Theta Burst Stimulation for Male Sexual Dysfunction in Bipolar Depression—A Case Series

Gunjan Malik¹, Namdev Chawan², Preeti Mishra¹, Shobit Garg¹, Sai Krishna Tikka⁴ and Priya Tyagi³

Bipolar disorder (BD) is a chronic, recurrent often disabling mood disorder affecting approximately 1% to 3% of the population.¹ In BD, depression has predominant polarity and is associated with marked impairment in (social and occupational) functioning and increased risk of suicide. Sexual dysfunction, specifically decreased libido, is an important symptom domain of bipolar depression.² It has been noted that 20% to 30% of adult men, among general population, have at least 1 manifest sexual dysfunction.³ Compared to other medical patients (~20%), greater number of male psychiatric patients (~50%), specifically 55% of those with BD, have been shown to have sexual dysfunctions.⁴ Management of BD involves the use of mood stabilizers, antipsychotics, antidepressants, and benzodiazepines, depending on the phase of the illness.⁵ Apart from the role of illness characteristics, psychotropic medications used in the treatment of bipolar depression are implicated to have an adverse effect of the sexual function too.⁶ Greater sexual dysfunction involves high personal distress and negative impact on treatment compliance and prognosis.⁷ Unfortunately, nonpharmacological treatment options including psychotherapeutic interventions are relatively limited, apart from with the very fact that sexual dysfunction in the context of depression is underreported by the patients as well as underestimated by clinicians.⁸ These facts have led to the investigation of other possible interventions, such as noninvasive brain stimulation in this regard.

A new noninvasive and potentially quite promising form of repetitive transcranial magnetic stimulation (rTMS), called theta-burst stimulation (TBS), applies short bursts (typically 3 pulses) at 50 Hz (within the gamma range of endogenous brain oscillations). These short bursts occur every 200 ms, or at 5 Hz, which is within the theta oscillation range.⁹ TBS is more potent when compared with conventional repetitive TMS. While continuous TBS (cTBS) has inhibitory effects, intermittent TBS (iTBS) has been shown to have excitatory effects.¹⁰

The literature pertaining to use of rTMS/TBS is very limited and specific mechanisms underlying the effect of rTMS in treating the domains of sexual dysfunctions, more specifically in the context of psychiatric disorders, have not yet been explored systematically. However, there are anecdotal reports of low frequency (inhibitory) rTMS delivered to supplementary motor area and deep TMS targeting the anterior cingulate cortex for the treatment of compulsive/hypersexual behaviors.¹¹ Paus et al.¹² investigated the influence of both cTBS and iTBS on sexual behaviors. They found that both iTBS and cTBS, delivered to the left dorsolateral prefrontal cortex (dLPC), modulate the sensitivity to rewards that predict sexual behaviors. More recently, Schecklmann et al.¹³ found that stimulation of right dorsolateral prefrontal cortex (rDLPFC) using a single session of high-frequency rTMS, which leads to cortical excitation similar to iTBS, significantly reduced subjective sexual arousal; stimulation delivered to the rDLPFC had no effect. Therefore, on the premise of this background literature, we aimed at delivering inhibitory stimulation (i.e., cTBS) to target the rDLPFC for improving the predominantly hypoactive sexual dysfunctions.

This case series included 3 male patients with bipolar affective disorder, current episode depression (moderate to severe) complaining of sexual difficulties—reduced sexual desire, erectile dysfunction, and delayed ejaculation, and received an adjunctive cTBS treatment. The diagnosis was made according to the diagnostic criteria for research (DCR)
of International Classification of Diseases-tenth edition (ICD-10). Subjects were evaluated, pre and post the stimulation sessions, on the Hamilton Depression Rating Scale (HAM-D) and the 14-item Changes in Sexual Functioning Questionnaire (CSFQ-14). The male version of the CSFQ-14 was used. It measures sexual dysfunction in 5 domains (subscales), that is, Pleasure (item—1); Desire/Frequency (items—2 and 3); Desire/Interest (items—4, 5, and 6); Arousal/Excitement (items—7, 8, and 9); and Orgasm/Completion (items—11, 12, and 13). Write about cut-offs here. The values of responses for all 14 items are added up to calculate the total CSFQ score and the subscale scores are calculated by adding up values for only the items that correspond to a particular subscale. Scores “at or below” 47 for total CSFQ score; and 4, 8, 11, 12, and 11 for subscales—Pleasure, Desire/Frequency, Desire/Interest, Arousal/Excitement, and Orgasm/Completion, were considered cut-off points indicative of sexual dysfunction for males (note: scores received on items 10 and 14 are not counted in the calculation of subscale scores). The rTMS-Side-Effects Checklist was used to assess the side-effects of rTMS after each session.

Informed consent to undergo cTBS as well as to report their case was taken from all the 3 patients. All the 3 patients were delivered 15 cTBS sessions (3 sessions per day each spaced half an hour apart 5 days in a week, intensive protocol) targeting the rDLPFC (right dorsolateral prefrontal cortex). cTBS protocol consisted of a burst of 3 pulses delivered at 50 Hz, which was repeated every 200 ms (at 5 Hz) for a total of 600 pulses and lasted the 40s. A total of 1,800 pulses was delivered per day. Treatment, that is, dosage of medications remained unchanged throughout the course of 15 days from the start of cTBS (see Table 1 for treatment details).

A MagVenture-MagPro-R30 device with Theta Burst booster and B65 coils (figure-of-8 shaped coil) was utilized in the delivery of items. The standard 10-20 international electroencephalogram (EEG) system was used for positioning the TMS coil as it accounts for variability in participant skull size and is consistently used in clinical TMS applications. The coil was centered over the rDLPFC (F4, 10-20 international system). All 3 patients reported improvement in sexual dysfunction after cTBS treatment. The CSFQ scores increased from baseline to posttreatment indicating improvement. None of the patients reported any side-effects and they tolerated the sessions well.

Subject 1, a 28-year-old, unmarried male presented to us with 5 years history of BD and 4 months of a current depressive episode. Since the beginning of this episode, he complained of less desire to engage in sexual activity and inability to achieve or maintain an erection. He also reveals that even reading erotic literature to get engaged in sexual fantasies doesn’t work. In addition, the patient reported not having the same level of pleasure or enjoyment from sexual arousal and orgasm as experienced since the onset of BD. He was drug free for >1 year, that is, since the remission of the previous episode. At baseline, the total CSFQ-14 score of 45 was lower than the cut-off point. The scores obtained in each subscale were: Pleasure (3); Desire-Frequency (6); Desire-Interest (9); Excitement (12); and Completion (10). The values for all scales lower than the cut-off points indicated overall sexual dysfunction. Postintervention, he showed enhanced performance on all subscales of CSFQ-14 including Pleasure; Desire-Frequency; Desire-Interest; Excitement; and Completion (see Table 1). After 15 days of treatment, his total CSFQ-14 score of 54 was higher than cut-off point suggesting the absence of overall sexual dysfunction (Table 2). Although all subscale scores were improved, he reports a mild increase in his sexual drive and improvement in penile erection but is not fully satisfied, complaint of not being able to reach the levels of sexual arousal and enjoyment that he experienced before the treatment of disease persist.

Table 1. Clinical Characteristics

| Patient | Age Gender | Total Duration of Illness in Years | Number of Depressive Episodes | Duration of Current Episode | Duration of Sexual Dysfunction in Months | Medications the Patients Received (Dose, Duration) During the Current Episode | Scores on the Hamilton Depression Rating Scale |
|---------|------------|-----------------------------------|------------------------------|-----------------------------|----------------------------------------|-------------------------------------------------|---------------------------------|
| P1      | 28 years M | 5 years                            | 3                            | 4 months                    | 4 months                               | • Bupropion (150 mg, 3 months) • Levosulpiride (40 mg, 3 months) | 18 Preintervention 10 Postintervention |
| P2      | 22 years M | 2 years                            | 2                            | 5 months                    | 5 months                               | • Lithium (800 mg, 6 months) • Lamotrigine (50 mg, 6 months) • Propranolol (10 mg, 6 months) | 25 21 |
| P3      | 28 years M | 2 years                            | 2                            | 3 months                    | 24 months                              | •                                        | 31 13 |
Subject 2 is a 22-year-old unmarried male patient with 2 years history of BD and 3 months of a current depressive episode. He also reports that despite having a strong desire to engage in sexual activity, he could not ejaculate when he wants to, decreased quantity of ejaculate, and poor quality of orgasm for last 5 months. He was receiving Bupropion 150 mg and Levosulpiride 40 mg daily for 3 months. On assessing the frequency and severity of sexual problems on the CSFQ-14, he scored a total of 57, at baseline, which was higher than the cut-off value. Although his total score and score on Pleasure (4), Desire-Frequency (9), and Desire-Interest (15) reached cut-off points and indicated the absence of sexual dysfunction, the scores obtained in the Excitement (11) and Completion (9) subscale were lower than cut-off points. Postintervention, he showed increased performance on all subscales, including Pleasure; Frequency; Desire; Excitement; and Completion. After 15 days of treatment, his total CSFQ-14 score of 65, which was again higher than the reference value or cut-off point, suggesting the absence of overall sexual dysfunction (Table 2). These results indicate that the patient made progress considering the recovery of most sexual functions after receiving cTBS treatment.

The third subject was a 28-year-old married patient with 2 years history of BD and 3 months of a current depressive episode. For the last 2 years, he complained of a complete loss of sexual interest and inability to achieve or maintain an erection causing significant problems in marital life. The patient was receiving Lithium 800 mg, Lamotrigine 50 mg, and propranolol 10 mg. At baseline, the total CSFQ-14 score was 32, which was lower than the reference value. The scores obtained in each subscale were: Pleasure (1); Frequency(2); Desire/Interest(5); Excitement (5); and Completion(9). The values for all scales were lower than the cut-off points and indicated overall sexual dysfunction in all phases of sexual functioning. Postintervention, all subscale scores improved. However, only the scores for Excitement (13) and Completion (12) crossed the cut-off points. After 15 days of treatment, his total CSFQ-14 score was 51, which was higher than the reference value or cut-off point, suggesting the absence of overall sexual dysfunction (Table 2).

Our study is the first to use TBS, targeted to the DLPFC, with stimulation intensity moderated by patient tolerability and with sexual dysfunction as a primary outcome. We showed changes in sexual function in patients with BD with cTBS. Although this case series includes only 3 subjects, it was encouraging that all 3 showed increase in CSFQ score with cTBS. The TBS treatment might have produced positive results because among benefits on mood patients reported to be more confident during sexual activity and participated more in the relationship.

The present study provides evidence of feasibility in using cTBS in patients with bipolar depression, and given the demonstration of the possibility of TBS in affecting sexual dysfunction, suggests that a larger clinical trial might be fruitful. Future endeavors, controlling for state-dependent effects and studying the effects of varying stimulation parameters, would also require TMS/electroencephalogram monitoring as well as online TMS/functional magnetic resonance imaging-based approaches to examine the effect of cTBS on functional connectivity between DLPFC and other brain regions. We consider our study to be a pilot for research leading in this direction.

Declaration of Conflicting Interests
The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: We wish to draw the attention of the editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work “Theta Burst for Sexual Dysfunction in Bipolar Depression—A Case Series.” We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs
Shobit Garg https://orcid.org/0000-0001-5913-9021
Sai Krishna Tikka https://orcid.org/0000-0001-9032-1227

References
1. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication [published correction appears in Arch Gen Psychiatry. 2007 Sep;64(9):1039]. Arch Gen Psychiatry. 2007;64(5):543-552. doi:10.1001/archpsyc.64.5.543.
2. Fagiolini A, Forgione R, Maccari M, et al. Prevalence, chronicity, burden and borders of bipolar disorder. *J Affect Disord*. 2013;148(2–3):161–169. doi:10.1016/j.jad.2013.02.001.

3. Elkhiat YI, Abo Seif AF, Khalil MA, Gamal El, Din SF, Hassan NS. Sexual functions in male and female patients with bipolar disorder during remission. *J Sex Med*. 2018;15(8):1111-1116. doi:10.1016/j.jsxm.2018.06.002.

4. Nizamie SH, Tikka SK. Sexual dysfunction in males. In: Kar NM, Kar GC (Eds). *Comprehensive Textbook of Sexual Medicine*, 2nd Edition. Jaypee Brothers Medical Publishers Private Limited; 2014:149–166.

5. Abdelatti SI, Ismail RM, Hamed RA. Sexual dysfunctions in a sample of male psychiatric patients compared to medically ill patients. *Middle East Curr Psychiatry*. 2020;27.12. doi:10.1186/s43045-020-00022-3.

6. Fountoulakis KN, Kasper S, Andreassen O, et al. Efficacy of pharmacotherapy in bipolar disorder: a report by the WPA section on pharmacopsychiatry. *Eur Arch Psychiatry Clin Neurosci*. 2012;262 Suppl 1:1–48. doi:10.1007/s00430-012-0323-x.

7. Montejo AL, Montejo L, Baldwin DS. The impact of severe mental disorders and psychotropic medications on sexual health and its implications for clinical management. *World Psychiatry*. 2018;17(1):3–11. doi:10.1002/wps.20509.

8. Gitlin MJ. Psychotropic medications and their effects on sexual function: diagnosis, biology, and treatment approaches. *J Clin Psychiatry*. 1994;55(9):406–413.

9. Chokka PR, Hankey JR. Assessment and management of sexual dysfunction in the context of depression. *Ther Adv Psychopharmacol*. 2018;8(1):13–23. doi:10.1177/2045125317720642.

10. Dutta P, Dhyani M, Garg S, et al. Efficacy of intensive orbitofrontal continuous Theta Burst Stimulation (oOFcTBS) in obsessive compulsive disorder: a randomized placebo controlled study. *Psychiatry Res*. 2021;298:113784. doi:10.1016/j.psychres.2021.113784.

11. Tripathi A, Singh A, Singh H, Kar SK. Successful use of transcranial magnetic stimulation in difficult to treat hypersexual disorder. *J Hum Reprod Sci*. 2016;9(3):207–209. doi:10.4103/0974–1208.192074.

12. Blum AW, Grant JE. Positive response of compulsive sexual behavior to transcranial magnetic stimulation. *Prim Care Companion CNS Disord*. 2020;22(1):1902469. doi:10.4088/PCC.1902469.

13. Prause N, Siegle GJ, Deblieck C, Wu A, Iacoboni M. EEG to primary rewards: predictive utility and malleability by brain stimulation. *PLoS One*. 2016;11(11):e0165646. doi:10.1371/journal.pone.0165646.

14. Schecklmann M, Sakreida K, Oblinger B, Langguth B, Poeppl TB. Repetitive transcranial magnetic stimulation as a potential tool to reduce sexual arousal: a proof of concept study. *J Sex Med*. 2020;17(8):1553–1559. doi:10.1016/j.jsxm.2020.05.002.

15. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research*. WHO; 1992.

16. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62. doi:10.1136/jnnp.23.1.56.

17. Keller A, McGarvey EL, Clayton AH. Reliability and construct validity of the Changes in Sexual Functioning Questionnaire short-form (CSFQ-14). *J Sex Marital Ther*. 2006;32(1):43–52. doi:10.1080/00926230500232909.

18. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? a meta-analysis of the efficacy of rTMS in psychiatric disorders. *J Clin Psychiatry*. 2010;71(7):873–884. doi:10.4088/JCP.08m04872gre.