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TMS and CBT-I for comorbid depression and insomnia. Exploring feasibility and tolerability of transcranial magnetic stimulation (TMS) and cognitive behavioral therapy for insomnia (CBT-I) for comorbid major depressive disorder and insomnia during the COVID-19 pandemic

Michael A. Norred*,

Department of Psychiatry, Medical University of South Carolina, SC, USA

Lindsay C. Haselden,

Medical University of South Carolina College of Medicine, SC, USA

Gregory L. Sahlem,

Department of Psychiatry, Stanford University, CA, USA

Allison K. Wilkerson,

Department of Psychiatry, Medical University of South Carolina, SC, USA

E. Baron Short,

Department of Psychiatry, Medical University of South Carolina, SC, USA

Lisa M. McTeague,

Department of Psychiatry, Medical University of South Carolina, SC, USA

Ralph H. Johnson VA Medical Center, SC, USA

Mark S. George

Department of Psychiatry, Medical University of South Carolina, SC, USA

Ralph H. Johnson VA Medical Center, SC, USA

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Dear Editor,

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*Corresponding author. Department of Psychiatry, 67 President St. Charleston, SC, 29425, michael.norred2@va.gov (M.A. Norred).

Declaration of competing interest

None.

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An estimated 90% of those with Major Depressive Disorder (MDD) report sleep related problems [1] and as many as 40% meet criteria for Insomnia Disorder [2]. MDD in the setting of Insomnia Disorder has been associated with more severe symptoms, increased risk of suicidal planning [3], as well as an increased risk of relapse when treated [4]. Residual insomnia symptoms may persist in as many as 72% of patients in remission from depression [5]. Repetitive Transcranial Magnetic Stimulation (rTMS) is an evidence-based treatment for MDD with proven efficacy and effectiveness [6]. Despite the proven benefit of rTMS, however, it is not 100% efficacious, and it does not specifically treat sleep dysfunction [7]. Treating comorbid Insomnia Disorder while treating MDD with rTMS may subsequently have a beneficial effect.

Cognitive Behavioral Therapy for Insomnia (CBT-I) is the gold standard treatment for Insomnia Disorder and has been shown to have an antidepressant effect in those with comorbid MDD and Insomnia Disorder [8]. Despite the proven efficacy of CBT-I in the treatment of Insomnia Disorder and promising early work suggesting CBT-I may improve mood symptoms in comorbid MDD and Insomnia Disorder [9], further work in this area has been limited in those treated with rTMS. The most substantial risk for those being treated with rTMS is seizure [9] and sleep deprivation is known to lower the seizure threshold. Sleep restriction is a core component of CBT-I that limits a patient's time in bed, transiently resulting in sleep deprivation, and subsequently could increase the risk of seizure with concurrent rTMS treatment. Before engaging in a larger-scale trial attempting to augment the efficacy of rTMS by addressing Insomnia Disorder symptoms using CBT-I, we first sought to determine whether it was safe and feasible to deliver both interventions concurrently. We completed a preliminary open-label study to determine if treatment with CBT-I is tolerable and feasible for patients with comorbid MDD and Insomnia Disorder being treated with rTMS using a figure-of-8-coil (36 treatments delivered on weekdays, 10-Hz, 3000-pulses, 4-s on, 26-s off).

We recruited participants who were being prescribed rTMS for MDD with clinically meaningful sleep disturbance defined as a PHQ-9, item-3 score >1. We included participants that met criteria for Insomnia Disorder on the Structured Clinical Interview for Sleep Disorders Revised (SCISD-R) and had an Insomnia Severity Index (ISI) score ≥ 15 . We excluded participants if another untreated sleep disorder was identified on the SCISD-R, they had initiated a new sedating medication within 2-weeks of enrollment, had an obligation to an irregular sleep schedule, comorbid psychotic or bipolar disorder, pregnancy, active substance use disorder, or were using a medication that reduces the seizure threshold. We asked enrolled participants to fill out surveys both before and after treatment with CBT-I including the ISI, the Pittsburgh Sleep Quality Index (PSQI), the 24-item Hamilton Rating Scale for Depression-24 (HRSD₂₄), and the Epworth Sleepiness Scale (ESS).

We performed manualized CBT-I [10] which consisted of six weekly 1-h sessions delivered through telehealth in appointments distinct from rTMS visits. We asked participants to complete daily sleep diaries which were used to guide the core components of CBT-I including stimulus control, sleep restriction and sleep titration, sleep education, sleep hygiene, relaxation, cognitive restructuring, and problem solving. At each visit we asked

participants about any perceived adverse events from the CBT-I either during their daily life or in relation to receiving rTMS.

We screened a total of 6 participants, of which two enrolled and followed the study procedures to completion. No adverse events were reported or observed during the study. Both participants saw improvements in their scores on several sleep and mood surveys by the end of the six weeks. ISI scores decreased from 24 (severe clinical insomnia) and 19 (moderate clinical insomnia) to 12 (subthreshold insomnia) and 7 (no clinically significant insomnia), respectively. Both participants had baseline PSQI scores of 16 which decreased to 6 and 7 by the end of the study. Average sleep efficiency from week 1 and week 6 showed improvement from 86% to 75%–93% and 97%, respectively. Baseline HRSD₂₄ scores of 21 (severe) and 16 (moderate) at the outset of the study decreased to 8 (remission) for both participants. Table 1 provides an outline of participant characteristics as well as a summary of the results.

Conclusions from this study are limited by the enrollment of only two participants. We suspect that recruitment was lower than anticipated due to factors related to the COVID-19 pandemic, with the largest contributor likely being the reduced number of patients being seen in consultation for rTMS treatment. The transition of patient visits to virtual platforms likely contributed to limited recruitment as virtual visits limited advertisement of the study and available information to patients. For participants that opted not to enroll following the initial phone call, it is possible that these participants were hesitant to participate in two separate interventions (rTMS and CBT-I), both of which are time consuming and require multiple visits. Further investigation is required to determine and parse out the advantage and safety profile of both treatments together for treating comorbid Insomnia Disorder and MDD and consideration of factors impacting recruitment will be imperative. Nevertheless, we were able to safely deliver CBT-I to patients receiving rTMS. Sleep restriction did not seem to negatively impact treatment, nor did it result in any seizures. In addition, both participants met criteria for remission from their depressive episodes and Insomnia Disorders. Given these promising findings, our study suggests both treatments can likely be safely given together with potentially additive efficacy.

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Table 1

Demographics and summary of results.

Participant Characteristics				
Participants: N = 2				
1. 52 year old Caucasian female.				
a. Antidepressant medications: Escitalopram 10 daily				
b. Anxiolytic/Sedating medications: Alprazolam 1 mg daily as needed; Hydroxyzine 25 mg every 6 hours as needed				
2. 55 year old Caucasian female.				
a. Antidepressant medications: Vortioxetine 20 mg daily				
b. Anxiolytic/Sedating medications: Ativan 1 mg daily as needed; Zolpidem 6.25 mg extended release tablet as needed at night				
c. Other: Dextroamphetamine-Amphetamine 20 mg at 8 a.m. and 12 p.m.				
Summary of Results				
Completion of Enrolled Participants		N = 2 (100%)		
Reported Adverse Events		None		
Participant 1		Participant 2		
Pre-rTMS + CBT-I		Post-rTMS + CBT-I	Pre-rTMS + CBT-I	Post-rTMS + CBT-I
SE	86	92.5	75.4	97
ISI	24	12	19	7
PHQ-9	17	8	20	15
HRSD-24	21	8	16	8
ESS	6	7	2	2
PSQI	16	6	16	7

* Repetitive Transcranial Magnetic Stimulation (rTMS); Cognitive Behavioral Therapy for Insomnia (CBT-I); Sleep efficiency (SE) – Reported as percentage; Insomnia Severity Index (ISI); Public Health Questionnaire-9 (PHQ-9); Hamilton Rating Scale for Depression-24 (HRSD-24); Epworth Sleepiness Scale (ESS); Pittsburgh Sleep Quality Index (PSQI).