

Rapid Transcranial Magnetic Stimulation (rTMS) and Normalisation of the
Dexamethasone Suppression Test (DST).

Short Title: Normalisation of DST with rTMS

Saxby Pridmore, M.D

Department of Psychological Medicine, Royal Hobart Hospital, Tasmania, Australia

Address correspondence and reprint requests to Prof. Saxby Pridmore, Department of
Psychological Medicine, Royal Hobart Hospital, Hobart, Tasmania, Australia.

Telephone: +61 3 62228804

Fax: +61 3 62347889

e-mail: s.pridmore@utas.edu.au

Rapid Transcranial Magnetic Stimulation (rTMS) and Normalisation of the Dexamethasone Suppression Test (DST).

Summary: Non-suppression of post dexamethasone cortisol is a feature of endogenous/melancholic depression. Normalisation of the DST response is a feature of remission and antidepressant treatment. Twelve consecutive depressed non-suppressors were treated with rTMS. Six demonstrated normalisation and good clinical improvement which was sustained for at least one month. Thus, rTMS has some biological effects in common with other antidepressant treatments.

Key Words: transcranial magnetic stimulation, dexamethasone suppression test

The dexamethasone suppression test ¹ is the most studied state marker of depression. ^{2,3} Non-suppression is associated with endogenous/melancholic features ^{1,4} and indicates a need for somatic intervention. ⁵ Non-suppression occurs when patients are symptomatic and normalisation of response usually accompanies remission. ⁶⁻⁸ Failure to normalise indicates a poor prognosis. ^{2,9}

Recent animal ¹⁰ and clinical ⁸ studies suggest that normalisation of hypothalamic-pituitary-adrenocortical function, as reflected in a return of DST suppression, is integral to the pharmacological action of amitriptyline and not secondary to recovery.

Transcranial magnetic stimulation (TMS) was described by Barker *et al.* in 1985.¹¹ Machines capable of rapid stimulation (rTMS) have recently become available. A strong current in an insulated electromagnet applied to the head produces a small eddy current at about the junction of the grey and white matter.^{12,13} Three blind trials¹⁴⁻¹⁶ have demonstrated that rTMS can have an antidepressant effect.

Our group has been using rTMS for one year as a clinical option for individuals with severe depression which has failed to respond to medication and for whom ECT is being considered. We have prospectively collected comprehensive data. The aim of this paper is to report the short term effects and the DST response to a course of rTMS in depressed patients who are at baseline dexamethasone non-suppressors.

METHOD

Consecutive patients with DSM-IV major depressive episode, which had failed to respond to an trial of at least one antidepressant medication at maximum recommended doses for one month and for whom the next treatment option was electroconvulsive therapy were offered rTMS. Sex, age, diagnosis, ECT history and current medication were recorded. Baseline Montgomery Asberg Depression Rating Scale¹⁷ (MADRS) Self-rating Depression Scale¹⁸ (SDS) and DST were completed. Dexamethasone 1 mg was given at 11 pm and blood was taken at 8 am and 4 pm the following day - the threshold for suppression was defined as 138 nmol/litre (5

microg/dl) cortisol. This paper reports on the progress of all the non-suppressers who were detected at baseline. For all patients, these assessments and the DST were repeated on the day of completion of the course of treatment.

Patients remained in the care of their treating psychiatrist who referred them to the author for rTMS. The treating psychiatrists were aware that systematic assessments were being compiled but did not access them. Diagnosis was determined by the author in collaboration with the treating psychiatrist. Ratings were performed by nursing staff and registrars trained in the use of these psychological instruments. The raters were not blind in so far as they were aware that a study was proceeding, but they were not involved in the management of the patients they assessed and they were not aware of the stage of treatment.

The patients were maintained on the least possible medication. With one exception, no new medications were commenced in the month before the course of rTMS. The exception was patient 4 who had been commenced on a very low dose of venlafaxine two weeks earlier. These patients were followed up through their treating psychiatrists for one month after the rTMS.

Treatment was with a Magstim Super Rapid stimulator with a double 70 mm coil.

One treatment session was given each day. Ten to 14 treatments were given over 12 to 16 days, depending on clinical response. A treatment sessions was 20, 5 second trains

of 10 Hz at 90-100 % of motor threshold, separated by 25 second rest periods, applied to the left prefrontal cortex.

RESULTS

Twelve different patients were discovered to be dexamethasone non-suppressers at baseline. One patient was treated four times, each time with marked reduction in symptoms and normalisation of the DST response, however, to simplify these results, only the findings relating to the first treatment are given. The age, sex diagnosis, ECT history and current medication are presented in Table 1. The before and after treatment MADRS, SDS and DST results are presented in Table 2.

The major finding was that six patients normalised during treatment. Five suppressed at both morning and afternoon samples. The remaining individual escaped suppression in the afternoon, but suppressed in the morning and had an overall reduction in post dexamethasone cortisol of 56%. For these six patients the average MADRS moved from 31 to 9 and the average SDS moved from 54 to 33. All achieved good clinical improvement and in all cases this improvement was maintained for at least four weeks after rTMS.

Six patients did not normalise. Three initially showed some clinical improvement. Their average MADRS and SDS showed moderate change. However, deterioration soon followed and ECT was required within two weeks of completion of the course of

rTMS. These patients took a DST prior to ECT and all escaped suppression at both the morning and afternoon samples. The other three patients who did not normalise did not show clinical improvement. Their average MADRS and SDS showed little change. On completion of the course of rTMS, but before discharge, a course of ECT was administered. For this latter group of patients a DST prior to ECT was not possible.

The numbers are small. On average, those who normalised were younger than those who did not normalise (50 vs 64 years) and were less depressed, as determined by lower baseline MADRS (31 vs 41) and SDS (54 vs 67). Also, those who normalised had a lower average baseline post dexamethasone cortisol levels (272 vs 413 nmol/l)

DISCUSSION

Among the shortcoming is that this work was not fully blind. The MADRS was scored by nurses and doctors who were aware that the patients were participating in an rTMS study. The SDS was scored by the patient, but this could not have been otherwise. The clinical decisions such as whether to discharge or commence ECT were made by the treating psychiatrists and they may have been biased to please the author, however, their primary responsibility was to their patients and these doctors had to meet the consequences of any wrong decisions. The most important findings emanate from the DST results and these were determined by technicians who had no knowledge whatsoever of our clinical activities.

In six cases there was DST normalisation and good clinical improvement. Medication was continued in five of these cases, however, it is unlikely that this was responsible for the changes. In four cases the medication had been in place without success for one month, and in the fifth case, in which medication had been more recently commenced, the dose was very small.

There were no detectable side-effects of rTMS other than an occasional transient headache. This is consistent with the findings of the double blind studies of Pascual-Leone *et al.*¹⁴ and George *et al.*¹⁵

These patients all suffered severe mood disorder. One inclusion criterion was that the current episode had failed to respond to an adequate trial of at least one antidepressant. The majority had failed to respond to medication from two or more different families. Ten of the had been hospitalised and received ECT for the treatment of a previous major depressive episode. On the baseline MADRS and SDS scores all at least reached the lower level of severe depression. Another inclusion criterion was initial DST non-suppression. Thus, from a clinical^{19,20} and biological^{2,9} perspective, clinical improvement in these patients in response to placebo was most unlikely.

Three non-suppressors showed some clinical improvement but relapsed within two weeks and required ECT. This is entirely consistent with the findings that non-suppression indicates a poor prognosis in spite of apparent clinical improvement.^{2,9}

Increasing age in both the presence²¹ and absence²² of depression has been associated with increased hypothalamic-pituitary-adrenocortical dysregulation as reflected by the DST. Common clinical experience is that depression in later life may prove less responsive to treatment than depression of early adult life. These factors may have been influential in the present study as the group which did not show normalisation of the DST was on average older than the group which showed normalisation. There also appeared to be a suggestion that those with higher baseline MADRS, SDS and post dexamethasone cortisol level may be less responsive to rTMS. However, the numbers are small and indicate only that an examination of the effect of age and severity of depression, as revealed by baseline assessments, on the outcome of rTMS treatment of depression may be justified. Very recent reports suggest that rTMS is less effective in older as compared to younger patients²³ and in psychotic as compared to non-psychotic depression.²⁴

While six patients achieved a favourable outcome during rTMS, six did not. It is reasonable to expect that a greater yield of favourable outcomes can be achieved with, as yet undetermined, optimum treatment parameters (frequency, train length, inter-train interval, number of trains and intensity) and number of treatments. There is very little information to guide the choice of parameters at the moment. Those we used are very similar to those used by Pascual-Leone *et al.*¹⁴ and dissimilar to those used by George *et al.*¹⁵ Our immediate plan is to continue to use these parameters, but to treat people twice each day, morning and afternoon.

The important finding of this report is that rTMS resulted in the normalisation of the DST response (accompanied by a good clinical improvement which persisted for at least one month) of six patients with severe, medication resistant depression who had not suppressed at baseline DST. This demonstrates that rTMS has some biological effects in common with other antidepressants⁸ and that this revolutionary technology can have effects within and beyond the nervous system.

Acknowledgement: Thanks to the Hobart Clinic and Kevin Clamp for financial assistance.

REFERENCE

1. Carroll B, Feinberg M, Greden J, Tarika J, Albala A, Haskett R, James N, Kronfol Z, Lohr N, Steiner M, de Vigne J, Young E. A Specific Laboratory Test for the Diagnosis of Melancholia. *Arch. Gen. Psychiatry* 1981;38: 15-22.
2. American Psychiatric Association Task Force on Laboratory Tests in Psychiatry. The dexamethasone suppression test: an overview of its current status in psychiatry. *Am. J. Psychiatry* 1987;144: 1253-62.
3. Rush A, Giles D, Schlessner M, Orsulak P, Weissenburger J, Fulton C, Fairchild C, Roffwarg H. Dexamethasone response, thyrotropin-releasing hormone stimulation, rapid eye movement latency, and subtypes of depression. *Biol Psychiatry* 1997;41: 915-28.

4. Rush A, Weissenburger J. Melancholic symptom features and DSM-IV. *Am. J. Psychiatry* 1994;151: 489-98.

5. Thase M, Dube S, Bowler K, Howland R, Myers J, Friedman E, Jarrett. Hypothalamic-pituitary-adrenocortical activity and response to cognitive behaviour therapy in undedicated, hospitalised depressed patients. *Am. J. Psychiatry* 1996;153; 886-91.

6. Carroll B. The hypothalamic-pituitary-adrenal axis in depression. In Davies B, Carroll B, Mowbray R eds. *Depressive illness: Some research studies*. Springfield, Ill. Charles C Thomas, 1972: 23-201.

7. Greden J, Gardner R, King D, Grunhaus L, Carroll B, Kronfol Z. Dexamethasone suppression tests in antidepressant treatment of melancholia. *Arch. Gen. Psychiatry* 1983; 40: 493-500.

8. Heuser I, Schweiger U, Gotthardt U, Schmider J, Lammers C-H, Dettling M, Yassouridis A, Holsboer F. Pituitary-adrenal-system regulation and psychopathology during amitriptyline treatment in elderly depressed patients and normal comparison subjects. *Am. J. Psychiatry* 1996;153: 93-9.

9. Ribeiro S, Tandon R, Grunhaus L, Greden J. The DST as a predictor of outcome in depression: a meta-analysis. *Am. J. Psychiatry* 1993;150: 1618-29.
10. Barden N, Reul J, Holsboer F. Do antidepressants stabilise mood through actions on the hypothalamic-pituitary-adrenocortical system? *Trends Neurosci* 1995;18: 6-11.
11. Barker A, Jalinous R, Freeston I. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985; 1: 1106-1107.
12. George M S, Wassermann E, Post R. Transcranial magnetic stimulation: a neuropsychiatric tool for the 21st century. *J. Neuropsychiatry Clin. Neurosci.* 1996;8: 373-82.
13. Kirkcaldie M, Pridmore S, Reid P. Electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS): the case of the skull. *Convulsive Therapy* 1997;13: 83-91.
14. Pascual-Leone, A, Rubio, B., Pallardo, F Catala M. Beneficial effect of rapid-rate transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 1996;348: 233-238.
15. George M S, Wassermann E, Kimbrell T, Little J, Williams W, Danielson A, Greenberg B, Hallett M, Post R. Daily left prefrontal rTMS improves mood in

- depression: a placebo-controlled crossover trial. *Am. J. Psychiatry* 1997;154: 1752-6.
16. Padberg F, Haag C, Zwanzger P, Thoma H, Kathmann N, Stubner S, Hampel H, Moller H. Rapid and slow transcranial magnetic stimulation are equally effective in medication-resistant depression: a placebo-controlled study. *International Journal of Neuropsychopharmacology* 1998, 1, Suppl. 1: S30.
17. Montgomery S, Asberg M. A new depression scale designed to be sensitive to change. *Br. J. Psychiatry* 1979;134: 1165-71.
18. Zung W. A self-rating depression scale. *Arch. Gen. Psychiatry* 1965;12: 63-70.
19. Fairchild C, Rush A, Vasavada N. Which depressions respond to placebo? *Psychiatry Res.* 1986;18: 217-26.
20. Zimmerman M, Spitzer R. Melancholia: from DSM-III to DSM-III-R. *Am. J. Psychiatry* 1989;146: 20-8.
21. von Bardeleben U, Holsboer F. Effect of age upon the steroid response to human CRH in depressed patients pre-treated with dexamethasone. *Biol. Psychiatry* 1991;29: 1042-50.

22.Heuser I, Gotthardt U, Schweiger U, Schmider J, Lammers C-H, Dettling M,

Holsboer F. Age-associated changes of pituitary-adrenocortical hormone regulation in humans: importance of gender. *Neurobiol. Aging* 1994;15: 227-31.

23.Figiel G, Epstein C, McDonald W, Amazon-Leece J, Figiel L, Saldivia a, Glover S.

The use of rapid rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. *J Neuropsychiatry Clin Neurosci* 1998; 10: 20-25.

24.Grunhaus L, Dannon P, Schreiber S. Effects of transcranial magnetic stimulation on

sever depression. Similarities with ECT. *Biol Psychiatry* 1998; 43: 76S-77S.

Patient	AGE	SEX	DIAGNOSIS	ECT PAST	MEDICATION (DAILY TOTAL)
1	75	F	BP	Y	nil
2	55	F	BP	Y	lithium 1.25 g, valproate 1.25 g
3	45	F	MDD	Y	moclobemide 1.2 g, valproate 600 mg
4	36	F	MDD	Y	venlafaxine 75 mg
5	50	F	MDD	Y	sertraline 100 mg, alprazolam 0.75 mg
6	41	M	MDD	N	sertraline 200 mg
Average	50				
7	56	M	BP	Y	venlafaxine 150 mg
8	61	F	MDD	Y	trimipramine 150 mg, lorazepam 3 mg
9	71	M	MDD	Y	sertroline 200 mg
10	50	M	MDD	N	paroxetine 40 mg
11	70	F	MDD	Y	sertroline 100 mg
12	78	F	MDD	Y	venlafaxine 225 mg
Average	64				

Table 1. The age, sex, diagnosis, ECT history (whether or not ECT has been received in the past) and current medication of patients; listed in order of age. BP = bipolar disorder; MDD = major depressive disorder. Shading indicates those who did not normalise.

Patient	MADRS BEFORE	MADRS AFTER	SDS BEFORE	SDS AFTER	DST * BEFORE	DST* AFTER
1	32	16	64	55	197, 233	76, 56
2	24	5	47	30	292	33
3	33	15	60	45	278, 234	60, 71
4	39	18	36	26	28, 475	28, 130
5	23	0	57	30	64, 290	36, 37
6	33	0	58	21	386, 513	45, 337
Average	31	9	54	33	272	88
7	38	10	67	20	397, 551	192, 205
8	55	13	72	57	454, 211	419, 270
9	34	16	74	58	454	383
10	37	18	69	48	620, 299	NA
11	42	53	60	60	557, 521	NA
12	40	37	57	54	234, 247	NA
Average	41	25	67	50	413	-

Table 2. The results of MADRS, SDS and DST conducted before and after a course of rTMS. Patients listed in order of age. NA = not available. Shading indicates those who did not normalise. * = expressed in nmol/litre.