Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation

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Abstract
This review focused on the treatment-emergent mania/hypomania (TEM) associated with repetitive transcranial magnetic stimulation (rTMS) treatment of depression. English-language literature published from 1966–2006 and indexed in Medline was searched. Ten of 53 randomized controlled trials on rTMS treatment of depression specifically addressed TEM. The pooled TEM rate is 0.84% for the active treatment group and 0.73% for the sham group. The difference is not statistically significant. Along with case reports, a total of 13 cases of TEM associated with rTMS treatment of depression have been published. Most of these patients were diagnosed with bipolar disorder and the majority of patients experiencing TEM took medication concurrent with rTMS. The parameters of rTMS used in these cases were scattered over the spectrum of major parameters explored in previous studies. Most train durations and intervals were within the published safety guidelines of the field. Reducing the frequency of sessions from two per day to one per day might be associated with a lower likelihood of TEM recurrence. The severity of manic symptoms varied significantly, but all cases responded to treatment that included a decrease or discontinuation of antidepressant and/or rTMS treatment and/or use of anti-manic medication. Current data suggests that rTMS treatment carries a slight risk of TEM that is not statistically higher than that associated with sham treatment. More systematic studies are needed to better understand TEM associated with rTMS. Special precautions and measures should be adopted to prevent, monitor, and manage TEM in research and practice.

Introduction
Almost all effective treatments for major depressive episodes (MDE) are complicated by low rates of treatment-emergent mania including hypomania (TEM) in the acute treatment of recurrent major depressive disorder (MDD) (Montgomery et al., 2000) and higher rates in bipolar depression (BD) (Calabrese et al., 1999). Whereas significant numbers of studies have demonstrated the acute efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) in recurrent MDD (Avery et al., 2006; Fitzgerald et al., 2006a; Hausmann et al., 2004b), the efficacy and safety of rTMS in the acute treatment of BD has not yet been established.

Further, in contrast to TEM in recurrent MDD, the phenomenon of TEM in BD has special relevance because of the prevalence of this adverse event; TEM has a higher overall rate of occurrence in BD, especially associated with the use of traditional antidepressants (Calabrese et al., 1999; Thase, 2005). Mood stabilizers that possess acute antidepressant properties, such as lithium and lamotrigine, do not appear to have this liability (Calabrese et al., 1999; Thase, 2005); instead, they exhibit the ability to stabilize mood from below baseline by delaying relapse and recurrence into depression (Calabrese et al., 2002b; Muzina and Calabrese, 2005).

Extensive literature exists on the phenomenon of TEM in acute BD treatment using traditional

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antidepressants (Calabrese et al., 1999; Post et al., 2003), traditional mood stabilizers (Bowden, 2003; Fawcett, 2003; Goodwin, 2003), and antipsychotic medications (Calabrese et al., 2005; Gao et al., 2005; Tohen et al., 2003). These data suggest that TEM is associated with tricyclic antidepressants in 7.7% of patients on mood stabilizers (Nemeroff et al., 2001) and in 11.2% patients of the studies collected in Peet’s review (Peet, 1994), with the adjunctive selective serotonin reuptake inhibitors in 3.0–6.4% of patients (Gijsman et al., 2004; Peet, 1994; Tohen et al., 2003), with the traditional mood stabilizers in 2.3–3.5% (Cohn et al., 1989; Nemeroff et al., 2001), and with the atypical antipsychotic agents in 2.2–5.7% (Calabrese et al., 2005; Tohen et al., 2003). This review evaluates the extent to which TEM is associated with the acute rTMS treatment of depression, including bipolar and unipolar depressive disorders.

Methods

Scientific articles published from 1966 to September 2006 and indexed in Medline were searched for the combinations of terms ‘rTMS’, ‘depression’, and ‘bipolar depression’. Bibliographies of articles were also scrutinized for primary source articles reporting on TEM associated with rTMS.

Priority was assigned to randomized, blinded, controlled clinical trials (RCTs) that addressed safety and tolerability of rTMS in the treatment of depression and specifically discussed the occurrence of TEM. In addition to the trials that addressed TEM directly, we also examined descriptive data from case reports of TEM associated with rTMS to better understand this phenomenon.

Results

Among a total of 53 RCTs of rTMS treatment for depression found in the literature search, ten trials specifically reported on the phenomenon of TEM. Seven of these ten trials included mixed samples in which the majority of the participants had MDD. Two other trials studied only unipolar participants and one trial studied only bipolar participants (see Table 1). Dolberg and colleagues’ (2002) trial was excluded because they did not specifically address TEM in their brief report. It is unclear whether their reported two cases of TEM (Dolberg et al., 2001) came from the sample of the published trial or a different study.

The TEM occurrence rate in a pooled sample of both unipolar and bipolar disorders was 0.84% for the active rTMS treatment group and 0.73% for the sham group (1.1% vs. 0% if case 9 is categorized into active rTMS). This difference is not statistically significant (Fisher’s two-tailed test). For the pooled total of 65 bipolar patients, the switching rate in the active rTMS treatment group was estimated to be 3.1%, close to the rate of traditional mood stabilizers. This estimation is subject to selection bias and limitations brought by the small sample size of each trial. The switching rate for unipolar was much lower, at 0.34%.

There were another ten cases of TEM associated with rTMS treatment of depression besides the three cases reported in the RCTs: a single case from an open trial (George et al., 1995) and nine cases from six case reports (Dolberg et al., 2001; Ella et al., 2002; Garcia-Toro, 1999; Hausmann et al., 2004a; Huang et al., 2004; Sakkas et al., 2003). Ten of these 13 case reports included detailed information about each case; these are listed in Table 2. The patients’ ages ranged from 31 yr to 79 yr, and no significant gender differences were observed.

Diagnosis and concurrent use of medication

Among the 13 cases of TEM associated with rTMS treatment of depression collected in this review, there were a total of nine TEM cases with BD, three cases with recurrent MDD, and two cases with unspecified depression (Dolberg et al., 2001; Ella et al., 2002; Garcia-Toro, 1999; Hausmann et al., 2004a; Huang et al., 2004; Sakkas et al., 2003). The majority of patients experiencing TEM were taking medication concurrent with rTMS treatment (see Table 2). The most frequently used medications were antidepressant monotherapy or antidepressants combined with other medication(s), such as mood stabilizers, anticonvulsants, anxiolytics, and/or antipsychotics. Two patients were receiving valproic acid (VPA) monotherapy. Concurrent use of VPA did not seem to prevent TEM from occurring.

The parameters of rTMS treatment

The rTMS modalities used in these reported cases varied widely over the spectrum of parameters that have been explored in previous rTMS clinical trials. Currently available data are insufficient to conclude a heightened risk of TEM with any explored parameter, although decreasing session frequency was successfully used in the management of TEM (George et al., 1995; Sakkas et al., 2003).

Laterality of rTMS stimulation

In the collected cases of TEM with detailed information, the most frequently used site for rTMS

...
<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>Randomization</th>
<th>Blind</th>
<th>Design</th>
<th>Group</th>
<th>n</th>
<th>Diagnoses</th>
<th>Switching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szuba et al.</td>
<td>2001</td>
<td>Randomized</td>
<td>Double</td>
<td>Parallel</td>
<td>10 Hz rTMS</td>
<td>9</td>
<td>5 MDD/4 BD</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90° sham</td>
<td>5</td>
<td>4 MDD/1 BD</td>
<td>0</td>
</tr>
<tr>
<td>Janicak et al.</td>
<td>2002</td>
<td>Randomized</td>
<td>Double</td>
<td>Parallel</td>
<td>10 Hz rTMS</td>
<td>15</td>
<td>10 MDD/4 BD</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECT</td>
<td>11</td>
<td>7 MDD/4 BD</td>
<td>0</td>
</tr>
<tr>
<td>Fitzgerald et al.</td>
<td>2003</td>
<td>Randomized</td>
<td>Double</td>
<td>Parallel</td>
<td>10 Hz L-DLPFC rTMS</td>
<td>20</td>
<td>19 MDD/1 BD</td>
<td>1 BD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 Hz R-DLPFC rTMS</td>
<td>20</td>
<td>19 MDD/1 BD</td>
<td>1 BD</td>
</tr>
<tr>
<td>Fitzgerald et al.</td>
<td>2003</td>
<td>Randomized</td>
<td>Double</td>
<td>Parallel</td>
<td>45° sham</td>
<td>20</td>
<td>16 MDD/4 BD</td>
<td>0</td>
</tr>
<tr>
<td>Nahas et al.</td>
<td>2003</td>
<td>Randomized</td>
<td>Double</td>
<td>Parallel</td>
<td>5 Hz rTMS</td>
<td>11</td>
<td>BD</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45° sham</td>
<td>12</td>
<td>BD</td>
<td>0</td>
</tr>
<tr>
<td>Su et al.</td>
<td>2005</td>
<td>Randomized</td>
<td>Double</td>
<td>Parallel</td>
<td>5 Hz rTMS</td>
<td>10</td>
<td>8 MDD/1 BD-I/1 BD-II</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 Hz rTMS</td>
<td>10</td>
<td>9 MDD/1/BD-II</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90° sham</td>
<td>10</td>
<td>8 MDD/1 BD-I/1 BD-II</td>
<td>1 BD*</td>
</tr>
<tr>
<td>Rossini et al.</td>
<td>2005a</td>
<td>Randomized</td>
<td>Double</td>
<td>Parallel</td>
<td>100% MT</td>
<td>18</td>
<td>12 MDD/6 BD</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80% MT</td>
<td>18</td>
<td>13 MDD/6 BD</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90° sham</td>
<td>16</td>
<td>12 MDD/5 BD</td>
<td>0</td>
</tr>
<tr>
<td>Rossini et al.</td>
<td>2005b</td>
<td>Randomized</td>
<td>Double</td>
<td>Parallel</td>
<td>Escitalopram + 15 Hz rTMS</td>
<td>17</td>
<td>MDD</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Escitalopram + sham rTMS</td>
<td>17</td>
<td>MDD</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sertraline + 15 Hz rTMS</td>
<td>16</td>
<td>MDD</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sertraline + sham rTMS</td>
<td>16</td>
<td>MDD</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Venlafaxine + 15 Hz rTMS</td>
<td>17</td>
<td>MDD</td>
<td>0</td>
</tr>
<tr>
<td>Fitzgerald et al.</td>
<td>2006</td>
<td>Randomized</td>
<td>Double</td>
<td>Parallel</td>
<td>1 Hz then + 10 Hz</td>
<td>25</td>
<td>21 MDD/4 BD-I</td>
<td>0</td>
</tr>
<tr>
<td>Rosa et al.</td>
<td>2006</td>
<td>Randomized</td>
<td>Rater</td>
<td>Parallel</td>
<td>rTMS</td>
<td>25</td>
<td>21 MDD/4 BD-I</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECT</td>
<td>16</td>
<td>MDD</td>
<td>1 MDD</td>
</tr>
<tr>
<td>Fitzgerald et al.</td>
<td>2006</td>
<td>Randomized</td>
<td>Double</td>
<td>Parallel &amp;</td>
<td>1 Hz rPFC rTMS</td>
<td>67</td>
<td>105 MDD/14 BD-I/11 BD-II</td>
<td>1 BD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>crossover</td>
<td>2 Hz rPFC rTMS</td>
<td>63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total n = 520
Switching rate = 0.84% for active rTMS treatment group, 0.73% for sham group.

rTMS, Repetitive transcranial magnetic stimulation; L- & R-DLPFC, Left and right dorsal lateral prefrontal cortex; MT, motor threshold; ECT, electroconvulsive therapy; MDD, major depressive disorder; BD, bipolar depression; MDE, major depressive episode.

aSame case as no. 9 in Table 2.
Table 2. Cases of treatment-emergent mania/hypomania (TEM) associated with repetitive transcranial magnetic stimulation (rTMS)

<table>
<thead>
<tr>
<th>Case</th>
<th>Author, year</th>
<th>rTMS site</th>
<th>RTMS frequency</th>
<th>Pulses session</th>
<th>Patient age, sex</th>
<th>Diagnosis</th>
<th>Medication use</th>
<th>Switching time</th>
<th>Treatment and response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>George et al., 1995</td>
<td>LDLPFC</td>
<td>20 Hz</td>
<td>400</td>
<td>NR</td>
<td>MDD</td>
<td>NR</td>
<td>After 9 daily rTMS sessions, patient developed hypomanic symptoms</td>
<td>Reduced the session frequency into a session every other day and hypomania resolved</td>
</tr>
<tr>
<td>2</td>
<td>Garcia-Toro, 1999</td>
<td>LDLPFC</td>
<td>20 Hz</td>
<td>1200</td>
<td>44, M</td>
<td>BD</td>
<td>Zuclopenthixol, carbamazepine, clonazepam, biperiden</td>
<td>During the 1st session with acute mood elevation and fluctuations. Similar acute effect in the following 2 d</td>
<td>Withhold of rTMS for 2 wk, then treated the patient with the same protocol &amp; derived a significant clinical benefit without a manic episode</td>
</tr>
<tr>
<td>3</td>
<td>Dolberg et al., 2001</td>
<td>LDLPFC</td>
<td>10 Hz</td>
<td>1200</td>
<td>46, F</td>
<td>BD × 15 yr</td>
<td>VPA 800 mg/d (blood level: 75); (haloperidol 5 mg/d DC)</td>
<td>End of 3rd wk and worsened in the 4th wk</td>
<td>Restarted haloperidol and the manic episode abated within one month</td>
</tr>
<tr>
<td>4</td>
<td>Dolberg et al., 2001</td>
<td>10 Hz</td>
<td>1200</td>
<td>54, M</td>
<td>BD II × 22 yr</td>
<td>BD</td>
<td>5 d after rTMS course</td>
<td>VPA 800 mg/d, episode lasted about 2 months</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ella et al., 2002</td>
<td>RDLPC</td>
<td>1 Hz</td>
<td>1200</td>
<td>79, F</td>
<td>Recurrent MDD</td>
<td>Tranylcypromine, haloperidol &amp; lorazepam</td>
<td>3 d after rTMS course (10 sessions in 2 wk)</td>
<td>Severe mania (YMRS = 32) for 2 d then switched to depression, recovered on VPA + sertraline</td>
</tr>
<tr>
<td>6</td>
<td>Ella et al., 2002</td>
<td>1200</td>
<td>46, M</td>
<td>BD I</td>
<td>Sertraline &amp; quetiapine</td>
<td>7 d after the rTMS course (15 sessions in 3 wk), YMRS = 23</td>
<td>Lamotrigine &amp; quetiapine plus tapering off sertraline, recovered with risperidone + VPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Sakkas et al., 2003</td>
<td>LDLPFC</td>
<td>20 Hz</td>
<td>1600 × 2 sessions/d</td>
<td>55, M</td>
<td>Drug-resistant depression × 3 yr</td>
<td>Citalopram 80 mg/d</td>
<td>3 wk after combined rTMS with SSRI*</td>
<td>First tapering down citalopram 1 wk later rTMS. Then put on thioridazine 300 mg/d and zuclopenthixol 40 mg/d, 1 wk later improved and tapered to 50 mg thioridazine/d*</td>
</tr>
<tr>
<td></td>
<td>Authors, Year</td>
<td>DLPFC Location</td>
<td>Frequency</td>
<td>Intensity</td>
<td>Duration</td>
<td>Initial Treatment</td>
<td>Outcome</td>
<td></td>
<td></td>
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<tr>
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<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Sakkas et al., 2003</td>
<td>L &amp; R-DLPFC</td>
<td>20 Hz</td>
<td>1600</td>
<td>2 sessions/d</td>
<td>46, M</td>
<td>BD, 1yr episode resistant to SSRI &amp; TCA; HDRS14 = 30.</td>
<td>Fluoxetine 80 mg/d, self-DC then free of med. for 2 mo.</td>
<td>2 rTMS sessions/d, 3 d/wk for 1 mo.; then 5 d/wk for 2 wk. Then hypomanic so reduce to 3 d/wk and pt became euthymic with only slight depressive symptoms</td>
</tr>
<tr>
<td>9</td>
<td>Huang et al., 2004*</td>
<td>L-DLPFC</td>
<td>5 Hz</td>
<td>1600</td>
<td></td>
<td>43, F</td>
<td>BD I for 8 yr resistant to antidepressant &amp; mood stabilizer</td>
<td>VPA 500 mg + venlafaxine 150 mg + flunitrazepam 6 mg/d</td>
<td>Depression resolved in 3 d and developed full-blown manic episode</td>
</tr>
<tr>
<td>10</td>
<td>Hausmann et al., 2004a</td>
<td>L- &amp; R-DLPFC</td>
<td>L 20 Hz then R 1 Hz</td>
<td>2000 of 20 Hz + 1200 of 1 Hz</td>
<td>31, F</td>
<td>BD I, 17 yr</td>
<td>Citalopram 40 mg + lorazepam 10 mg the 1st day. Paroxetine tapered over 4 d.</td>
<td>HDRS from 23 down to 3 by day 7 and start to develop manic symptoms</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Cohen et al., 2004, 2005</td>
<td>R-DLPFC</td>
<td>10 Hz</td>
<td>NR</td>
<td>NR</td>
<td>PTSD with previous episodes of major depression</td>
<td>Paroxetine No antidepressant</td>
<td>After 3 sessions, severity between hypomania &amp; mania. Most manic symptoms without being psychotic or dangerous to self/others</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Cohen et al., 2004, 2005</td>
<td>R-DLPFC</td>
<td>1 Hz</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

L- & R-DLPFC: Left and right dorsal lateral prefrontal cortex; NR, Not reported; M, male; F, female; MDD, major depressive disorder; BD, bipolar depression; PTSD, post-traumatic stress disorder; VPA, valproic acid; DC, discontinue; YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale; d, day; wk, week; mo., month; yr, year.

* The rTMS was re-administered 4 months later upon relapse, 2 sessions/d intensive rTMS resulted in hypomania after 2 wk, when changed to once a day the patient returned to normothymic state. Then once per week maintenance for 1 month. Thereafter well on VPA only until 1 yr follow-up.

* The same case as in Su et al. (2005).
stimulation was the left dorsal lateral prefrontal cortex (DLPFC). However, TEM did occur with stimulation of the right DLPFC (Ella et al., 2002). There was also a case of TEM where first the left, then the right DLPFC was stimulated (Hausmann et al., 2004a). There is not enough data available to evaluate which side is more likely to trigger TEM.

**Frequency of rTMS stimuli**

The frequencies of rTMS used in these 13 cases of TEM ranged over the spectrum that has been explored in previous rTMS clinical trials for depression, including 20 Hz, 10 Hz, and 5 Hz on the left DLPFC (Dolberg et al., 2001; Garcia-Toro, 1999; Hausmann et al., 2004a; Huang et al., 2004; Sakkas et al., 2003) and 10 Hz and 1 Hz on the right DLPFC (Cohen et al., 2004; Ella et al., 2002). One rTMS protocol combined high-frequency (20 Hz) and low-frequency (1 Hz) stimulation on the left DLPFC in the same session (Hausmann et al., 2004a). No specific frequency appears to increase the occurrence of TEM.

**Intensity of rTMS stimuli**

The intensities of rTMS used in these cases ranged from 80% to 110% of motor threshold (MT) in single frequency protocol. The case that combined 20 Hz on the left DLPFC and 1 Hz on the right DLPFC (Cohen et al., 2004; Ella et al., 2002). One rTMS protocol combined high-frequency (20 Hz) and low-frequency (1 Hz) stimulation on the left DLPFC in the same session (Hausmann et al., 2004a). No specific frequency appears to increase the occurrence of TEM.

**The duration of stimulus train and the interval between trains of rTMS**

Although some cases used a longer train duration (Garcia-Toro, 1999; Sakkas et al., 2003; Hausmann et al., 2004a) and a few cases did not report the inter-train interval (Sakkas et al., 2003; Hausmann et al., 2004a), most of the cases were within the safety guidelines published in the field (Wassermann, 1998). Since the guidelines for the safe ranges of parameters were mainly based on the likelihood of undesired seizures, their usefulness is questionable for the prevention of TEM.

**Number of pulses per session**

The total number of pulses delivered per session has been an important dosing index in clinical trials. There were four patients treated with ≥1600 pulses per session and five patients treated with <1600 pulses per session, a dose considered to be the recommended average dose. It was noticed that some patients treated with 1200 pulses/d had a past history of switching, indicated by numerical switch events during previous treatment with antidepressants (Dolberg et al., 2001).

**Frequency of sessions**

Treatment sessions were typically scheduled once daily, although some patients received two rTMS sessions per day (George et al., 1995; Sakkas et al., 2003). It is worth noting that these patients who experienced TEM while receiving two sessions of rTMS per day did not experience switching on a one session/d schedule. At less frequency, rTMS produced the desired antidepressant effects without mania-like symptoms.

**TEM and management**

The observed mania/hypomania switches occurred from as early as the first session after starting rTMS treatment (Garcia-Toro, 1999) to as late as 1 wk post-rTMS treatment (Ella et al., 2002). The durations of mania-like symptoms lasted from 2 d (Garcia-Toro, 1999) to 1 month (Dolberg et al., 2001).

The reported methods of managing TEM included tapering or stopping concurrent antidepressants, reducing the frequency of rTMS sessions or discontinuing rTMS treatment, and/or adding anti-manic medications. In a case reported by Garcia-Toro (1999), the patient experienced ‘laughing and repeatedly expressed elation and sexual desires’ during the first three sessions of rTMS. After rTMS had been held for 2 wk, he did benefit from the rTMS treatment of the same protocol without experiencing the sudden mood elevation. Manic symptoms typically resolved with discontinuation of rTMS or antidepressant medications and/or with mood stabilizer treatment within a few days to a few weeks. In an extreme case, the mania episode lasted for 2 months and required the use of VPA treatment at a dose of 800 mg/d (Dolberg et al., 2001).

**Discussion**

Almost every category of antidepressant medication has been linked to a risk of switching patients with BD into the manic or hypomanic phases; thus, antidepressant monotherapy in BD remains controversial (Calabrese et al., 1999; Montgomery et al., 2000). The switch rate in the acute treatment has been reported in the range of 0–25% or even higher in various groups (Bottlender et al., 1998; Calabrese et al., 1999; Muzina and Calabrese, 2003). TEM may occur with non-pharmacological antidepressant treatment modalities, such as electroconvulsive therapy (ECT) (Devanand et al., 1988; Lewis and Nasrallah, 1986), vagus nerve
stimulation (VNS) (Rush et al., 2005; Sackeim et al., 2001), phototherapy (Labbate et al., 1994), and therapeutic sleep deprivation (Colombo et al., 1999). TEM has also been reported as a side-effect in studies of deep brain stimulation (DBS) for the treatment of obsessive–compulsive disorder (Greenberg et al., 2006).

The pooled TEM occurrence rate in this review yields a quite low rate of 0.84% in rTMS treatment of depression and 3.1% for BD only; not significantly different from the rate of sham treatment. This suggests that rTMS may not be associated with an increased risk of switching compared to other antidepressant treatments. It should be taken into account that rTMS treatment was given for 2 wk and followed for another 2 wk in most rTMS trials reviewed. The duration of treatment and observation is much shorter than the usual length of trials for pharmacological agents and gives less chance for TEM to occur.

**Potential factors related to occurrence of TEM**

The occurrence of TEM in placebo groups in controlled trials and almost every kind of treatment suggests that the phenomenon is related to the nature of the disease itself. Estimates of natural switch rates in BD range from 4.6% (Calabrese et al., 1999) to 6.7% (Tohen et al., 2003) in placebo groups. These numbers represent the natural occurrence of the switching phenomenon without the iatrogenic effects of medication. At least part of the switch risk is probably accounted for by the natural course of bipolar disorder, although antidepressant treatment may provoke it (Altshuler et al., 2006).

The pooled switching rate from the RCT data with BD is more than nine times the switching rate associated with unipolar depression. As there is a proportion of undiagnosed bipolar disorder in those diagnosed as unipolar (Hirschfeld et al., 2003; Perlis, 2005), it is possible that some of these unipolar patients might actually suffer from bipolar disorder instead of the diagnosed MDD. The special relevance of TEM in bipolar disorder needs to be further studied.

Factors potentially related to mood switching may include aggressive dosing of treatment as well as the natural course of the disorder. Interestingly, the two switching cases using 20 Hz rTMS reported by Sakkas and colleagues (2003) and another case reported by Hausmann and colleagues (2004a) were all quite aggressively dosed during the first trial that resulted in mood switching. When dosing was decreased in their later trials, switching did not occur again in the same patient. This also suggests that occurrence of TEM should not be an absolute contraindication for the later use of rTMS at a less aggressive dosage. Individualized dosing should be considered.

**Propylaxis strategies for preventing switch into mania**

Because of the risk of TEM, it is advisable to use mood stabilizers in the antidepressant treatment of BD (APA, 2002; Calabrese et al., 2004a; Suppes et al., 2005). Although the use of mood stabilizers may not always prevent mania/hypomania status from occurring (Bottlender et al., 1998; Calabrese et al., 1999, 2002a; Leverich et al., 2006), the role of mood stabilizers in the treatment of BD is supported by some double-blind, placebo-controlled trials (see Table 3).

The large-scale trials of antidepressant treatments for BD have shed more light on the dispute in the literature about the rates of mood polarity switching in patients during the treatment of BD and the role of mood stabilizers. Switch rates in pure placebo treatment without any mood stabilizers or antidepressants were in the range of 4.6% (Calabrese et al., 1999) to 6.7% (Tohen et al., 2003). When the placebo treatment group included some patients on lithium, the switch rate was 3.45% (Cohn et al., 1989); when all patients were on lithium or another mood stabilizer, the switch rate was 2.3% (Nemeroff et al., 2001). Increased proportion of patients on mood stabilizers is associated with a decreasing TEM rate although the differences between the designs of these trials make a direct comparison less reliable. Longer and more rigorous prospective studies might clarify how much the mood stabilizers can help prevent switching during acute treatment of BD.

The atypical antipsychotics and other newer medications used in the treatment of bipolar disorders have not been associated with increased switch rates as either monotherapy or in conjunction with an SSRI in large-scale trials for the acute treatment of BD (Amsterdam and Shults, 2005; Calabrese et al., 2005; Tohen et al., 2003). In a placebo-controlled study by Calabrese and colleagues on 133 patients, the switch rate of the lamotrigine-treatment group, 5.4%, was not significantly different from that of the placebo group, 4.6% (Calabrese et al., 1999).

**Proposed safety measure for experimental rTMS treatment of BD**

To maximize safety in patients receiving rTMS for the treatment of BD, it appears reasonable to keep subjects on a mood-stabilizing medication while receiving rTMS. However, since the interaction between rTMS treatment and most of the medications used to treat...
**Table 3. Medications and treatment-emergent mania/hypomania (TEM) in bipolar depression treatment**

<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Year</th>
<th>Study site</th>
<th>n</th>
<th>Response rate comparison</th>
<th>Concurrent medication</th>
<th>Wk</th>
<th>Switch rate with medication group</th>
<th>Switch rate with placebo group</th>
<th>Definition of TEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calabrese et al.</td>
<td>2005</td>
<td>USA</td>
<td>360 + 180</td>
<td>None (except limited zolpedem, lorazepam at first 3 wk)</td>
<td>Quetiapine</td>
<td>8</td>
<td>2.2% at 600 mg/d, n = 98; 3.9% at 300 mg/d, n = 121</td>
<td>3.9%, n = 107</td>
<td>YMRS ≥16 on any 2 consecutive visits</td>
</tr>
<tr>
<td>Tohen et al.</td>
<td>2003</td>
<td>Thirteen countries</td>
<td>833</td>
<td>None</td>
<td>Fluoxetine + olanzapine 48.8%, n = 82; olanzapine 32.8%, n = 351; placebo 87/355 (24.5% remission)</td>
<td>None</td>
<td>8</td>
<td>Fluoxetine + olanzapine 6.4%, n = 76; olanzapine 5.7%, n = 335</td>
<td>6.7%, n = 345</td>
</tr>
<tr>
<td>Nemeroff et al.</td>
<td>2001</td>
<td>USA</td>
<td>117</td>
<td>All on lithium (Li), some combined with valproic acid (VPA) or carbamazepine (C)</td>
<td>Fluoxetine + olanzapine (response = HDRS ≤8 or CGI ≤2)</td>
<td>10</td>
<td>Paroxetine + MS (4 Li + VPA, 1 Li + C): 0%; imipramine + MS (1 Li + VPA, 1 Li + C): 7.7%; n = 36 (2 cases with low Li level 10.5%, 1 with high Li level 5.9%)</td>
<td>2.3%, n = 43</td>
<td>‘TEM’ but not meet the DSM-III-R criteria for hypomania/mania at screening</td>
</tr>
<tr>
<td>Calabrese et al.</td>
<td>1999</td>
<td>USA, UK, France &amp; Australia</td>
<td>196</td>
<td>None</td>
<td>Lamotrigene (both 5 mg and 200 mg better than placebo), placebo</td>
<td>7</td>
<td>5.4%, n = 129</td>
<td>4.6%, n = 65</td>
<td>Manic, hypomanic or mixed episodes (Note: rapid cycling bipolar was excluded at enrolment)</td>
</tr>
<tr>
<td>Cohn et al.</td>
<td>1989</td>
<td>USA</td>
<td>89</td>
<td>25% on Li</td>
<td>Fluoxetine 86%, imipramine 57%, placebo 38%</td>
<td>6</td>
<td>Fluoxetine 0; imipramine 3.33%, n = 60</td>
<td>3.45%, n = 29</td>
<td></td>
</tr>
</tbody>
</table>

YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale; CGI, Clinical Global Impression illness severity scale; MS, mood stabilizer.
bipolar disorder has not been well studied, the specific medication that should be used to prevent switching in the acute treatment remains inconclusive.

In the large-scale studies on acute pharmacological treatment of BD, the use of mood stabilizers did not totally stop switching from occurring; this is also true for rTMS treatment of BD. It is necessary for future studies on rTMS treatment of BD to define the standard for switching events, to closely monitor emergence of manic symptoms, and to treat TEM. This brings an urgent need for the field to establish standard definitions of switching phenomena, including switching into hypomania and mania. Using a standard mania rating scale to define TEM would be an option. Standardizing the definition may also benefit the clinical management of bipolar disorder.

The symptoms of manic/hypomanic switches tend to be less severe, last for shorter periods, and respond better to antidepressant dose adjustments and anti-manic treatment than naturally occurring manic episodes (Tamada et al., 2004). Discontinuation of antidepressant treatment may be one, but not always the first or best option. Measures to treat switching should be tailored to the individual case, depending upon the severity of symptoms in switching and the treating physician’s judgement of the overall clinical picture. When deterioration is observed in a clinical trial, a research physician should evaluate the participant to determine if he/she needs an rTMS dose/schedule adjustment or an additional rescue medication. Anti-manic treatment may be needed if there is no response after discontinuing the ongoing antidepressant treatment.

Summary

Like other antidepressant treatments in BD, rTMS carries the risk of TEM. Although TEM was interpreted as an undesirable adverse event (Gijssman, 2005) it might also be indicative of the potential capacity for rTMS to elevate subjects’ mood. Overall, the rate of switching to mania during rTMS treatment of depression did not appear higher than that for sham rTMS treatments or pharmacological antidepressant treatments. Available data did not link TEM occurrence with a specific frequency, intensity, number, or laterality of rTMS stimulation. The positive response to the decrease of session frequency in some TEM cases suggested that the dosing of rTMS treatment may be more important than the frequency and intensity of stimuli or the laterality of rTMS stimulation. It is possible that the observed switch phenomena were determined, at least to some degree, by the natural course of bipolar disorder itself. Further studies are required to better elucidate which variables make mood switching more likely during rTMS treatment.

In future studies of rTMS in BD, screening high-risk patients and monitoring for TEM is warranted. Measures to prevent mania from occurring should also be considered, especially in patients who may already be at increased risk for manic switching, such as patients with rapid-cycling bipolar disorder and/or with a past history of mood switching related to other antidepressant treatments (Calabrese et al., 2004b; MacQueen et al., 2002).

Since further study of the relationship between dosing and switch rate is needed, it should be acceptable to allow flexible or individualized strategies of tapering antidepressant treatments, including rTMS, as the first step in the treatment/response to switch events with mild symptoms or in dealing with potential switching. However, anti-manic medication may be necessary to control the manic symptoms in severe cases in addition to the discontinuation of antidepressant and/or rTMS treatment.

Acknowledgements

Supported by funding from the Research Center for Bipolar Disorders at Case Western Reserve University (CWRU), Department of Psychiatry of CWRU, and Medical School of Case Western Reserve University. We thank our staff members including Eve Laidman, Sarah Bilali, Carla Conroy, and Tanya Smith and outside editors for their assistance in collecting data and proof reading/editing the manuscript.

Statement of Interest

Dr Joseph Calabrese (Research funding: Abbott, AstraZeneca, The Cleveland Foundation, Department of Defense, GlaxoSmithKline, Health Resources and Services Administration, Janssen, Lilly, NARSAD, National Institute of Mental Health, Pfizer, Stanley Medical Research Institute; Consulting agreements/Advisory boards/Honoraria for lectures: Abbott, AstraZeneca, Bristol–Myers Squibb/Otsuka, Lilly, GlaxoSmithKline, Janssen, Servier, and Solvay/Wyeth). Dr Prashant Gajwani (Research funding: Bristol–Myers Squibb, and Pfizer; Consulting agreements/Speaker: Abbott, AstraZeneca, Bristol–Myers Squibb/Otsuka, Lilly, GlaxoSmithKline, Janssen, Servier, and Solvay/Wyeth). Dr Keming Gao (Grant support and honoraria from AstraZeneca). Dr David Kemp (Research support: GSK; Educational grant: Bristol–Myers Squibb, Abbott). Dr David J. Muzina: (Research support:...
Abbott, CSK, Repligen; Speaker: Astra, Eli Lilly (not in the last 12 months), CSK, Pfizer, and Zeneca; Consultant: AstraZeneca. Dr Guohua Xia (Research funding: NARSAD).

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