Published in final edited form as:

J Clin Psychiatry. 2018 ; 79(2): . doi:10.4088/JCP.16m11089.

Effects of a course of right unilateral ultrabrief pulse electroconvulsive therapy (ECT) combined with venlafaxine on insomnia symptoms in elderly depressed patients

W. Vaughn McCall, M.D. M.S.^(a), Sarah H. Lisanby, M.D.^{(b),*}, Peter B. Rosenquist, M.D.^(a), Mary Dooley, M.S.^(c), Mustafa M. Husain, M.D.^(d), Rebecca G. Knapp, Ph.D.^(c), Georgios Petrides, M.D.^(e), Matthew V. Rudorfer, M.D.^(f), Robert C. Young, M.D.^(g), Shawn M. McClintock, Ph.D., M.S.C.S.^(d), Martina Mueller, Ph.D.^(c), Joan Prudic, M.D.^(h), Robert M. Greenberg, M.D.⁽ⁱ⁾, Richard D. Weiner, M.D.^(b), Samuel H. Bailine, M.D.^(e), Mary Anne Riley, M.S.^(a), Laryssa McCloud, Ph.D.^(a), Charles H. Kellner, M.D.⁽ⁱ⁾ CORE/PRIDE Work Group

^(a)Department of Psychiatry and Health Behavior; Augusta University/Medical College of Georgia, Augusta, Georgia ^(b)Department of Psychiatry and Behavioral Sciences; Duke University School of Medicine, Durham, North Carolina ^(c)Department of Psychiatry and Behavioral Sciences; Medical University of South Carolina, Charleston, South Carolina ^(d)Department of Psychiatry; University of Texas Southwestern Medical Center, Dallas, Texas ^(e)Zucker Hillside Hospital/North Shore-LIJ Health System, New York ^(f)National Institute of Mental Health, Bethesda, Maryland ^(g)Department of Psychiatry; Weill Cornell Medicine; New York, New York ^(h)Department of Psychiatry; Columbia University and New York State Psychiatric Institute, New York, New York ⁽ⁱ⁾Department of Psychiatry; NYU School of Medicine; New York, New York ^(j)Department of Psychiatry; Icahn School of Medicine at Mount Sinai, New York, New York

Abstract

Objective: Antidepressant medications have a variety of effects on sleep, apart from their antidepressant effects. It is unknown whether electroconvulsive therapy (ECT) has effects on perceived sleep in depressed patients. This secondary analysis examines the effects of ECT on perceived sleep, separate from its antidepressant effects.

Method: Elderly patients with major depressive disorder, as defined by DSM-IV, received open-label high-dose, right unilateral ultrabrief pulse ECT, combined with venlafaxine, as part of participating on Phase 1 of the NIMH-supported study “Prolonging Remission in Depressed Elderly” (PRIDE). Phase 1 of PRIDE participant enrollment period extended from February 2009 to August 2014. Depression severity was measured with the Hamilton Rating Scale for Depression-24 item (HRSD₂₄), and measures of insomnia severity were extracted from the

Address correspondence to Dr. W. Vaughn McCall; Dept. Psychiatry and Health Behavior; Medical College of Georgia; Augusta University; 997 St Sebastian Way; Augusta, Georgia, 30912. Phone 706-721-6719. Fax 706-721-1793 (wmccall@augusta.edu).

*Now at the National Institute of Mental Health. Dr. Sarah H. Lisanby contributed to this article while at Columbia University and Duke University, prior to joining NIMH. The views expressed are her own and do not necessarily represent the views of the National Institutes of Health or the United States Government.”

Data previously presented as a poster at the International Society for Electroconvulsive Therapy and Neurostimulation annual meeting May 15, 2016 in Atlanta Georgia

HRSD₂₄. Participants were characterized at baseline as either ‘high-insomnia’ or ‘low-insomnia’ subtypes, based upon the sum of the three HRSD₂₄ sleep items as either 4–6, or 0–3, respectively. Insomnia scores were followed during ECT, and were adjusted for the sum of all the HRSD₂₄ non-sleep items. Generalized linear models were used for longitudinal analysis of insomnia scores.

Results: Two hundred and forty patients participated, with 48.3% in the high-insomnia and 51.7% in the low-insomnia group. Although there was a reduction in the insomnia scores in the high-insomnia group, only 12.4% of them experienced remission of their insomnia after a course of ECT, despite an increase in utilization of sleep aids across the course of ECT, from 8.6% to 23.2%. The degree of improvement in insomnia symptoms paralleled the degree of improvement in non-insomnia symptoms. A “low” amount of improvement on the sum of the HRSD-non-insomnia items (HRSD-sleep) was accompanied by a “low” amount of improvement in insomnia scores (change of -1.6 ± 1.2 , $p < 0.0001$), while a “high” amount of improvement on the sum of the HRSD-non-insomnia items was accompanied by a “higher” amount of improvement in insomnia scores (change of -3.1 ± 1.6 , $p < 0.0001$). After adjustment for non-insomnia symptoms, there was no change in insomnia in the low insomnia group.

Conclusions: We found that ECT, combined with VLF, has a modest anti-insomnia effect that is linked to its antidepressant effect. While most patients will have some degree of residual insomnia after ECT, and will require some consideration of whether additional, targeted assessment and treatment of insomnia is warranted.

ClinicalTrials.gov Identifier: ClinicalTrials.gov Identifier:

Clinicaltrials.gov link <https://clinicaltrials.gov/ct2/show/NCT01028508?term=NCT01028508&rank=1>

Introduction

Sleep disturbance is common among older people, with more than 50% of people older than 65 years reporting sleep difficulties.¹ Insomnia is among the symptoms of major depressive disorder (MDD),² and older MDD patients more often state insomnia is a focus of concern, while younger patients do not.^{3;4} The presence of insomnia complicates the presentation of MDD. It was an independent risk factor for poorer quality of life in a mixed-age sample of patients with MDD,⁵ and treatment of insomnia has been shown to improve the quality of life in middle aged patients with MDD.⁶ Further, the presence of sleep problems was found to be an independent risk factor for greater intensity of suicidal ideation in a mixed-age sample of MDD,⁷ and is associated with greater rates of suicide death in the elderly.^{8;9} The persistence of insomnia in older MDD patients, after otherwise successful resolution of an MDD episode, forebodes increased risk of MDD relapse, at least in older MDD patients who achieved remission through interpersonal psychotherapy.¹⁰ Thus, optimum treatment of MDD ought to include relief from insomnia symptoms.

Most treatments of MDD produce improvement in insomnia symptoms. Early comparisons of psychotherapy versus tricyclic antidepressants (TCAs) reported that insomnia symptoms were among the first symptoms to improve with TCAs, before general improvement in mood was seen. This pattern of change was not seen with psychotherapy.¹¹ Some sedating antidepressants have benefits for insomnia symptoms that occur independent of a diagnosis

of MDD or any other psychiatric disorder. For example, low doses of either trazodone or the TCA doxepin are associated with improvement in sleep in non-depressed insomniacs, and these benefits are evident both in patient self-report and in polysomnography (PSG).^{12;13} This pattern is not seen with selective serotonin reuptake inhibitors (SSRIs), as these medicines may improve sleep complaints in patients with MDD, without necessarily improving objective sleep as reflected in PSG.¹⁴

Information regarding the impact of electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) on insomnia symptoms in MDD is limited. More is known about the impact of ECT on PSG sleep than is known regarding ECT and self-reported sleep. The methodology is inconsistent across studies of ECT's effects on PSG sleep, but the general finding is that ECT is associated with increases in PSG total sleep time and suppression of rapid eye movement (REM) sleep.¹⁵ rTMS is associated with reduction in insomnia symptoms, but the improvement in insomnia symptoms is linked with improvement in the overall MDD syndrome, that is, rTMS does not seem to have an anti-insomnia effect apart from its antidepressant effect.¹⁶

We have recently completed a study of ECT in the elderly, entitled "Prolonging Remission in Depressed Elderly" (PRIDE). Phase 1 of PRIDE was an open label study of the effects of high-dose, right unilateral ultrabrief pulse (RUL-UBP) ECT augmented with venlafaxine in a large sample of elderly MDD patients, while Phase 2 was a randomized comparison of outpatient continuation ECT plus pharmacotherapy versus pharmacotherapy alone in prolonging remission for those participants who had remitted in Phase 1. The primary aim of Phase 1 was to describe the efficacy and safety of RUL UBP ECT, and the methods and efficacy results of Phase 1 are reported elsewhere.¹⁷ We conducted a secondary analysis of Phase 1 PRIDE data for the purpose of (1) describing the impact of RUL UBP ECT on insomnia complaints in elderly MDD patients, and (2) assessing whether ECT has benefits for sleep, apart from ECT's antidepressant effect.

METHOD

Patients

Full details of the methods of Phase 1 of the PRIDE study can be found elsewhere.¹⁷ Recruitment occurred at multiple sites from February 2009 to August 2014, and approval for the study was obtained from the IRB at each site. Participants provided their own, written, informed consent. Briefly, participants were in- or outpatients, age ≥ 60, with a diagnosis of unipolar major depressive episode as defined by DSM IV,¹⁸ and Hamilton Rating Scale for Depression-24 item (HRSD₂₄) total score ≥ 21.¹⁹ Exclusion criteria were bipolar disorder, schizoaffective disorder, dementia, substance abuse/dependence in last 6 months, active general medical or neurological conditions that would have affected cognition or treatment response, contraindications to lithium (Li) or venlafaxine (VLF), or failure to respond to an adequate trial of Li + VLF, or any ECT in the current episode.

Procedures

Medication Washout and Concomitant Medications.—Psychotropic medications were discontinued within 1 week of starting Phase 1. Rescue medication for agitation, anxiety, or insomnia was limited to lorazepam up to 3 mg/day, or equivalent.

ECT.—ECT procedures were standardized as follows: 3x weekly, standard RUL placement (D’Elia placement).²⁰ A dose titration procedure to determine seizure threshold was carried out at the initial session, and subsequent sessions were administered at 6x seizure threshold. Seizure adequacy criterion was a motor seizure ≥ 15 s, and restimulation, if needed. If the HRSD₂₄ demonstrated $<25\%$ drop from baseline by treatment 6, the stimulus dose was increased by 50%. If the HRSD₂₄ demonstrated $<25\%$ drop from baseline by treatment 9, the stimulus dose was increased again by 50%.

Medication.—VLF was started 1–5 days prior to ECT or up to 2 days after the first treatment at an initial dosage of 37.5 mg *po*, increased by 37.5 mg every 3 days or as tolerated, with a target dose of 225 mg *qD*.

Assessments

Diagnostic, Demographic and Baseline Clinical Assessments.—Baseline assessments were obtained for eligible patients who provided informed consent. Diagnosis was established using either the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)²¹ (study years 1–2) or the Mini-International Neuropsychiatric Interview (MINI)²² (years 3–6). The change to the MINI as a diagnostic instrument was made to minimize the baseline assessment time burden on patients.

Depression outcome measures.—The HRSD₂₄ was administered three times per week, before each ECT. The primary outcomes in Phase 1 were remission status and the longitudinal trajectory of HRSD₂₄ total scores. Patients were classified as *remitters* based on: (a) HRSD₂₄ ≤ 10 on two consecutive ratings, and (b) HRSD₂₄ did not increase > 3 points on the second consecutive HRSD₂₄, or remained ≤ 6 . The minimum number of ECT required for remission was 2, but there was no maximum. *Non-remitters*: (a) did not reach above remission criteria, (b) had at least 12 treatments, and (c) reached a plateau defined as no clinical improvement (< 3 point decrease in HRSD₂₄ after last 2 consecutive treatments). Participants were classified as drop outs if they left the study after fewer than 12 sessions of ECT and had not yet met criteria for remission.

Standardization and Quality Control for HRSD₂₄.—Raters at all sites were trained to criteria using a set of videotaped clinical interviews. Ongoing consistency across sites and clinical raters was insured by having each rater rate a new set of videotapes annually for comparison with ratings of a “gold standard” rater.

Insomnia severity—Insomnia severity was measured by the sum of the three insomnia items of the HRSD₂₄, measuring initial, middle, and terminal insomnia, respectively. Each of the three items is scored 0–2, creating a range for their sum of 0–6. Notably, the use of any dose of any hypnotic medication resulted in a score of at least “1” on the middle

insomnia item. The psychometric properties of the sum of the three insomnia items have been previously reported, showing that the sum loads on to a single factor when the HRSD₁₇ is subjected to a factor analysis,²³ and this measure is sensitive to treatment effects in samples of patients with MDD.²⁴ For the purpose of the present investigation, baseline insomnia sum scores of 0–3 were characterized as the ‘low insomnia’ group, while baseline sum scores 4–6 were characterized as the ‘high-insomnia’ group. At the end of treatment, ‘remission of insomnia’ was declared when the insomnia sum score became “0” and remained “0” through the end of the course of ECT. ‘Partial remission’ was declared when the insomnia sum score became 2 and remained 2 for the remainder of the ECT course.

Suicidal Ideation—The intensity of suicidal ideation was measured with the Beck Scale for Suicide Ideation (SSI).²⁵ and the HRSD₂₄ (item #3).

Non-insomnia depression symptoms, cognition, and medical comorbidity—

Non-insomnia depressive symptoms were calculated by subtracting the insomnia sum scores from the HRSD₂₄, to create the HRSD-sleep. Global cognitive function was measured with the Mini Mental State Examination,²⁶ and severity of general medical conditions was measured with the Cumulative Illness Rating Scale – Geriatric (CIRS-G).²⁷

Statistical Analysis

Sample description.—Frequency distributions for categorical variables and measures of central tendency (mean) and variability (standard deviation) were used to describe the baseline characteristics for the Phase 1 study sample. For group comparisons, t-test and chi-square test were used for continuous and categorical variables, respectively. Generalized linear models were used for longitudinal analysis of insomnia scores with subjects as the unit of analysis to account for within subject variability. To investigate the effect of non-insomnia symptoms on insomnia scores over time, observed (unadjusted) insomnia scores were compared with scores adjusted for non-insomnia symptoms (HRSD₂₄ total score minus insomnia sum score). For multiple comparisons of insomnia scores between observed and predicted means at each time point, p-values were adjusted using Bonferroni correction. Change from baseline insomnia scores to the last observed insomnia score adjusted for change in non-insomnia symptoms were compared between high and low insomnia groups. In order to detect whether ECT had an impact on sleep, apart from its antidepressant effect, we used percent change in HRSD-sleep from baseline to last measurement to determine patients for whom ECT worked (high percent change) and those for whom it did not work (no or minimal change). From the two upper and the two lower quintiles of HRSD-sleep, we included only patients with high insomnia scores at baseline to explore whether insomnia scores changed differently for those for whom ECT was effective compared to those for whom ECT was not effective. In addition, we compared the means for change from baseline to last observed insomnia score in the high ($\geq 50\%$ improvement) versus low ($< 25\%$ improvement) groups based on change in non-insomnia symptoms (HRSD-sleep). Significance level alpha was maintained at 0.05. All analyses were conducted using SAS 9.4 (Cary, NC).

RESULTS

Two hundred and forty patients entered Phase 1 and contributed to the present report, including 148 remitters, 24 non-remitters, and 68 drop outs. The treatment response of the drop outs was very similar to the non-remitters.¹⁷ The sample was mostly female and white, with a high baseline degree of depressive symptom severity, well-preserved global cognitive function, and a moderate degree of overall insomnia severity.(Table 1) Most patients were taking a benzodiazepine at the time of being evaluated for participation (63.8%), but summed-insomnia scores were not significantly different in those who did versus those who did not take a benzodiazepine at baseline. Only 22.9% were taking an SSRI. Patients were nearly evenly split between the high-insomnia (48.3%) and low-insomnia groups (51.7%). In the low-insomnia group at study entry, three of 124 patients were taking a sleep aid, but by the end of Phase 1, 24 patients (19.4%) were taking a sleep aid. Similarly, in the high-insomnia group at study entry 10 of 116 patients were taking a sleep aid, but by the end of Phase 1, 27 patients (23.2%) were taking a sleep aid. The high-insomnia group was distinguished by younger age, history of greater severity of general medical illness, more psychiatric hospitalizations, greater severity of suicidal ideation intensity, and greater severity of non-insomnia symptoms of depression (Table 2).

Among the patients in the high-insomnia group, only 12.4% met our definition of full remission from insomnia, but 59.3% reached partial remission. The average number of ECT sessions required to reach full remission of insomnia in the high-insomnia group was 6.1 ± 2.2 , while the number of sessions required to reach partial remission was 5.1 ± 3.4 . The mean change in the insomnia score for the high-insomnia group was 2.7 ($p < 0.0001$). Insomnia scores showed very little change across the course of ECT in the low-insomnia group. (Figure 1) When insomnia scores were adjusted for non-insomnia depression symptoms, comparison with the observed scores showed little change; all p -values were $> .05$ except at baseline and visit 1 in the low insomnia group. Mean insomnia scores, adjusted for change in non-insomnia depression symptoms, decreased by 0.50 for the low insomnia group and by 2.56 for the high insomnia group ($p = 0.002$ and $p < .0001$ respectively). The change in scores for the high insomnia group was statistically significantly greater than for the low insomnia group ($p < 0.0001$). Of the 124 patients in the low-insomnia group, 112 remained in the low-insomnia group, but 12 (9.6%) transitioned from the low insomnia group to the high-insomnia group by the end of the ECT course.

We found that insomnia scores decreased regardless of whether ECT had a strong versus a weak antidepressant effect ($p > 0.5$), and the change was statistically significant over time ($p < 0.05$). (Figure 2) Further, we found that a “low” amount of improvement on the sum of the HRSD-non-insomnia items (HRSD-sleep) was accompanied by a “low” amount of improvement in insomnia scores (change of -1.6 ± 1.2 , $p < 0.0001$), while a “high” amount of improvement on the sum of the HRSD- non-insomnia items was accompanied by a “higher” amount of improvement in insomnia scores (change of -3.1 ± 1.6 , $p < 0.0001$). When further adjusting for age, recurrent episode, melancholia, psychiatric hospitalizations, CIRGS severity and CGI severity no statistically significant relationship with insomnia scores was observed (all $p > 0.1$).

Discussion

The main findings of the study were that only 12.4 % of the high-insomnia sample experienced full remission of insomnia symptoms by the end of ECT, but 59.3% met our definition of “partial remission” for insomnia symptoms by the end of the ECT course. Remission and/or partial remission for insomnia symptoms occurred relatively early – after 5–6 ECT sessions. The adjusted mean improvement in insomnia symptoms across both the low-insomnia group and the high insomnia group could be partially explained by the increased use of sleep aids across the course of ECT in both groups. The increased prescription of sleep aids during the course of ECT is noteworthy and may be related to the fact that VLF is known to disrupt polysomnographic sleep.²⁸

The high-insomnia group showed a greater degree of improvement in insomnia symptoms compared with the low –insomnia group. However, when changes in the insomnia scores were contrasted between those with strong antidepressant response to ECT versus those with weaker antidepressant response to ECT, we found that the degree of change in insomnia scores was related to overall change in non-insomnia symptoms, suggesting that improvement in insomnia symptoms is part of the antidepressant effect of ECT. This finding is similar to what has been reported regarding the impact of rTMS and tDCS on insomnia symptoms in MDD,^{16;29} suggesting that therapeutic brain stimulation for MDD exerts its effect differently from antidepressant medication.

The overall sample exhibited a high degree of depressive symptoms at baseline, with 56% reporting some degree of suicidal ideation, and 48% reporting a high degree of insomnia symptoms. The high-insomnia group had a greater proportion of recurrent episodes of MDD, more psychiatric hospitalizations, greater suicidal ideation, and a greater intensity of non-insomnia MDD symptoms. The association between insomnia and suicide has been reported many times,³⁰ including in samples of elderly MDD patients, but our report is the first to confirm this association in an ECT sample. The use of sleep aids increased over the course of study participation, with similar rates of use in the low-insomnia and high-insomnia groups.

This report is subject to a number of limitations. First, the findings are limited to elderly adults with MDD who are taking concomitant VLF and low dose, as-needed lorazepam in the context of RUL UBP ECT. Other forms of ECT, higher doses of benzodiazepines, or different concomitant antidepressants could have produced different results. As mentioned, VLF has been reported to have some sleep-disturbing effects, and this could have affected the results of this study.²⁸ However, the combination of antidepressant medications with ECT is more effective than ECT alone in the treatment of MDD, and hence the results of this study are likely to be of relevance as more practitioners adopt the combination of antidepressants and ECT.³¹ Second, as this was an open label study with no comparison group, the improvement in the high-insomnia group could be related to regression to the mean, and the lack of change in the low-insomnia group may be explained by a floor effect with the HRSD₂₄ insomnia sum score. Third, using only the HRSD₂₄ insomnia sum score may have produced different results from other insomnia assessment methods, including patient-report sleep diaries, the Insomnia Severity Index,³² actigraphy, or PSG. Fourth, as

PSG was not conducted, it is unknown what portion of the sample was experiencing primary sleep disorders, such as sleep apnea or periodic limb movement disorder, both of which show increasing prevalence with age. In earlier work, we have reported a rate of 16% of unsuspected primary sleep disorders in a sample of young and middle-aged MDD patients.³³ It is likely that the rate of primary sleep disorders was higher in the present sample, and it is unknown whether the presence of primary sleep disorders might affect clinical outcomes in ECT.

The findings of this report provide several clinical lessons: first, that the intensity of insomnia symptoms is positively associated with the intensity of suicidal ideation, implying that ECT practitioners should view the progression or remission of insomnia as a potential indirect indicator of suicidal ideation. Second, most elderly MDD patients can expect improvement in insomnia during ECT, especially those with the most extreme symptoms, but most will also be left with some residual insomnia symptoms. Indeed, in this study, the rate of prescription of sleep aids actually increased over the course of ECT, and ECT practitioners should be alert to the need to assess and treat incompletely resolved insomnia complaints in elderly depressed patients. Third, improvement in insomnia can usually be expected early, and it is unclear that lengthening the course of ECT will lead to further improvement in residual insomnia.

The persistence of insomnia symptoms in otherwise successfully treated patients could result in residual deficits in quality of life or greater risk of relapse; these questions will be examined in future reports. If residual insomnia symptoms represent regression to population means (since insomnia complaints are common in population studies of the elderly) and are benign, they might require no special treatment; alternatively, if they confer some ongoing risk of relapse or poor quality of life, they may require unique treatment strategies. Disrupted sleep is a major concern for elderly patients with MDD;⁴ and these data provide evidence that RUL-UBP ECT, combined with VLF, can result in some relief from insomnia symptoms.

Acknowledgements:

The authors thank the following persons for their assistance in this study: Ahmad Raza, M.D. University of Texas Southwestern Medical Center, Dallas, Texas served as a study psychiatrist, and reports no conflicts of interest.

Styliani Kaliora, M.D., Zucker Hillside Hospital/North Shore-LIJ Health System, New York served as a study psychiatrist, and reports no conflicts of interest.

Vassilios Latoussakis, M.D., Weill Cornell Medicine, New York, New York served as a study psychiatrist, and reports no conflicts of interest.

Kristen G. Tobias, M.A., Mimi C. Briggs, B.A., Lauren S. Liebman, B.A., Emma T. Geduldig, B.A., all from Icahn School of Medicine at Mount Sinai, New York, New York and served as study managers. They report no conflicts of interest.

Abeba Teklehaimanot, M.S. Medical University of South Carolina, Charleston, South Carolina, served to clean data and help with statistical analyses. She reports no conflicts of interest.

Supported by NIMH grant U01MH055495-09 (Mt Sinai); U01MH055495-09., 1U01MH086127-01 (Wake Forest); 7U01MH086127 and 3U01MH086127-06S1 (Medical College of Georgia); U01MH081362 (Medical University of South Carolina); 5U01-MH086122 (Weill Cornell Medicine); 5U01MH84241-5 (Duke); 5U01MH086130 (Mayo); 5U01MH08612005 (UTSW); U01 MH084241 (Duke); U01-MH086123 (LIJ). The NIMH provided an internal data

safety monitoring board (DSMB) to oversee the conduct of the study. The NIMH had no role in the writing or approval of this paper.

Dr. McCall has been a scientific advisor for Merck, and Israeli Growth Partners, and a consultant to Luitpold Pharmaceuticals, Inc and Multiple Energy Technologies, LLC. Dr. Kellner receives honoraria from UpToDate, Psychiatric Times, and Northwell Health, Inc. Dr. Husain has received grant support from NIDA, NINDS, NIA, NARSD, Stanley Foundation, Cyberonics, Neuronetics, St. Jude medical (ANS), MagStim, Brainsway, NeoSync, Alkermes, and Corcept, and has been a consultant to Cerebain Inc. Dr. Young is a consultant to the NIH. Dr. Lisanby has received grant support from NINDS, NIBIB, Brain and Behavior Research Foundation, Stanley Medical Research Foundation, Neosync, Nexstim, and Brainsway. Dr. Petrides has received research support from Amgen, Astra Zeneca, Corcept, Eli Lilly, Proteus, St. Jude Medical, and Sunovion, and he has served on an advisory panel for Corcept. Dr. McClintock has received grant support from the NIMH and Brain and Behavior Foundation, and honoraria from TMS Health Education. Dr. Weiner is co-inventor on a Duke University Patent licensed to MECTA, Corp, but does not individually receive royalties. The other authors report no financial relationships with commercial interests.

Reference List

1. Foley D, Monjan A, Brown S, et al. Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep* 1995;18: 425–432 [PubMed: 7481413]
2. American Psychiatric Association American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, Virginia: APA; 2013
3. Ismail Z, Fischer C, McCall WV. What characterizes late life depression? *Psychiatric Clinics of North America* 2013; in press
4. Hegeman J, Kok R, van der Mast R, et al. Phenomenology of depression in older compared with younger adults: a meta-analysis. *British Journal of Psychiatry* 2012;200: 275–281 [PubMed: 22474233]
5. McCall WV, Reboussin BA, Cohen W. Subjective measurement of insomnia and quality of life in depressed inpatients. *J Sleep Res* 2000;9: 43–48 [PubMed: 10733688]
6. McCall WV, Blocker JN, D'Agostino RB Jr., et al. Treatment of insomnia in depressed insomniacs: effects on health-related quality of life, objective and self-reported sleep, and depression. *Journal of Clinical Sleep Medicine* 2010;6: 322–329 [PubMed: 20726279]
7. McCall WV, Blocker JN, D'Agostino R Jr, et al. Insomnia severity is an indicator of suicidal ideation during a depression clinical trial. *Sleep Medicine* 2010;11: 822–827 [PubMed: 20478741]
8. Fujino Y, Mizoue T, Tokui N, et al. Prospective Cohort Study of Stress, Life Satisfaction, Self-Rated Health, Insomnia, and Suicide Death in Japan. *Suicide Life Threat Behav* 2005;35: 227–237 [PubMed: 15843339]
9. Turvey CL, Conwell Y, Jones MP, et al. Risk factors for late-life suicide: a prospective, community-based study. *Am J Geriatr Psychiatry* 2002;10: 398–406 [PubMed: 12095899]
10. Reynolds CF III, Frank E, Houck PR, et al. Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? *Am J Psychiatry* 1997;154: 958–962 [PubMed: 9210746]
11. DiMascio A, Weissman MM, Prusoff BA, et al. Differential symptom reduction by drugs and psychotherapy in acute depression. *Arch Gen Psychiatry* 1979;36: 1450–1456 [PubMed: 518245]
12. Roth A, McCall W, Vaughn, Liguori A. Cognitive, psychomotor and polysomnographic effects of trazodone in primary insomniacs. *J Sleep Res* 2011;20: 552–558 [PubMed: 21623982]
13. Lankford A, Rogowski R, Essink B, et al. Efficacy and safety of doxepin 6mg in a four-week outpatient trial of elderly adults with chronic primary insomnia. *Sleep Medicine* 2012;13: 133–138 [PubMed: 22197474]
14. Gillin JC, Rapaport M, Erman MK, et al. A comparison of nefazodone and fluoxetine on mood and on objective, subjective, and clinician-rated measures of sleep in depressed patients: a double-blind, 8-week clinical trial. *J Clin Psychiatry* 1997;58: 185–192 [PubMed: 9184611]
15. McCall WV, Rosenquist PB. The effect of ECT on sleep - a comment to Winkler et al. *Journal of Psychiatric Research* 2015;61: 239–240 [PubMed: 25434521]

16. Rosenquist PB, Krystal A, Heart KL, et al. Left dorsolateral prefrontal transcranial magnetic stimulation (TMS): sleep factor changes during treatment in patients with pharmacoresistant major depressive disorder. *Psychiatry Research* 2013;205: 67–73 [PubMed: 23021320]
17. Kellner CH, Husain MM, Knapp RG, et al. Right unilateral ultrabrief pulse electroconvulsive therapy (ECT) in geriatric depression: phase 1 of the PRIDE study. *American Journal of Psychiatry* 2016; epub before print: appiajp201615081101
18. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Fourth ed. Washington, DC: American Psychiatric Association; 1994
19. Hamilton M A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23: 56–62 [PubMed: 14399272]
20. D'Elia G, Raotma H. Is unilateral ECT less effective than bilateral ECT? *Br J Psychiatry* 1975;126: 83–89 [PubMed: 1092400]
21. Spitzer RL, Williams JB, Gibbon M, et al. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Arch Gen Psychiatry* 1992;49: 624–629 [PubMed: 1637252]
22. Sheehan D, Lecrubier Y, Harnett-Sheehan K, et al. The Mini International Neuropsychiatric Interview (M.I.N.I.) the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* 1998; 22–33
23. Fleck M, Chaves M, Poirier-Littre M, et al. Depression in France and Brazil: factorial structure of the 17-item Hamilton Depression Scale in inpatients. *Journal of Nervous and Mental Disorders* 2004;192: 103–110
24. Asnis GM, Chakraborty A, DuBoff EA, et al. Zolpidem for persistent insomnia in SSRI-treated depressed patients. *J Clin Psychiatry* 1999;60: 668–676 [PubMed: 10549683]
25. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *J Consult Clin Psychol* 1979;47: 343–352 [PubMed: 469082]
26. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12: 189–198 [PubMed: 1202204]
27. Linn B, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc* 1986;16: 622–626
28. Salin-Pascual RJ, Galicia-Polo L, Drucker-Colin R. Sleep changes after 4 consecutive days of venlafaxine administration in normal volunteers. *J Clin Psychiatry* 1997;58: 348–350 [PubMed: 9515972]
29. Brunoni AR, Junior RF, Kemp AH, et al. Differential improvement in depressive symptoms for tDCS alone and combined with pharmacotherapy: and exploratory analysis from the sertraline vs electrical current therapy for treating depression clinical study. *International Journal of Neuropsychopharmacology* 2014;17: 53–61 [PubMed: 24060107]
30. McCall W, Black C. The link between suicide and insomnia: theoretical mechanisms. *Current Psychiatry Reports* 2013;15: 389 [PubMed: 23949486]
31. Sackeim HA, Dillingham E, Prudic J, et al. Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes. *Archives of General Psychiatry* 2009;66: 729–737 [PubMed: 19581564]
32. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine* 2001;2: 297–307 [PubMed: 11438246]
33. McCall WV, Kimball J, Boggs N, et al. Prevalence and prediction of primary sleep disorders in a clinical trial of depressed patients with insomnia. *Journal of Clinical Sleep Medicine* 2009;5: 454–458 [PubMed: 19961031]

CLINICAL POINTS:

- Complaints of insomnia are common in elderly patients, especially those with major depression (MDD). As insomnia is associated with adverse outcomes such as suicide, we aimed to examine whether electroconvulsive therapy (ECT) had an anti-insomnia effect, apart from its effect on MDD, in a sample of elderly MDD patients receiving ECT and venlafaxine.
- We found that ECT, combined with VLF, has a modest anti-insomnia effect that is linked to its antidepressant effect. Further, residual insomnia was common in our sample, despite otherwise successful ECT. Providers should consider targeted assessment and treatment of insomnia in elderly MDD patients receiving ECT.

Figure 1.
Changes in Insomnia Scores According to High Versus Low Baseline Insomnia Scores

Figure 2.
Changes in Insomnia Scores According to High Versus Low Change in Overall Depression Severity

TABLE 1

Demographic and Clinical Characteristics of Entire Sample at Baseline

Characteristic	N	Total Sample
DEMOGRAPHICS		
Age (y)	240	69.9 ± 7.6
Education (y)	239	14.5 ± 3.3
Female	240	138 (57.5%)
White	240	228 (95.0%)
Hispanic	240	9 (3.8%)
BASELINE CLINICAL CHARACTERISTICS		
Recurrent Episode	240	210 (87.5%)
Psychosis	240	28 (11.7%)
Melancholia	239	141 (59.0%)
Atypical	239	5 (2.1%)
Psychiatric Hospitalizations	229	2.4 ± 3.4
HRSD ₂₄	240	31.2 ± 7.3
MMSE (Raw Score)	239	27.5 ± 2.4
CIRGS Total Categories	240	4.6 ± 2.3
CIRGS Total Score	237	8.6 ± 4.2
CIRGS Severity Index	237	1.9 ± 0.5
CGI Severity	239	6.3 ± 0.9
Benzodiazepine Use	240	153 (63.8%)
SSRI Antidepressant Use	240	55 (22.9%)
FAMILY HISTORY OF MENTAL DISORDERS		
Psychiatric Illness	233	160 (68.7%)
Mood Disorder	231	143 (61.9%)
Major Depressive Disorder	230	136 (59.1%)
Bipolar Disorder	231	33 (14.3%)
BASELINE INSOMNIA AND SUICIDALITY MEASURES		
HRSD Insomnia Score ¹	240	3.4 ± 1.8
0–3 (low)	124	51.7%
4–6 (high)	116	48.3%
HRSD ₂₄ Question 3	240	1.6 ± 1.1
Beck SSI Total Score	202	4.6 ± 7.3
Beck SSI Index		
0	105	52.0%
1–2	29	14.4%
3–15	39	19.3%
16	29	14.4%
Adjusted HRSD ₂₄ Total Score ²	240	27.9 ± 6.6

Data are represented as mean ± SD for continuous variables and number (%) for categorical.

¹Insomnia score=Sum of HRSD₂₄ Items 4,5,6; range =0–6

²Adjusted HRSD₂₄ Total score=HRSD₂₄ Total score-Insomnia Score (Sum Items 4–6); range=0–54

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2.

Demographic and Baseline Clinical Characteristics by Insomnia Score (High/Low) at Baseline

	Baseline Insomnia Score				
Characteristic	N	Low (0–3)	N	High (4–6)	P-Value
DEMOGRAPHICS					
Age (y)	124	70.9 ± 7.9	116	68.8 ± 7.1	0.027
Education (y)	124	14.7 ± 3.4	115	14.4 ± 3.1	0.412
Female	124	68 (54.8%)	116	70 (60.3%)	0.389
White	124	121 (97.6%)	116	107 (92.2%)	0.058
Hispanic	124	3 (2.4%)	116	6 (5.2%)	-
BASELINE CLINICAL CHARACTERISTICS					
Recurrent Episode	124	103 (83.1%)	116	107 (92.2%)	0.032
Psychosis	124	11 (8.9%)	116	17 (14.7%)	0.163
Melancholia	123	64 (52.0%)	116	77 (66.4%)	0.024
Atypical	123	3 (2.4%)	116	2 (1.7%)	-
Psychiatric Hospitalizations	117	1.8 ± 1.7	112	3.0 ± 4.4	0.006
MMSE (Raw Score)	123	27.5 ± 2.3	116	27.5 ± 2.4	0.836
CIRGS Total Categories	124	4.6 ± 2.3	116	4.6 ± 2.3	0.797
CIRGS Total Score	122	8.4 ± 4.3	115	8.8 ± 4.2	0.415
CIRGS Severity Index	122	1.9 ± 0.4	115	2.0 ± 0.5	0.010
CGI Severity	123	6.1 ± 0.8	116	6.4 ± 0.9	0.011
Benzodiazepine Use	124	76 (61.3%)	116	77 (66.4%)	0.412
SSRI Antidepressant Use	124	27 (21.8%)	116	28 (24.1%)	0.663
FAMILY HISTORY OF MENTAL DISORDERS					
Psychiatric Illness	120	82 (68.3%)	113	78 (69.0%)	0.909
Mood Disorder	119	77 (64.7%)	112	66 (58.9%)	0.366
Major Depressive Disorder	119	74 (62.2%)	111	62 (55.9%)	0.329
Bipolar Disorder	119	17 (14.3%)	112	16 (14.3%)	1.000
BASELINE INSOMNIA, SUICIDALITY, AND DEPRESSION MEASURES					
Insomnia Score	124	1.9 ± 1.0	116	5.0 ± 0.8	<.0001
HRSD ₂₄ Question 3	124	1.5 ± 1.1	116	1.7 ± 1.2	0.165
Beck SSI Total Score	105	3.2 ± 5.6	97	6.2 ± 8.4	0.004
Beck SSI Index					0.012
0	61	58.1%	44	45.4%	
1–2	15	14.3%	14	14.4%	
3–15	22	21.0%	17	17.5%	
16	7	6.7%	22	22.7%	
Adjusted HRSD ₂₄ Total Score ²	124	26.2 ± 5.4	116	29.7 ± 7.3	<.0001

Data are represented as mean ± SD for continuous variables and number (%) for categorical.

¹ Insomnia score=Sum of HRSD₂₄ Items 4,5,6; range =0–6² Adjusted HRSD₂₄ Total score=HRSD₂₄ Total score-Insomnia Score (Sum Items 4–6); range=0–54