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Benzodiazepine use and response to repetitive transcranial magnetic stimulation in Major Depressive Disorder

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To the editor,

Repetitive transcranial magnetic stimulation treatment (rTMS) is an established and increasingly widely used treatment for patients with Major Depressive Disorder (MDD) whose use is supported by multiple positive meta-analyses (for example [1,2]). Despite several decades of research into the use of rTMS, there remain a number of important clinical questions that still need to be answered to inform optimal clinical practice. One of these questions concerns the concurrent use of psychotropic medications and whether these may reduce or enhance the likelihood of clinical response to rTMS. Previous analyses have indicated that concurrent use of antidepressant medication, mood stabilizers or antipsychotics does not have a meaningful negative effect on the likelihood of antidepressant response to rTMS: for example, we have previously found that concurrent antidepressant or mood stabilizer therapy was associated with a higher rate of response [3].

Several recent studies have suggested that concurrent benzodiazepine use may be associated with poorer clinical outcomes. One of these studies reported on outcomes seen in 181 patients who had received a 6 week course of rTMS [4] and benzodiazepine use was associated with less overall improvement. The second report, analyzing patterns of response in patients from a large trial of 10Hz stimulation compared to intermittent theta burst (iTBS), found that low dose benzodiazepine use was associated with a lower likelihood of being in the 'rapid response' group and came close to being associated with overall non-response (odds ratio = 2.25, CI = 0.99 and 5.11) [5]. Due to these concerns, we conducted an analysis of pooled data from two recently published rTMS clinical trials (both exploring the efficacy of standard high-frequency left sided rTMS versus a form of accelerated rTMS or accelerated iTBS) to explore whether benzodiazepine use was related to clinical response to rTMS therapy.

For this analysis, we pooled data from two recently completed clinical trials (Trial 1 [10] and Trial 2 [11]) that were parallel superiority trials comparing an accelerated rTMS protocol (multiple treatments per day) with a standard once daily rTMS protocol. For Trial 1 the accelerated protocol used standard high frequency left sided rTMS, while for Trial 2 it was iTBS stimulation. Further details about Trial 1 and 2 can be found in their original publications. This provided data on 185 subjects (83 who received standard rTMS, 59 who received accelerated TMS and 33 who received accelerated iTBS). There were 99 female and 86 male patients with a mean age of 47.4 ± 13.4. The mean age of depression onset was 26.9 ± 13.3 years, the patients had an average of 4.0 ± 7.7 depressive episodes and they had received a total of 6.8 ± 8.6 previous medication trials. The mean baseline Montgomery Asberg Depression Rating Scale score (MADRS) was 31.8 ± 5.7.

In both clinical trials, data on the use of benzodiazepines was collected for the period of rTMS treatment. Benzodiazepine use (regular or as needed (PRN)) was recorded along with drug type but not dose. We analyzed the effect of any benzodiazepine use (yes or no) or the effect of regular use on change in MADRS scores from baseline to week 8 follow up (independent samples t-tests) as well as on response rates (chi-squared) for the total group and treatment subgroups. A total of 121 patients were taking no benzodiazepines, 37 patients were taking diazepam, 4 patients alprazolam, 8 patients clonazepam and 15 patients another benzodiazepine.

For the analysis of any benzodiazepine use, there was no difference in overall change of MADRS scores between patients taking benzodiazepines or not (taking: n = 64, mean MADRS change: 27.0 ± 29.6, not taking: n = 121, mean change: 27.0 ± 34.3, t = −0.2, p = 0.99). There was also no difference in response rate (BZD users: 25%, non-users: 24.8%, p = 0.98). There were also no differences in overall change of MADRS scores comparing patients who took benzodiazepine regularly or not at all (regular users, n = 17: 34.4 ± 26.9%, non-users, n = 121: 27.0 ± 34.3%, p = 0.40) or the response rates comparing these 2 groups (regular BZD users: 23.5%, non-users: 24.8%, p = 0.91). There was also no difference in the degree of MADRS change or response rates when analyzed separately by type of TMS treatment (standard rTMS, accelerated rTMS, accelerated iTBS). In addition to these analyses, we conducted a series of linear and binary regressions to see if there was any relationship between benzodiazepine use and clinical response but found no effect on any of these analyses.

In conclusion, we found no relationship between any form of benzodiazepine use and clinical outcomes of rTMS treatment in this analysis. This conclusion obviously differs from that of the two previous reports cited above that found an effect of benzodiazepine use in the context of either standard high-frequency left-sided TMS or left-sided iTBS therapy, the two treatment groups included in our analysis. There were some differences in the duration of treatment provided across the studies (for example Hunter

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et al. [4] provided six weeks of standard treatment whereas four weeks was provided by Kaster et al. [5] and in our current report) but these do not seem sufficient to explain the difference in the current result. One of the major limitations of our report, the binary coding of benzodiazepine use as a yes or no variable rather than analysis of a dose effect, was also the approach used in the other two studies and again is not likely to explain the difference in the results. Clearly whether or not patients should be weaned off benzodiazepine use prior to rTMS treatment is an important clinical question that requires further exploration in larger prospectively assessed samples of patients undergoing rTMS therapy with greater detail included in the analysis of the form of benzodiazepine use.

It is also important to note that the studies reporting a relationship between benzodiazepine use and poorer response do not provide any direct evidence that benzodiazepine use lessens the likelihood of response as these relationships are purely correlative. It is possible that patients taking benzodiazepines are different in some illness characteristics (for example anxiety as an obvious one) that are associated with poorer response which are not accounted for in these analysis. Papers in the literature are already falling into the trap of assuming this correlation implies causation and it is important that this assumption doesn't get embedded in TMS folk law until it is properly tested in studies able to overcome these limitations.

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