The Efficacy of rTMS in the Treatment of MDD with Concomitant Benzodiazepine Use

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Introduction / Background

Repetitive Transcranial Magnetic Stimulation (rTMS) has been shown to be effective for Treatment Resistant (TR) Major Depressive Disorder (MDD).[1,2] Previous studies have shown concomitant medication use may negatively impact treatment outcomes, and there is limited data on rTMS efficacy in patients with TR-MDD concurrently taking benzodiazepines.[3,4,5]

The aim of this study was to determine the efficacy and safety profile of rTMS in patients with TR MDD who are concomitantly taking benzodiazepines.

Methods

This study included 195 patients with TR-MDD who had rTMS (59 patients were concurrently taking benzodiazepines and 136 patients were not taking benzodiazepines over the course of their rTMS treatment).

Patients were referred for rTMS by private psychiatrists associated with The Adelaide Clinic Services in an outpatient setting. A diagnosis of a Major Depressive Episode was made using DSM-IV-TR criteria; by a TMS psychiatrist and the Mini International Neuropsychiatric Interview was used to assess for comorbidities (e.g. Generalised anxiety disorder, OCD, etc.). Participants completed the HAM-D17, HAM-A, MADRS and ZUNG at baseline and at the end of treatment, and treatment outcomes were compared between patients concurrently taking and not concurrently taking benzodiazepines.

STAR*D criteria for Response and Remission[6] were used:
- Partial response: ≥25% improvement on HAM-D
- Response: ≥50% improvement on HAM-D
- Remission: Score of ≤7 on HAM-D

Figure 1. Rating scales (HAM-D17, HAM-A, MADRS & ZUNG):

HAM-D – 17 Item (Depression)	
Normal	0 – 7
Mild	8 – 13
Moderate	14 – 18
Severe	19 – 22
Very Severe	23+

HAM-A (Anxiety)	
Normal	<14
Mild	14 – 17
Moderate	18 – 24
Severe	25 – 30

MADRS (Depression)	
Normal	<7
Mild	7 – 19
Moderate	20 – 34
Severe	35+

ZUNG (Depression)	
Normal	20 – 44
Mild	45 – 59
Moderate	60 – 69
Severe	70+

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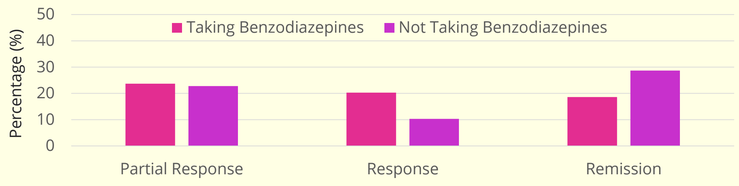
Results

Figure 2. Demographic characteristics among people not taking benzodiazepines and people taking benzodiazepines during rTMS treatment

	Not taking Benzodiazepines (n = 136)	Taking Benzodiazepines (n = 59)	Test, p value
Age (years) M(SD)	48.16 (14.51)	52.19 (12.27)	t (193) = -1.86, p = 0.064
Gender			
Male	62 (45.6%)	16 (27.1%)	$\chi^2(1) = 5.10$, p = 0.024
Female	74 (54.4%)	43 (72.9%)	
Total number of years depressed M (SD)*	19.09 (14.12%)	22.45 (11.30%)	t (190) = -1.60, p = 0.112
Duration of current depressive episode (months) M(SD)*	25.23 (46.22%)	13.71 (12.95%)	t (39) = 1.82, p = 0.072
Episodic Depression			$\chi^2(2) = 5.39$ p = 0.067
Yes	70 (51.5%)	32/58 (55.2%)	
No (continuous)	66 (48.5%)	24/58 (41.4%)	
Antidepressant Trials (five or more)	99/131 (75.6%)	46/56 (82.1%)	
Previous ECT	59/135 (43.7%)	34/58 (58.6%)	$\chi^2(1) = 3.04$, p = 0.081
Unipolar Depression	109 (80.1%)	44 (74.6%)	$\chi^2(1) = 0.46$, p = 0.497
Generalised Anxiety Disorder	45 (33.1%)	29 (49.2%)	$\chi^2(1) = 3.85$, p = 0.050
Obsessive Compulsive Disorder	20 (17.7%)	3 (5.1%)	$\chi^2(1) = 2.80$, p = 0.095
Post-Traumatic Stress Disorder	15 (11.0%)	4 (6.8%)	$\chi^2(1) = 0.43$, p = 0.512
Panic Disorder (with Agoraphobia)	13 (9.6%)	12 (20.3%)	$\chi^2(1) = 3.37$, p = 0.066

Figure 3. Response and remission rates in patients receiving rTMS with and without concurrent benzodiazepine use

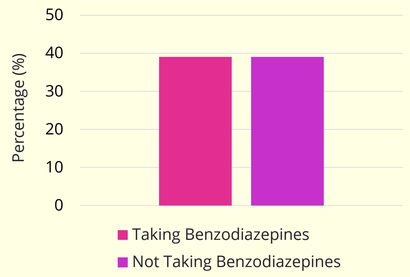


No significance difference shown between groups for response or remission: $\chi^2(3)=1.34$, $p=0.720$

Figure 2 reports descriptive statistics for people of the study population. 72.9% of female patients were treated with benzodiazepines prior to commencing rTMS treatment, which was significantly greater than the 27.1% proportion of male patients who were taking benzodiazepines at the time of rTMS treatment ($\chi2(2) = 5.10$ p = 0.024). Approx. half of the patients (49.2%) who had GAD were also being treated with benzodiazepines, and this was significantly greater than for people who did not have GAD (33.1%) ($\chi2(1) = 3.85$, p = 0.050.

Figure 3 illustrates findings from the Chi-squared test which showed **no significant difference** in partial response ($\chi2(1) = 0.00$, p = 1.000), response (including remission) ($\chi2(1) = 0.00$, p = 1.000) and remission only ($\chi2(1) = 1.68$, p = 0.195) between the two treatment groups. Figure 4 further depicts this similarity by showing that the proportion of responders (including remitters) in both groups were found to be the same (39%).

Figure 4. The proportion of responders (including remitters) in each of the treatment groups



Conclusions

This study found that **being treated with benzodiazepines does not make any difference to the outcome of rTMS**. rTMS has efficacy in patients both with or without concurrent benzodiazepine use – an important finding for evaluating rTMS effectiveness and safety.

Our findings suggest that concomitant benzodiazepine treatment should not be a contraindication to a trial of rTMS, and that these patients are likely to have similar outcomes as those not taking benzodiazepines. Withdrawal from benzodiazepines, which can be a slow and difficult process, is not supported as necessary prior to a trial of rTMS.

Further studies with larger datasets are needed. In the future it may be helpful to explore the impact of other factors associated with the prescription of benzodiazepines. Further work would benefit by investigating the efficacy of rTMS in patients with TR-MDD using other pharmacological medications such as mood stabilisers and antipsychotics.

Limitations with this study included that the indication for, as well as the type, frequency and dosage of benzodiazepine, were not defined. Due to this study being conducted in a private hospital outpatient clinic, results may also be impacted by selection bias involving possible differences in the clinical characteristics of private patients.

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