*Original article / Araştırma*

# Combining transcranial magnetic stimulation and cognitive-behavioral therapy in treatment resistant obsessive-compulsive disorder

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***ABSTRACT***

***Objective:*** *A non-negligible percentage of patients with obsessive-compulsive disorder (OCD) do not respond satisfactorily to treatments. Inpatient cognitive-behavioral therapy (CBT) has provided some relief in even refractory and chronic patients. Repetitive transcranial magnetic stimulation (rTMS) has also provided promising results. However, no studies have combined these two strategies.* ***Methods:*** *Eighteen patients with treatment resistant and chronic OCD who had been hospitalized in order to receive pharmacotherapy, inpatient CBT and rTMS were evaluated on the Yale-Brown Obsession and Compulsion Scale (Y-BOCS) and the Hamilton Depression Rating Scale-17 (HDRS-17). rTMS was applied every day over the left dorsolateral prefrontal cortex for 5 days in a week with parameters of 25 Hz and 1000 pulses.* ***Results:*** *Y-BOCS scores decreased by 59.14%, from 30.72±6.12 at admission to 12.55±7.44 when discharged. HDRS-17 scores decreased by 56.80%; from 18.38±3.94 at admission to 7.94±5.70 at discharge. The mean numbers of rTMS and CBT sessions were 23.28±6.78 and 17.17±5.04 respectively.* ***Discussion:*** *The combination of pharmacotherapy, CBT and rTMS may be effective in treatment resistant and chronic OCD in the short term.* ***(Anatolian Journal of Psychiatry 2015; 16(3):180-188)***

***Key words:*** *obsessive-compulsive disorder, OCD, transcranial magnetic stimulation, cognitive-behavioral therapy*

# Tedaviye dirençli obsesif kompulsif bozuklukta transkranyal manyetik uyarım ve bilişsel-davranışçı terapinin birlikte kullanımı

***ÖZET***

***Amaç:*** *Obsesif kompulsif bozukluk (OKB) hastalarının azımsanamayacak bir kısmı tedaviye yeterli yanıt vermezler. Yataklı tedavide uygulanan bilişsel davranışçı terapiler (BDT) kronik ve dirençli olgularda dahi bir yarar sağlayabilir. Yineleyen transkranyal manyetik uyarım tedavisi (TMU) ile de umut verici sonuçlar bildirilmiştir, ancak bu iki etkin tedavi yöntemini bir arada kullanan çalışma bulunmamaktadır.* ***Yöntem:*** *Tedaviye dirençli ve kronik OKB tanısı olan 18 olgu farmakoterapi, BDT ve TMU tedavisi kombinasyonu uygulanmak üzere yatırıldı. Olgular Yale-Brown Obsesyon ve Kompulsiyon Ölçeği (Y-BOCS) ve Hamilton Depresyon Dercelendirme Ölçeği-17 (HDRS-17) ile değerlendirildiler. TMU 20 seans, 25 Hz, 1000 vuru parametreleri ile sol dorsolateral prefrontal kortekse uygulandı.* ***Bulgular:*** *Tedavi öncesinde ortalama 30.72±6.12 olan Y-BOCS puanları tedavi bitiminde 12.55±7.44 puana inerek %59.14 gerilemiş bulundu. Tedavi öncesinde ortalama 18.38±3.94 olan HDRS-17 puanlarında ise tedavi bitiminde 7.94±5.70 puan ile %56.80 azalma saptandı. Uygulanan tedavi seanslarının ortalama sayıları TMU için 23.28±6.78 ve BDT için 17.17±5.04 olarak gerçekleşti.* ***Tartışma:*** *Tedaviye dirençli ve kronik OKB olgularında farmakoterapi, BDT ve TMU kombinasyonu ile yapılacak tedavi etkili bir seçenek olabilir.* ***(Anadolu Psikiyatri Derg 2015;***

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***Anahtar sözcükler:*** *Obsesif kompulsif bozukluk, OKB, transkranyal manyetik uyarım, bilişsel davranışçı terapi*

## INTRODUCTION

Obsessive-compulsive disorder (OCD) has a lifetime prevalence of 2.3% and is the tenth leading cause of disability amongst all diseases.[1] Although clomipramine and selective serotonin re-uptake inhibitors are beneficial in OCD, 40-60% of patients only respond partially or not at all.[2] Similarly, while cognitive-behavioral therapy (CBT) is another effective treatment modality, it is useful in only 50-60% of patients and only 25% recover completely.[3] CBT can be effective in partial responders to pharmacotherapy[4] and even non-responders may benefit to some degree.[5] The combination of pharmacotherapy and psychotherapy has been shown to be an effective choice of treatment.[6] However, some authors have reported that, despite the use of appropriate medication, alone or in combination with CBT, up to 40% of OCD patients continue to suffer from obvious symptoms and 10% do not improve at al.[7]

Although OCD has traditionally been treated in outpatient settings, intensive inpatient psychotherapy combined with pharmacological treatment has been reported to be helpful for the patients with severe, refractory OCD.[8,9] Given the high prevalence and lack of satisfactory improvement in a significant percentage of patients there is an obvious need to develop novel treatments. Repetitive transcranial magnetic stimulation (rTMS) has emerged as a neuromodulation technique and been applied to various psychiatric disorders, providing the best results in the treatment of depression.[10] The first studies that used rTMS in the treatment of OCD targeted the dorsolateral prefrontal cortex (DLPFC), with no significant effect when compared to sham rTMS; however, recent studies targeting the supplementary motor area (SMA) and the orbitofrontal cortex (OFC) have produced promising results.[11]

As far as we know, no study has yet been published in which rTMS has been combined with standard therapeutic OCD tools, namely pharmacological treatment and CBT. Here we report the results from 18 inpatients with OCD who were treated with all three approaches.

## METHODS

The study protocol conformed to the Helsinki declaration; all patients were fully informed and signed consent forms. Eighteen patients who had been admitted to the Neuropsychiatry Istanbul Hospital between December 2010 and February 2013 suffering from a severe loss of functioning due to OCD, diagnosed according to the DSM-IV and who were 'treatment-resistant' participated to study.

In this study 'treatment resistance' was described as failure to remit or respond clinically (50% reduction in symptoms) despite ≥2 adequate trials of standard therapies with clomipramine or a selective serotonin reuptake inhibitor. None of the patients had a trial of electroconvulsive therapy, transcranial magnetic stimulation or any other neuromodulatory treatment. Although all patients had received pharmacotherapy, only 38% had also received CBT (n=7) before the current hospitalization. Forty-four percent of patients (n=8) had been admitted previously and 16% (n=3) had repeated hospitalizetions.

Exclusion criteria were applied to patients who had suffered from a concurrent mental illness that had caused more severe problems than OCD and those with mental retardation or retarded depression that was severe enough to limit the effectiveness of CBT. The sample did not include OCD patients with psychotic symptoms or a history of psychosis. One patient was excluded due to the aggravation of depressive symptoms after five sessions of rTMS to the extent that CBT became impossible.

All subjects received a combination of pharmacotherapy, CBT and rTMS. All patients received one hour of CBT focused on OCD on every weekday and were continuously monitored by psychiatric nurses. The nurses helped them with their behavioral homework that consisted of preventing patients' compulsive behavior and their avoidance of anxiety-provoking situations. rTMS was administered with a Magstim Super Rapid stimulator (Magstim, Whitland, United Kingdom) with a figure-of-eight-shaped coil. Stimulation lasted two seconds at a frequency of 25 Hertz. One thousand pulses and 20 trains were given over the left DLPFC. The motor threshold was determined by inspecting the movement of the abductor pollicis brevis. Stimulation up to 110% of the motor threshold was exerted over the DLPFC, which was assumed to be five centimeters anterior to the area that

caused the thumb to contract. Pharmacotherapy and rTMS were given together. The ongoing medications of the patients when they were participated to the study were not changed but doses were adjusted by therapeutic drug monitoring (TDM). All the patients were on pharmacotherapy as given in detail on Table 1. Discharge decision was based on either the improvement of symptoms to a significant degree or the patient's request.

The severity of OCD was assessed according to the Yale-Brown Obsession and Compulsion Scale (Y-BOCS).[12,13] Specifically, the measure used was percentage of patients showing at least a 40% decrease in their Y-BOCS scores as this degree of improvement has generally been accepted as an indication of a good response to treatment. A secondary outcome was the severity of associated depression, as measured by the Hamilton Depression Rating Scale-17 (HDRS-17), which is a 17-item instrument used to measure the severity of depression.[14,15] The percentage of patients showing at least a 50% decrease in their HDRS-17 scores were calculated, as this degree of improvement has been accepted as a response to treatment in most studies. In this study, response rate was defined as a 40% decrease in Y-BOCS score and a 50% decrease in HDRS-17 scores.

The Wilcoxon signed-rank test was used to test for a significant difference between patient scores at admission and at discharge. This method is a non-parametric statistical hypothesis test that is used when comparing two related samples, matched samples, or repeated measurements on a single sample.

## RESULTS

The demographic and clinical characteristics of patients are shown in Table 1. Treatment outcomes are shown in Table 2. The mean age of patients was 30.67±11.30. In terms of gender, 44.4% of patients were male and 55.6% were female, while 33.3% were married and 66.7% were single.

Y-BOCS scores showed a 59.14% decrease between admission and discharge (30.72 ± 6.12 at admission and 12.55±7.44 at discharge). The proportion of patients who had a 40% or more decrease in their Y-BOCS score was 83.3%. Similarly, HDRS-17 scores improved by 56.80% between admission and discharge (18.38±3.94 at admission and 7.94±5.70 at discharge). There was a minimum 50% decrease HDRS-17 scores in 83.3% of patients. The mean number of days of hospitalization was 24.39±8.36. Patients had suffered a mean 11.72±9.51 years of illness. They received a mean number of 23.28±6.78 sessions of rTMS and of 17.17±5.04 sessions of CBT. The mean number of previous hospitalizetions was 0.72±1.07.

## DISCUSSION

We employed a combination of medication, intensive inpatient CBT and rTMS in patients with chronic and severe OCD who were refracttory to previous interventions. What is new in the present study is the application of rTMS, the effectiveness of which is not clear in OCD though its role in depression treatment has been established. Most patients significantly improved in less than a month.

Calvocoressi et al. reported that scores on the Y-BOCS of 66 OCD inpatients improved significantly (from a mean of 27.6 at admission to 18.3 at discharge) after a mean hospital stay of 102 days.[16] In a sample of 403 individuals receiving intensive residential treatment for severe, refracttory OCD over an average period of 66 days, mean Y-BOCS scores decreased by 30.1% from 26.6 to 18.6.[17] Similarly, a partial hospitalization program that combined behavioral and pharmacological therapy to treat 58 patients with severe OCD resulted in a minimum 25% decrease in Y-BOCS scores (a successful outcome) in 71% of patients.[18] The same study reported that 55% of patients had Y-BOCS scores of 16 or less (i.e. mild symptoms) at the end of the hospitalization program. McKenzie and Marks reported a 30-50% decrease in symptom severity in 218 patients with chronic and severe OCD.[19]

Our trial of pharmacotherapy, applied together with inpatient CBT and rTMS resulted in a greater decrease in Y-BOCS scores and higher response and remission rates than those reported in previous studies. Furthermore, one of the most remarkable results of our study is the short length of hospitalization compared to previous research. The length of stay in the largest (n=403) study of inpatient psychotherapy was 66 days.[17] Other studies reported even longer hospital stays; for example, 102 days in the study by Calvocoressi et al.[16] and 104 days in the study by Drummond et al.[8]

To the best of our knowledge, ten randomized controlled studies using rTMS in the treatment of OCD had been published before the end of

**Table 1.** Demographic and clinical characteristics of patients

| Age (years) | Sex (M = male; F = female) | Marital (M=married; S=single) status | Days of hospitalization | Previous hospitalizations | Duration of illness (years) | Number of TMS sessions | Number of CBT sessions | Medication (mg) | Obsessions | Compulsions | Y-BOCS on admission | Y-BOC on discharge | HDRS-17 on admission | HDRS-17 on discharge |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 53 | M | M | 28 | 1 | 35 | 20 | 13 | Clomipramine 300<br>Lamotrigine 100<br>Chlorpromazine 100<br>Clonazepam 3 | Somatic (P)<br>Aggressive<br>Religious | Checking<br>Others | 33 | 2 | 19 | 8 |
| 23 | M | S | 30 | 4 | 5 | 30 | 22 | Venlafaxine 75<br>Mirtazapine 15<br>Sulpiride 400 | Others (P)<br>Sexual (P)<br>Aggressive<br>Contamination<br>Hoarding<br>Religious | Cleaning<br>Checking<br>Repetitive behav. (P)<br>Ordering<br>Hoarding<br>Symmetry | 26 | 17 | 17 | 11 |
| 24 | F | S | 22 | 0 | 4 | 20 | 14 | Fluvoxamine 200<br>Paroxetine 20<br>Aripiprazole 10 | Contamination (P)<br>Repetitive beh.(P)<br>Sexual (P)<br>Aggressive<br>Religious | Cleaning (P)<br>Others | 32 | 11 | 23 | 9 |
| 24 | F | S | 20 | 0 | 13 | 20 | 15 | Sertraline 200<br>Aripiprazole 20<br>Carbamazepine 400 | Sexual (P)<br>Religious (P)<br>Aggressive | Checking<br>Counting<br>Others | 20 | 7 | 17 | 3 |
| 43 | F | S | 40 | 2 | 32* | 40 | 30 | Fluvoxamine 100<br>Clomipramine 50<br>Risperidone 2<br>Biperiden 2 | Contamination (P)<br>Aggressive<br>Symmetry<br>Others | Cleaning (P)<br>Checking<br>Others | 28 | 7 | 19 | 9 |
| 22 | F | S | 30 | 0 | 7 | 30 | 22 | Fluvoxamine 200<br>Paroxetine 60<br>Aripiprazole 10 | Contamination (P)<br>Checking<br>Hoarding<br>Religious<br>Symmetry (P)<br>Somatic | Cleaning (P)<br>Hoarding<br>Ordering<br>Repetitive behav.<br>Others | 40 | 4 | 15 | 0 |
| 46 | M | M | 39 | 1 | 13 | 30 | 22 | Fluvoxamine 150<br>Clomipramine 75<br>Aripiprazole 15 | Contamination (P)<br>Hoarding<br>Aggressive<br>Sexual<br>Others | Cleaning (P)<br>Checking<br>Repetitive behav.<br>Counting<br>Hoarding | 39 | 12 | 22 | 7 |
| 45 | F | M | 11** | 1 | 20 | 20 | 15 | Clomipramine 150<br>Flupentixol 8<br>Valproic acid 750 | Hoarding (P)<br>Aggressive<br>Contamination<br>Symmetry | Hoarding (P)<br>Ordering<br>Repetitive behav. | 34 | 26 | 13 | 6 |
| 19 | M | S | 35 | 0 | 3 | 30 | 22 | Fluvoxamine 200<br>Clomipramine 75<br>Paliperidone 6<br>Clonazepam 3 | Religious (P)<br>Aggressive<br>Hoarding<br>Symmetry | Repetitive behav. (P)Others<br>Counting<br>Ordering | 30 | 14 | 23 | 8 |

**Table 1.** Demographic and clinical characteristics of patients (continue)

| Age (years) | Sex (M = male; F = female) | Marital (M=married; S=single) status | Days of hospitalization | Previous hospitalizations | Duration of illness (years) | Number of TMS sessions | Number of CBT sessions | Medication (mg) | Obsessions | Compulsions | Y-BOCS on admission | Y-BOC on discharge | HDRS-17 on admission | HDRS-17 on discharge |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 27 | M | S | 21 | 2 | 14 | 20 | 15 | Sertralin 200<br>Fluvoxamine 100<br>Paliperidone 6<br>Chlorpromazine 200<br>Valproic acid 1500 mg<br>Lorazepam 2 mg | Sexual (P)<br>Aggressive | Repetitive behav. | 24 | 6 | 14 | 4 |
| 29 | F | S | 20 | 0 | 5 | 20 | 15 | Fluoxetine 60<br>Clomipramine 150<br>Sulpiride 100 | Contamination (P)<br>Symmetry<br>Aggressive | Cleaning (P) | 36 | 15 | 19 | 11 |
| 35 | M | S | 25 | 1 | 15 | 20 | 15 | Fluvoxamine 300<br>Pimozide 4 | Sexual (P)<br>Contamination (P)<br>Biperiden 4 mg | Cleaning (P)<br>Checking | 28 | 13 | 18 | 7 |
| 20 | M | S | 20 | 0 | 6 | 20 | 15 | Paroxetine 40<br>Clomipramine 150<br>Sulpiride 250 | Others (P)<br>Religious<br>Symmetry | Checking (P)<br>Ordering<br>Others | 40 | 17 | 8 | 4 |
| 19 | M | S | 20 | 0 | 7 | 21 | 16 | Fluoxetine 40<br>Fluvoxamine 100<br>Sulpiride 200 | Contamination (P)<br>Aggressive<br>Sexual | Cleaning (P)<br>Checking | 30 | 8 | 22 | 9 |
| 40 | F | M | 30 | 0 | 18 | 30 | 22 | Paroxetine 30<br>Amisulpride 100<br>Quetiapine 50<br>Clonazepam 1 | Contamination (P)<br>Ordering<br>Symmetry | Cleaning (P) | 38 | 14 | 19 | 6 |
| 42 | F | M | 15 | 1 | 6 | 15 | 11 | Sertraline 200<br>Fluvoxamine 200<br>Pimozide 4<br>Quetiapine 200<br>Clonazepam 2 | Others (P)<br>Somatic | Others (P)<br>Checking | 25 | 13 | 22 | 7 |
| 23 | F | S | 13 | 0 | 3 | 13 | 10 | Fluoxetine 60<br>Fluvoxamine 200<br>Methylphenidate 10 | Religious (P)<br>Aggressive<br>Sexual | Others (P)<br>Checking | 26 | 32 | 21 | 28 |
| 18 | F | S | 20 | 0 | 5 | 20 | 15 | Sertraline 200<br>Flupentixol 6<br>Topiramate 200 | Contamination (P)<br>Others<br>Aggressive | Cleaning (P) | 24 | 8 | 20 | 7 |

** Aged 25 when treatment began, ** 20 rTMS, 11 rTMS sessions of rTMS were applied during hospitalization and 9 additional sessions were applied in outpatient settings. The second Y-BOCS was assessed one month after discharge.*
*Y-BOCS: Yale-Brown Obsession and Compulsion Scale, HDRS-17: Hamilton 17-Item Depression Rating Scale, (P): Principal obsessions and compulsions*

**Table 2.** Treatment outcomes

| | Y-BOCS | Obsession scores | Compulsion scores | HDRS-17 |
|---|---|---|---|---|
| On admission (mean±SD) | 30.72±6.12 | 16.11±2.94 | 14.05±4.13 | 18.38±3.94 |
| On discharge (mean±SD) | 12.55±7.44 | 6.77±4.02 | 5.77±3.70 | 7.94±5.70 |
| Decrease from admission to discharge (mean) | 18.17 | 9.34 | 8.28 | 10.44 |
| Decrease from admission to discharge (percent) | 59.14 | 57.97 | 58.93 | 56.80 |
| Response rate* (percentage of patients) | 83.3 | - | - | 83.3 |

** Response rate was defined as a 40% decrease in Y-BOCS score and a 50% decrease in HDRS-17 scores.*
*Y-BOCS: The Yale-Brown Obsession and Compulsion Scale, HDRS-17: The 17-Item Hamilton Depression Rating Scale*
*SD: Standard deviation*

2012. These studies inspected 282 subjects (161 received active treatment, 121 received sham rTMS), with a mean of 14.8±6.5 sessions.[11] In all of these studies, all or most of the subjects were taking medication in addition to receiving rTMS. Patients in most studies were somewhat resistant to treatment. Overall, changes in their Y-BOCS scores were significant and moderate. Thirty-five percent of patients who received active rTMS and 13% who received sham rTMS responded to treatment, with a decrease in Y-BOCS scores of 25-40%.

In similar works, Prasko et al.,[20] Sachdev et al.[21] and Badawy et al.[22] applied rTMS over the left DLPFC. However, Prasko et al. employed low-frequency (1 Hz) rTMS, while Sachdev et al. employed 10 Hz and Badawy et al. 20 Hz. Neither Prasko et al. nor Sachdev et al. found any difference between active and sham rTMS. In their study of 60 patients who received 20 sessions of rTMS, rTMS was particularly more effective than a placebo when given as an add-on therapy; initial YBOCS scores (25.85±4.88) decreased to 20.60±4.30.[22] Therefore, the comparison of high-frequency versus low-frequency rTMS over the left DLPFC merits further investigation.

Of those researchers who applied rTMS over the right DLPFC, Alonso et al.[23] applied 1 Hz, Sarkhel et al.[24] and Mansur et al.[25] applied 10 Hz. Also several researchers applied 1 Hz rTMS over the pre-SMA.[26-28] Ruffini et al.[29] applied rTMS at a frequency of 1 Hz for 15 sessions over the left orbitofrontal cortex (OFC). Unlike earlier studies that in general support the finding that low-frequency rTMS on the pre-SMA and OFC is more effective than high-frequency rTMS on the DLPFC,[11] we found that high frequency rTMS in combination with CBT and pharmacotherapy was an effective treatment. This is consistent with the study by Badawy et al. who applied a higher frequency (20 Hz) than in any previous investigation (10 Hz had been the highest frequency used).[22]

Low-frequency rTMS has been reported to exert an inhibitory effect on the neural tissue while high-frequency stimulation is thought to have the opposite effect.[30] The orbitofronto-striatal circuitry has been observed to exhibit hyperactivity in OCD.[31] Therefore, it is plausible that low-frequency rTMS, which inhibits those parts of the brain, can relieve the symptoms of OCD, which is a disease of neural hyperactivity. How then, can we explain the effectiveness of high-frequency rTMS in OCD? Badawy et al. found that the motor threshold increased in OCD patients who responded to TMS after 15 sessions, while non-responders showed non-significant changes.[22] As a result, it can be concluded that although high-frequency rTMS is excitatory, it could decrease the hyperexcitability in neurocircuitry when some critical upper limit is exceeded. If these findings are evaluated in the context of the reported cortical hyperexcitability in OCD,[32] the efficacy of high-frequency stimulation in OCD patients seem reasonable. The GABAergic system may also be important in the effectiveness of rTMS in OCD. rTMS has been reported to potentiate GABAergic neurotransmission, particularly at high frequencies.[33] rTMS can also modulate NMDA neurotransmitter mechanism both of which have been associated with dysfunction in OCD.[34]

The efficacy and safety of rTMS of 25 Hz has been shown in studies with depressive patients.[35,36] In this study, we did not observe any seizure or serious side effect that lead to stop the rTMS. Three of the patients reported mild headache continuing 1 or 2 hours after each session. Patients did not report any tinnitus, dizziness,

nausea, or cognitive adverse effects, however, one patient was excluded due to the aggravation of depressive symptoms after five sessions of rTMS.

Our results suggest that the combination of pharmacotherapy, high-frequency rTMS over the left DLPFC and inpatient CBT is effective in patients with severe and chronic OCD. The length of stay, treatment cost, and time away from school or work are important issues in inpatient OCD treatments.[17] Given that a significant clinical response of OCD symptoms -even in milder and less chronic forms of OCD- often requires up to three months of treatment with pharmacological agents or weekly CBT, the time to achieve a satisfactory improvement can be significantly shortened by the addition of rTMS to classical therapeutic approaches.

This study has some limitations. First, we did not include a sham rTMS group; however, the fact that our patients were severely and chronically ill decreased the chance of spontaneous improvement, although it cannot be ruled out. Second, we cannot exclude the possibility that rTMS primarily helped relieve depression, thus increasing the motivation of patients to participate in CBT, rather than acting specifically on their OCD. Compared to previous studies of inpatient treatment of OCD, depression scores in our patients decreased very rapidly, which confirms the well-known finding that rTMS acts more rapidly in ameliorating depression than pharmacotherapy or CBT. Third, all patients continued to take medication. Although the duration of hospitalization was too short for the clinical effects of pharmacotherapy to become apparent, maintaining the drugs that patients had already been using might have contributed to the improvement of their OCD, given that relief from symptoms begins late in OCD treatment. Increasing or adjusting drug dosage according to TDM might have also increased treatment efficiency. Nevertheless, although most patients in previous studies had also been medicated they did not recover as fast as the patients in this study, which confirms the efficacy of rTMS. Fourth, intensive CBT might have been primarily responsible for the improvement in our patients. However, results from previous studies that assessed intensive inpatient CBT were not as successful as ours. This difference may be related to differences in the intensity of the CBT, which is a factor that is difficult to measure and compare. Nevertheless, a rough comparison based on the information reported in the 'methods' sections of previous trials indicates that we offered more intensive CBT than in earlier studies. Fifth, only the results at the time of discharge from hospital are presented and have no indication of the rate of recurrence at follow-up.

The results of this study should be evaluated carefully due to the lack of a comparison group. The results are published with the purpose of sharing the treatment effect of a combination treatment with the colleagues.

## CONCLUSION

The combination of pharmacotherapy, CBT and rTMS may be effective in treatment resistant and chronic OCD in the short term. Future studies based on larger samples that include control groups and have long-term follow-up findings will be valuable for the treatment of OCD. Finally, the selection of suitable patients and appropriate rTMS parameters (the site of application and the problem of low- or high-frequency stimulation) requires further investigation.

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