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Research paper

Add-on deep Transcranial Magnetic Stimulation (dTMS) for the treatment of chronic migraine: A preliminary study

Chiara Rapinesi[a], Antonio Del Casale[a,b,*], Paola Scatena[a], Georgios D. Kotzalidis[a], Simone Di Pietro[a], Vittoria Rachele Ferri[a], Francesco Saverio Bersani[c], Roberto Brugnoli[a], Ruggero Nessim Raccah[d], Abraham Zangen[e], Stefano Ferracuti[c], Francesco Orzi[a], Paolo Girardi[a], Giuliano Sette[a]

[a] NESMOS (Neurosciences, Mental Health, and Sensory Organs) Department, Sapienza University of Rome, School of Medicine and Psychology, Sant'Andrea Hospital, Rome, Italy
[b] Department of Psychiatric Rehabilitation, P. Alberto Mileno Onlus Foundation, Vasto, Italy
[c] Department of Neurology and Psychiatry, Policlinico Umberto I University Hospital, Sapienza University of Rome, Rome, Italy
[d] ATID Ltd. Advanced Technology Innovation Distribution, Rome, Italy
[e] Department of Life Sciences, Ben Gurion University of the Negev, Be'er Sheva, Israel

HIGHLIGHTS

- dTMS can improve treatment-resistant chronic migraine (CM).
- Bilateral DLPFC dTMS reduced attack frequency, drug overuse, and depressive symptoms.
- dTMS is safe and effective in treatment-resistant CM, with or without depression.

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ABSTRACT

Introduction: Deep Transcranial Magnetic Stimulation (dTMS) can be an alternative treatment to relieve pain in chronic migraine (CM). The aim of this study was to evaluate the effect of high-frequency dTMS in add-on to standard treatment for CM in patients not responding to effective abortive or preventive drug treatment.
Methods: We randomized 14 patients with International Classification of Headache Disorders, 3rd Edition (ICHD-3) treatment-resistant CM to add-on dTMS (n = 7) or standard abortive or preventive antimigraine treatment (n = 7). Three sessions of alternate day 10 Hz dTMS consisting of 600 pulses in 10 trains were delivered to the dorsolateral prefrontal cortex (DLPFC), bilaterally, but with left hemisphere prevalence, for 12 sessions spread over one month.
Results: The add-on dTMS treatment was well tolerated. Patients treated with dTMS showed significant reduction of pain intensity, frequency of attacks, analgesic overuse, and depressive symptoms during treatment and one month later, compared to the month preceding treatment and at the same time-points compared to the control group.
Conclusions: As compared to standard pharmacological treatment alone, add-on high-frequency dTMS of the bilateral DLPFC reduced the frequency and intensity of migraine attack, drug overuse, and depressive symptoms. This study supports the add-on dTMS treatment in treatment-resistant CM.

1. Introduction

Approximately 2% of the global population suffers from chronic migraine (CM), a quality-of-life—impairing condition [1]. Patients with chronic pain may not respond to standard drug treatment and may require alternative approaches to relieve symptoms. The search for other than drug treatment is further justified by the fact

* Corresponding author at: NESMOS (Neurosciences, Mental Health, and Sensory Organs) Department, Sapienza University, School of Medicine and Psychology, Psychiatry Unit, Sant'Andrea Hospital, Via di Grottarossa 1035-1039, 00189 Rome, Italy.
E-mail address: antonio.delcasale@uniroma1.it (A. Del Casale).

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that prophylactic migraine drugs may trigger drug overuse, which is in turn complicated by drug overuse headache.

High frequency double-pulse magnetic stimulation over the frontal cortex has been shown to transiently suppress central pain perception and to increase the threshold to painful stimuli [2]. Other cortical areas, in particular the dorsolateral prefrontal cortex (DLPFC), have been considered as potential targets for nociceptive control [3]. The DLPFC actively modulates cortico-subcortical and cortico-cortical pathways and is involved in nociceptive transmission, having an inhibitory role on tonic pain [4].

Transcranial Magnetic Stimulation (TMS) has been proposed as an alternative treatment to improve CM pain [3] and prevent further episodes [5,6], while reducing drug overuse and their side effects.

Given the above considerations, in this preliminary study we aimed to further assess the efficacy of add-on dTMS in CM patients and its effect on mood during a 1-month follow-up period. We hypothesized that high frequency dTMS over the left DLPFC, by enhancing cortical activity, would reduce CM pain; we also supposed an interplay between improved mood and treatment response in case of correlation between the two.

2. Materials and methods

The study was conducted at the Psychiatry and Neurology Units of the Sant'Andrea Hospital, Sapienza University, Rome, Italy.

To address potential sources of bias (i) we have selected patients from our Psychiatry and Neurology Units; (ii) we have targeted patients fitting our main aims on the basis of inclusion and exclusion criteria; (iii) we have made a data analysis plan; and (iv) we have created a database for the statistical analyses.

2.1. Patients and inclusion criteria

We recruited 14 patients (mean age = 51.714 years, standard deviation [SD] ± 6.81) with CM, who were randomized to add-on dTMS (dTMS-AO) (n = 7) or standard treatment (SDT) (n = 7). CM diagnosis was established according to the ICHD-3 criteria [7]. All patients had severe daily or almost daily (≥15 days/month) headaches in the last three months (of which ≥8 headache days/month met criteria for migraine without aura), and did not respond to ≥3 preventive medications and to drug overuse (defined as a regular use for at least 10 days a month and for at least three months of ergotamine, triptans, opioid receptor agonists, combination analgesics, or unverified use of multiple drug classes; or a regular use of at least 15 days a month for at least three months of acetylsalicylate, paracetamol, and other nonsteroidal anti-inflammatory drugs [7]).

We included in this study medically refractory patients whose headaches significantly interfere with functioning or quality of life in spite of paying attention to triggers and lifestyle, and despite adequate trials (for dose and duration) of abortive (both a triptan and an intranasal or injectable DHE or nonsteroidal anti-inflammatory drugs or combination analgesics) and preventive (at least two of four drug classes, alone or in combination, from the following: beta-blockers; anticonvulsants/stabilizers; tricyclic antidepressants; calcium channel blockers) medications with evidence of efficacy [8].

All patients were on stable drug treatment since at least one month; treatment remained unchanged for the whole duration of the study. Three patients in each group met also criteria for major depressive disorder.

2.2. Exclusion criteria

Patients with pregnancy, liver or kidney disease, malignancy, severe hypertension, pacemaker or metallic implants, and history of seizure or structural brain lesions have been excluded. The study was approved by the Sant'Andrea Ethical Board; all patients provided free, informed consent.

2.3. Clinical measures and assessment tools

Patients scored daily their pain intensity on Visual Analogue Scale (VAS) score on a 0–100 scale and were required to report on a daily record the number and quality of their headache attacks and all medication. The Hamilton Depression Rating Scale (HDRS) was used to rate depression at baseline and each control visit, i.e., at the 2nd and 4th (last dTMS session) week, and at the 1-month post-treatment follow-up.

2.4. Deep TMS protocol

For dTMS sessions we used Brainsway's H1 coil deep TMS System (Brainsway, Har Hotzvim, Jerusalem, Israel). The H1 coil is designed to elicit neuronal activation in medial and lateral prefrontal regions, including the orbitofrontal cortex, with a preference for the left hemisphere. H1 coils were positioned over patient's scalp. The optimal spot on the scalp for stimulation of the right abductor *pollicis brevis* muscle was located, and the motor threshold established by delivering single stimulations to the motor cortex. The motor threshold, defined as the lowest stimulation intensity producing five motor evoked potentials (MEPs) of at least 50 μV in 5 of 10 stimulations, was measured by gradually increasing stimulation intensity. The site of stimulation was located 5.5 cm anterior to the point at which maximum stimulation of the *abductor pollicis brevis* muscle was reached. dTMS treatment was delivered by expert, trained, certified physicians (CR, VRF, PS, SDP) in trains of 10 Hz at 100% of the measured motor threshold. Each patient received 10 10-Hz trains per session at 100% of the measured motor threshold, with 2-s duration each and 20 s inter-train intervals for a total of 360 stimuli per session, a total of 4320 impulses. The complete cycle of the dTMS treatment consisted of three weekly sessions on alternate days for 4 consecutive weeks, for a total of 12 sessions. We introduced the above mentioned specific dTMS parameters and stimulation frequency for the treatment of CM.

2.5. Standard treatment

Patients in both the dTMS-AO and SDT groups received drug treatment aimed at preventing migraine attacks as well as abortive medications, once the attack was on the way. Among the latter, our patients used triptans (mainly sumatriptan and zolmitriptan), ergot alkaloids like ergotamine, nonsteroidal anti-inflammatory drugs (mainly ketorolac, ibuprofen, paracetamol, acetylsalicylate, and nimesulide), while prophylactic drugs were calcium channel blockers (cinnarizine), beta-adrenoceptor blockers (propranolol), anticonvulsant drugs like valproate, antidepressants (mostly the tricyclic amitriptyline), and any combination of these. The dTMS and control groups did not differ for use of medications at baseline. dTMS was added on ongoing prophylactic treatment, while patients were allowed to use abortive drugs *p.r.n.*

2.6. Outcome measures

The primary outcome measure was the difference in headache frequency from baseline to endpoint. The secondary outcomes were

Table 1
Sociodemographics of the two samples at baseline and clinical characteristics throughout the study.

Variable	dTMS-AO group (N = 7)	SDT group (N = 7)	Test (value)	*p*
Mean Age, years (SD)	53.28 (5.76)	50.14 (7.84)	Mann-Whitney ($U = 19$)	0.522
Gender, male/female ratio	2/5	3/4	Chi-squared test ($\chi^2 = 0.311$)	0.577
Mean migraine crises, number (SD)				
Baseline	5.43 (0.97)	5.42 (1.90)	Mann-Whitney ($U = 23.5$)	0.952
2 weeks	1.28 (1.11)	5.86 (1.86)	Mann-Whitney ($U = 2$)	**0.004****
4 weeks	0.71 (0.49)	2.86 (2.27)	Mann-Whitney ($U = 0$)	**0.002****
6-week follow-up	2.71 (1.11)	5.57 (2.22)	Mann-Whitney ($U = 6$)	**0.021***
Mean rescue treatments, number (SD)				
Baseline	7.43 (2.82)	6.71 (2.05)	Mann-Whitney ($U = 21.5$)	0.748
2 weeks	1.00 (1.15)	7.14 (2.27)	Mann-Whitney ($U = 0.5$)	**0.003****
4 weeks	0.71 (0.49)	6.86 (2.79)	Mann-Whitney ($U = 0$)	**0.002****
6-week follow-up	3.14 (1.68)	6.28 (1.98)	Mann-Whitney ($U = 4.5$)	**0.013***
Mean VAS scores (SD)				
Baseline	83.57 (6.90)	79.28 (8.38)	Mann-Whitney ($U = 17$)	0.373
2 weeks	60.00 (7.64)	78.57 (6.90)	Mann-Whitney ($U = 1$)	**0.003****
4 weeks	45.71 (9.76)	79.28 (13.05)	Mann-Whitney ($U = 0.5$)	**0.003****
6-week follow-up	58.57 (10.29)	74.28 (9.76)	Mann-Whitney ($U = 5.5$)	**0.018***
Mean HDRS scores (SD)				
Baseline	10.00 (2.08)	9.28 (2.36)	Mann-Whitney ($U = 20.5$)	0.652
2 weeks	6.57 (2.70)	8.14 (1.95)	Mann-Whitney ($U = 15.5$)	0.276
4 weeks	4.42 (1.90)	8.71 (1.70)	Mann-Whitney ($U = 1.5$)	**0.004****
6-week follow-up	3.00 (1.29)	8.14 (2.03)	Mann-Whitney ($U = 0$)	**0.002****

dTMS-AO, add-on deep transcranial magnetic stimulation; HDRS, Hamilton Depression Rating Scale; SD, standard deviation; SDT, standard treatment; VAS, visual analog scale. All significant results in **bold**.
* $p < 0.05$.
** $p < 0.01$.

change from baseline to endpoint of VAS scores (headache severity) and change in the number of rescue medications.

2.7. Statistical analysis

Baseline socio-demographic and clinical characteristics of the two groups of patients (dTMS-AO and SDT) were compared with the Mann-Whitney *U*-test for the continuous variable age, and the Chi-squared test for the categorical variable, gender. The number of migraine crises, number of rescue medications, VAS and HDRS scores were calculated at baseline (T1), 2-weeks (T2), 4-weeks (T3), and 6-weeks (T4).

Changes were then analyzed by mixed-model analysis of variance (ANOVA), with treatment (dTMS-AO vs. SDT) as the distinguishing between-subject factor, and time (T1, T2, T3, T4) as the repeated-measures factor. Sphericity assumption was tested through Mauchly's Test of Sphericity. Post-hoc multiple comparisons were performed with the Bonferroni test, to assess differences at each timepoint.

The cut-off for statistical significance was set at $p < 0.05$. All *P* values were two-tailed. We used the IBM SPSS Statistics 21.0 (IBM Corporation, 2012) for all analyses.

3. Results

There were no significant differences between the dTMS-AO and SDT groups regarding both gender and age, and no significant baseline differences in number of migraine crises, number of rescue medications, VAS and HDRS scores (Table 1).

3.1. Number of migraine crises

Mean differences in the number of migraine crises from baseline in the two treatment groups are shown in Fig. 1a. We found significant within-subjects main effects of time ($F[3,36] = 11.8$; $p < 0.001$; $\eta^2 = 0.496$) and treatment group-by-time interaction ($F[3,36] = 17.422$; $p < 0.001$; $\eta^2 = 0.592$), and significant between-subjects effect of group ($F[1,12] = 19.168$, $p < 0.001$; $\eta^2 = 0.615$). Bonferroni adjustment for multiple comparisons showed that the reduction of migraine crises from baseline was significantly larger in the dTMS-AO than in the SDT group at T2 ($p = 0.006$), T3 ($p < 0.001$), and T4 ($p = 0.005$); no significant differences were observed between T2 and T3, T2 and T4, and T3 and T4. Means analyses showed significant effect of group ($F[1,12] = 19.168$; $p < 0.001$; $\eta^2 = 0.615$) and a significant multivariate effect of time ($F = 13.297$; $p < 0.001$; $\eta^2 = 0.800$).

3.2. Rescue medications

Mean differences in the number rescue treatments from baseline in the two treatment groups are shown in Fig. 1b. We found significant within-subjects main effects of time ($F[3,36] = 13.400$; $p < 0.001$; $\eta^2 = 0.759$) and treatment group-by-time interaction ($F[3,36] = 15.919$; $p < 0.001$; $\eta^2 = 0.661$), and significant between-subjects effect of group ($F[1,12] = 19.454$, $p < 0.001$; $\eta^2 = 0.618$). Bonferroni adjustment for multiple comparisons showed that reduction in rescue medication use from baseline was significantly larger in the dTMS-AO than in the SDT group at T2 ($p = 0.007$), T3 ($p = 0.002$), and T4 ($p < 0.001$); no significant differences were observed between the T2 and T3, T2 and T4, and T3 and T4. Means analyses showed significant effect of group ($F[1,12] = 19.454$; $p < 0.001$; $\eta^2 = 0.618$) and a significant multivariate effect of time ($F = 11.367$; $p < 0.001$; $\eta^2 = 0.773$).

3.3. VAS scores

Mean differences in VAS scores from baseline in the two treatment groups are shown in Fig. 1c. We found significant within-subjects main effects of time ($F[3,36] = 15.036$; $p < 0.001$; $\eta^2 = 0.556$) and treatment group-by-time interaction ($F[3,36] = 13.656$; $p < 0.001$; $\eta^2 = 0.532$), and significant between-subjects effect of group ($F[1,12] = 22.250$; $p < 0.001$; $\eta^2 = 0.650$). Bonferroni adjustment for multiple comparisons showed that VAS score reduction from baseline was significantly larger in the

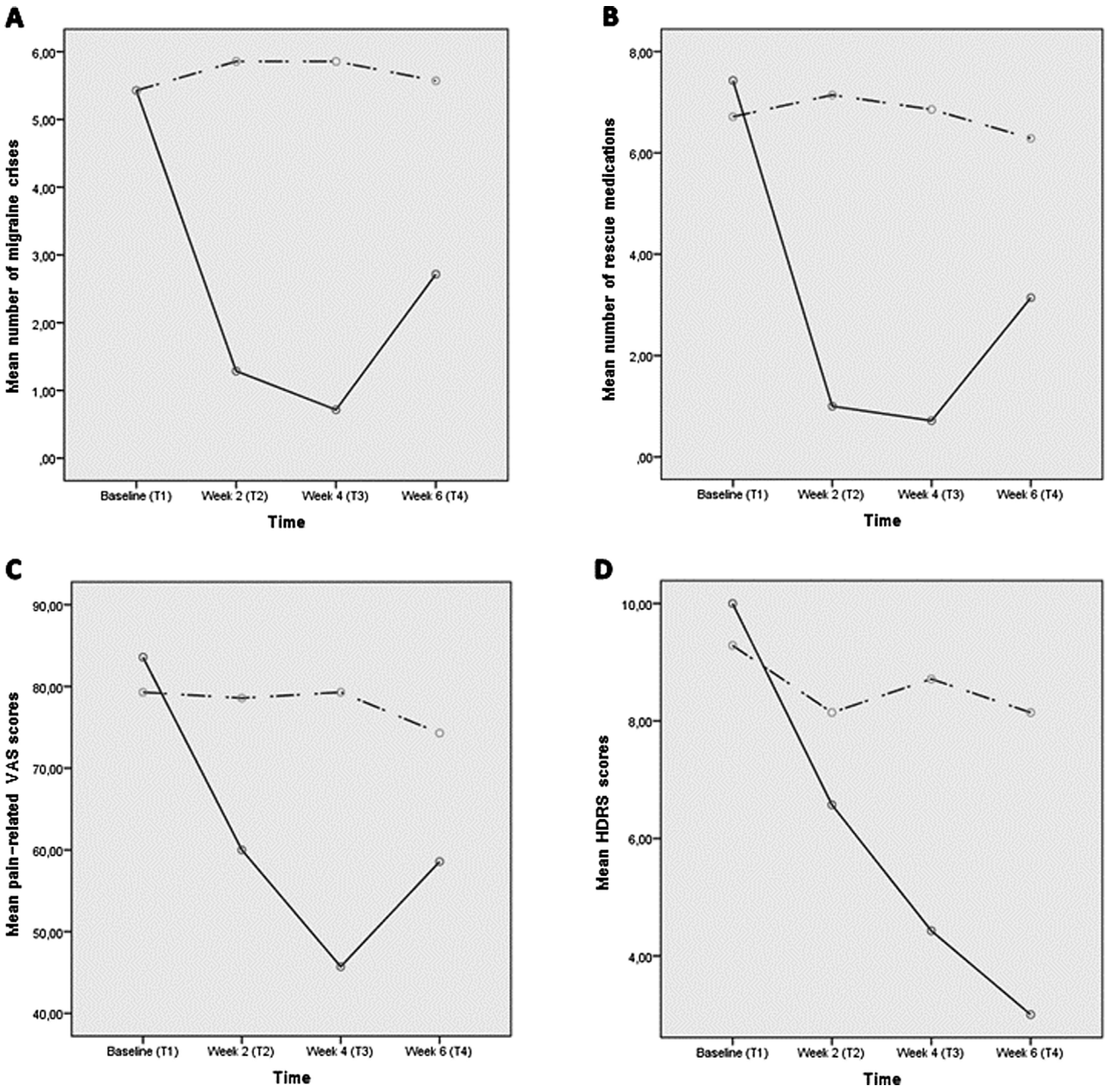

Fig. 1. Time course of migraine episodes (a), rescue medication use (b), and VAS (c) and HDRS scores (d) in the dTMS add-on group (straight lines) and in the standard treatment-only group (broken lines).

dTMS-AO than in the SDT at T2 ($p = 0.012$), T3 ($p < 0.001$), and T4 ($p = 0.004$); no significant differences were found between T2 and T3, T2 and T4, and T3 and T4. Means analyses showed significant effect of group ($F[1,12] = 22.250$, $p < 0.001$; $\eta^2 = 0.650$) and a significant multivariate effect of time ($F = 11.839$; $p < 0.001$; $\eta^2 = 0.780$).

3.4. HDRS

Mean HDRS score differences from baseline in the two treatment groups are shown in Fig. 1d. We found significant within-subjects main effects of time ($F[3,36] = 27.451$; $p < 0.001$; $\eta^2 = 0.696$) and treatment group-by-time interaction ($F[3,36] = 33.384$; $p < 0.001$), and significant between-subjects effect of group ($F[1,12] = 7.669$; $p = 0.017$; $\eta^2 = 0.390$). Bonferroni adjustment for multiple comparisons showed that HDRS score reduction from baseline was significantly larger in the dTMS-AO than in the SDT group at all timepoints ($p < 0.001$); no significant differences were observed between T2 and T3, and between T3 and T4, while between T2 and T4 we found a significant HDRS drop ($p = 0.044$). Means analyses showed significant effect of group ($F[1,12] = 7.669$; $p = 0.017$; $\eta^2 = 0.390$) and a significant multivariate effect of time ($F = 25.073$; $p < 0.001$; $\eta^2 = 0.883$).

4. Discussion

To the best of our knowledge, this is the first dTMS study conducted on patients affected by CM. High-frequency dTMS delivered over the bilateral DLPFC with left prevalence was effective and well tolerated in medically-resistant CM patients. Add-on dTMS treatment reduced migraine frequency, severity, use of rescue medications, and depressive symptoms significantly up to 6 weeks compared to baseline. Our results match previous studies with

superficial high-frequency repetitive TMS (rTMS) over the DLPFC [3,5], but are in contrast with those of another rTMS study that found no benefit for DLPFC stimulation as compared to M1 stimulation in migraine patients [9]. It is possible that the deep technique recruits more pain-suppressing circuits than does superficial repetitive transcranial magnetic stimulation and this accounts for the differences encountered between our study and Schulman et al. [8]. In fact, it has been shown that the H-coil elicits a wider stimulation field than the classical figure of 8 coil [10]. The effect of rTMS treatment, which is able to stimulate cortical areas noninvasively, could be attributed to the putative role of DLPFC in mechanisms of pain control; DLPFC seems to exert an inhibitory effect on pain perception by negatively modulating central supraspinal pain pathways [11]. Inter-regional correlation of midbrain and medial thalamic activity was significantly reduced during high left DLFPC activity, suggesting that its negative correlation with pain might result from dampening of midbrain-medial thalamic pathway effective connectivity. DLPFC activation has been temporally related to amelioration of pain sensation in capsaicin-induced acute pain [12].

In line with the results of recent meta-analyses [12,13], our data also showed dTMS-associated improvement of depressive symptoms after four weeks of bilateral DLPFC stimulation. DTMS was found to be safe and efficacious in the treatment of depressive episodes and comorbid anxiety in major depressive [12,13] and bipolar disorders [14], alcohol use disorder and alcohol use-related dysthymia and depression [15–17].

The differences between the two groups cannot be accounted for by differences in drug intake, as patients in the two groups received similar doses of similar drugs. It is possible that dTMS enables the pain circuitry to be more responsive to drugs.

Interestingly, the effect on migraine-related measures tended to decrease after the completion of the dTMS treatment cycle and in the absence of maintenance sessions, while the effect on depression mounted even after the treatment was stopped. This fact could point to the need for maintenance sessions in patients with CM. At any rate, CM measures at follow-up were significantly better than at baseline. This study supports dTMS treatment also in patients with comorbid CM and depressive symptoms. Our data indicate efficacy for dTMS in reducing migraine episodes and severity, number of rescue medications, and comorbid depressive symptoms.

4.1. Limitations

This is a one-center open-label study with a limited sample size and not including a sham dTMS control group. Further studies with larger samples and double-blind methodology can be useful to confirm the effectiveness of the dTMS for patients with treatment-resistant CM.

5. Conclusions

High-frequency dTMS delivered over the bilateral DLPFC with left prevalence was effective and well tolerated in medically-resistant CM patients as add-on treatment to medications. In this study a standard pharmacological treatment with add-on dTMS for four weeks, as compared to standard pharmacological treatment alone, significantly reduced migraine frequency, severity, use of rescue medications, and depressive symptoms up to six weeks from baseline. It is highly likely that dTMS enables the pain circuitry to be more responsive to drugs. This study also supports add-on dTMS treatment in patients with comorbid CM and depressive symptoms.

Financial and competing interests disclosure

R.N.R. is scientific consultant to ATID Ltd., distributor of deep r-TMS (Brainsway) technology in Italy. All other authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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