

# Risk of seizures in transcranial magnetic stimulation: a clinical review to inform consent process focused on bupropion

Christine E Dobek<sup>1</sup>  
Daniel M Blumberger<sup>2</sup>  
Jonathan Downar<sup>3</sup>  
Zafiris J Daskalakis<sup>2</sup>  
Fidel Vila-Rodriguez<sup>1</sup>

<sup>1</sup>Department of Psychiatry,  
Faculty of Medicine, Non-Invasive  
Neurostimulation Therapies  
(NINET) Laboratory, University of  
British Columbia, Vancouver, BC,

<sup>2</sup>Department of Psychiatry, Centre  
for Addiction and Mental Health,

<sup>3</sup>Department of Psychiatry, University  
Health Network, University of  
Toronto, Toronto, ON, Canada

**Objective:** When considering repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder, clinicians often face a lack of detailed information on potential interactions between rTMS and pharmacotherapy. This is particularly relevant to patients receiving bupropion, a commonly prescribed antidepressant with lower risk of sexual side effects or weight increase, which has been associated with increased risk of seizure in particular populations. Our aim was to systematically review the information on seizures occurred with rTMS to identify the potential risk factors with attention to concurrent medications, particularly bupropion.

**Data sources:** We conducted a systematic review through the databases PubMed, PsycINFO, and EMBASE between 1980 and June 2015. Additional articles were found using reference lists of relevant articles. Reporting of data follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

**Study selection:** Two reviewers independently screened articles reporting the occurrence of seizures during rTMS. Articles reporting seizures in epilepsy during rTMS were excluded. A total of 25 rTMS-induced seizures were included in the final review.

**Data extraction:** Data were systematically extracted, and the authors of the applicable studies were contacted when appropriate to provide more detail about the seizure incidents.

**Results:** Twenty-five seizures were identified. Potential risk factors emerged such as sleep deprivation, polypharmacy, and neurological insult. High-frequency-rTMS was involved in a percentage of the seizures. None of these seizures reported had patients taking bupropion in the literature review. One rTMS-induced seizure was reported from the Food and Drug Administration in a sleep-deprived patient who was concurrently taking bupropion, sertraline, and amphetamine.

**Conclusion:** During the consent process, potential risk factors for an rTMS-induced seizure should be carefully screened for and discussed. Data do not support considering concurrent bupropion treatment as contraindication to undergo rTMS.

**Keywords:** repetitive transcranial magnetic stimulation, seizures, bupropion, consent process, interaction

## Background

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neurostimulation treatment that is evolving toward a mainstream therapeutic option for major depression.<sup>1</sup> rTMS can be used in monotherapy as well as in combination with antidepressant medications, particularly when facing treatment-resistant depression.<sup>2</sup> In this regard, during the assessment and consent process, clinicians and patients still face important questions with regard to the interaction of pharmacological interventions with rTMS, specifically in terms of safety of the combined intervention. When discussing medications

Correspondence: Fidel Vila-Rodriguez  
Department of Psychiatry, Faculty of  
Medicine, Non-Invasive Neurostimulation  
Therapies (NINET) Laboratory, UBC  
Hospital, University of British Columbia,  
Detwiller Pavilion, 2255 Wesbrook Mall,  
Vancouver, BC V6T 2A1, Canada  
Tel +1 604 827 0175  
Email fidelvil@mail.ubc.ca

and potential hazards for rTMS, current guidelines on use of rTMS establish a categorization of medications that can pose a potential hazard for rTMS.<sup>3</sup> Under category 1, there are compounds listed which state that the intake of one or a combination of the following drugs forms a strong potential hazard for application of rTMS due to their significant seizure threshold-lowering potential. Thus, a recommendation is made that rTMS should be performed, when required, with particular caution. Tricyclic antidepressants, some antipsychotics, and stimulants are included. However, other antidepressants, mostly selective serotonin reuptake inhibitors (SSRIs) and bupropion as well, are listed under category 2 and categorized as posing a relative hazard for the application of rTMS, and the recommendation is to perform rTMS, when required, with caution.<sup>3</sup>

Nonetheless, cases in which patients are on bupropion and are referred for consideration of rTMS can raise legitimate questions during the assessment and consent process in clinicians and patients alike with regard to the safety of such combined treatment. Although bupropion is classified in category 2 with other SSRI or serotonin norepinephrine reuptake inhibitor (SNRI), such as fluoxetine or venlafaxine,<sup>3</sup> the perception of risk with regard to the combination of rTMS–bupropion might have suffered from a similar situation to that in eating disorders whereby a culture of considering all formulations of bupropion as an absolute contraindication seemed to permeate into clinical practice.<sup>4</sup>

Despite more recent evidence suggesting that extended-release (XR) formulations of bupropion may not pose any higher seizure risk than other antidepressants, clinicians often remain reluctant to prescribe bupropion in the setting of eating disorders.<sup>4</sup> A similar reluctance may also persist in some clinicians regarding the use of rTMS in patients taking bupropion. In order to provide with accurate and current information on the topic, we wanted to provide clinicians with a systematic review of the literature on the occurrence of rTMS-induced seizures with a special focus on the role of concurrent medications, including bupropion. The ultimate goal is to provide clinicians and patients alike with a detailed review of the topic in order to aid in informing the consent process of patients who are on bupropion and are contemplating a course of rTMS.

## Pharmacodynamic profile of bupropion and risk of seizure

Bupropion is a commonly prescribed noradrenaline–dopamine reuptake inhibitor antidepressant indicated for the treatment of major depressive disorder as well as an aid in smoking cessation. In depression, it can be used on

monotherapy or as an add-on medication for patients with an insufficient response to first-line SSRI antidepressants.<sup>5,6</sup> First released in the United States market in 1985 (1998 in Canada), it is currently available in three oral formulations that have bioequivalent systemic exposure to bupropion, in both rate and extent of absorption.<sup>7</sup> The first oral formulation is an immediate release (IR) formulation and is administered three times per day; the second is sustained release (SR) and is administered twice per day; the third is extended/modified release administered once per day. Primarily, bupropion acts as a dopamine–norepinephrine reuptake inhibitor and a nicotinic acetylcholine receptor antagonist.<sup>8</sup> This unique pharmacodynamic profile differentiates bupropion from other antidepressants and results in lower rates of side effects such as sexual dysfunction, somnolence, or weight gain that are prevalent in SSRIs and SNRIs.<sup>9–12</sup> The differential side-effect profile of bupropion compared to other antidepressant medications might contribute some patients to prefer bupropion over other antidepressant medications<sup>13</sup> or clinicians to consider bupropion as a first alternative when patients cannot tolerate side effects associated to SSRIs or SNRIs.<sup>14</sup>

The most common side effects of bupropion (SR, 300–400 mg) compared to placebo include headache (25%–26% vs 23%), dry mouth (17%–24% vs 7%), and nausea (13%–18% vs 8%).<sup>12</sup> Seizures are the most serious side effects associated with bupropion, with a 0.4% risk of seizure when taking bupropion IR at 300–450 mg/d. Due in part to this higher risk, the IR formulation of bupropion has been discontinued in many jurisdictions of the United States and Canada, in favor of slower-release formulations carrying a lower risk of seizure induction.

There is a dose–response effect in the association of seizures with bupropion: the higher the dose of bupropion, the higher the risk of seizures. For example, the risk of seizure increases from 0.1% to 0.4% when taking bupropion SR 100–300 mg/d to 400 mg/d, respectively.<sup>12</sup> When bupropion was first introduced in the United States in 1985, the recommended dosage was 400–600 mg/d. Immediately upon introduction, a study conducted resulted in bupropion being temporarily withdrawn from the market between 1986 and 1989.<sup>15</sup> Horne et al<sup>15</sup> conducted a double-blind placebo-controlled study on eating disorders patients (bulimia) and bupropion. After four out of 55 participants taking bupropion experienced grand-mal seizures, the high frequency (HF) of seizures in the study was alarming and bupropion was temporarily suspended. Postmarketing research showed that the incidence of seizure rates was directly proportional to both dosing and type of oral formulation used. Specifically, the higher the dose, the higher the risk of seizures,

and IR formulations carry a higher risk compared to SR or XR formulations. In addition, seizure risk was found to be associated with patient factors, clinical situations, and concomitant medications. As a result of new data, modifications to the medication information sheet were made regarding reduction of dosing as well as additional contraindications such as history of head trauma or prior seizure, brain tumor, severe hepatic cirrhosis, concomitant medications that lower seizure threshold, excessive use of alcohol or sedatives (including benzodiazepines), drug addictions, and diabetes.<sup>12</sup>

## rTMS and risk of seizure

rTMS was approved for the treatment of depression in Canada (2002) and in the United States (2008) and has been used to effectively treat thousands of patients with depression. The rTMS treatment protocol is noninvasive and capitalizes on the principle of electromagnetic induction to elicit an electrical current in brain tissue of enough magnitude to depolarize neurons within the cerebral cortex; these neurons are part of relevant circuits involved in emotional regulation.<sup>16</sup> The most common side effects include headache (5%–23%) and discomfort at the site of stimulation (20%–40%).<sup>17–22</sup> The most serious side effect associated with rTMS is the accidental induction of a seizure. Although accidental seizures occur at a frequency of <0.1%, there are factors that may increase the risk of rTMS triggering a seizure such as sleep deprivation, family history of seizures, alcohol use, and previous neurological condition.<sup>20,23</sup>

## Methods

We conducted a systematic review of rTMS-related accidental seizures. Inclusion criteria were 1) case reports or case series or studies, where the occurrence of a seizure was reported, 2) using rTMS or TMS, 3) any language, 4) any age, and 5) studies on humans. Exclusion criteria were 1) rTMS/TMS studies in samples afflicted by epilepsy, 2) not enough information to establish that a seizure had occurred, and 3) reports of non-seizure side effects. A total of 1,197 records were identified through the databases PubMed, PsycINFO, and EMBASE with the search terms “rTMS” or “TMS” or “transcranial magnetic stimulation” or “repetitive transcranial magnetic stimulation” and “ictal activity” or “seizure” or “convulsion” or “epilepsy” or “epileptic” (detailed information is given in Figure S1). The search was conducted in between June 6 and 10, 2015, and included papers in all languages since the year 1980. An additional seven records were identified through other sources, namely references from original records. All records were initially screened, and 1,154 were excluded due to the following reasons: investigated epilepsy and/or chronic

seizure patients, was a review paper, unrelated to the topic, used animal subjects, had no seizures induced, or was a duplicate record. Following the initial screening, 43 full-text articles were assessed for eligibility. Out of the 43 assessments, 22 articles were excluded, as four reported rTMS-induced syncope, 13 were comments/reviews on rTMS, one used an H-coil for deep rTMS, three did not induce a seizure, and one article investigated an epilepsy patient. Therefore, 21 articles that reported 25 rTMS-induced seizures were included in the final literature review.<sup>23–42</sup> Two raters conducted the search and went through the selection process and reviewed the full-text papers. Another investigator independently rated the 43 full-text articles selected to confirm that the final articles were properly selected based on the criteria.

Authors were contacted for further information regarding missing information in the 25 seizure reports. Those contacted include A Chervyakov, K Brogmus, E Wassermann, M Rosa, and R Kandler. Additional information extracted pertained to the paper by Kandler, dictated that the stimulation would have been using a large coil placed at the vertex to stimulate the small hand and foot muscles, and that the frequency of the stimuli would have been no more than 0.3 Hz (–RH Kandler, Department of Clinical Neurophysiology, Royal Hallamshire Hospital, electronic communication, February 6, 2014). Chervyakov et al<sup>42</sup> also described the two seizures reporting their stroke location (left and right middle cerebral artery basin), the rTMS session that the seizures occurred (single pulse during diagnostic mapping, 1<sup>st</sup> session of high frequency rTMS), also that both seizures were associated with underestimation of the EEG data during screening (A Chervyakov, electronic communication, June 15, 2015, Research center of neurology, Russian Academy of Medical Science, Moscow, Russia).

## Results

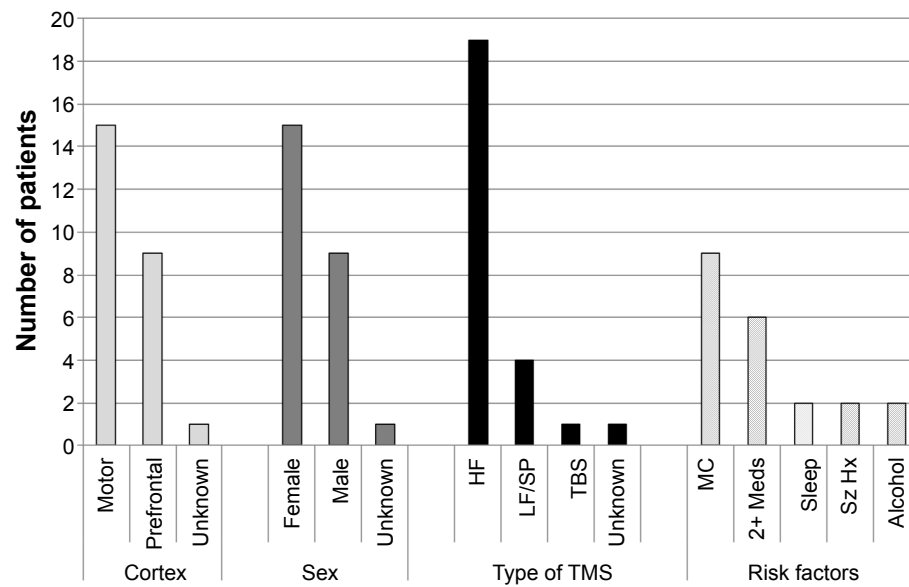
Our systematic review yielded 25 reports of rTMS-induced seizures; 23 reports were from peer-reviewed journals and two were from conference abstracts. All data included fulfilled our inclusion criteria (Figure S1). Case series are summarized in Table 1 (detailed information is given in Table S1). There was 15 women, nine men, and one unknown reported to have experienced TMS-induced seizures. Women were significantly younger than men with women’s having a mean age of 31 vs men’s mean age of 49 years old (independent *t*-test; *P*>0.005, two-tailed). In terms of diagnoses, nine were receiving rTMS in the context of a depressive episode, nine for neurological conditions, six were healthy volunteers, and one had a pain syndrome.

Details on TMS parameters are provided in Table 1 and summarized in Figure 1. Briefly, 19 cases had HF-rTMS

**Table 1** Summary table of rTMS induced accidental seizures including the author, type of TMS, location, medications, risk factors, type of seizure, and diagnosis.

| ID | Author   | Type of TMS | Location | Medication         | Risk factor   | Type of seizure                      | Diagnosis  |
|----|--|-------------|----------|--------------------|---|--------------------------------------|--|
| 1  | Chervyakov et al <sup>12</sup>                                   | SP          | L-MC     | NR                 | Pre-existing condition  | Secondarily generalized              | Stroke   |
| 2  | Chervyakov et al <sup>12</sup>                                   | HF          | R-MC     | NR                 | Pre-existing condition  | Secondarily generalized              | Stroke   |
| 3  | Chiramberro et al <sup>24</sup>                                  | HF          | L-DLPFC  | SRT, OLZ, HDX      | High blood alcohol, multiple medications, over OLZ recommended dose | Asymmetric twitching of both arms    | MDD  |
| 4  | Bagati et al <sup>25</sup>                                       | HF          | L-DLPFC  | PRX, DVF           | Multiple medications  | Generalized                          | MDD  |
| 5  | Hu et al <sup>26</sup>   | HF          | L-PFC    | SRT                | Youth   | Generalized                          | Adolescent onset MDD   |
| 6  | Harel et al <sup>27</sup>  | HF          | L-PFC    | Li                 | No risk factors   | Generalized                          | BD   |
| 7  | Gomez et al <sup>28</sup>  | HF          | R-MC     | CZX                | Pre-existing condition, frequent alcohol use (withdrawal)           | Jacksonian                           | Stroke -MCA  |
| 8  | Oberman and Pascual-leone <sup>39</sup>                          | cTBS        | L-MC     | None               | No risk factors   | Generalized                          | Healthy  |
| 9  | Sakkas et al <sup>30</sup>                                       | HF          | R-PFC    | QTP, DZP, GP       | Multiple medications  | Jacksonian                           | BD: Type I   |
| 10 | Rosa et al <sup>29</sup>   | HF          | L-MC     | NR                 | Pre-existing condition  | Generalized                          | Complex pain regional syndrome                                     |
| 11 | Tharayil et al <sup>35</sup>                                     | SP          | R-MC     | Li, CPZ            | Sleep deprived  | Generalized                          | BD- current hypomania  |
| 12 | Prikryl and Kucerova <sup>31</sup>                               | HF          | L-DLPFC  | NR                 | Sleep deprived  | Generalized                          | MDD  |
| 13 | Bernabeu et al <sup>32</sup>                                     | HF          | MC       | FLX                | Pre-existing condition, multiple medications                        | Secondarily generalized              | Possible Traumatic Brain Injury                                    |
| 14 | Conca et al <sup>33</sup>  | HF          | L-DLPFC  | VFX, TZD, LOR, THR | History of seizure  | Frontal lobe complex partial seizure | Mixed depressive-anxious state, dependent personality, hypothyroid |
| 15 | Brogmus <sup>40</sup>  | NR          | NR       | NR                 | NR  | Secondarily generalized              | Hydrocephalus and chronic inflammatory CNS process                 |
| 16 | (NINDS) Wassermann <sup>23</sup>                                 | HF          | MC       | NR                 | NR  | Secondarily generalized              | Healthy  |
| 17 | Wassermann et al <sup>34</sup>                                   | HF          | L-PFC    | NR                 | NR  | Generalized                          | Healthy  |
| 18 | Wassermann et al <sup>34</sup>                                   | HF          | MC       | NR                 | NR  | Generalized                          | Healthy  |
| 19 | Pascual-leone et al <sup>41</sup>                                | HF          | L-MC     | None               | Family history of seizures  | Generalized                          | Healthy  |
| 20 | Fauth et al <sup>36</sup>  | SP          | MC       | NR                 | Pre-existing condition  | Jacksonian                           | Stroke   |
| 21 | Kandler <sup>38</sup>  | HF          | MC       | None               | Pre-existing condition  | Jacksonian                           | Multiple sclerosis   |
| 22 | Kandler <sup>38</sup>  | HF          | MC       | None               | Pre-existing condition  | 2 generalized same day               | Multiple sclerosis   |
| 23 | Homburg and Netz <sup>37</sup>                                   | SP          | MC       | NR                 | Pre-existing condition  | Generalized                          | Large ischaemic scar after MCA infarction                          |
| 24 | Wassermann <sup>23</sup>   | HF          | MC       | NR                 | NR  | Partial motor                        | Healthy  |
| 25 | Pascual-Leone not published (reported Wassermann <sup>23</sup> ) | HF          | PFC      | AMT, HLD           | Investigators unaware of medications                                | Secondary generalized                | Psychotic depression   |

**Abbreviations:** HF, High Frequency; SP, Single Pulse; cTBS, continuous theta burst stimulation; MC, Motor Cortex; PFC, Prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; L, Left; R, Right; MDD, Major Depressive Disorder; BD, Bipolar Depression; MCA, Middle Cerebral Artery; NR, Not Reported; AMT, Amitriptyline; CPZ, Chlorpromazine; CZX, Chlordiazepoxide; DVF, Desvenlafaxine; DZP, Diazepam; GP, Gabapentin; FLX, Fluoxetine; HLD, Haloperidol; HDX, Hydroxyzine; Li, Lithium; LOR, Lorazepam; OLZ, Olanzapine; PRX, paroxetine; QTP, Quetiapine; SRT, Sertraline; THR, Thyroxine; TZD, Trazodone; VFC, Venlafaxine.



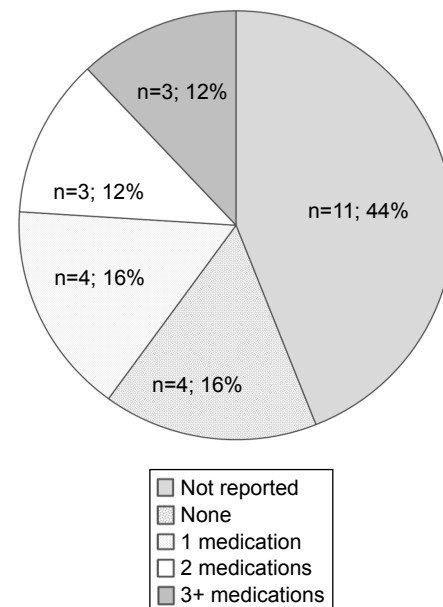
**Figure 1** Patients with an rTMS-induced seizure categorized by area of cortex stimulated (cortex), sex, type of TMS administered, and possible risk factors. **Abbreviations:** rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation; HF, high frequency; LF, low frequency; SP, single pulse; TBS, theta-burst stimulation; MC, preexisting medical condition; Meds, medications; Sleep, sleep deprived; Sz Hx, history of seizures; Alcohol, influence of alcohol.

(>3 Hz),<sup>23–34,42</sup> four cases with multiple single-pulse stimulations,<sup>23,35–38,42</sup> one continuous theta-burst stimulation (cTBS),<sup>39</sup> and one not reported.<sup>40</sup> Fifteen reports were cases where motor cortex was stimulated,<sup>23,28,29,32,35–39,41,42</sup> nine where prefrontal cortex was stimulated,<sup>24–27,30,31,33,34</sup> and one not reported.<sup>40</sup> The intensity of stimulation used is very heterogeneous and ranges from 40% to 130% resting motor threshold (RMT). Of note, there were no TMS-induced seizures with intermittent theta-burst stimulation or with 1 Hz over the right prefrontal cortex.

Reports were heterogeneous when reporting potential risk factors for seizures, but most identified at least one potential risk factor that could contribute to increasing the probability of inducing a seizure during rTMS treatment. These risk factors include neurological insult or preexisting condition, including multiple sclerosis, stroke, and traumatic brain injury,<sup>28,29,32,36–38,40,42</sup> interrupted sleep pattern,<sup>31,35,39</sup> and a history of seizures.<sup>33,41</sup> The six remaining case reports did not contain enough information to determine if risk factors were present.<sup>23,27,34</sup> With regards to the event reported by Chiramberro et al,<sup>24</sup> Wall and colleagues<sup>43</sup> suggested that rTMS may have not been the primary factor in inducing the seizure. Wall et al discussed that the adolescent patient was taking multiple psychotropic medications, where olanzapine was given outside of the acceptable dosing range at 75 mg/d. They further discussed that with the high blood alcohol content, rTMS should not have been delivered that day. Thus, this case exemplifies the importance of having definitive guidelines based on the risk factors for rTMS treatment.<sup>43</sup>

In terms of medications, all patients who had a mood disorder were on at least one medication, the majority being on two or three medications (Figure 2). The antidepressants are varied, and no particular antidepressant is overrepresented. There are no cases of rTMS-induced seizures where the patient was taking bupropion.

Only one seizure has been documented by the US Food and Drug Administration (FDA) involving a patient taking



**Figure 2** The number and combination of medications that each of the patients (n=25) was taking during the time of accidental rTMS-induced seizure: including no medication (none, n=4, 16%), one medication (n=4, 16%), two medications (n=3, 12%), three medications or more (n=3, 12%), and medications not reported (n=11, 44%). **Abbreviation:** rTMS, repetitive transcranial magnetic stimulation.

bupropion during rTMS treatment.<sup>44</sup> The patient was on the tenth rTMS treatment session of the second course of rTMS therapy when she began to have tonic-clonic movements. The patient was taking other medications other than bupropion that also decreased seizure threshold, namely, sertraline and amphetamine. In addition, the patient was likely sleep deprived as she worked a night shift before treatment. The patient made a full recovery, and the supervising psychiatrist declared that the seizure was due to an “equipment failure” (from report on FDA).<sup>44</sup>

## Discussion

Data available on the rare occurrence of TMS-induced seizures do not show an overrepresentation of any particular antidepressant. However, there are some factors that seem to be more prevalent in rTMS-induced seizures, namely HF-rTMS, motor cortex stimulation, pre-existing conditions, polypharmacy, sleep deprivation, and past history of seizures.

Currently, standard guidelines of rTMS do not exclude the use of bupropion while receiving rTMS treatment, including the suggested guidelines from the International Workshop on the Safety of rTMS<sup>23</sup> or with the FDA. Based on the current evidence, a low dose (<400 mg XR and <300 mg SR) of bupropion taken by patients undergoing rTMS seems to be a safe means of delivering treatment to those with clinical depression. As there is limited research investigating this area, the issue still remains controversial. More studies are needed to look at bupropion and its effect on the seizure threshold to accurately determine if the caution behind bupropion and rTMS is justified.

In addition to well-known risk factors of inducing an accidental rTMS seizure, medication has been suggested to

also pose as a possible risk factor.<sup>20</sup> As described earlier, bupropion IR was found to be associated with increased rate of seizures in a dose-dependent manner in particular populations, which led some authors to hypothesize that it might decrease seizure threshold in rTMS. In this regard, Mufti and Holtzheimer<sup>45</sup> showed in a case study of an individual patient that RMT determined by rTMS was reduced from a mean of 71% device output to 64% mean device output when a patient was concurrently taking 300 mg/d of bupropion compared to taking no bupropion or 150 mg/d of bupropion. Although this anecdotal piece of evidence is interesting, its inferential capacity is very limited (note the authors used an independent-samples *t*-test for repeated measures of RMT on that single patient, which can misrepresent significance). RMT has also been shown to be quite variable between treatment days as it can be influenced by electrode and coil placement errors as well as other influences on cortical and spinal excitability such as circadian rhythms and circulating hormone levels.<sup>46</sup> Therefore, a small fluctuation in RMT within a participant is not a determinant factor when investigating bupropion's influence on motor threshold.

Based on this study and the past seizure history of bupropion in the late 1980s, some physicians and patients might raise the question as to what is the potential risk when contemplating a course of rTMS while taking bupropion. This might represent a barrier to a significant number of depressed patients as bupropion is a popular antidepressant that lacks the undesirable side effects of other antidepressants. Unbeknownst to many, most antidepressants taken alone have a similar risk of seizure to bupropion ranging from 0.1% to 0.4% (Table 2),<sup>47–56</sup> with popular antipsychotics ranging from

**Table 2** Seizure incidence rates (in percent) for popular antidepressants and antipsychotics based in the literature

| Antidepressant       | Source   | Dose (mg/d) | Seizure rate (%)       |
|----------------------|--|-------------|------------------------|
| Bupropion SR         | US Food and Drug Administration <sup>12</sup>              | 100–300     | 0.1                    |
| Bupropion IR         | US Food and Drug Administration <sup>12</sup>              | 300–450     | 0.4                    |
| Citalopram           | Lundbeck Canada Inc. <sup>53</sup>                         |             | 0.25 (vs 0.23 placebo) |
| Duloxetine           | Eli Lilly and Company <sup>51</sup>                        |             | 0.2                    |
| Fluoxetine           | Eli Lilly and Company <sup>48</sup>                        | 20–60       | 0.2                    |
| Fluvoxamine          | Edwards et al <sup>52</sup>                                | <100        | 0.2                    |
| Mirtazapine          | GenMed PC <sup>49</sup>                                    |             | 0.04                   |
| Paroxetine           | GlaxoSmithKline Inc. <sup>54</sup>                         |             | 0.1                    |
| Sertraline           | Pfizer-Roerig <sup>47</sup>                                |             | 0.0–0.2                |
| Venlafaxine          | Pfizer <sup>50</sup>                                       | <150        | 0.3                    |
| Venlafaxine XR       | Pfizer <sup>50</sup>                                       |             | 0                      |
| Tricyclics           | Preskorn & Fast <sup>56</sup>                              |             | 0.1–0.4                |
| <b>Antipsychotic</b> | US Food and Drug Administration; Alper et al <sup>55</sup> |             |                        |
| Olanzapine           |  |             | 0.9                    |
| Quetiapine           |  |             | 0.8                    |
| Aripiprazole         |  |             | 0.4 (vs 0.1 placebo)   |
| Ziprasidone          |  |             | 0.4                    |
| Risperidone          |  |             | 0.3                    |

**Note:** Dosing information is available for some of the medications.

**Abbreviations:** IR, immediate release; SR, sustained release; XR, extended release.

0.5% to 0.9%. In comparison, the incidence of seizure on the general population without medication is 0.07%–0.09%.<sup>57</sup>

Over a thousand treatments have been documented, which have allowed patients to concomitantly receive bupropion and rTMS treatment successfully. Janicak et al<sup>58</sup> had 34 out of 36 patients on bupropion who received a total of 1,053 rTMS treatments (average 20 treatments/person) for up to 12 weeks without inducing a seizure. Kleinjung et al<sup>59</sup> investigated bupropion as an add-on medication with rTMS for tinnitus treatment as bupropion is a noradrenaline and dopamine reuptake inhibitor that may potentiate low-frequency (LF)-rTMS by enhancing neuroplasticity. Eighteen patients received 150 mg of bupropion XR 4 hours before each rTMS session, for a total of ten sessions, while 100 matched tinnitus patients received rTMS treatment alone. They found that there was no difference between the 100 matched controls to those who received bupropion as an add-on medication and also reported no serious adverse events during the study. In addition, the University Health Network rTMS Clinic at Toronto Western Hospital has administered ~20,000 treatments without accidental seizure and regularly treat patients taking bupropion (up to 300 mg, divided into two doses). Similarly, the Temerty Centre for Therapeutic Brain Intervention has administered >20,000 treatments without inducing a seizure in a bupropion patient, with estimates of 5%–10% of the patients on bupropion. There are no restrictions at the Temerty Centre on bupropion other than the daily dose should not exceed 300 mg.

When considering all rTMS-induced accidental seizures reported in the literature (Table 1), none of the patients were taking bupropion with one report from the FDA outlining multiple risk factors. Further, bupropion was not stated as an exclusion criterion for any of the aforementioned research studies. The higher proportion of seizures reported using HF-rTMS compared to LF-rTMS might be related to the fact that HF-rTMS acutely increases cortical excitability, whereas LF-rTMS decreases cortical excitability. Furthermore, LF-rTMS has been explored as a therapeutic tool to treat refractory epilepsy.<sup>60</sup> Based on the literature, other popular medications for mood disorders including antidepressants (SSRIs, SNRIs, atypical), antipsychotics, benzodiazepines, and mood stabilizers were present when a seizure was initiated. Thus, it seems that rTMS may be a viable option for patients taking appropriate doses of bupropion, and certainly data do not support a change in the classification on the guidelines by The Safety of TMS Consensus Group to class 1 (strong potential hazard).<sup>3</sup> Also, data do not support considering bupropion as an absolute contraindication to receive rTMS in the context

of mood disorders. A systematic and comprehensive approach to reporting rTMS side effects, including seizures, would benefit clinicians and patients alike. Specifically, a system akin to the pharmacovigilance programs for medications could be established for medical devices. This medical-device-vigilance program would set standards for reporting adverse events associated with medical devices, thereby increasing the reporting rates and information accuracy.

## Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary materials

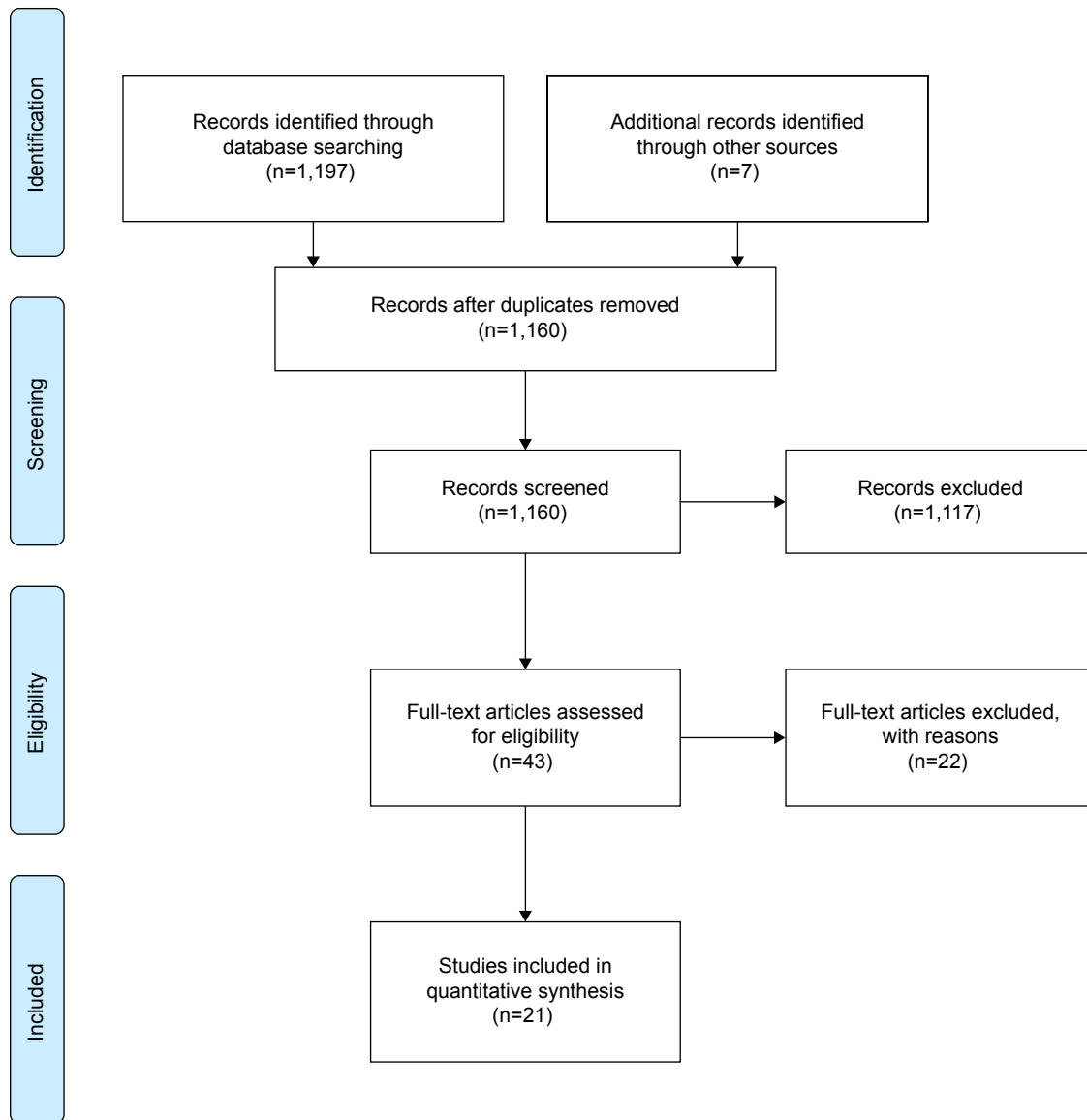


Figure S1 PRISMA flow diagram.<sup>1</sup>

**Abbreviation:** PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Table S1** rTMS characteristics and information on seizures

| ID | Patient    | Type of TMS   | Location | Medication  | Sleep hx | Session number | Other risk factors   | Outcome of seizure  | Type of seizure                   | Diagnosis            | Others   |
|----|------------|---|----------|---|----------|----------------|--|---|-----------------------------------|----------------------|--|
| 1  | F          | SP, diagnostic mapping  | L-MC     | NR  | NR       | Map (1)        | Stroke patient and no hx of seizures   | Developed symptomatic poststroke epilepsy   | Secondarily GEN                   | Stroke, left MCA     | Epileptiform signs seen on EEG during screening                                      |
| 2  | NR         | 10 Hz, 80% MT 2-second stimulation, 58 second-rest-8 session  | R-MC     | NR  | NR       | I              | Stroke patient and no hx of seizures   |   | Secondarily GEN                   | Stroke, right MCA    | Epileptiform signs seen on EEG during screening                                      |
| 3  | 16 yo F    | 10 Hz, 60 trains of 5 seconds, intertrain intervals of 25 seconds and 3,000 stimuli/d; 5 days a week for 4 weeks  | L-DLPFC  | SRT (150 mg/d), OLZ (75 mg/d), and HDX (24 mg/d)                          | NR       | 12             | 0.20% alcohol concentration on the 12th session  | Neurological examination, blood work, and EKG fine  | Asymmetric twitching of both arms | MDD                  | Alcohol complication, outside range of OLZ dosage                                    |
| 4  | 44 yo male | 15 Hz, 110% of motor threshold, 35 pulses/train, 35 trains/session, intertrain interval 26 seconds, 1,225 pulses/d  | L-DLPFC  | PRX (37.5 mg), DVF (100 mg), and etizolam (2 mg/d)                        | NR       | 4              | Not any known  | Showed diffuse, mild cerebral atrophy on MRI  | GEN                               | MDD                  | Resumed rTMS at subthreshold power level (90% of MT) under sodium valproate coverage |
| 5  | 15 yo F    | 20 trains per session with the coil turned on for 4 seconds at a frequency of 10 Hz and MT intensity of 80% and then turned off for 26 seconds (ie, one train lasted 30 seconds in total) | L-PFC    | SRT (100 mg/d)  | NR       | I              | ECG, EEG, MRI, and blood tests all came back fine during screening                           | No abnormality in neurological examination; EEG did not indicate any focal lesions or epileptiform discharge, hypomania first night | GEN                               | Adolescent onset MDD | Sertraline use continued   |
| 6  | F          | 20 Hz at 120% MT. 42 trains each and a 20-second intertrain interval (total 1,680 pulses/session)   | L-PFC    | Li (900 mg/d) (blood level of 0.79 mEq/L before entering study)           | NR       | 12             | No risk factors  | No lasting effects determined by cognitive examination  | GEN                               | BD                   | Limited information on this case   |
| 7  | 58 yo M    | 10 trains, 10 Hz of rTMS with 2-second duration each train, at 90% of RMT   | R-MC     | CZX (10 mg at night) for a slight anxiety disorder; acetyl salicylic acid | NR       | I              | Chronic stroke patient, MCA; frequent alcohol use; current withdrawal; and no hx of seizures | Abnormal EEG 1 hour after   | Jacksonian                        | Stroke, MCA          | Frequent alcohol consumer, eliminated intake for 2 weeks before                      |
| 8  | 33 yo M    | 50 trains of cTBS at RMT  | L-MC     | None  | Yes      | NR             | No   | MRI, neurological examination and blood tests normal; no EEG done   | GEN                               | Healthy              | Recent large time zone change  |

|    |         |   |         |  |                                  |  |   |                                      |  |  |
|----|---------|---|---------|--|----------------------------------|--|---|--------------------------------------|--|--|
| 9  | 30 yo F | 100% MT; constant frequency (20 Hz), duration of each train (2 seconds), ~40 trains, with an intertrain interval of 1 minute              | R-PFC   | QTP (600 mg/d), DZP (20 mg/d), and GP (150 mg/d)                   | 9th                              | No hx of epilepsy and normal MRI                           | EEG normal  | Jacksonian, left arm                 | BD: type I   | Patient decided to go off diazepam for it was made her sleepy. Unknown to staff. Continued treatment when back on diazepam |
| 10 | 24 yo F | 25 trains per session, intensity of 100% MT, frequency of 10 Hz, 10 seconds turned on and 20 seconds turned off (total of 2,500 pulses/d) | L-MC    | NR   | 1st                              | No hx of seizures or other risk factors                    | Clinical and neurological examinations, blood work, EEG, and CT all normal            | GEN                                  | Complex pain regional syndrome   |  |
| 11 | 35 yo M | Single pulse, 58% delivered the stimulus at the same spot twice 60 seconds apart  | R-MC    | Li (900 mg/d) and CPZ (50 mg/d)                                    | 1st                              | No hx or seizures or risk factors and no hx drugs/ alcohol | Found out after brother had one episode of convulsions; EEG showed mostly alpha waves | GEN                                  | BD-current hypomania   | Lack of sleep due to hypomania   |
| 12 | 45 yo M | 15 Hz, 100% MT, 10-second train, 30-second intertrain   | L-DLPFC | NR   | 6th                              | Healthy  | Free of health problem and EEG normal   | Grand mal                            | MDD  | Did not sleep over week-end  |
| 13 | 28 yo F | Single 2-second train of 20 Hz at 110% MT   | MC      | FLX (20 mg for anxiety 3 days prior)                               | 1st                              | Normal physical and neurological examinations              | Neurological examination, MRI, and EEG normal   | Secondarily GEN                      | Possible traumatic brain injury  | Fluoxetine was unknown to staff  |
| 14 | 36 yo F | Underwent 110% of MT with 20 Hz, 10-second duration and ten trains with an intertrain interval of 60 seconds                              | L-DLPFC | VFX (112.5 mg/d), TZD (500 mg/d), LOR (3 mg/d), and THR (100 µg/d) | First session of second protocol | Yes. EEG showed mild generalized slowing                   | EEG recorded bifrontopolar paroxysmal delta activities and abnormal SPECT scan        | Frontal lobe complex partial seizure | Mixed depressive ± anxious state; codiagnosed personality, hypo-thyroidism | Add-on antidepressant strategy. One maprotiline-induced generalized seizure in 1996  |
| 15 | 66 yo F |   | NR      | NR   |                                  |  |   | Secondarily GEN                      | Hydrocephalus and chronic inflammatory process in CNS                      |  |
| 16 | 26 yo F | 120% MT, 15 Hz, 2.5 seconds, intertrain 120 seconds   | MC      | None   | NR                               | NR   | No lasting effects  | Secondarily GEN                      | Healthy  |  |
| 17 | 27 yo F | 1%-5%, 15 Hz, three trains ×0.75 seconds, intertrain interval 250 ms  | L-PFC   | None   | I                                | Neurological examination fine                              | EEG, neurological, pulse, and cognitive tests normal                                  | GEN                                  | Healthy  |  |

(Continued)

Table S1 (Continued)

| ID | Patient | Type of TMS   | Location | Medication  | Sleep hx   | Session number | Other risk factors  | Outcome of seizure   | Type of seizure  | Diagnosis                                | Others  |
|----|---------|---|----------|-------------|------------|----------------|---|--|------------------|--|---|
| 18 | 39 yo F | 110%, 25 Hz, four trains x0.8 seconds, intertrain interval 1 second   | MC       | None        | NR         | I              | Neurological examination fine                                   | EEG, neurological, pulse, cognitive tests normal   | GEN              | Healthy                                  |   |
| 19 | 35 yo F | 10 seconds, frequency 25 Hz, intensity of 2.5x the MEP threshold  | L-MC     | None        | Slept well | Day 1          | Found out after had a first degree relative with hx of seizures | Neurological examination, EEG, and neuropsychological tests normal. Anxiety about having another seizure | GEN              | Healthy                                  |   |
| 20 | 62 yo M | Intensity (30%, 40%, and 50% maximum), 51 stimuli given 5–30 seconds apart with a stimulus intensity of 70% | MC       | NR          | NR         | Possibly Day 1 | No hx of seizures and EEG and CT normal                         | Postical paresis resolved in 4 days, two further seizures on days 7 and 15                               | Jacksonian       | Stroke                                   |   |
| 21 | 60 yo M | 24 cortical stimuli, <3 Hz  | MC       | None        | NR         | After 4 weeks  | NR  | NR   | Jacksonian       | Multiple sclerosis                       |   |
| 22 | 30 yo F | 50 cortical stimuli, <3 Hz  | MC       | None        | NR         | After 3 weeks  | NR  | EEG high voltage rhythmic and sharp activities suggest low epileptic threshold                           | Two GEN same day | Multiple sclerosis                       | Session before convulsions she had 50 stimuli. This was her fifth series of tests; on four earlier ones over the past 5 months, 40 stimuli had been given |
| 23 | 57 yo M | Single pulse. 40% maximum intensity of stimulator output (2 T pulsed for 100 ns) at intervals of 2 minutes  | MC       | NR          | NR         | First          | No hx of seizures; EEG and CT demonstrated the MCA infarction   | 2 seizures 4 weeks later, seizure free since taking phenytoin (100 mg three times per day)               | GEN              | Large ischemic scar after MCA infarction |   |
| 24 | M       | 130% intensity, 3 Hz, 7 seconds, "long" intertrain interval   | MC       | None        | NR         | NR             | NR  | No lasting effects   | Partial motor    | Healthy                                  |   |
| 25 | F       | 10-second trains, rTMS, frequency 10 Hz, intensity 0.9x MEP threshold, intertrain interval 1 minute         | PFC      | AMT and HLD | Several    |                |   | No lasting effects   | Secondarily GEN  | Psychotic depression                     | Investigators were unaware that she was on medications  |

**Abbreviations:** AMT, amitriptyline; BD, bipolar depression; CNS, central nervous system; CPZ, chlorpromazine; cTBS, continuous theta-burst stimulation; CZX, chlorzazepoxide; DLPCF, dorsolateral prefrontal cortex; DVF, desvenlafaxine; DZP, diazepam; F, female; FLX, fluoxetine; GEN, generalized; GP, gabapentin; HDX, hydroxyzine; HF, high frequency; HLD, haloperidol; hx, history; L, left; LF, low frequency; Li, lithium; LOR, lorazepam; M, male; MC, motor cortex; MCA, middle cerebral artery; MDD, major depressive disorder; NR, not reported; OLZ, olanzapine; PFC, prefrontal cortex; PRX, paroxetine; QTP, quetiapine; R, right; rTMS, repetitive transcranial magnetic stimulation; cTBS, continuous theta-burst stimulation; SP, single pulse; SRT, sertraline; THR, thyroxine; TZD, trazodone; VFX, venlafaxine; yo, year old; RMT, resting motor threshold; TMS, transcranial magnetic stimulation; MT, motor threshold; ECG, electrocardiogram; EEG, electroencephalogram; MRI, magnetic resonance imaging; EKG, electrocardiogram; SPECT, single-photon emission computer tomography; MEP, motor evoked potential; CT, computerized tomography.

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