World Journal of Medical Research

Original Article Open Access

Transcranial Magnetic Stimulation and psychological therapies: Considering the benefits of a combined treatment approach for depression.

[1, 2]Shane Gill, [1, 2]Patrick Clarke, [2]Ashlee Rigby, [2]Benjamin Carnell,[1, 2, 3]Cherrie Galletly

[1] Discipline of Psychiatry, School of Medicine, the University of Adelaide, Adelaide, Australia
[2] Ramsay Mental Health Services (SA), Ramsay Health Care, Adelaide, Australia
[3] Northern Adelaide Local Health Network, SA, Australia

Abstract

Background: Repetitive TMS (rTMS) has been found to be an effective treatment for major depression. A number of psychological therapies have also been shown to be effective. We hypothesized that the efficacy of rTMS could be increased by combining this treatment with psychological therapies in an Enhanced rTMS program.

Study design: Within a clinical rTMS service, we designed a pilot study to evaluate the effects of combining rTMS and psychological therapies, having already delivered rTMS alone for previous patients.

Materials and methods: In an Enhanced rTMS program, patients attended a half day program, which included both psychological therapies and a session of rTMS, three days a week, for six weeks. The program included mindfulness based cognitive therapy, problem-solving therapy, computerized Cognitive Behavioral Therapy, exercise, and relaxation. The outcomes of the combined program were compared with patients who previously received only rTMS.

Results A total of 18 people commenced the Enhanced rTMS program, with 14 completing the program. Patients who completed the full program showed a similar improvement in depressive symptoms to those treated with rTMS alone (59 patients), suggesting that there may be limited advantage in adding psychological therapies.

Conclusions: The addition of psychological therapies to rTMS did significantly not improve the rate of beneficial outcomes in comparison to rTMS alone; however the sample size was relatively small. There was low adherence to the full program in some patients, with some preferring to attend only certain program components.

Key Words **:** neurostimulation, CBT, exercise, mood disorders, problem solving therapy

Address for correspondence and reprint requests to:
Shane Gill, Eastwood House, 29 Hauteville Terrace, Eastwood SA 5063, Australia
email: sgill@chariot.net.au

(NPPL) Submitted Friday, September 26, 2014Accepted Sunday, November 30, 2014Published Monday, December 08, 2014

Introduction

Major depression is a leading cause of functional impairment and disability [1]. A significant proportion of people with depression are treatment resistant, responding poorly to various antidepressant

medications [2, 3]. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial showed that after trialing two antidepressants without response, cognitive behavioral therapy (CBT) is as effective as a medication switch or augmentation strategies [3]. The two forms of treatment can be combined, and there is evidence that CBT combined with antidepressant therapy is associated with a higher improvement rate than drug treatment alone [4]. Similarly, Brakemeier *et al*., [5] compared CBT in addition to antidepressant medication, maintenance electroconvulsive therapy (ECT) plus antidepressant medication, and antidepressant medication alone, in patients who had responded to ECT. At a 6 month follow-up, CBT and medication was more effective in maintaining remission than either of the other treatments. However, it is possible that patients with more severe depression are less likely to respond to cognitive therapies and are more likely to drop out [6], so combined therapies may not be suitable for all patients.

Repetitive transcranial magnetic stimulation (rTMS) is an effective alternative for individuals with treatment resistant depression [7, 8]. The efficacy of rTMS has been demonstrated in both randomized controlled trials [8] and clinical settings [9], with an average of 30-40% of patients remitting. In rTMS trials, the majority of patients usually also receive antidepressant medication. However, there have not been any previous studies evaluating the combination of rTMS and psychological therapies, and it is possible that there may be a further additive effect with better results for patients who receive combined treatment.

Anovel pilot program was developed which consisted of three evidence-based therapies: mindfulness based cognitive therapy [10, 11], problem-solving therapy [12] and an internet-based CBT program. In addition to these therapies, the program included sessions of exercise and relaxation. The program was conducted three times a week on the same days as patients had rTMS. The program ran for six weeks, resulting in patients attending a total of 18 sessions for each. We had previously collected efficacy data for rTMS alone, using the same protocol, on a different group of patients [9]. We hypothesized that combining evidence-based psychological therapies with rTMS, and Enhanced rTMS program, would result in greater improvement in depressive symptoms than rTMS alone, and provide another alternative for treatment resistant depression.

Patients and Methods

Participants

While this study was running, patients referred by their private psychiatrist for the rTMS service could only be accepted for treatment if they participated in the enhanced program. Thirty one eligible patients were offered the Enhanced TMS program; thirteen did not want to participate but advised that they would have attended for rTMS alone. Eighteen patients were accepted into the Enhanced rTMS program. Prior to the commencement of the Enhanced rTMS program, rTMS was offered as part of the clinical service whereby bilateral rTMS was offered in isolation, thus providing a suitable comparison group. There were 65 patients previously treated with rTMS alone following the same protocol.

All patients met the DSM-IV criteria for major depressive disorder (three patients across the two programs had bipolar affective disorder). In the Enhanced rTMS program, all patients were taking psychiatric medications, none of which were changed during their course. In the rTMS Alone program, 53 (89.8%) patients were taking psychiatric medication, 10 of whom changed their medication during their treatment course. Written informed consent was obtained from all patients. The study

was approved by the Ramsay Health Care (SA) Mental Health Services Research and Ethics Committee.

Study Design

There were two programs operating subsequently in this service: rTMS Alone and Enhanced rTMS. In both, patients attended their respective programs three days a week for six weeks; 18 treatments in total. In the Enhanced rTMS program, patients rotated through the different therapy sessions each day they attended, including; mindfulness based cognitive therapy, problem-solving therapy, computerized Cognitive Behavioral Therapy, exercise, relaxation, and rTMS. Each therapy session lasted approximately 45 minutes. Details of the two programs, and the therapy sessions they included, are provided in what follows.

Enhanced rTMS program

Mindfulness-based cognitive therapy

Mindfulness-based cognitive therapy (MBCT) is a group-based clinical intervention which has been shown to be efficacious in reducing relapse of major depressive disorder [13] particularly in treatment resistant depression, with a risk for relapse reduction of 34% [14]. A trained mental health nurse facilitated the groups. The mindfulness-based cognitive therapy followed the manualized 8-week skills training program by Segal, Williams and Teasdale [10], but the program was condensed such that all sessions were delivered in six weeks.

Problem solving therapy

Problem-Solving Therapy (PST) is a cognitive-behavioral intervention that focuses on training in adaptive problem-solving attitudes and skills. A recent meta-analysis found PST to be as effective as other psychosocial therapies and medication treatments and significantly more effective than no treatment and support/attention control groups (d=.40) [15]. The PST sessions were based on "Problem-Solving Therapy: A Positive Approach to Clinical Intervention" [16].

Internet-based CBT

MoodGYM is an internet-based CBT intervention designed to treat and prevent depression and anxiety, which has been shown to be effective in reducing symptoms of depression and anxiety [17].Patients were given access to a computer and provided with a unique login code for their internet CBT sessions.

Physical Activity

Exercise has been shown to improve depressive symptoms, particularly for people with treatment resistant depression [18], and has additional beneficial effects across several physical and mental health outcomes [19].During 45 minute physical activity sessions, patients either went for a low-intensity walk, or took part in an unstructured but guided gym session involving strengthening exercises and cardio equipment (e.g. exercise bike, cross trainer, rowing machine).

Relaxation

The Cochrane review on relaxation for depression found that relaxation techniques were more effective at reducing self-rated depressive symptoms than no or minimal treatment [20]. During each 45 minute session, patients were asked listen to a CD player with non-verbal 'soothing' sounds whilst sitting in a reclining chair in a secluded room

Bilateral rTMS

Repetitive TMS was administered using a MagPro R30 stimulator and MCF B65 figure-of-eight coil (MagVenture A/S, Denmark). The location of stimulation was identified through finding the point at which maximum stimulation of the

abductor pollicis brevis muscle was reached, and measuring six centimeters anterior to this point. Standard visual methods, as outlined in Pridmore *et al*., [21] were used to measure this resting motor threshold. Patients sat in a reclining chair, and were offered disposable earplugs during treatment sessions. All patients were treated at 110% of the resting motor threshold with high frequency rTMS (10Hz) to the left dorsolateral prefrontal cortex (DLPFC) in 5-s trains with a 25-s intertrain interval (1500 pulses), followed by low-frequency rTMS for 15 minutes applied to the right DLPFC(900 pulses). Treatment duration was 15 minutes on each side; 30 minutes in total. The coil was held in place during treatments using a flexible stand attached to a machine trolley.

rTMS Alone program

Prior to the Enhanced rTMS program, rTMS was delivered within our service to patients without added psychological interventions. Within this initial program, rTMS treatments were delivered utilizing the same bilateral protocol, as outlined previously. This data therefore provides a valuable comparison. Further information describing the method can be found in our previous paper [9].

Measures

Patients in both the Enhanced rTMS and initial rTMS Alone program were assessed at baseline and after the 6 week program by a trained mental health research officer. The primary outcome measure was the17-item Hamilton Depression Rating Scale (HAMD) [22]. Patients were also assessed using the 14-item Hamilton Anxiety Rating Scale (HAMA) [23] and the Zung Self-Rating Depression Scale (Zung) [24]. Based on the STAR*D trial, [25] a clinical response was defined as an decrease of 50% in the HAMD score and remission was defined as a score of less than 7 on the HAMD.

Results

Patients for both the Enhanced rTMS and rTMS Alone programs are described in Table 1. There were two patients that dropped out from the Enhanced rTMS program. A further two patients did not complete a sufficient number of the required sessions for their results to be included in the analysis (22.2% non-completion rate). In the rTMS alone program, four patients dropped out, and

Descriptive statistics, mental illness history, and previous treatments for both the Enhanced rTMS and rTMS alone treatment programs

Variable		Enhanced rTMS	rTMS Alone
		M (SD) or N (%)	M (SD) or N (%)
Number of Patients		14	59
Age (years)		53.64 (15.32)	51.46 (13.47)
Total Number of Years Depressed		21.2 (16.47)#	22.71 (14.40) #
Gender	Male	5 (35.7%)	21 (35.6%)
	Female	9 (64.3%)	38 (64.4%)
Episodic Depression	Yes	5 (41.7%)#	37 (62.7%)
	No (continuous)	7 (58.3%)#	22 (37.3%)
Antidepressant Trials	Less than Five	6 (46.2%)#	14 (24.6%)#
	More than Five	7 (53.8%)#	43 (75.4%)#
Previous ECT		7 (53.8%)#	31 (52.5%)
Previous rTMS		5 (35.7%)	10 (16.9%)
Previous Psychotherapy*		5 (35.7%)#	Data not available
Individual Psychologist		4 (28.6%)#	Data not available

*Dialectical Behavioral Therapy or Cognitive Behavior Therapy.
#Data not available for all patients.

Mean (SD) pre and post-treatment scores, mean difference, and significance of independent *t*-tests for patients treated with Enhanced rTMS and rTMS alone.

Rating Scale	Program	N	Mean (SD)		Mean Difference (SD)	*t*	*p*
			Pre	Post			
HAM-D	Enhanced rTMS	14	19.71 (4.21)	12.36 (9.94)	-7.36 (7.93)	3.47	.004*
	rTMS Alone	59	20.42 (5.70)	11.29 (7.00)	-9.14 (7.66)	9.16	>.001*
HAM-A	Enhanced rTMS	14	19.29 (6.38)	13.64 (11.63)	-5.64 (8.68)	2.43	.03
	rTMS Alone	59	21.15 (7.58)	12.93 (7.82)	-8.22 (7.07)	8.94	>.001*
Zung	Enhanced rTMS	14	55.54 (9.68)	49.61 (15.58)	-5.93 (14.35)	1.55	.146
	rTMS Alone	59	56.75 (7.11)	45.61 (10.64)	-11.14 (11.03)	7.75	>.001*
*statistically significant $p<0.05$							

follow-up data was not obtained for two patients (6.2% non-completion rate).

For those in the Enhanced rTMS program, as indicated in Table 2, paired samples *t*-tests revealed that there was a statistically significant decrease in symptom severity as rated by the HAM-D and HAM-A, but not the Zung self-rated depression scale. As is also indicated in Table 2, paired samples *t*-tests highlighted that there was a significant decrease in symptom severity across these three measures for patients that received only rTMS.

Comparison of Enhanced rTMS and rTMS Alone: Results from the Enhanced rTMS program were compared to the data from previous patients who had received only rTMS. Independent *t*-tests were used to analyse any difference between the two programs regarding the extent of change in scores across the three measures. These tests revealed there were no significant differences between Enhanced rTMS and rTMS Alone on the HAMD ($t(71)=-.78$, $p = 0.44$), and the HAMA ($t(71)=-1.17$, $p = 0.25$). A Mann-Whitney test indicated that there were no significant differences regarding change in Zung scores between the two programs ($U = 321.50$, $p = 0.20$).

At the end of the Enhanced rTMS program eight (57.1%) patients met the criteria for response, six (42.9%) of whom were in remission. In the rTMS Alone program, 26 (44.1%) patients met the criteria for response. There were 21 (35.6%) patients in remission. There were no significant differences in rates of response ($\chi^2(1,73)=.78$, $p=.38$) or remission ($\chi^2(1,73)=.26$,$p=.61$) between the two groups. These results suggest that the effectiveness of rTMS was not improved by adding psychological therapies.

Discussion

The present study investigated a novel approach to treatment resistant depression, combining rTMS, a biological treatment, with a selection of psychological therapies. It has been suggested that rTMS might influence neuroplasticity in the brain [26], so perhaps the ability to take in information and skills learned in the psychological therapy sessions might be greater while people are having the rTMS treatment. In turn, adding the psychological therapies may improve depression independently of the improvement due to rTMS, so the overall benefits may be combined.

However, whilst there was a considerable proportion of patients that did respond to treatment to in the Enhanced rTMS program, the results indicated that there was no significant difference in response and remission rates between the two programs. As a result, it cannot be concluded that a combined treatment approach may necessarily lead to improved outcomes.

Further to this, some patients did not complete the full course, perhaps as a result

of not perceiving any benefit or possibly due to the intensive commitment. The lack of efficacy shown by the Zung scores may reflect a lack of perceived benefit or dissatisfaction with the program. There was a greater dropout rate for the Enhanced rTMS program, and it became increasingly difficult to recruit new participants into the Enhanced rTMS program. There was also a 45% drop in referrals to the rTMS service from our referral base of private psychiatrists when the Enhanced rTMS program was running. Although there was no formal measure, it was noted by some patients that the demands of the program (e.g. time commitments) were too great. It is possible that for at least some patients, the Enhanced rTMS program would have been more accepted and successful if the program was less intensive or more specifically targeted. Some patients also had a higher attendance at some program components over others, particularly at rTMS sessions. It is therefore also possible that patients referred for rTMS preferred biological treatments (e.g. medication and rTMS) that did not involve individual psychological and physical effort.

As a pilot study, there are limitations that present themselves. Firstly, this study had a relatively small sample size, thus making it difficult to draw strong conclusions. Additionally, some of the program components were adjusted. For example, we compressed the typical eight week mindfulness program in to a six week course which may have affected efficacy. Furthermore, there was low attendance from some patients to various program components on occasions. The Enhanced rTMS program discontinued after 18 patients because of the lack of referrals. One strength of the study was that there was a control group of patients who had rTMS alone. However, there was no control group of patients who only participated in the psychological interventions. Had our study shown a benefit from combining psychological therapies with rTMS then further research would have been needed to identify which of the specific psychological therapies were most useful. If further studies are undertaken to investigate these combined treatments, measures would need to be taken to ensure the program is appropriately tailored to improve patient acceptability, and potentially the efficacy of the program. For example, our patients were all outpatients and may have found the time commitment difficult; the program might have been more acceptable to inpatients. Or, a program focusing on fewer therapy approaches may be better suited. Follow-up data, to detect a delayed response, may also be useful.

Conclusion

In conclusion, despite the theoretical benefits of combining psychological therapies with rTMS to treat treatment resistant depression, our results did not demonstrate a significant improvement in outcome compared to receiving just rTMS. Contrary to expectations, the combination of therapies in a day program was not highly accepted by some patients. Whilst there were no significant differences reported, the present pilot study provides a useful platform for exploring further benefits of combined approaches to treatment resistant depression.

Learning Points

The addition of psychological therapies to rTMS did not significantly improve remission rates beyond just rTMS alone.

Careful consideration needs to be given to tailoring a combination program to ensure patient acceptability.

Further research may be warranted with greater patient numbers.

Authors' contributions

The study was conceived by PC, SG, AR, and CG, with each involved in its design. AR carried out the literature search and

prepared the draft manuscript, including interpretation of results, with the assistance of BC. BC, PC, SG and AR were involved in carrying out the experiment. All authors were involved in the preparation of the final manuscript.

Conflicts of Interests

The authors declare that there are no conflicts of interests

Ethical Considerations

The study was approved by the Institute Ethics Committee

Acknowledgements

The authors wish to acknowledge Cassandra Burton (research officer) for her assistance in the preparation of the manuscript and Carol Turnbull (Ramsay Health Care (SA) Mental Health Services CEO) for her ongoing support and encouragement for the rTMS research.

References

1. World Health Organisation. The global burden of disease: 2004 Update. Geneva, Switzerland: WHO Press, 2008.
2. Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What did STAR* D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatric Services 2009; 60: 1439-1445. [Pubmed]
3. Sinyor M, Schaffer A, Levitt A. The sequenced alternatives to relieve depression (STAR*D) trial: A review. Canadian Journal of Psychiatry 2010;55: 126-135.[Pubmed]
4. Wiles N, Thomas L, Abel A, Ridgway N, Turner N, Campbell J, Garland A, Hollinghurst S, Jerrom B, Kessler D, Kuyken W, Morrison J, Turner K, Williams C, Peters T, Lewis G. Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial. Lancet 2013; 381: 375-384. .[Pubmed]
5. Brakemeier EL, Merkl A, Wilbertz G, Quante A, Regen F, Bührsch N, van Hall F, Kischkel E, Danker-Hopfe H, Anghelescu I, Heuser I, Kathmann N, Bajbouj M. Cognitive-Behavioral Therapy as continuation-treatment to sustain response after electroconvulsive therapy in depression-a randomized controlled Trial. Biol Psychiatry. 2014 Aug 1;76(3):194-202. doi: 10.1016/j.biopsych.2013.11.030. Epub 2013 Dec 12. [Pubmed]
6. Jarrett RB, Minhajuddin A, Kangas JL, Friedman ES, Callan JA, Thase ME. Acute phase cognitive therapy for recurrent major depressive disorder: Who drops out and how much do patient skills influence response? Behav Res Ther 2013: 51; 221-230. [Pubmed]
7. George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. Current Opinion in Psychiatry 2013;26: 13–18. .[Pubmed]
8. Berlim MT, McGirr A, Beaulieu MM, Turecki G. High frequency repetitive transcranial magnetic stimulation as an augmenting strategy in severe treatment-resistant major depression: a prospective 4-week naturalistic trial. J Affect Disord. 2011 Apr; 130(1-2): 312-7. doi: 10.1016/j.jad.2010.10.011. Epub 2010 Nov 5. [Pubmed].
9. Galletly C, Gill S, Clarke P, Burton C, Fitzgerald P. A randomised trial comparing repetitive Transcranial Magnetic Stimulation given three days/week and five days/week for the treatment of major depression- is efficacy related to the duration of treatments or the number of treatments? Psychol Med. 2012 May;42(5):981-8. doi: 10.1017/S0033291711001760. Epub 2011 Sep 13. [Pubmed].
10. Segal ZV, Williams JMG, Teasdale JD. Mindfulness-based cognitive therapy for depression: a new approach to preventing relapse. New York: The Guilford Press, 2002.
11. Kabat-Zinn J. Mindfulness-based interventions in context: past present, and future. Clin Psychol Sci Prac 2003;10: 144-156.
12. D'Zurilla TJ, Goldfried MR. Problem solving and behaviour modification. Journal of Abnormal Psychology 1971; 78: 107-126. .[Pubmed]
13. Hoffman SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on

anxiety and depression: A meta-analytic review. Journal of Consulting and Clinical Psychology 2010;78: 169–183 [Pubmed].
14. Piet J, Hougaard E. The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: A systematic review and meta-analysis Clin Psychol Rev. 2011 Aug; 31(6): 1032-40. doi: 10.1016/j.cpr.2011.05.002. Epub 2011 May 15. [Pubmed]
15. Bell AC, D'Zurilla TJ. Problem-solving therapy for depression: A meta-analysis. Clinical Psychology Review 2009;29: 348–353. [Pubmed]
16. Nezu AM, Nezu CM, D'Zurilla TJ. Solving Life's Problems: A 5-Step Guide to Enhanced Well-Being. New York: Springer Publishing Company, 2007.
17. Proudfoot J, Ryden C, Everitt B, Shapiro DA, Goldberg D, Mann A, Tylee A, Marks I, Gray JA. Clinical efficacy of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. British Journal of Psychiatry 2004;185: 46-54. [Pubmed]
18. Mota-Pereira J, Silverio J, Carvalho S, Ribeiro JC, Fonte D, Ramos J. Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. Journal of Psychiatric Research 2011;45: 1005-1011 [Pubmed].
19. Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. Current Opinion in Psychiatry 2005;18: 189–193.[Pubmed]
20. Jorm AF, Morgan AJ, Hetrick SE. Relaxation for depression. Cochrane Database of Systematic Reviews 2008; 4: CD007142. .[Pubmed]
21. Pridmore S, FernandesFilho JA, Naha Z, Liberatos C, George MS. Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and visualisation method. Journal of ECT 1998;14; 25-27. [Pubmed]
22. Hedlund JL, Vieweg BW. The Hamilton Rating Scale for Depression: a comprehensive review. Journal of Operational Psychiatry 1979; 10: 149–165.
23. Hamilton M. The assessment of anxiety states by rating. British Journal of Medical Psychology 1959;32: 50–55.[Pubmed]
24. Zung W. A self-rating depression scale. Archives of General Psychiatry 1965;12: 63–70.[Pubmed]
25. Rush AJ, Fava M, Wisniewski SR, Lavori PW, et al. Star*D Investigators Group. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Controlled Clinical Trials 2004;25: 119-142.[Pubmed]
26. Leuchter AF, Cook IA, Jin Y, Phillips B. The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. Front Hum Neurosci. 2013 Feb 26;7:37. doi: 10.3389/fnhum.2013.00037. eCollection 2013. [Pubmed].

World Journal of Medical Research