Brain Stimulation 11 (2018) 1098–1102

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Early relapse (ER) transcranial magnetic stimulation (TMS) in treatment resistant major depression

Saxby Pridmore [a, b, *], Sheila Erger [b], Marzena Rybak [b], Erin Kelly [b], Tamara May [c]

[a] School of Medicine, University of Tasmania, Hobart, Tasmania, Australia
[b] TMS Department, Saint Helen's Hospital, Hobart, Tasmania, Australia
[c] School of Psychology, Deakin University, Burwood, Victoria, Australia

ARTICLE INFO

Article history:
Received 22 January 2018
Received in revised form
11 May 2018
Accepted 19 May 2018
Available online 22 May 2018

Keywords:
TMS
Treatment resistant depression
Early relapse
Maintenance TMS

ABSTRACT

Background: There is interest in using TMS to keep patients with severe relapsing depression as well as possible, once remission has been achieved. This has been conceptualized as 'maintaining' the remission. One protocol employs series of 5 TMS sessions over 3 or 5 days, at about monthly intervals. We have suggested this practice is better conceptualized as early relapse (ER) TMS.
Aim: To determine whether 5 TMS sessions at about monthly intervals are effective in keeping patients relatively well, and whether the concept of ER-TMS can be supported.
Method: Prospective, naturalistic, 10-month study, administering pre- and post-TMS series, HAMD6, visual analogue scale for mood, and CGI-S.
Results: Thirty-nine patients (72% female) received 168 series of 5 TMS sessions and remained in the program for 21 weeks on average. Pre-post-treatment scores showed significant reductions on all measures. Post-series HAMD6 score 3.30 (2.28) indicates remission has been achieved. Pre-series scores of 6.24 (2.78) indicate a post-series decline in mood, in the direction of relapse. Before TMS series 70% were no longer in remission (being in partial remission or relapse), and after TMS series, 79% were in remission.
Conclusion: In severe relapsing depression, monthly series of TMS move mood from the relapse/partial remission range in the direction or remission and is appropriately termed early relapse ER-TMS. Long-term availability of ER-TMS to patients with severe relapsing depression deserves consideration.

1. Introduction

Major depressive disorder (MDD) is common, painful and disabling. Remission is difficult to achieve [1], relapse is common [2], and 30–60% of those who have one episode will have further episodes, with increasing frequency and severity over time [3].

The initial aim of acute treatment is 'remission', a state of low levels of, or absent, symptoms [4]. An intermediate state of 'partial remission with residual symptoms' reflects persistence of the original disorder, in a milder form [4,5]. 'Relapse' describes the return of the depressive episode [4,6]. 'Recovery' involves a prolonged period of remission, and indicates that depressive illness is no longer present (however, 'recurrence' remains a possibility) [7].

The term 'treatment-resistant depression' (TRD) is widely used and variously defined. Fava [8] states TRD refers to inadequate response to at least one trial of an antidepressant, at an adequate dose, for an adequate duration. Souery et al. [9] refer to an inadequate response to two adequate trials of different classes of antidepressants – this is more widely accepted and the definition we adopted. Patients who come to TMS have almost universally failed to respond to many treatment trials and by definition, suffer TRD, with the classic features of slow/minimal improvement and a tendency to relapse/deteriorate.

Resistance is a grave complication which can develop in patients who were previously responsive to a treatment [10]. When residual symptoms are present in the post-treatment state, relapse is more likely [5,11,12].

Transcranial magnetic stimulation (TMS) is effective in the acute treatment of TRD [13,14], but as with remissions induced by other

* Corresponding author. School of Medicine, University of Tasmania, Hobart, Tasmania, Australia.
E-mail addresses: s.pridmore@utas.edu.au (S. Pridmore), Sheila.Erger@healthscope.com.au (S. Erger), mrybak@netspace.net.au (M. Rybak), Erin.Kelly@healthscope.com.au (E. Kelly), tamara.may@deakin.edu.au (T. May).

https://doi.org/10.1016/j.brs.2018.05.013
1935-861X/

means, relapse may occur. One report [15] found 10% had relapsed at 6 months. A comparison of ECT and TMS found the relapse rate to be similar, approximately 20% at 6 months [16].

In addition to producing remission in depressive episodes, there is interest in TMS as a means of keeping people well, subsequent to the acute treatment. The term "maintenance" (M –) TMS was coined. One protocol continues stimulation sessions (following TMS induced remission) but less frequently, for example, twice weekly sessions in the early weeks, reducing over time, to a single monthly treatment [17]. Such work has produced occasionally encouraging results, but none have emphatically indicated the way forward.

The concept of 'clustered maintenance' (CM-) TMS was introduced by Fitzgerald et al. [18] and refers to (following TMS induced remission), series of 5 TMS sessions over three days, at monthly intervals – the aim being to 'maintain the remission'. In our clinical practice we have adopted a slightly modified model, providing 5 TMS sessions over either 3 or 5 days, and allowing/encouraging the extension of the time between TMS series, beyond one month, according to clinical progress.

We retrospectively studied 16 patients who had been treated using the Fitzgerald CM-TMS model and found evidence of reduced hospital admission rates [19]. We prospectively studied 33 CM-TMS treatment series, and found evidence, in 29 presentations, of early signs of relapse [20]. This led us to conceptualize the activity called CM-TMS, not as a means of maintaining remission, but as a form of early relapse (ER) treatment.

The aim was to determine whether patients (with TRD and a history of recurrent relapse) who had responded well to sessions of TMS, 1) suffered a measurable lowering of mood by 4 weeks (or slightly more), and 2) experienced improved mood in response to series of 5 TMS sessions over 3 or 5 days. Should this be the case, a useful form of assistance for those with TRD would be demonstrated, as would some theoretical support the concept and term: ER-TMS.

2. Method

This study was approved by the institutional ethics committee and all participants provide written informed consent. The design was a large, prospective, naturalistic study of the effects of series of 5 sessions of TMS over 3 or 5 days, at monthly or greater intervals, administered to patients with a history of TRD who had responded well to two acute courses of TMS.

2.1. Participants

Participants were recruited from a private psychiatric hospital in Australia. Patients were included in the study if they had responded to at least 2 courses of acute treatment TMS (left DLPFC, 110% RMT, 10 Hz, 4s trains, 75 trains, 20 sessions over 4 weeks) and had experienced relapse within 3 months following the second last successful acute course. Demographic details including age, gender, and details of the periods between series of 5 TMS sessions were collected and are displayed in Table 1.

2.2. Procedure

Four weeks after successful completion of the last acute course of TMS, series of 5 TMS sessions were commenced on a monthly basis (using the above parameters). The period between the series of 5 TMS sessions was extended (if possible) according to clinical progress.

Before and after each series of 5 TMS sessions, the following were administered: 1) the six-item clinician rated Hamilton Depression Rating Scale (HAMD6) [21], 2) a six-item patient rated visual analogue scale (VAS6) [22], and 3) the clinician rated Clinical Global Impression Scale for Severity (CGI-S) [23].

2.3. Measures

HAMD6: The HAMD6 was our primary outcome measure of severity. Remission, the state when symptom levels are low or absent [4], has been operationalized as a HAMD6 score of <4 [6,23]. Relapse describes the return of the depressive episode after remission [4,6] has been operationalized as a HAMD6 score of ≥7 [24,25]. An intermediate state of partial remission with residual symptoms sits between remission and relapse [4,5] and corresponds to HAMD6 scores of 5 and 6.

VAS6: The VAS6 anchor points reflected the items of the HAMD6 and were placed either end of 10 cm lines: No depression – Worst possible depression; Activities give normal pleasure – Activities give no pleasure; No physical health concerns – Extreme physical health concerns; No feelings of guilt – Extreme feelings of guilt; Not anxious – Most anxious possible. The 6th HAMD6 item concerns 'retardation' - in an inexact match we chose the (subjective) anchor points: No concentration problems – Most possible concentrations possible.

CGI-S: The CGI-S, an objective metric based on the clinical experience of staff, was used as the indicator of the severity in another TMS study [26] and we selected it as a secondary measure.

2.4. Data analysis

Descriptive statistics were used to present participant characteristics. Paired samples t-tests were used to understand changes in the pre-post scores for each treatment series using Cohen's d for

Table 1
Participant characteristics.

	N	M	SD	Range
Age	39	49.4	16.3	25–86
Sex	28 female (72%)			
	11 male (28%)			
SEIFA		994	65	851–1084
Prior ECT	26 (67%)			
Average number of psychotropic medication types		2.2	0.8	1–4
Currently taking 1 antidepressant	11			
Currently taking >1 antidepressant	26 (97%)			
Current anticonvulsant	10 (26%)			
Currant antipsychotic	11 (28%)			
Current lithium	6 (15%)			
Current other psychotropic medication	17 (44%)			
Length psychiatric history (years)		11.8	9.2	1–30

ECT, Electroconvulsive Therapy; SEIFA, socio-economic indexes for areas.

effect sizes. Chi square tests were used to explore differences in diagnostic categories pre and post treatment. Mixed modelling using random effects was used to understand the influence of number of treatment series and time between treatment series on the pre, post and change scores of the primary outcome variable for participants commencing the maintenance program for the first time during the study period. All data were entered into SPSS 24 for analysis.

3. Results

In the 10 months from Jan 1, 2017, 39 patients presented. Twelve patients were already in the program on January 1, 19 were in the program at the end of the period, and 20 patients had entered and left the program. Table 1 shows the demographic details of the participants. On average, the participants had over 10 years of psychiatric history, were taking over 2 types of psychotropic medications, and 67% had previous electroconvulsive treatment.

Neighbourhood socioeconomic disadvantage was measured using the Socio-Economic Indexes for Areas (SEIFA) Disadvantage Index corresponding to the participant's postcode of residence (Australian Bureau of Statistics, 2013). The SEIFA of participants was similar to the Australian average ($M = 1000, SD = 100$), $t(38) = 0.586$, $p = 0.651$, indicating the treatment group was of average socio-economic status.

Over the 10 months we delivered 168 series of 5 TMS sessions. The mean number of series delivered to each individual was 3.6 (range 1–10), and the mean number of weeks between series was 4.9 weeks (SD = 1.6, range = 2–14). Patients remained in the program for an average of 21 weeks (SD = 14.4, range = 4–45).

Of those who left the program during the year, none were lost to follow-up, one remained well and discontinued with clinician support, 5 experienced insufficient benefit to justify patient inconvenience, 6 had extenuating circumstances, including pregnancy, and 8 experienced relapse.

3.1. Pre-post scores

Paired samples *t*-test showed a significant reduction in HAMD6 total, VAS6 total and CGI-S pre and post scores with large effect sizes, Table 2. On the HAMD6 the average pre-treatment score was within the partial remission stage and the average post-treatment score was within the remission range. Patient and clinician reported depression change scores showed significant positive agreement (VAS6 and HAMD6 $r = .613$, $p < .001$; VAS6 and GGI-S $r = .534$, $p < .001$).

The post-treatment outcome on the HAMD6 total score for patients in 3 pre-treatment categories (Remission, Partial Remission, and Relapse) are displayed in Table 3. A chi square analysis showed there was a significant difference in categories pre and post treatment on the HAMD6. At the beginning of treatment 30% of patients were in remission, 70% of patients were in partial remission (28%) or relapse (42%). Following treatment only 14 patients were in relapse (8%), 22 cases were in partial remission (13%) and 132 cases were in remission (79%). In brief, before TMS series 70% were no longer in remission (being in partial remission or relapse), and after TMS series, 79% were in remission.

Table 2
Pre-post scores for combined series of 5 TMS sessions (N = 168).

	Pre	Post	t	p	Cohen's d
HAMD6 Total M (SD)	6.24 (2.78)	3.30 (2.28)	16.37	<.001	1.29
VAS6 Total M (SD)	24.62 (12.18)	16.53 (10.90)	11.96	<.001	0.92
CGI-S Total M (SD)	2.99 (0.93)	1.96 (0.85)	16.10	<.001	1.25

Table 3
Pre- and Post-treatment HAMD6 scores (raw numbers and % totals across rows).

Pre-treatment	Post-treatment			Totals
	Remission[a]	Partial Remission[b]	Relapse[c]	
Remission[a]	49 (98%)	0 (0%)	1 (2%)	50 (30%)
Partial Remission[b]	43 (92%)	3 (6%)	1 (2%)	47 (28%)
Relapse[c]	40 (56%)	19 (27%)	12 (17%)	71 (42%)
Totals	132 (79%)	22 (13%)	14 (8%)	168 (100%)

[a] Remission ≤4.
[b] Partial remission 5&6.
[c] Relapse ≥7.

3.2. Number of, and time between, TMS series

The new patients (N = 27; those who commenced the program during the study period) were explored to understand if there was an influence of number of series of TMS, or time between TMS series, on depression scores. This was 1) to explore whether additional series of treatments influenced whether the patient continued to relapse, and 2) to explore whether there was an increase in the time between treatment series which may have related to patients remaining well for longer.

Fig. 1 shows the average HAMD6 scores pre and post each treatment series for the new group of patients.

There was no significant influence of the number of series or number of weeks between series on the HAMD6 pre scores (series number $p = .554$, time between $p = .773$), post scores (series number $p = .884$, time between $p = .494$), or change in HAMD6 scores (series number $p = .561$, time between $p = .683$). This indicated that HAMD6 scores at the start of each treatment series, end of each treatment series and the change in scores before and after treatment series were not influenced by the number of series received or the time between series.

4. Discussion

This study aimed to understand if 'clustered maintenance' TMS was better conceptualized as ER-TMS. Our finding of the majority of patients (70%) not being in remission (that is, partial remission or relapse) at the beginning of each treatment series confirms this notion. That at the conclusion of each treatment series the majority of patients (79%) were in remission highlights the effectiveness of ER-TMS to bring about symptom reduction.

We chose the HAMD6 as it is superior to the HAMD17 in terms of transferability, scalability and responsiveness [27,28]; it is unidimensional [29] and can be managed in a busy service clinic.

From one point of view, limitations of this study include its open nature and lack of a placebo group. However, our point of view is from the real world, where patients suffer comorbidities (including personality issues), use substances, and have received only modest benefit from the recommended pharmacological agents.

All the patients in this study suffer TRD, a group which is extremely difficult to help. Thase and Swartz [10] have described TRD as demonstrating a progressive deteriorating illness course over time. Such patients are difficult to move to remission, and often, for no apparent reason, slip back into partial remission or relapse. In the presence of residual symptoms, relapse is common, and Paykel [4, page 435] states the presence of residual symptoms indicates the "persistence of the original disorder".

It is important to emphasize that HAMD6 scores at the start of each series, end of each series and the change in scores before and after series were not influenced by the number of series received or the time between series. This indicates a chronic disorder which is

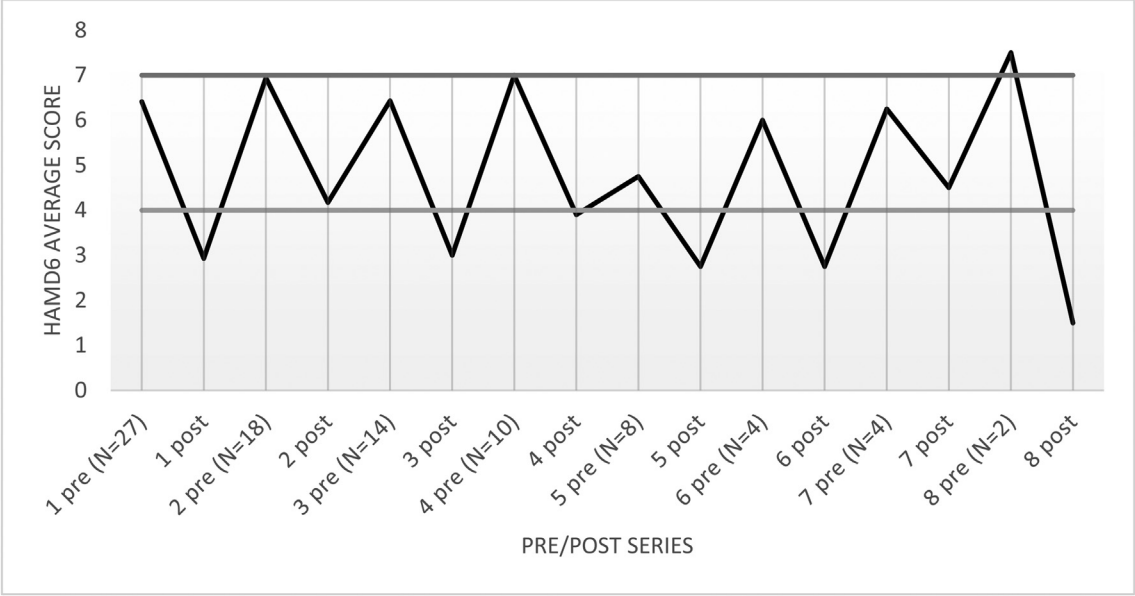

Fig. 1. Average pre and post scores on the HAMD6 for new patients across TMS series. Horizontal lines at 4 and 7: ≤4 indicates remission, >4 to <7 indicates partial remission with residual symptoms, and ≥7 indicates relapse. Eight cycles are depicted.
I cannot afford colour – but, if colour is free [not mentioned in advice to authors] – the following may be acceptable.

relieved, but not cured, by this form of treatment. In other words, this treatment needs to be continued.

Thus, the patients here described suffer a painful, dangerous disorder which is generally unresponsive to treatment, and which is associated relapse and disability [30]. This study demonstrates that some patients with difficult to manage depression can be kept well with series of 5 TMS sessions delivered at about monthly intervals. By "kept well" we mean that such patients remain and function in the community. There is some lowering of mood over weeks, but acute, prolonged and disruptive episodes of illness and treatment were avoided by planned, brief series of treatment. While there was lowering of mood over weeks, using this regimen, over the 10-month period, of 39 patients, only 8 relapsed. Following their second last acute (20 session course) of TMS, all of these patients had relapsed and required a further acute, protracted course of treatment. With the assistance of ER-TMS, at the time of reporting, these patients had remained in the program, not needing protracted treatment, for more than 21 weeks. Our earlier retrospective study also found an increased time to relapse [20].

Fitzgerald et al. [18] found that, following successful acute treatment, clusters of 5 TMS sessions at monthly intervals extended patients periods of wellness. They attributed this to the maintenance of the remission. The current study demonstrates that patients treated with this protocol may drift from remission into partial remission or relapse in a period of weeks, but remain relatively well because the early application of 5 TMS sessions restores remission, or at least, improves mood. These results support our earlier theory (Pridmore et al., 2017) that CM-TMS would be better conceptualized as ER-TMS.

TMS is not widely available in any country. Should the findings of this study be replicated, the question becomes, to what extent is society prepared to assist people with TRD who are responsive to ER-TMS? Continuous psychotherapy [4] and indefinite pharmacotherapy [31] have been described. Deep brain stimulation [32] and physician-assisted death [33] are potential future strategies. In this context, long-term ER-TMS may have a place. It is our clinical experience that after months or even years, some patients have achieved recovery.

It is important to highlight that, due to the current lack of funding for TMS in Australia, patients must be admitted to private hospitals, so that the cost of their treatment can be covered by the hospitalization rebate. Thus, in addition to ER-TMS, our patients receive the benefits of removal from stressors and the support and encouragement of hospital staff. However, while periods of hospitalization may please some, regular hospitalization is an annoyance to many individuals who wish to be at home or work, to the extent that some have refused this form of help because of the hospitalization requirement.

The next step, and one we are considering, is to determine whether out-patient ER-TMS provides the same benefits as in-patient ER-TMS.

Conflicts of interest

The authors have no conflicts of interest. They received no monies in return for this work, other than their routine employment. They have no links with commercial operations connected with TMS

References

[1] Trivedi M, Rush A, Wisniewski S, Nierenberg A, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D, implications for clinical practice. Am J Psychiatr 2006;163:28–40.
[2] Berwain I, Walter H, Seifritz E, Huys Q. Predicting relapse after antidepressant withdrawal – a systematic review. Psychol Med 2017;47:426–37.
[3] Akil H, Gordon J, Hen R, Javitch J, Mayberg H, McEwen B, et al. Treatment resistant depression: a multi-scale, systems biology approach. pii: S0149–7634(17)30368-8 Neurosci Biobehav Rev 2017. https://doi.org/10.1016/j.neubiorev.2017.08.019 [Epub ahead of print].
[4] Paykel E. Partial remission, residual symptoms, and relapse into depression. Dialogues Clin Neurosci 2008;10:431–7.
[5] Rush A, Kraemer H, Sackheim H, Fava M, Trivedi M, Frank E, et al. Report by the ACNP Taskforce on response and remission in major depressive disorder. Neuropsychopharmacology 2006;31:1841–53.
[6] Kyle P, Lemming O, Timmerby N, Sondergaard S, Andreassen K, Bech P. The validity of the different versions of the Hamilton Depression Scale in separation revision rates of placebo and antidepressants in clinical trials of major depression. J Clin Psychopharmacol 2016;36:453–6.

[7] Moller H, Riedel Seemuller F. Relapse or recurrence in depression: why has the cutoff been set at 6 months. Medicographia 2011;33:125–31.
[8] Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatr 2003;53:649–59.
[9] Souery D, Amsterdam J, de Montigny C, Lecubier Y, Montgomery S, Lipp O, et al. Treatment resistant depression: methodological overview and operational criteria. Eur Neuropsychopharmacol 1999;9:83–91.
[10] Thase M, Schwartz T. Choosing medications for treatment-resistant depression based on mechanism of action. J Clin Psychiatr 2015;76:720–7.
[11] Paykel E, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A. Residual symptoms after partial remission, an important outcome in depression. Psychol Med 1995;25:1171–80.
[12] Van Londen L, Molenaar R, Goekoop J, Zwinderman A, Rooijmans H. Three- to 5-year follow-up of outcome in major depression. Psychol Med 1998;28:731–5.
[13] O'Reardon J, Solvason H, Janicak P, Sampson S, Isenberg K, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatr 2007;62:1208–16.
[14] George M, Lisanby S, Avery D, McDonald W, Durkalski B, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatr 2010;67:507–16.
[15] Janicak P, Nahas Z, Lisanby S, Solvason H, Sampson H, Sampson S, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. Brain Stim 2010;3:187–99.
[16] Dannon P, Dolberg O, Schreiber S, Grunhaus L. Three and six-month outcome following courses of either ECT or TMS in a population of severely depressed individuals – preliminary report. Biol Psychiatr 2002;51:687–90.
[17] Rachid F. Maintenance repetitive transcranial magnetic stimulation (rTMS) for relapse prevention in with depression: a review. pii: S0165–1781(17)30473-0 Psychiatr Res 2017. https://doi.org/10.1016/j.psychres.2017.09.009 [Epub ahead of print].
[18] Fitzgerald P, Grace N, Hoy K, Bailey M, Daskalakis Z. An open label trial of clustered maintenance rTMS for patients with refractory depression. Brain Stimul 2013;6:292–7.
[19] Rybak M, Kelly E, Erger S, Pridmore S. A system of TMS Maintenance for depressed mood. (Conference Poster). Brain Stim 2017;10:361.
[20] Pridmore S, Erger S, Rybak M, Kelly E, Lawson F. Early relapse treatment (ERT) or "maintenance" transcranial magnetic stimulation (TMS)? Am. J. Med. Biol. Res. 2017;4:111–7.
[21] O'Sullivan R, Fava M, Agustin C, Baer L, Rosenbaum J. Sensitivity of the six-item Hamilton depression rating scale. Acta Psychiatr Scand 1997;95:379–84.
[22] Cowdry R, Gardner D, O'Leary K, Leibenluft E, Rubinow D. Mood variability: a study of four groups. Am J Psychiatr 1991;148:1505–11.
[23] Guy W, editor. ECDEU assessment manual for psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.
[24] Bech P, Lunde M, Bech-Andersen G, Lindberg L, Martiny K. Psychiatric outcome studies (POS): does treatment help the patients? A Popperian approach to research in clinical psychiatry. Nord J Psychiatr 2007;46(61 Suppl):4–34.
[25] Bachner Y, O'Rourke N, Goldfracht M, Bech P, Ayalon L. Psychometric properties of responses by clinicians and older adults to a 6-item Hebrew version of the Hamilton Depression Rating Scale (HAMD6). BMC Psychiatry 2013;13:2.
[26] Dunner D, Aaronson S, Sackheim H, Janicak P, Carpenter L, Boyadjis T, et al. A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. J Clin Psychiatr 2014;75:1394–401.
[27] Timmerby N, Andersen J, Sondergaard S, Ostergaard S, Bech P. A systematic review of the clinimetric properties of the 6-item version of the Hamilton Depression Rating Scale (HAM-D6). Psychother Psychosom 2017;86:141–9.
[28] Hooper C, Bakish D. An examination of the sensitivity of the six-item Hamilton Rating Scale for Depression in a a sample of patients suffering from major depressive disorder. J Psychiatry Neurosci 2000;25:178–84.
[29] Primo de Carvalho Alves L, Pio de Almeida Fleck M, Boni A, Sica da Rocha N. The major depressive disorder hierarchy: rasch analysis of 6 items of the Hamilton depression scale covering the continuum of depressive syndrome. PLoS One 2017;12, e0170000.
[30] World Health Organization (WHO). Depression and other common mental disorders. 2017 (WHO reference number: WHO/MSD/MER/2017.2).
[31] Bauer M, Pfennig A, Severus E, Wybrow P, Angst J, Moller H. World Federation of Societies of Biological Psychiatry, Task Force on Unipolar Depressive Disorders, 2013. World Federation of societies of biological psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, Part 1: update on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatr 2013;(14):334–85.
[32] Barrett K. Psychiatric neurosurgery in the 21st century: overview and the growth of deep brain stimulations. BJPsych Bull 2017;41:281–6.
[33] Steinbock B. Physician-assisted death and severe. Treatment-resistant depression. Hastings Cent Rep 2017;47:30–42.