

Transcranial magnetic stimulation–associated mania with psychosis: A case report

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How to cite: Knox ED, Bota RG. Transcranial magnetic stimulation–associated mania with psychosis: A case report. *Ment Health Clin* [Internet]. 2021;11(6):373-5. DOI: 10.9740/mhc.2021.11.373.

Submitted for Publication: May 6, 2021; **Accepted for Publication:** October 4, 2021

Abstract

Transcranial magnetic stimulation (TMS) is a noninvasive procedure used in the treatment of depression. We observed TMS-associated mania with psychotic symptoms in a 55-year-old male diagnosed with MDD and generalized anxiety disorder without history of psychosis or mania. Owing to poor pharmacotherapeutic response and worsening symptomatology, TMS was introduced while continuing phenelzine; this was initially successful in demonstrating positive effects on mood. However, the patient began to develop symptoms consistent with mania with psychosis and was hospitalized. Both TMS and phenelzine were discontinued, leading to significant improvement of the symptoms of mania and psychosis. Phenelzine was later reintroduced for maintenance treatment of depression and anxiety, with no recurrence of mania or psychosis. This case report implicates TMS as a possible cause of mania and psychosis symptoms.

Keywords: transcranial magnetic stimulation, TMS, treatment-emergent mania

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Disclosures: The authors have no conflicts of interest to disclose.

Background

Transcranial magnetic stimulation (TMS) is a procedure indicated for the treatment of MDD in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.¹ Using a computerized, electromechanical device, brief magnetic pulses are applied to the head to induce electrical currents of targeted neuronal pathways. Several advantages exist for the use of TMS over traditional antidepressant treatments, including fewer side effects, a less invasive nature than vagal nerve stimulation or ECT, and targeting of specific parts of the brain. A review of TMS trials

identified the risk of treatment-emergent mania to be 0.84%, statistically similar to sham-TMS treatment risk of 0.73%, with TMS-induced mania more commonly diagnosed in patients with a history of bipolar disorder.² Case reports^{3,4} have described a switch to mania or hypomania during the course of right-side or bilateral application of TMS when used for depression treatment in patients continuing antidepressant pharmacotherapy. One case series⁵ had described treatment-emergent hypomania related to left-sided application of TMS for the treatment of unipolar depression in 4 patients without a history of hypomanic or manic episodes. In addition, cases⁶⁻⁸ of hypomania not progressing to mania have been described in patients receiving TMS, either with or without concurrent antidepressant use. Although these cases report mania and hypomania with TMS treatment, literature is scarce in describing TMS-induced mania with psychosis. Only 1 such case was identified in published literature,⁹ describing sertraline and TMS-related mania with psychosis in a patient with no history of bipolar disorder. In this case report, we describe a patient with



treatment-resistant depression with no history of bipolar disorder or mania who developed a manic episode with psychosis during treatment with phenelzine and left-sided application of TMS.

Patient Case

A 55-year-old white male presented with a 9-year history of depression leading to significant functional impairment including loss of employment and marital strain. He had no documented chronic medical illness, no medical medications, and routine laboratory monitoring indicated normal metabolic, thyroid, renal, and hepatic function. The patient denied use of any illicit substances or alcohol, and his urine drug screen was negative. Upon presentation to psychiatry, his symptoms included anhedonia, insomnia, guilt, hopelessness, amotivation, apathy, cognitive impairment, dysphoric mood, and ruminations, with significant worsening over the past 6 months. The patient's pharmacotherapeutic interventions for past episodes of depression and symptoms of anxiety include therapeutic trials of several antidepressants at maximally tolerated doses, including SSRIs, SNRIs, MAOIs, and bupropion; antidepressant augmentation with second-generation antipsychotics, buspirone, and benzodiazepines; and an ineffective 4-week course of ECT. Phenelzine was initiated within 6 months of initial TMS session, with improvement noted in anxiety symptoms, but limited benefit on mood. Treatment with TMS was initiated and phenelzine 30 mg orally per day was continued. After 6 weeks of TMS treatment, totaling 30 sessions as a standard 5-day per week course, the patient began to develop symptoms consistent with mania, including a decreased need for sleep, delusional symptoms including persecutory paranoia related to local arson events as well as grandiosity, rapid speech, racing thoughts, impulsivity, irritability, and significant increases in energy and spending. After several days of manic and psychotic symptoms, the patient was hospitalized owing to significant functional impairment. Phenelzine and TMS treatments were ceased, and the episode of mania was successfully treated with oxcarbazepine 300 mg orally twice a day and olanzapine titrated to 30 mg orally at bedtime, with significant improvement noted over several days. Phenelzine was slowly reintroduced upon discharge, titrated to 15 mg orally 3 times a day. Both olanzapine and oxcarbazepine were discontinued within 3 weeks. Over the course of 26 months of active monitoring with phenelzine monotherapy, the patient did not experience reemergence of manic or psychotic symptoms.

Transcranial Magnetic Stimulation

The procedure was administered via TMS protocol as follows: application to left dorsolateral prefrontal cortex,

75 trains 120% individual motor threshold, 10 Hz for a duration of 4 seconds on, with usual 26 seconds off. Over the entire course of TMS, the patient received TMS 5 times per week for 6 weeks while continuing phenelzine.

Discussion

There is indication of a relationship between the TMS treatment and development of mania with psychosis in our patient. Although this patient had previously been trialed on several antidepressants, each carrying a risk of treatment-emergent mania, the onset of manic symptoms from antidepressants is often within 1 year and the risk of switch generally does not persist months beyond medication discontinuation.^{10,11} Tricyclic antidepressants demonstrate a higher risk of switch to mania than MAOIs or serotonin reuptake inhibitors, and the risk of affective switch appears to be higher in those with earlier age of disease onset or in patients with a history of bipolar disorder than those without.¹² Studies have also identified antidepressant resistance as a risk factor for development of mania.¹³ This patient had no documented history of bipolar disorder, mania, or hypomania, and depression onset was not at a young age. He had not been trialed on higher-risk treatment with tricyclic antidepressants, although he may have been at higher risk for affective switch owing to antidepressant resistance. The recent medication change may have contributed to this mood disturbance, most notably the initiation of phenelzine in the year leading up to TMS treatment.¹⁴ However, this patient was re-trialed on therapeutic phenelzine after hospital discharge without reemergence of manic or psychotic symptoms after continuous 26 months post-stabilization with phenelzine monotherapy.

Conclusion

The lack of manic symptom reemergence after a prolonged period of antidepressant treatment with phenelzine suggests the initiation of TMS as the culprit in the development of mania with psychosis in this patient. Although the risk of mania is considered low in TMS clinical trials, this patient's severe presentation requiring hospitalization warrants consideration of TMS as the possible and likely cause of mania with psychosis.

References

1. Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS. The Clinical TMS Society consensus review and treatment recommendations for TMS therapy for major depressive disorder. *Brain Stimul.* 2016;9(3):336-46. DOI: [10.1016/j.brs.2016.03.010](https://doi.org/10.1016/j.brs.2016.03.010). PubMed PMID: [27090022](https://pubmed.ncbi.nlm.nih.gov/27090022/); PubMed Central PMCID: [PMC5612370](https://pubmed.ncbi.nlm.nih.gov/PMC5612370/).
2. Xia G, Gajwani P, Muzina DJ, Kemp DE, Gao K, Ganocy SJ, et al. Treatment-emergent mania in unipolar and bipolar depression:

- focus on repetitive transcranial magnetic stimulation. *Int J Neuropsychopharmacol*. 2008;11(1):119-30. DOI: [10.1017/S1461145707007699](https://doi.org/10.1017/S1461145707007699). PubMed PMID: [17335643](https://pubmed.ncbi.nlm.nih.gov/17335643/).
3. Ella R, Zwanzger P, Stampfer R, Preuss UW, Muller-Siecheneder F, Moller H-J, et al. Switch to mania after slow rTMS of the right prefrontal cortex. *J Clin Psychiatry*. 2002;63(3):249. DOI: [10.4088/JCP.v63n0312d](https://doi.org/10.4088/JCP.v63n0312d). PubMed PMID: [11926727](https://pubmed.ncbi.nlm.nih.gov/11926727/).
 4. Hausmann A, Kramer-Reinstadler K, Lechner-Schoner T, Walpott M, Rupp CI, Hinterhuber H, et al. Can bilateral prefrontal repetitive transcranial magnetic stimulation (rTMS) induce mania? *J Clin Psychiatry*. 2004;65(11):1575-6. DOI: [10.4088/JCP.v65n1122a](https://doi.org/10.4088/JCP.v65n1122a). PubMed PMID: [15554775](https://pubmed.ncbi.nlm.nih.gov/15554775/).
 5. Ozten E, Sayar GH, Karamustafalioglu O. Hypomanic shift observed during rTMS treatment of patients with unipolar depressive disorder: four case reports. *Ann Gen Psychiatry*. 2013;12(1):12. DOI: [10.1186/1744-859X-12-12](https://doi.org/10.1186/1744-859X-12-12). PubMed PMID: [23618105](https://pubmed.ncbi.nlm.nih.gov/23618105/); PubMed Central PMCID: [PMC3639843](https://pubmed.ncbi.nlm.nih.gov/PMC3639843/).
 6. Sakkas P, Mihalopoulou P, Mourtzouhou P, Psarros C, Masdrakis V, Politis A, et al. Induction of mania by rTMS: report of two cases. *Eur Psychiatry*. 2003;18(4):196-8. DOI: [10.1016/S0924-9338\(03\)00048-8](https://doi.org/10.1016/S0924-9338(03)00048-8). PubMed PMID: [12814856](https://pubmed.ncbi.nlm.nih.gov/12814856/).
 7. Arul-Anandam AP, Loo C, Mitchell P. Induction of hypomanic episode with transcranial direct current stimulation. *J ECT*. 2010;26(1):68-9. DOI: [10.1097/YCT.obo13e3181a744bf](https://doi.org/10.1097/YCT.obo13e3181a744bf). PubMed PMID: [19483641](https://pubmed.ncbi.nlm.nih.gov/19483641/).
 8. Baccaro A, Brunoni AR, Bensenor IM, Fregni F. Hypomanic episode in unipolar depression during transcranial direct current stimulation. *Acta Neuropsychiatr*. 2010;22(6):316-8. DOI: [10.1111/j.1601-5215.2010.00495.x](https://doi.org/10.1111/j.1601-5215.2010.00495.x).
 9. Brunoni AR, Valiengo L, Zanao T, de Oliveira JF, Bensenor IM, Fregni F. Manic psychosis after sertraline and transcranial direct-current stimulation. *J Neuropsychiatry Clin Neurosci*. 2011;23(3):E4-E5. DOI: [10.1176/jnp.23.3.jnpe4](https://doi.org/10.1176/jnp.23.3.jnpe4). PubMed PMID: [21948925](https://pubmed.ncbi.nlm.nih.gov/21948925/).
 10. Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry*. 2006;163(2):232-9. DOI: [10.1176/appi.ajp.163.2.232](https://doi.org/10.1176/appi.ajp.163.2.232). PubMed PMID: [16449476](https://pubmed.ncbi.nlm.nih.gov/16449476/).
 11. Tondo L, Vázquez G, Baldessarini RJ. Mania associated with antidepressant treatment: comprehensive meta-analytic review. *Acta Psychiatr Scand*. 2009;121(6):404-14. DOI: [10.1111/j.1600-0447.2009.01514.x](https://doi.org/10.1111/j.1600-0447.2009.01514.x). PubMed PMID: [19958306](https://pubmed.ncbi.nlm.nih.gov/19958306/).
 12. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. *Bipolar Disord*. 2003;5(6):407-20. DOI: [10.1046/j.1399-5618.2003.00067.x](https://doi.org/10.1046/j.1399-5618.2003.00067.x). PubMed PMID: [14636364](https://pubmed.ncbi.nlm.nih.gov/14636364/).
 13. Patel R, Reiss P, Shetty H, Broadbent M, Stewart R, McGuire P, et al. Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study. *BMJ Open*. 2015;5(12):e008341. DOI: [10.1136/bmjopen-2015.008341](https://doi.org/10.1136/bmjopen-2015.008341)
 14. Stoll AL, Mayer PV, Kolbrener M, Goldstein E, Suplit B, Lucier J, et al. Antidepressant-associated mania: a controlled comparison with spontaneous mania. *Am J Psychiatry*. 1994;151(11):1642-5. DOI: [10.1176/ajp.151.11.1642](https://doi.org/10.1176/ajp.151.11.1642). PubMed PMID: [7943454](https://pubmed.ncbi.nlm.nih.gov/7943454/).