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EARLY RELAPSE TREATMENT (ERT) OR "MAINTENANCE" TRANSCRANIAL MAGNETIC STIMULATION (TMS)?

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ABSTRACT. *Background:* Major depressive disorder (MDD) commonly takes a relapsing form. Transcranial magnetic stimulation (TMS) has be suggested as a means of maintaining remission. Brief courses of TMS at about monthly intervals appear to provide health benefits. *Objective:* To examine whether such brief courses of TMS are better conceptualized as maintaining remission, or as the provision of early relapse treatment. *Method:* 25 series of treatment (18 different patients) were considered. Pre- and post-treatment 6-item Hamilton Depression Rating Scale (HAMD6) and 7 visual analogue scales (VASs) were collected, along with pre-treatment Clinical Global Impression-Severity (CGI-S) and post-treatment CGI-Improvement (I). *Results:* Pre-treatment HAMD6 and CGI-S indicated that many patients were symptomatic and in early relapse. Post-treatment HAMD6 indicated that many patients had achieved remission, and this was supported by the CGI-I. The

VAS scores also improved. *Conclusions:* Short courses of TMS at about monthly intervals have beneficial results and are better conceptualized as early relapse treatment (ERT).

Keywords: major depressive disorder; transcranial magnetic stimulation; early relapse treatment

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Introduction

Major depressive disorder (MDD) is painful and disabling. Remission is difficult to achieve (Trivedi et al., 2006), and relapse commonly occurs (Berwain et al., 2016). Should the remitted state feature any residual symptoms, relapse is even more likely (Paykel et al., 1995).

Transcranial magnetic stimulation (TMS) has proven to be effective in acute treatment of drug resistant MDD (Fitzgerald et al., 2016), but as with remissions induced by other treatments, relapse is common in the following months (Dannon et al., 2002). One study found that following TMS-induced remission, relapse occurred at approximately 5 months, and importantly, that the reintroduction of TMS often effected a further remission (Demirtas-Tatlidede et al., 2008).

There is interest in TMS not only as a treatment of acute MDD, but also, as a means of keeping people well, once remission has been achieved. This particularly applies to those patients with well-established MDD and a history of frequent relapse. The term "maintenance" (M-)TMS has frequently been employed – reflecting the hope that occasional TMS may be effective in maintaining hard-won remissions. The term continuing (C-)TMS has been used interchangeably with M-TMS and there is a need for terminological agreement (Levkovitz et al., 2015). A popular protocol, has been, once remission has been achieved, to continue providing stimulation sessions, but less frequently, such as twice per week (Perera et al., 2016) and once per month (Philip et al., 2016).

Clustered maintenance (CM-)TMS is the term applied to clusters of 5 TMS sessions delivered over 2 days, at monthly intervals (Fitzgerald et al., 2013). The authors found this form of care successfully reduced the frequency of relapses (or in other words, kept patients well for longer). In conversation with our group, the devisor of CM-TMS (Prof Paul Fitzgerald, Monash University) advised that the 5 sessions could also be delivered over 3 or 5

days. We adopted this model of care, hoping to reduce the suffering and costs of chronic MDD. (Stimulation parameters: 120% MT, 10Hz, 4s trains, 75 trains.)

In an in-press poster (Rybak et al., 2017) we offered an account of our experience with 16 patients treated with CM-TMS in a non-academic inpatient setting. In the early stages of this service, the period between series is set at 4 weeks, but this varied according to clinical response and patient preference. Recently, the average period between series was 5.8 weeks (Rybak et al., 2017). These patients had remained relatively well for an average of 21.7 months. In a cross-sectional prospective assessment, we found their average Clinical Global Impression – Severity (CGI-S) indicated a point between borderline and mildly ill. Following treatment, visual analogue scale (VAS) responses for depression and sleep problems both improved, and the CGI-Improvement indicated a point between minimally and much improved.

These results raised the possibility that CM-TMS, in our hands, at least, was not maintaining remission, but rather, providing early remission treatment [ERT]. The current paper describes an investigation as to whether our service would be better described as providing ERT-TMS.

Method

Ethical approval for this study was not required as we used only data collected in routine clinical practice and the identity of no patient was revealed.

In accordance with the latest standards (Perera et al., 2016) we recently upgraded our outcome assessment methods. Before and after series of treatments, clinicians administer the six-item Hamilton Depression Rating Scale (HAMD6) (O'Sullivan et al., 1997) in the structured/scripted form (Williams, 1988). Totals were calculated. Five (5) or more was taken as indicating relapse (Kyle et al., 2016).

Before and after each series we also administer a battery of visual analogue scales (VASs) (Cowdry, 1991). For this subjective instrument to retain congruity with the HAMD6, we have chosen anchor points reflecting of the items of that instrument: No depression – Worst possible depression; Activities give normal pleasure – No activities give pleasure; No physical health concerns – Extreme health concerns; No feelings of guilt – Extreme feelings of guilt; Not anxious – Most anxious possible; No concentration problems – Most possible concentrations possible. In addition, we included a 7^{th} item; No sleep problems – Most sleep problems possible. These are constructed on a 10-cm line; totals were calculated and compared.

Before each series, we administer the Clinical Global Impression Scale for Severity (CGI-S) (Guy, 1976), and on completion of each series we administered the CGI-Improvement (I) (Guy, 1976). These are both 7 point

scales; in the CGI-S, 1 indicates “normal, no illness,” while in CGI-I, 4 indicates “no change.”

All patients were referred by non-academic, private psychiatrists and were taking at least one antidepressant medication.

We were interested in the response to a stimulation series, and the response to more than one series by a single individual was acceptable.

Results

25 series were identified (18 individuals, of whom 7 experienced 2 series). The average age was 53 years, and 13 (72%) were female.

Before the series of sessions of stimulation, the average HAMD6 score was 7.4 – that is, the average score was in the relapse range (Table 1). Before the series of stimulation, HAMD6 scores indicated 22 examples of relapse.

After the series of sessions of stimulation, the average HAMD6 score was 3.3 – that is, the average score was in the remission range (Table 1). After the series of stimulation, HAMD6 scores indicated only 6 examples of relapse. That is, there were 16 examples of movement from relapse to remission.

Before the series of sessions of stimulation, the average CGI-S score was 3.4 (indicating a position between mildly and moderately ill. There was 1 case of severe illness, 3 of markedly ill and 6 of moderate illness. There were no examples of “normal, no illness.”

After the series of sessions of stimulation, the average CGI-I score was 1.96 (indicating a position between much improved and very much improved. There were 5 examples of “very much improved,” 16 of “much improved” and none of “no change.”

Before treatment the VASs for MDD related symptoms total was 898, and after this was 565, indicating a 37% improvement.

In summary, before treatment, the HAMDS indicated relapse, and after, remission. Before treatment the CGI-S also indicated the presence of illness, and after, the CGI-I indicted considerable improvement. The VASs also indicated improvement.

Discussion

This bears the hallmarks of a non-blinded study. Bias may have played a hand. But, it is difficult to see how or why. Ours is a non-academic working facility. We have recently upgraded our outcome measures collection system, and staff were going about their daily activities, rather than being concerned about which form of treatment produced the greatest effect.

There may be debate that the HAMDS6 score of <5, for remission, given by Kyle et al. (2016), is too low. Another group argues that for the Hebrew version of HAMD6, the remission point should be <7 (Bachner et al., 2013). This needs to be seen in context, the remission point for HAMD17 is universally accepted as <8. To a large extent, the accepted integer is less important than the direction of changes.

As a subjective measure, we chose VASs for depression related symptoms. These are not standardized and are of modest use in diagnosis. However, they are quick and simple and provide evidence of change. We used a 7-item battery, based on the HAMD6 questions plus one dealing with sleep problems. We report a 37% reduction in the pre-treatment score. This is consistent with our earlier VAS findings (Rybak et al., 2017) of a 47% reduction in depression and a 32% reduction in sleep problems.

It is important to remember that in the pre-series assessments, the high HAMD6 findings are supported by the low CGI-S scores. Together, these indicate that many of the people in this study were in early relapse before they received treatment. Post-series assessments revealed a lowering of HAMD6 scores being substantiated by CGI-I scores indicating clear improvement. This evidence suggests that in the early stages of relapse, a short course of TMS is sufficient to improve the mood, possibly to the point of remission.

For those patients with well-established MDD and history of frequent relapse, who respond to TMS, there is some evidence that 5 day courses of TMS at about monthly intervals provide benefits (Fitzgerald et al., 2013). This paper strongly indicates that, at least in our hands, rather than maintain remission, these short courses are better conceptualized as early relapse treatment (ERT).

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Table 1 Pre- and Post-treatment metrics

Client	Pre-treatment HAMD6 Total	Post-treatment HAMD6 Total	Pre-treatment VASs Total	Post-treatment VASs Total	CGI-S	CGI-I
1	11	7	54.3	47	5	3
2	8	2	38.3	7.4	3	1
2	7	3	35.4	22.9	4	2
3	4	3	32.3	15.5	2	2
3	8	3	39.3	18.5	3	2
4	5	2	32.8	20.6	3	2
4	6	2	40	34.4	3	2
4	4	2	37.9	24.1	3	3
5	2	0	22.1	15.6	2	2
6	7	5	25.1	29.7	3	2
6	6	6	38.1	44.4	3	2
7	9	2	21.2	4.5	4	2
7	10	4	29.5	11	5	2
8	15	7	39.1	33.4	5	2
9	12	5	48.8	30.9	4	2
9	8	3	53.2	24.9	3	2
9	5	3	26.9	16	3	1
10	5	2	45.9	12.5	3	2
10	8	4	42.4	20.4	4	1
11	10	6	19.8	21.8	4	2
12	6	1	48.4	21	3	2
13	5	1	10.7	0.7	2	3
14	4	1	31.9	13.8	2	1
15	5	1	42.4	33.9	3	2
15	11	4	33	27.3	6	2
15	6	5	28.6	34	4	3
16	7	0	44.1	3.1	3	1
17	5	4	37.3	31.4	3	3
17	9	6	37.3	34.8	4	3
18	11	8	59	46	4	3
19	10	5	26.9	21.8	4	3
20	5	5	27.1	25.8	3	3
21	5	3	27.3	13.3	3	2
Aver-age	7.2	3.5	35.6	23	3.4	2.1