascular, and hepatic side effects. Urinary symptoms include frequency, dysuria, and nocturia and may lead to ulcerative cystitis; however, these potential side effects tend to be dose-related and reversible with cessation of the ketamine infusions [28, 29]. Cardiovascular side effects are commonly reported including tachycardia and hypertension, however uncommonly life-threatening [28, 30]. Hepatotoxicity may occur with increases in transaminases, alkaline phosphatase, and gamma-glutamyl transferase and have normalized with discontinuation of ketamine [28, 31].

While still lacking definitive data, some researchers propose that the effect on glutamatergic *N*-methyl-D-aspartate receptors is integral to ketamine's mechanism of action [32]. Age-related changes in glutamate receptors both through *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors are well described in preclinical and clinical studies [33]. There are studies discussing the different mechanisms of late-life depression compared to early-life depression such as differences in NMDA receptors with aging [34] which is thought to be related to ketamine's antidepressant effect [35]. Whether this directly affects response to ketamine in older patients remains unknown to the field.

We present two cases of patient with treatment-resistant late-life depression. Both patients received ketamine 0.5 mg/kg in a continuous 40 min intravenous infusion.

Case 1

The first patient was a 72-year-old female first diagnosed with bipolar disorder type I in her 50s but with lifelong symptoms of depression and mania/hypomania. The patient

had been on multiple medications with limited/short lasting effects or intolerable side effects. These medications included fluoxetine, paroxetine, sertraline, citalopram, escitalopram, bupropion, duloxetine, mirtazapine, lithium, and lamotrigine with limited efficacy or intolerable side effects. After a severe depressive episode, the patient underwent a course of ECT, initially right unilateral electrode placement and later bilateral electrode placement due to lack of response. The patient received a total of 8 right unilateral and 51 bilateral ECT including maintenance ECT over a period of 3 years; however, she developed increasing cognitive side effects and the response to treatment gradually diminished. There was difficulty in spacing out the ECT treatment without a recurrence of depressive symptoms, and the closer the ECT treatments were, the more cognitive problems arose. Her subjective cognitive complaints related to ECT included word finding difficulty, stuttering, and feeling "less sharp" than previously.

The patient agreed to a trial of off-label ketamine infusions. The first infusion (0.5 mg/kg over 40 min) was well tolerated and patient reported transient psychotomimetic effects, described by her as "time running faster." She reported no side effects in between infusions. The infusion schedule was biweekly for 2 weeks, followed by weekly administrations for 8 weeks. The patient reported a sustained and gradual antidepressant response, with the response lasting until subsequent infusions. She received a total of 11 infusions. The Quick Inventory of Depressive Symptoms-Self-Report (QIDS-SR) was administered prior to each infusion (Fig. 1). Her initial baseline QIDS was 14, indicating moderate to severe depression. After six infusions, QIDS-SR decreased to 6, and with weekly maintenance ketamine, it was persistently low, with the last infusion QIDS-SR at 7 points. In a similar manner, the Beck Depression Inventory II (BDI-II) was 22 at baseline prior to the infusions, 6 after six infusions, and 11 at the last infusion. The patient reported the improvement in her symptoms of depression was significant and allowed her to resume many of her daily activities. She had no complaints of worsening cognitive function.

Case 2

The second patient was a 64-year-old female diagnosed with major depressive disorder in her 20s who presented with depression and suicidal ideation. Previous trials with fluoxetine, venlafaxine, desvenlafaxine, duloxetine, and lurasidone were of limited efficacy. The patient had experienced approximately one depressive episode yearly with a usual duration of 1 month since her young adulthood. The length of index episode was 3 months at presentation, leading to hospitalization for the severity of symptoms. The patient refused to undergo and ECT course out of concern for cognitive side effects and was consented to receive off-label intravenous ketamine.

Ketamine infusions were started using standard dose of 0.5 mg/kg over 40 min. The infusions were well tolerated, and she described the acute effect of the ketamine as if "the doors in my mind have opened" and feeling calmer. Her initial QIDS-SR was 20, and after six infusions (over a period of 3 weeks), it decreased to 6. She continued receiving weekly and then every other week infusions with a sustained antidepressant response. After 11 weeks, patient had received a total of 13 infusions initially biweekly then once every 2 weeks, and her QIDS-SR remained in the low range (6 points). The patient stopped coming to the ketamine clinic for about 5 weeks, returning to the clinic with a recurrence of symptoms. When she was reevaluated, her QIDS-SR was 18. After resuming the intravenous infusions with the same frequency (once every other week), she showed again a good response to ketamine, and at last observation after 11 weeks of restarting infusions, her QIDS had returned again to 6 points. Patient received a total of 22 infusions and continues to receive maintenance ketamine infusions.

Both patients had tolerated the intravenous infusions of ketamine and had minimal psychotomimetic effects that cleared rapidly after the end of the infusions. Vital signs remained stable during all infusions; no significant elevations in blood pressure or heart rate occurred, and psychotomimetic

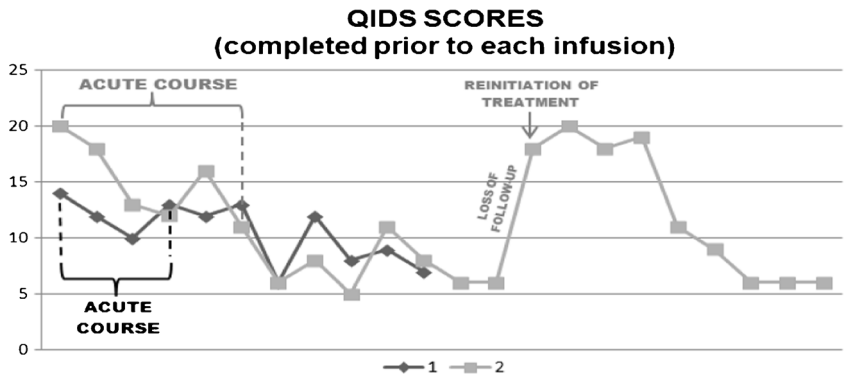

Fig. 1 Quick Inventory of Depressive Symptomatology scores for each patient prior to each ketamine infusion

effects were mild and transient, resolving completely a few minutes after the infusion was finalized. None of the two patients reported inter-infusion psychotomimetic side effects or significant cognitive side effects, and they did not complain urinary or bladder problems. The trajectory of improvement is described in Fig. 1.

Conclusions

Current literature regarding use of ketamine for late-life depression remains scarce. The five prior case reports describing ketamine in elderly patients and cited above have variable response rates. One of the most important limitations of case reports, including the ones reported here, is that they are not generalizable to the entire population. While our cases fall in the same category, the positive outcomes observed in these patients challenge concerns that ketamine is unsafe or not effective in the elderly population. It is interesting to point out that the patient in the second case report responded to ketamine after relapsing. Reintroduction of ketamine in the second patient after loss of follow-up did not lose its effect.

Further research is needed to determine the role of ketamine therapy in the geriatric population. Additionally, the higher suicide rates in the elderly, compared to the general population, demand the search for therapeutic alternatives [36]. Studies in the geriatric populations should investigate alternative dosing and administration of ketamine. The current dose of IV ketamine is arbitrarily chosen at 0.5 mg/kg. In the geriatric population, who may be more prone to side effects and lower tolerability, lower doses or longer infusion times need to be explored, as well as different ways of administration (i.e., subcutaneous, intramuscular, or intranasal) [37]. Safety, both during the infusion (cardiovascular and psychotomimetic) and long term (cognitive, hepatic, and urinary side effects), may have a different incidence in older patients. A better understanding of the different aspects of the neurobiology of depression in the elderly as well as of the pharmacology of ketamine in this population will aid in the development of effective and safe treatments for this population.

Compliance with Ethical Standards

Conflict of Interest Carolina Medeiros da Frota Ribeiro declares no conflict of interest.

Patricio Riva-Posse has received consulting fees from Johnson & Johnson.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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