Bayesian adaptive randomization trial of intravenous ketamine for veterans with late-life, treatment-resistant depression

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A B S T R A C T

More than eleven million U.S. Veterans are at least 65 years of age, an age group of which almost 20% suffers from clinically significant depressive symptoms. Available pharmacological treatments are suboptimal for patients, including veterans, with late-life depression. Ketamine has emerged as a potentially promising rapid-acting therapy for treatment-resistant depression (TRD). However, few studies have examined the safety, tolerability and efficacy of ketamine therapy for older adults with late-life TRD (LL-TRD). This study uses an adaptive randomization design to test the safety, tolerability, efficacy, and durability of three distinct, single sub-anesthetic doses of intravenous (IV) ketamine versus a single dose of active placebo (midazolam) in older depressed veterans. As the study progresses, Bayesian adaptive randomization recalibrates randomization ratios to allocate more participants to conditions demonstrating greater promise and fewer participants to conditions with less promise. Secondary analyses explore clinical and biological moderating and mediating factors of rapid treatment response. Results are expected to inform both the viability of ketamine treatment and optimal dosing strategies for patients with LL-TRD.

1. Introduction

Late-life depression (LLD) is a common, disabling condition that affects up to 20% of older veterans [1]. It is associated with a variety of medical comorbidities and negative health outcomes including functional impairment and mortality. Further, up to one-third of older adults show resistance to available first-line treatments due to a more complex clinical picture and a greater risk of side effects associated with increased age [2–4].

Current therapies for treatment-resistant depression (TRD) include neuromodulation treatments [electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS)], augmentation with atypical antipsychotics or lithium, and monoamine oxidase inhibitors. However, these interventions may pose significant adverse effects on cognition, metabolic profile, weight, and movement disorders [5,6] and may take several weeks to months to achieve optimal benefit. Therefore, the development of new evidence-based, effective, safe, and rapidly-acting interventions for older adults with LL-TRD is critically needed.

Ketamine, a non-competitive NMDA-receptor antagonist initially FDA approved as an anesthetic agent in 1970, has emerged as a promising treatment for patients with TRD. Multiple randomized, placebo-controlled trials of single and repeated administrations of a sub-anesthetic dose of ketamine demonstrate rapid and robust antidepressant and anti-suicidal effects [7–9]. These studies have supported the treatment as safe and tolerable for short-term use in young and mid-life adult populations. Yet, very few studies have examined ketamine’s antidepressant efficacy, safety, and tolerability in an older population [10], significantly hampering evidence-based treatment guidelines for LL-TRD. As older patients may be more sensitive to ketamine’s dissociative, cognitive, and hemodynamic side effects, identifying a tolerable dose in this population is especially important.

1.1. Study aims and hypotheses

The Ketamine for Treatment Resistant Late-Life Depression study uses a double-blind, placebo-controlled, adaptive randomization design to examine the efficacy, safety and tolerability of three different dosages of intravenous ketamine (single-dose 0.1, 0.25 or 0.5 mg/kg over 40 min) compared to active placebo midazolam (0.03 mg/kg) in up to
66 U.S. military veterans with LL-TRD. This design will compare efficacy, tolerability, and duration of action across multiple subanesthetic doses of ketamine. We hypothesize the following: (1) the durability of antidepressant effect of a single ketamine 0.5 mg/kg infusion will be superior to a single ketamine 0.1 mg/kg infusion, a single ketamine 0.25 mg/kg infusion, and a single midazolam 0.03 mg/kg infusion 7 days after the infusion; (2) a single ketamine infusion at the most effective dose will be safe and well-tolerated.

Additional exploratory aims are to measure the effects of the most effective ketamine dose relative to midazolam on (a) neurocognitive performance; (b) peripheral markers of cellular plasticity; (c) neurophysiological measures, including resting-state quantitative electroencephalography (EEG) and the mismatch negativity (MMN) event-related potential (ERP).

2. Methods

2.1. Trial design overview

The trial employs a Bayesian Adaptive Randomization Design in which randomization ratios change after the first 20 participants and at regular intervals thereafter according to a priori specified rules. These rules make use of Bayesian posterior probabilities to recalibrate the randomization ratio such that more participants are allocated to conditions demonstrating greater promise while minimizing allocation to conditions demonstrating less promise. Based on pre-specified rules, if any condition demonstrates overwhelming evidence of superiority the trial will be stopped for utility. The study Stopping Rule is when the response rate of the best performing condition is large enough that the posterior probability is > 0.975 that it is better than the next best condition. Conversely, using similarly constructed a priori evidence rules, suspension of accrual will result for conditions demonstrating such poor performance that continuation of the condition is futile. Additional decision-rules will use Bayesian posterior probabilities to identify the best condition to carry forward into a larger clinical trial. Specific details on the study design and its operating characteristics are included in Appendix 1.

Eligible participants who enroll in the study are randomly assigned to one of 4 treatment arms: ketamine 0.10 mg/kg, ketamine 0.25 mg/kg, ketamine 0.50 mg/kg, or midazolam 0.03 mg/kg. An initial randomization will assign participants in a 1:3 ratio to receive midazolam or further adaptive randomization (Fig. 1). The 75% of participants allocated to adaptive randomization will receive ketamine 0.10 mg/kg, 0.25 mg/kg or 0.50 mg/kg or midazolam 0.03 mg/kg. The rationale for the initial 1:3 split is that if investigators’ expectations hold true, the adaptive algorithm will rapidly decrease the proportion of participants adaptively randomized to midazolam and increase those allocated to ketamine. The 1:3 split will guarantee a sufficient control group (i.e. midazolam) with which to credibly compare the best performing ketamine condition.

2.2. Study sample and setting

This trial and all its procedures were approved by the Baylor College of Medicine Institutional Review Board and the Research and Development Committee of the Michael E. Debakey VA Medical Center. This study is registered at ClinicalTrials.gov (NCT02556606).

The study enrolls depressed male and female veterans 55 years of age or older with TRD. There is no upper age limit. Recruitment strategies include facilitated provider referral, targeted outreach to non-VA affiliated organizations serving older Veterans, placing online advertisements through social media, and a recruitment booth at the VA Medical Center to distribute brochures containing information about the study.

2.3. Inclusion and exclusion criteria

To qualify for the study, participants must (i) meet DSM-5 criteria for Major Depressive Disorder based on a structured diagnostic interview; (ii) have a history of at least one previous episode of depression prior to the current episode (recurrent MDD) or chronic MDD of at least two years duration; (iii) have not responded to two or more adequate trials of FDA-approved antidepressants, determined by the MGH Antidepressant Treatment Response Questionnaire (ATRQ) [11] criteria. Participants are also screened for cognitive impairment and must obtain a minimum score of 25 on the Mini Mental Status exam (MMSE) [12] to be eligible. Full study inclusion and exclusion criteria are detailed in Table 1.

2.4. Study visits

Study visits take place on the day prior to the treatment infusion and at regular intervals after the infusion for 7 days. To continue in the study beyond day 7, participants must meet response or remission criteria (remission: Montgomery-Asberg Depression Rating Scale (MADRS) [13] ≤ 9; response: ≥ 50% reduction in MADRS from baseline visit; Clinician Global Improvement Scale (CGI-I) [14] = 1 or 2). Responders who are not remitters may have a maximum MADRS score of 15 (with ≤ 2 for MADRS items 1 and 2 of reported and apparent sadness). Responders who continue in the study are further assessed on a weekly basis 14, 21, and 28 days after the study infusion in order to continue monitoring durability of treatment effects. Non-responders are exited from the study at day 7. Participants are also exited if they earn 2 consecutive MADRS score ≥ 20 on weekly follow up visits after day 7.

2.5. Treatment intervention

The research pharmacist prepares the IV medication (ketamine or midazolam) in a 100 ml NS bag, and sends it to the treatment suite prior to the infusion, such that a fixed dose of ml per kg is administered. Treatment infusions take place in a hospital and in a private room equipped with vital sign monitoring. Infusion procedures are similar to prior ketamine studies [15–17]. Pulse, blood pressure, digital pulse-
oximetry, and ECG monitoring are instituted. A board-certified anesthesiologist administers the study drug and is present throughout the administration; a medical cart is available for emergencies.

Each participant receives a 40 min infusion of ketamine 0.10 mg/kg, 0.25 mg/kg or 0.50 mg/kg or midazolam 0.03 mg/kg under double-blind conditions. The study drug is dissolved in 0.9% saline in a total volume of 100 mL and administered with an infusion pump at a constant rate.

2.6. Measures

Table 2 provides a full list of measures and schedule of study procedures.

| Table 1 | Inclusion and Exclusion criteria. |
|-----------------|-----------------------------------|
| **Inclusion criteria** | **Exclusion criteria** |
| • Age ≥ 55 years | • Current VNS or rTMS therapy |
| • Current MDE (Unipolar) based on the MINI 7.0 | • ECT treatment within 6 months prior to Screening |
| • History of ≥ 1 previous episode of depression prior to the current episode (recurrent MDD) or chronic MDD (of at least two years’ duration) | • Ongoing use of the following medications: St John's Wort, theophylline, tramadol, metronidazole |
| • Failure to respond to ≥ 2 adequate trials of FDA-approved antidepressants determined by the ATRQ criteria | • MMSE < 25 at Screening, suggesting age-related cognitive decline or mild dementia |
| • QIDS-SR ≥ 14 | • Clinically significant personality disorder that would, in the investigator’s judgment, preclude safe study participation |
| • MADRS ≥ 27 | • Serious and imminent suicidal or homicidal risk |
| • CGI-S ≥ 4 | • Participants with one or more seizures without a clear and resolved etiology |
| • Able to understand and sign informed consent | • Hypertension (systolic BP > 160 mm Hg or diastolic BP > 90 mm Hg) |
| **Exclusion criteria** | • Clinically significant abnormal findings of laboratory parameters [including urine ECG, toxicology screen for drugs of abuse], physical examination, or ECG |
| • Currently taking psychotropic medications with consultation from the participant’s prescribing physician. | • Hypertension (systolic BP > 160 mm Hg or diastolic BP > 90 mm Hg) |
| • History of bipolar disorder, schizophrenia, schizoaffective disorder or any psychotic disorder | • Participants starting hormonal treatment in the 3 months prior to Screening |
| • Documented history of a psychotic disorder in a first-degree relative | • Past intolerance or hypersensitivity to ketamine, or history of recreational use of PCP or ketamine |
| • Current diagnosis of OCD or eating disorder | • Past intolerance or hypersensitivity to midazolam |
| • Alcohol or substance use disorder (except nicotine) within the preceding 3 months | • MMSE < 25 at Screening, suggesting age-related cognitive decline or mild dementia |
| • Clinically significant personality disorder that would, in the investigator’s judgment, preclude safe study participation | • Ongoing use of medications with known activity at the NMDA or AMPA glutamate receptor [e.g., riluzole, lamotrigine, memantine, topiramate, dextromethorphan, D-cycloserine], or the mu-opioid receptor |
| • Serious, unstable medical illnesses including respiratory (obstructive sleep apnea, or history of difficulty with airway management during previous anesthetics), cardiovascular [including ischemic heart disease and uncontrolled hypertension], and neurologic [including history of severe head injury] | • Ongoing use of the following medications: St John's Wort, theophylline, tramadol, metronidazole |
| • Clinically significant abnormal findings of laboratory parameters [including urine ECG, toxicology screen for drugs of abuse], physical examination, or ECG | • Decrease of > 25% in depressive symptoms as reflected by the QIDS-SR score from Screening to Randomization |
| • Hypertension (systolic BP > 160 mm Hg or diastolic BP > 90 mm Hg) | • ECT treatment within 6 months prior to Screening |
| • Participants with one or more seizures without a clear and resolved etiology | • Current VNS or rTMS therapy |
| • Participants starting hormonal treatment in the 3 months prior to Screening | **Table 2** | Measures & schedule of events. |

| Scale | Screen/ Washout | Intake | Study Infusion | Follow Up |
|-------|----------------|-------|----------------|----------|
| Day | −21 to −1 | 0 | 1 | 2 | 3 | 4 | 7b | 14 | 21 | 28 |
| MADRS | x | x | x | x | x | x | x | x | x | x |
| QIDS-SR | x | x | x | x | x | x | x | x | x | x |
| MMSE | x | | | | | | | | | |
| MCCB | x | | | | | | | | | |
| PROMIS | x | | | | | | | | | |
| CADSSa | x | x | x | x | x | x | x | x | x | x |
| CGI | x | x | x | x | x | x | x | x | x | x |
| QLESQ | x | x | x | x | x | x | x | x | x | x |
| CSSRS | x | x | x | x | x | x | x | x | x | x |
| BPRSb | x | x | x | x | x | x | x | x | x | x |
| PRISEx | x | x | x | x | x | x | x | x | x | x |
| EEG | x | x | x | x | x | x | x | x | x | x |

MADRS Montgomery-Asberg Depression Rating Scale. MMSE Mini Mental State Exam. MCCB MATRICS Consensus Cognitive Battery. PROMIS Patient Reported Outcomes Measurement Information System-Emotional Distress-Anxiety Short Form. CADSS Clinician Administered Dissociation Symptom Scale. CGI Clinician Global Improvement. QLESQ Quality of Life Enjoyment and Satisfaction Questionnaire. CSSRS Columbia-Suicide Severity Rating Scale. PRISE Patient Reported Inventory of Side Effects. QIDS-SR Quick Inventory of Depressive Symptomatology –Self Report. a CADSS and BPRS administered at 0, 40, 120, and 240 min on infusion days. b Day 7 follow up assessment is the primary efficacy rating for the study. Responders at day 7 continue weekly follow up assessments through day 28 to monitor treatment response and relapse. Non-responders at day 7 are exited from study.

2.6.1. Screening and eligibility

All participants sign an approved informed consent document that explains study procedures and subject rights before any study-related procedures take place. All consenting participants receive a psychiatric evaluation conducted by a study physician. Participants complete a structured diagnostic interview (MINI [18]), a neurocognitive measure (MCCB [19,20]), and a depression scale (Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR [21])) to confirm eligibility. A medical screening is also performed to rule out contraindicated conditions. If initial eligibility criteria are met, a taper is conducted if necessary such that prohibited medications are discontinued over 7 days or longer as determined by the medication's half-life. If patients are taking an antidepressant medication at Screening, they are tapered off over a period of up to 2 weeks and then are drug-free for a minimum of 1 week. Study physician investigators monitor the tapering or "washout" of psychotropic medications with consultation from the participant's prescribing physician.

2.6.2. Primary outcome and efficacy measures

The Montgomery-Asberg Depression Rating Scale (MADRS) is the primary outcome measure of change in depressive symptoms following treatment. The MADRS was selected for its strong psychometric properties and previous use in ketamine trials. Participants complete the MADRS with a trained research study staff member at baseline prior to infusion, 24 h post-infusion, and at regular intervals for 7 days thereafter. The 7-day post infusional assessment marks the primary outcome efficacy rating for all participants. Responders who continue in the study are re-administered the MADRS 14, 21, and 28 days post-infusion to continue monitoring treatment response and relapse. The QIDS-SR [21] is a secondary efficacy outcome measure and administered prior to infusion, immediately following infusion, and at every subsequent study visit.
2.6.3. Safety and tolerability measures

The Columbia Suicide Severity Rating Scale (CSSI) [22] is administered at each visit to assess for suicidal ideation and behavior. The scale is administered prior to infusion, re-administered immediately following infusion on day 1, and repeated at every subsequent visit to assess for changes since the previous study visit. There is no cut off score at which a patient would terminate or exited from the study. However, participants deemed at emergent risk by the study physician will be treated appropriately, including options such as increased contact, more frequent clinical visits, or psychiatric hospitalization. To assess for side effects of treatments, participants are administered the Patient Rated Inventory of Side Effects (PRISE) [23] the day before infusion, 24 h post-infusion, and at regular intervals for 7 days thereafter. Participants are administered the Clinician Administered Dissociative Symptoms Scale (CADSS) [24] 1 day before the infusion, immediately prior to infusion, and after 40, 120, and 240 min post-infusion Day 1 to assess for dissociative experiences and symptoms related to the infusion. The CADSS is re-administered at all follow-up visits. All aforementioned assessments are repeated on post-infusion days 14, 21 and 28 for responders.

2.6.4. Neurocognitive assessment

Neurocognitive performance is assessed with the MATRICS Consensus Cognitive Battery (MCCB) [25]. The battery of tests is administered to participants 1 day prior to infusion and is repeated 7 days after infusion and 28 days after the infusion for responders.

2.6.5. EEG

Pharmaco-EEG complements and extends clinical information that are historically used to predict treatment response or test treatment effects in TRD [26] and is translatable between animals and humans. Pharmaco-EEG allows testing how much and whether ketamine reaches the neocortex by indexing gamma band resting state quantitative EEG. Four minutes of eyes open and closed will be assessed pre-infusion, 30 min after start of infusion, 60 min after start of infusion, and 2 and 4 h after end of infusion. EEG is also assessed on 24 h and 7 days after ketamine infusion for all participants and 21 days after infusion for responders. We expect ketamine to acutely increase gamma band power as a biomarker of NMDA receptor engagement [27]. A secondary measure of engagement of ketamine with the NMDA receptor is mismatch negativity (MMN) amplitude which is a negative peak around 100–250 ms after an unexpected event [28]. Ketamine suppresses MMN amplitude [29–31] which is sustained for at least 30 min after the end of infusion [31]. We expect a suppression of MMN amplitude if ketamine engages the NMDA receptor.

2.6.6. Blood biomarkers

Brain-derived neurotrophic factor (BDNF) plays a critical role in depression pathophysiology and response to antidepressant treatment [32–35]. Recent preclinical work found that ketamine’s rapid antidepressant effect is mediated in part through enhancement of BDNF translation and signaling [32,34]. A previous study from our group supports plasma BDNF as a peripheral biomarker relevant to ketamine antidepressant response [15]. These pilot data, in concert with prior literature, suggest that (a) ketamine-related elevations in plasma BDNF may reflect central BDNF-mediated enhancements in synaptic plasticity potentially underlying the antidepressant effects; and (b) extent of ketamine-triggered increase in BDNF may mediate response to ketamine. Plasma will be isolated from participants for measurement of BDNF at baseline the morning of the infusion and then again 2, 4 and 8 h following the infusion. BDNF levels are measured again on day 7 for all participants and day 28 for responders.

There is also increasing evidence linking inflammation with depression [36–38] and with alterations in NMDA receptor-mediated signaling [39]. There is limited data, however, regarding the impact of ketamine treatment on neuroinflammatory markers in participants with depression [40]. Serum for cytokine analysis is obtained before the study infusion and on day 7 for all participants and day 28 for responders.

3. Statistical analysis plan and power

Preliminary data analyses will inspect baseline, group differences and compliance variables for correlations with specified outcomes. Variables demonstrating baseline group differences that correlate with outcomes, will be treated as potential confounders [41,42]. Analyses including and excluding the relevant variable as a covariate will determine the degree to which any group differences might confound conclusions regarding treatment.

Parallel Frequentist and Bayesian analyses will be conducted to evaluate the durability and efficacy of the three subanesthetic doses of a single ketamine (0.1 mg/kg, 0.25 mg/kg, and 0.50 mg/kg) or midazolam (0.03 mg/kg) infusion. Frequentist results yield the probability of the observed data, or data more extreme, given that the null hypothesis holds. Bayesian results address probability that the governing parameter for an observed process equals some value or range of values. This permits statements regarding the probability that treatment confers benefit of some magnitude; a critical issue in treatment development. Statistical analyses will use R [43].

Broadly, the analytic strategy will use generalized linear modeling. Continuous, dichotomous and time-to-event data will utilize linear, logistic, and proportional hazards regression respectively (Proc GENMOD and Proc PHREG; SAS v. 9.3). Longitudinal analyses will employ generalized linear mixed models (Proc GLIMMIX; SAS 9.3). Intention-to-treat analyses will evaluate time to relapse as a function of drug condition, collapsing participants initially randomized to midazolam with those assigned to the same condition via adaptive randomization. For intention-to-treat purposes, participants failing to demonstrate a response to treatment will be counted as having relapsed on the first day of follow-up. Per protocol analyses will subsequently estimate effects among only those participants who demonstrated an initial response to treatment. Multiple imputation and maximum likelihood solutions, which are robust under assumptions of that missing data are random, will address missing data in cross-sectional and longitudinal analyses respectively [44]. Sensitivity analyses will evaluate robustness of analytic conclusions to missing data. Non-ignorable missing data patterns will be addressed through pattern-mixture modeling methods [45].

For Bayesian analyses, unless otherwise indicated in the data analytic plan, priors will be neutral and diffuse. For linear, Poisson, and logistic and Cox Proportional Hazards regression, priors for coefficients will take the form ~ N(mean = 0, var = 1 x 106) in the linear, log, log (odds) and log(hazard) scales respectively. Evaluation of proportions will use beta-binomial models with both the previously stated Beta prior as well as with ~Beta(1,1) priors for the purposes of reporting. Priors for error or dispersion terms will use ~ Uniform(1,100), a ~Half-Normal (μ = 0, σ = 100) or a ~ Folded T-Distribution(df = 3, μ = 0, σ = 100). Sensitivity analysis using optimistic and pessimistic, skeptical priors will evaluate prior assumptions [46]. Assessing the convergence of Bayesian analyses on the posterior distributions via Monte-Carlo Markov chain (MCMC) will use graphical (Trace Plot, Autocorrelation Plot) and quantitative (Geweke Diagnostics, Gelman-Rubin Diagnostics, and Heidelberger-Welsh Diagnostics) evidence. Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data.

4. Discussion

The Ketamine for Treatment-Resistant Late-Life Depression study is the first randomized placebo controlled trial to evaluate the tolerability, efficacy, and durability of three distinct, single sub-anesthetic doses of IV ketamine in older depressed adults. This trial is especially important
because it (1) compares multiple doses of ketamine against an active placebo; (2) features an adaptive randomization design using Bayesian probabilistic analyses; and (3) explores moderating and mediating mechanisms of treatment response.

Ketamine’s appropriateness for late-life depression remains unclear. Preliminary evidence from a small double-blind, randomized, active placebo-controlled trial of different subcutaneous doses of ketamine supports the efficacy and safety of ketamine therapy for older adults with TRD [10]. However, these findings are limited by a small sample size and the exclusion of participants who were acutely suicidal. Further, the route of administration was subcutaneous rather than intravenous, treatment dosages ranged, and the majority of participants received multiple treatments.

An additional scientific gap relates to dose in this population. Although most controlled studies have used a 0.5 mg/kg slow infusion dosing strategy, recent evidence suggests that lower (0.1 mg/kg) or higher (1.0 mg/kg) doses may also be effective and in the case of the 0.1 mg/kg dose, potentially preferable due to minimal side effects [47].

A unique feature of the study is the use of Bayesian statistical methods. While Bayesian methods are increasingly used in early phase oncology clinical trials, they are still rare in psychiatry research [48]. Utilization of Bayesian methods allows for a smaller sample size and thus a more time- and cost-efficient study. The adaptive randomization design serves to maximize the number of participants receiving the best performing dose and minimizes the number of participants receiving less beneficial doses. We selected the 7 day post-infusion assessment as the time-point for the adaptive randomization decision rule because it is the one with the most clinical relevance and importance in TRD. A selected dose with an early, rapid antidepressant effect at 24 h but which dissipates by Day 7 is less clinically meaningful than a dose as- selected with an early, rapid antidepressant effect at 24 h but which dissipates by Day 7 is less clinically meaningful than a dose as selected with an early, rapid antidepressant effect at 24 h but which dissipates by Day 7 is less clinically meaningful than a dose as

References

[1] K.E. Kerfoot, L.L. Petrakis, R.A. Rosenheck, Dual diagnosis in an aging population: prevalence of psychiatric comorbidities, substance abuse, and mental health service utilization in the department of veterans affairs, J. Dual Diagnosis 7 (1–2) (2011) 1–13, https://doi.org/10.1080/15504263.2011.546096.
[2] T.L. Mark, V.N. Joish, J.W. Hay, D.V. Sheehan, S.S. Johnston, Z. Cao, Antidepressant use in geriatric populations: the burden of side effects and interactions and their impact on adherence and costs, Am. J. Geriatr. Psychiatry 19 (3) (2011) 211–221, https://doi.org/10.1097/JGP.0b013e318205156d.
[3] A. Van Damme, T. Declerq, L. Lemey, H. Taddei, M. Petrovic, Late-life depression: issues for the general practitioner, Int. J. Gen. Med. 11 (2018) 113–120, https://doi.org/10.2147/IGM.S154876.
[4] C. Knobel, G. Alves, B. Friedrichs, et al., Treatment-resistant late-life depression: challenges and perspectives, Curr. Neuropharmacol. 13 (2015) 577–591, https://doi.org/10.2174/157015911013150120003032.
[5] E. Verwijik, H.C. Comij, R.M. Kok, H.-P. Spaans, M.L. Stek, E.J.A. Scherder, Neurocognitive effects after brief pulse and ultrabrief pulse unilateral electroconvulsive therapy for major depression: a review, J. Affect. Disord. 140 (3) (2012) 233–243, https://doi.org/10.1016/j.jad.2012.02.024.
[6] A. Üçok, W. Gaebel, Side effects of atypical antipsychotics: a brief overview, World Psychiatry 7 (1) (2008) 58–62, https://doi.org/10.1002/j.2055-5458.2008.tb00154.x.
[7] R.M. Berman, A. Cappiello, A. Anand, et al., Antidepressant effects of ketamine in depressed patients, Biol. Psychiatry 47 (4) (2000) 351–354, https://doi.org/10.1016/S0006-3223(00)00902-7.
[8] S.T. Wilkinson, M. Toprak, M.S. Turner, S.P. Levine, R.B. Katz, G. Sanacora, Antidepressant use in geriatric populations: the burden of side effects and interactions, Clin. Drug Investig. 25 (11) (2017) 1199–1209, https://doi.org/10.1007/s44269-017-0166-6.
[9] M.S. Toprak, M.S. Turner, S.P. Levine, R.B. Katz, G. Sanacora, Antidepressant use in geriatric populations: the burden of side effects and interactions, Clin. Drug Investig. 25 (11) (2017) 1199–1209, https://doi.org/10.1007/s44269-017-0166-6.
[10] D. George, V. Gálvez, D. Martin, et al., Pilot randomized controlled trial of titrated subcutaneous ketamine in older patients with treatment-resistant depression, Am. J. Geriatr. Psychiatry 25 (11) (2017) 1199–1209, https://doi.org/10.1016/j.jagp.2017.06.007.
[11] G.M. Chandler, D.V. Josifescu, M.H. Pollack, S.D. Targum, M. Fava, Validation of a NIMH-funded dose-response study found no sex differences in response to multiple single infusion doses of ketamine [49]. Further studies are underway to investigate systematic differences in response to ketamine according to gender (ClinicalTrials.gov, Identifier: NCT01558063).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2019.100432.
