HHS Public Access

Author manuscript

Brain Stimul. Author manuscript; available in PMC 2022 July 15.

Published in final edited form as:

Brain Stimul. 2021 ; 14(6): 1508–1510. doi:10.1016/j.brs.2021.09.007.

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

Keywords

Transcranial magnetic stimulation; TMS; Depression; Insomnia; Cognitive behavioral therapy for insomnia; CBTI

Dear Editor,

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

Declaration of competing interest
None.

Clinicaltrials.gov identifier
NCT04258618.

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 ($HRSD_{24}$), 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 $HRSD_{24}$ 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.

References

[1]. Franzen PL, Buysse DJ. Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications. Dialogues Clin Neurosci 2008;10(4):473–81. [PubMed: 19170404]

[2]. Stewart R, Besset A, Bebbington P, Brugha T, Lindesay J, Jenkins R, Singleton N, Meltzer H. Insomnia comorbidity and impact and hypnotic use by age group in a national survey population aged 16 to 74 years. Sleep 2006;29(11): 1391–7. [PubMed: 17162985]

[3]. Soehner AM, Kaplan KA, Harvey AG. Prevalence and clinical correlates of cooccurring insomnia and hypersomnia symptoms in depression. J Affect Disord 2014;167:93–7. [PubMed: 24953480]

[4]. Cutler AJ. The role of insomnia in depression and anxiety: its impact on functioning, treatment, and outcomes. J Clin Psychiatr 2016;77(8):e1010.

[5]. Nierenberg AA, Husain MM, Trivedi MH, Fava M, Warden D, Wisniewski SR, Miyahara S, Rush AJ. Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. Psychol Med 2010;40(1):41–50. [PubMed: 19460188]

[6]. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipovic SR, Grefkes C, Hasan A, Hummel FC, Jaaskelainen SK, Langguth B, Leocani L, Londero A, Nardone R, Nguyen JP, Nyffeler T, Oliveira-Maia AJ, Oliviero A, Padberg F, Palm U, Paulus W, Poulet E, Quartarone A, Rachid F, Rektorova I, Rossi S, Sahlsten H, Schecklmann M, Szekely D, Ziemann U. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). Clin Neurophysiol 2020;131(2):474–528. [PubMed: 31901449]

[7]. Rosenquist PB, Krystal A, Heart KL, Demitrack MA, McCall WV. Left dorsolateral prefrontal transcranial magnetic stimulation (TMS): sleep factor changes during treatment in patients with pharmacoresistant major depressive disorder. Psychiatr Res 2013;205(1–2):67–73.

[8]. Carney CE, Edinger JD, Kuchibhatla M, Lachowski AM, Bogouslavsky O, Krystal AD, Shapiro CM. Cognitive behavioral insomnia Therapy for those with insomnia and depression: a randomized controlled clinical trial. Sleep 2017;40(4).

[9]. Stultz DJ, Osburn S, Burns T, Pawlowska-Wajswol S, Walton R. Transcranial magnetic stimulation (tms) safety with respect to seizures: a literature review. Neuropsychiatric Dis Treat 2020;16:2989–3000.

[10]. Taylor DJ, Peterson AL, Goodie JL, Grieser E, Hryshko-Mullen AS, Rowan A, Wilkerson A, Pruiksma KE, Dietch JR, Hall-Clark B, Fina B. Cognitive behavioral Therapy for insomnia in the military: therapist guide. 2019. Retrieved from, https://insomnia.arizona.edu/CBTI-M.

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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).