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Bupropion Decreases Resting Motor Threshold: A Case Report

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Abstract

Background—Bupropion is associated with a dose-related increased seizure risk. This effect could correlate with a change in motor cortex excitability. Transcranial magnetic stimulation (TMS) can assess changes in motor cortical excitability by measuring resting motor threshold (RMT).

Method—RMT was determined before and during two weeks concomitant administration of bupropion at two different doses (150 mg per day and 300 mg per day) in a 41 year old female enrolled in a study of repetitive TMS (rTMS) for the treatment of depression.

Results—RMT was significantly lower when the patient took 300 mg per day of bupropion compared to no bupropion and 150 mg per day of bupropion. When bupropion was reduced to 150 mg, RMT returned to the pre-medication level.

Conclusion—Bupropion 300 mg per day increased cortical excitability as demonstrated by decreased RMT. This finding emphasizes the importance of assessing RMT regularly during rTMS treatment – especially in the context of new or changed doses of medications.

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Keywords

Bupropion; Resting Motor Threshold; repetitive Transcranial Magnetic Stimulation; Cortical Excitability

Background

Bupropion is an aminoketone antidepressant with a dose related stimulant effect on the central nervous system (1). Although bupropion has been shown to have an overall good safety profile with minimal side effects, it is associated with a dose-related increased seizure risk (2). The mechanism of action of bupropion is not completely understood, but may relate to presynaptic norepinephrine and dopamine reuptake inhibition (3). The seizure risk of bupropion may therefore result from heightened cortical excitability induced by these noradrenergic and dopaminergic properties.

Single pulse transcranial magnetic stimulation (TMS) can noninvasively evaluate cortical excitability by assessing resting motor threshold (RMT) (4). TMS uses an electromagnetic coil to produce rapidly changing magnetic fields that can induce current in the cerebral cortex and depolarize neurons. In the case of TMS applied to the hand region of the motor cortex, corresponding muscles in the contralateral hand will contract. The minimal amount of energy required to cause movement in a relaxed muscle group in about half of a series of TMS pulses is defined as the RMT. The RMT is a proxy for motor cortex excitability (5) and decreases in RMT may be associated with an increased risk of seizures.

Recently, repetitive transcranial magnetic stimulation (rTMS) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of depression based on data from a multi-center clinical trial (6). This treatment has a good overall safety profile, but there are case reports of generalized tonic-clonic seizures associated with rTMS (7,8). It is likely that medications that increase seizure risk (such as bupropion) might further increase the likelihood of a seizure when used concomitantly with rTMS. Evidence of this might be demonstrated by a change in RMT suggesting altered cortical excitability. This case report describes a dose-related decrease in RMT in a patient undergoing rTMS while taking bupropion.

Methods

The patient was a 41 year old female who had given written informed consent to participate in a multicenter NIMH-sponsored rTMS trial (R01 MH069886) to evaluate the efficacy of rTMS for the treatment of major depression. The trial was approved by the Emory University Investigational Review Board. She had a history of numerous depressive episodes over the past 20 years. At time of enrollment into this study, her current episode was of three months duration. Her magnetic resonance imaging (MRI) scan, electrocardiogram and screening laboratory evaluation (including electrolytes, renal function, liver function, complete blood cell count, thyroid function, urinalysis and urine toxicology screen) were all within normal limits. She had no comorbid medical conditions and denied history of any neurological disorder; she had never had seizures, tics or any abnormal movements. She was taking Estrostep for birth control and no other medications.

rTMS treatments were delivered using an investigational Model 2100 CRS rTMS system that included a figure-8 coil and novel navigational system (Neuronetics, Inc., Malvern, PA, USA). To determine resting motor threshold (RMT), the TMS coil was firmly placed over the patient's scalp and moved over the left motor cortex in order to determine the best location for evoking a response in the right abductor pollicis brevis (APB) muscle. The coordinates for this position were recorded so that it could be reliably identified during future sessions.

RMT estimation was repeated weekly (before each series of five rTMS treatment sessions) by visual observation of thumb or other finger movement (9) using the MT Assist program – an interactive computer program that uses a mathematical algorithm to provide an iterated estimate of MT based on four individual MT determinations made during the RMT estimation session (6). The final estimate of RMT (based on these four individual values) was used for determining stimulation intensity for the next five rTMS sessions. No other measures of cortical excitability were collected as part of the clinical trial protocol. Prefrontal electroencephalography (EEG) was obtained during each treatment but not during motor threshold testing.

Following screening and baseline procedures (including a single RMT estimation session [Visit 1 in Table 1 and Figure 1] as described above), the patient was enrolled and randomized into Phase 1 (her treatment allocation in this phase remains unknown as the study continues to recruit subjects and the blind has not been broken). Phase 1 consisted of 3 weeks double-blind, sham-controlled rTMS of the left dorsolateral prefrontal cortex. rTMS parameters were 120% RMT, 10 Hz, 4 second trains with a total of 75 trains per treatment session. During this phase, RMT was determined at 3 separate times (Visits 2, 3, and 4).

Due to lack of antidepressant response after 3 weeks treatment in Phase 1, the patient continued to Phase 2 consisting of 3 weeks open-label rTMS (same parameters as in Phase 1 but with a known active coil). During Phase 2, the RMT was determined at 3 separate times (Visits 5, 6, and 7). The patient showed a robust antidepressant response in this phase. Per study protocol, she was therefore enrolled into Phase 3 which included taper of rTMS and institution of maintenance medication. Based on her prior medication history, bupropion sustained-release was started at 150 mg per day prior to Visit 8, and two RMT determinations were made on this dose (Visits 8 and 9). Dose was then increased to 300 mg twice daily (300 mg total daily dose), and two RMT determinations were made on this dose (Visits 10 and 11). Given the observed decrease in RMT, bupropion was decreased back to 150 mg per day, and a final RMT determination was made before TMS was discontinued and the patient completed Phase 3 (Visit 12).

Results

No seizure activity or abnormal movements were observed at any time. EEGs during all rTMS treatment sessions showed no ictal or interictal epileptiform activity. The patient reported feeling “jittery” at 300 mg per day but not 150 mg per day of bupropion; she reported no other adverse effects from the medication at any dose. Throughout the trial, she consistently denied any adverse effects related to TMS or rTMS. Table 1 gives the individual RMT determinations and estimated RMT for each session; these data show good reliability for RMT measurement within each session. Figure 1 shows the estimated RMT for each session over time. The patient had an estimated RMT of 73% maximum output of the TMS machine at both baseline and completion of the study. As can be seen in Table 1 and Figure 1, there was a clear decrease in RMT when the patient was taking bupropion at 300 mg (but not 150 mg) per day; RMT returned to the pre-bupropion level when the patient reduced dose to 150 mg per day. An independent samples t-test showed a statistically significant difference ($t=8.11$, $df=46$, $p<0.001$) between the mean of individual RMT determinations while on bupropion 300 mg (B300; mean = 64.8 (SD = 2.1); $n=8$ [4 per session for 2 sessions]) and the mean of all other RMT determinations (OTH; mean = 71.6 (SD = 2.2); $n=40$ [4 per session for 9 sessions before and 1 session after B300]).

Conclusion

Bupropion appeared to produce a dose-related decrease of RMT in a patient receiving therapeutic rTMS. There are no prior published reports of TMS changes with the use of bupropion, though there is some indication that other antidepressant medications may affect cortical excitability as measured by TMS (10). Given the consistency of RMT prior to co-treatment with bupropion 300 mg per day then following dose reduction, it is highly unlikely that the decrease in RMT at 300 mg bupropion was solely due to prior treatment with rTMS. Given the design of the clinical trial protocol, we cannot address whether the noted effect on RMT was due to an interaction between bupropion and rTMS treatments (i.e., whether bupropion alone would have induced this same decrease in resting motor threshold if the patient had not also been receiving rTMS).

Although rTMS has been approved by the FDA as monotherapy, it is likely that rTMS will be used in patients receiving concomitant antidepressant medications. Little is known about the risks and benefits of combining rTMS with such medications, though these data suggest that the combination of bupropion with rTMS may lead to an increase in cortical excitability that may further be associated with an increased risk of seizures. To mitigate this risk, it is critical that rTMS for depression be dosed according to the subject's motor threshold – i.e., the decrease in RMT with bupropion may not be clinically relevant as long as the rTMS treatment intensity is reduced accordingly. However, this emphasizes the importance of regularly checking RMT during an rTMS treatment course, especially in the context of medication additions or dose changes.

Beyond the safety implications, this case report reinforces the importance of considering the effects of *all* comorbid medications when treating with rTMS. For example, an extensive literature describes changes in TMS measures with anticonvulsants (11). As a class, anticonvulsants increase RMT and bias other measures of cortical excitability towards inhibition and away from excitation. However, it is relevant to note that valproate in combination with low frequency (1 Hz) rTMS has been demonstrated to change the proposed effects of this form of stimulation from inhibitory to excitatory (12). Additionally, rivastigmine has been shown to inhibit the induction of global excitability enhancement with anodal transcranial direct current stimulation (13). These findings emphasize that concomitant medications may have unintended effects that may be clinically relevant to not only the safety but also the efficacy of focal brain stimulation therapies.

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References

1. Foley KF, DeSanty KP, Kast RE. Bupropion: pharmacology and therapeutic applications. *Expert Rev Neurother* 2006;6(9):1249–1265. [PubMed: 17009913]
2. Rissmiller DJ, Campo T. Extended-release bupropion induced grand mal seizures. *J Am Osteopath Assoc* 2007;107(10):441–442. [PubMed: 17956996]
3. Ascher JA, Cole JO, Colin JN, Feighner JP, Ferris RM, Fibiger HC, et al. Bupropion: a review of its mechanism of antidepressant activity. *J Clin Psychiatry* 1995;56(9):395–401. [PubMed: 7665537]
4. Baykushev S, Struppler A, Gozmanov G, Mavrov R. Motor threshold as indicator of premotor and motor cortex excitability. *Electromyogr Clin Neurophysiol* 2008;48(6–7):256–264.

5. Conforto AB, Z'Graggen WJ, Kohl AS, Rosler KM, Kaelin-Lang A. Impact of coil position and electrophysiological monitoring on determination of motor thresholds to transcranial magnetic stimulation. *Clin Neurophysiol* 2004;115(4):812–819. [PubMed: 15003761]
6. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007;62(11):1208–1216. [PubMed: 17573044]
7. Rosa MA, Picarelli H, Teixeira MJ, Rosa MO, Marcolin MA. Accidental seizure with repetitive transcranial magnetic stimulation. *J ECT* 2006;22(4):265–266. [PubMed: 17143158]
8. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalogr Clin Neurophysiol* 1998;108(1):1–16. [PubMed: 9474057]
9. Pridmore S, Fernandes Filho JA, Nahas Z, Liberatos C, George MS. Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. *J ECT* 1998;14(1):25–27. [PubMed: 9661090]
10. Gerdelat-Mas A, Loubinoux I, Tombari D, Rascol O, Chollet F, Simonetta-Moreau M. Chronic administration of selective serotonin reuptake inhibitor (SSRI) paroxetine modulates human motor cortex excitability in healthy subjects. *Neuroimage* 2005;27(2):314–322. [PubMed: 16019236]
11. Ziemann U. TMS and drugs. *Clin Neurophysiol* 2004;115(8):1717–1729. [PubMed: 15261850]
12. Fregni F, Boggio PS, Valle AC, Otachi P, Thut G, Rigonatti SP, et al. Homeostatic effects of plasma valproate levels on corticospinal excitability changes induced by 1Hz rTMS in patients with juvenile myoclonic epilepsy. *Clin Neurophysiol* 2006;117(6):1217–1227. [PubMed: 16644277]
13. Kuo MF, Grosch J, Fregni F, Paulus W, Nitsche MA. Focusing effect of acetylcholine on neuroplasticity in the human motor cortex. *J Neurosci* 2007;27(52):14442–14447. [PubMed: 18160652]

Figure 1. Estimated visit RMT over time

Power is percent output of the TMS device. Visit number corresponds to an rTMS session at which RMT was estimated (approximately once per week). B-150 = bupropion 150 mg per day. B-300 = bupropion 300 mg per day. *Indicates time at which patient was on 300 mg bupropion per day and RMT was significantly lower; see text for details.

Table 1

RMT values determined at every study visit.

STUDY PHASE	RMT VISIT	RMT 1 (%)	RMT 2 (%)	RMT 3 (%)	RMT 4 (%)	EST RMT (%)
Baseline	1	70.3	73.6	73.3	73.6	73
Phase 1	2	66.3	70.0	70.4	72.6	70
Phase 1	3	70.3	70.4	68.5	71.0	70
Phase 1	4	70.3	69.4	70.4	69.5	70
Phase 2	5	72.9	69.4	70.4	70.0	71
Phase 2	6	68.8	71.0	72.6	72.6	71
Phase 2	7	72.7	73.6	71.0	72.6	72
Phase 3	8	72.7	75.9	74.3	74.6	74
Phase 3	9	71.2	73.6	76.0	69.4	73
Phase 3	10	65.3	66.0	64.1	68.5	66
Phase 3	11	63.1	64.0	65.6	61.6	64
Phase 3	12	75.4	69.4	73.5	72.6	73

RMT = resting motor threshold; EST RMT = estimated resting motor threshold; the patient was taking bupropion 150 mg daily at Visits 8, 9 and 12; she was taking bupropion 300 mg daily at Visits 10 and 11.