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ORIGINAL ARTICLE

Effect of repetitive transcranial magnetic stimulation on quality of life and comorbid anxiety in patients with depression

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Background In Egypt, major depressive disorder (MDD) is the most common mental disorder. Its prevalence is about 2.7% among other mental disorders. There is a significant effect of MDD on the quality of life (QOL) of the affected. Anxiety, a common co-occurring symptom in depression, affects as many as 90% of all patients with depression. Repetitive transcranial magnetic stimulation (rTMS) has become a clinically approved, recognized, and acceptable therapeutic intervention for treatment-resistant depression.

Patients and Methods We recruited 51 patients diagnosed with moderate to severe MDD in this double-blinded sham-controlled trial. Age range was from 18 to 60 years. Patients were randomly assigned (1:1:1) to three study groups [10-Hz rTMS, intermittent theta-burst stimulation (iTBS), or sham]. Sessions were conducted by applying 10-Hz rTMS, iTBS, or sham to the left dorsolateral prefrontal cortex with a schedule of five successive daily sessions a week for 4–6 weeks. Sessions were delivered through a figure-of-eight coil connected to the Neurosoft rTMS system. The outcome measures were the change in anxiety and QOL scores between baseline and after interventions as measured by Hamilton Anxiety Rating Scale and QOL scale, respectively.

Results The improvement of anxiety symptoms was measured by the change in scores of the Hamilton Anxiety Rating Scale between baseline and after 4 weeks of intervention. There were significant differences between active groups (10-Hz rTMS and iTBS) versus sham group with a highly statistically significant difference favoring 10-Hz rTMS (11.6±5.9; 48.9%) over sham (2.2±2.7; 8.4%) (P<0.001), also, there was a significant difference favoring iTBS (13.2±5.32; 54.3%) over sham (2.2±2.75; 8.4%) (P<0.001). Regarding QOL, the 10-Hz rTMS group showed a mean of improvement of 20±11.4 points on the scale (54.9%) in comparison with 2.2±2.33 (5.8%) in the sham group (P<0.001). Further, iTBS showed a change of 20.7±9.55 (63.18%) versus 2.2±2.34 (5.8%) in the sham group (P<0.001).

Conclusions Both conventional 10-Hz rTMS and iTBS are efficacious and tolerable not only in the management of treatment resistant MDD but also in improving comorbid anxiety and QOL.

Keywords Anxiety, Depression, Quality of life, Transcranial magnetic stimulations.
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INTRODUCTION

Depressive disorders represent the second leading cause of disability worldwide, and major depressive disorder (MDD) accounted for 2.5% of global disability-adjusted life years (Ferrari *et al.,* 2013). In Egypt, MDD is the most common mental disorder; its prevalence is ~2.7% among other mental disorders (Ghanem *et al.,* 2009).

Patients with mood disorders are at increased risk of experiencing one or more comorbid disorders (Garcia-

Toro *et al.,* 2013). MDD is commonly associated with other comorbid psychiatric disorders. These comorbid psychiatric disorders may affect clinical course of MDD (Garcia-Toro *et al.,* 2013), economic burden, suicidal risk (McIntyre *et al.,* 2012), and treatment response (Riper *et al.,* 2014). Anxiety disorders represent the most common and prevalent MDD comorbidity (Merikangas *et al.,* 2003).

Anxiety affects about 90% of patients with depression (Kaplan, 2016). Severe comorbid anxiety was associated with longer duration of illness, possible treatment nonresponse, and higher risk of suicide (American Psychiatric Association, 2013). So, it is of paramount importance to accurately detect the presence and severity of anxious distress in patients with MDD for planning treatment and response monitoring (American Psychiatric Association, 2013). For these reasons, DSM-5 stated the specifier 'with anxious distress' to remind and raise the attention of clinicians about comorbid anxiety symptoms in patients with MDD (Bentley *et al.,* 2014).

Moreover, comorbid psychiatric conditions (especially anxiety, personality disorders, and substance or alcohol use) were found to be associated with treatment-resistant depression (Souery *et al.,* 2001; Fagiolini and Kupfer, 2003).

Furthermore, MDD significantly influences quality of life (QOL) of patients. QOL refers to life satisfaction, subjective well-being, functioning in work and daily activities, perception of physical health, economic status, and social relationships. QOL is assessed through individual's subjective views of his/her family and social relationships, functioning at home and work, life circumstances, and perception of physical and mental health. Effective depression treatment can lead to improvement in depressive symptoms, psychosocial functioning, and greater QOL (Katschnig, 2006).

Although several treatment modalities for MDD are available and have evident efficacy including psychosocial and psychopharmacological interventions (Bentley *et al.,* 2014), where psychosocial interventions are recommended in mild depression and psychopharmacological interventions are recommended in moderate or severe depression (National Collaborating Centre for Mental, H., National Institute for Health and Clinical Excellence, 2010), a substantial number (10–30%) of patients with MDD have a debilitating chronic course despite adequate pharmacological and psychological interventions (Bromet *et al.,* 2011).

Repetitive transcranial magnetic stimulation (rTMS) through modulation of brain activity holds promise in treatment-resistant depression (George and Aston-Jones, 2010) and recently has become a clinically approved recognized and accepted therapeutic intervention for treatment-resistant depression (Lontis *et al.,* 2006).

The high-frequency (10-Hz) stimulation of the left dorsolateral prefrontal cortex (DLPFC) is the most frequently used rTMS protocol (Brunoni *et al.,* 2017). The course of treatment involves a daily rTMS session that lasts for 37.5 min, five successive days per week for 4–6 weeks (Berlim *et al.,* 2017). Intermittent theta-burst stimulation (iTBS) session typically lasts for about 3 min and induces a stimulation that is similar or more potent than 10-Hz rTMS (37.5 min)-induced stimulation (Di Lazzaro *et al.,* 2011).

Several studies have explored the effects of rTMS in anxiety spectrum disorders, but results were contradictory (Mantovani *et al.,* 2006; Boggio *et al.,* 2010; Paes *et al.,* 2011; Watts *et al.,* 2012). In this sham-controlled trial, we analyzed the effect of different active techniques of rTMS (10-Hz rTMS or iTBS) versus sham on levels of comorbid anxiety and QOL in patients with MDD.

PATIENTS AND METHODS

Study design and sampling

The study design was a randomized double-blinded sham-controlled trial. The study was conducted at Minia University Hospital, Minia, Egypt. We recruited patients through referrals from psychiatry outpatient clinics during the period from December 1, 2018 to October 1, 2019.

We recruited adults aged 18–60 years old, including both males and females. MDD diagnosis was stated according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria using Structured Clinical Interview for DSM-5 (SCID-5) as a single or recurrent episode (American Psychiatric Association, 2013).

Regarding severity of depressive symptoms, we recruited patients with moderate to severe symptoms in their current depressive episode who scored at least 18 on the 17-item Hamilton Rating Scale for Depression (Hamilton, 1967).

We recruited patients with previous antidepressant treatment failure that was defined according to Antidepressant Treatment History Form (Sackeim, 2001) either by failure of response to a previous antidepressant trial of adequate dose and duration (Antidepressant Treatment History Form score of 3 or higher) or intolerance to at least two separate trials of antidepressant treatment with inadequate dose and duration (score 1 or 2).

The patients were allowed to receive a stable antidepressant regimen for at least 4 weeks before TMS with no change of their antidepressant before intervention, and this regimen continued during the study. However, those who were unable to tolerate two previous antidepressant trials were allowed to receive TMS without concomitant antidepressants medications.

We excluded patients with current or previous history of psychotic symptoms, substance use disorders, and bipolar affective disorders. We also excluded patients with MDD who failed to respond to adequate electroconvulsive

therapy (ECT) course (eight sessions or more), patients who had a previous history of TMS treatment, and those having a vagus nerve stimulator implant.

In addition, general contraindications of TMS were verified before sessions as personal or a family history of epilepsy in a first-degree relative, presence of a metal in or close to the head, or unstable neurological, medical, or surgical conditions (seizures, stroke, brain tumor, or brain surgery).

Ethical approval was obtained from the ethical research committee of Minia University. The participants shared in the study voluntarily after informing them about the purpose and procedures of the study and after taking their consent.

Randomization

Randomization of the current study was ensured through random allocation of participants (1:1:1) to the study groups (10-Hz rTMS, iTBS, or sham). Additionally, the three groups were balanced regarding the number of antidepressants trials in the current episode, as this variable was significantly correlated with improvement by rTMS (the lower the number of failed antidepressant trials, the better the response with rTMS) (Lisanby *et al.,* 2009). The groups were randomized into two categories: more than one failed trial versus one or less than one antidepressant trial.

Blinding

Patients were informed that they will receive rTMS, but they did not know which type of stimulation they received or the differences between multiple approaches. A trained psychologist (rater) performed assessments of patients before, during, and after the course of stimulation. This rater did not know the type of stimulation received by each patient or whether he received sham or real TMS. So, neither the participants nor the rater knew the type of intervention applied. Moreover, the rater and the participants were instructed not to share any information about details of sessions.

Study procedures

A total of 51 participants diagnosed with MDD were enrolled, of whom six discontinued treatments (two from 10-Hz rTMS group, three from iTBS group, and one from sham group). The reason for dropout in all of them was because of difficulty in commitment to daily sessions.

Initial psychiatric assessments of all patients and assessment of contraindications of TMS were conducted by a psychiatrist with full psychiatric interview including a Structured Clinical Interview for DSM-5 (SCID-5) for MDD diagnosis. The assessments of scores of depression, anxiety, and QOL were done at baseline (before starting sessions) and after 4 weeks of regular sessions (five sessions per week).

The TMS sessions were delivered using a figure-of-eight coil connected to Neuro-MS/D magnetic stimulator (Neurosoft LLC, Ivanovo, Russia). Resting motor threshold (RMT) was determined by visual observation according to recent guidelines (McClintock *et al.,* 2018). The coil was advanced 5.5 cm anterior to the MT location along a right superior oblique plane with a rotation point about the tip of the patient's nose for proper localization of the left DLPFC.

Conventional 10-Hz rTMS was delivered based on conventional FDA-approved parameters (stimulation intensity: 120% RMT, frequency: 10-Hz, 4 s on and 26 s off, 3000 pulses per session, and total duration: 37.5 min) (O'Reardon *et al.,* 2007; George *et al.,* 2010).

iTBS was delivered with the same intensity (120% RMT) and at the same site of 10-Hz rTMS. It differs from 10-Hz rTMS in stimulation pattern and total number of pulses (triplet 50 Hz bursts, repeated at 5 Hz, 2 s on and 8 s off, 600 pulses/session, and total duration: 3 min and 9 s) (Huang *et al.,* 2005).

Sham TMS was delivered as recommended by Lisanby *et al.,* (2001), through tilting the figure-of-eight coil 90° from tangential, as it was shown to be devoid of biological effects at that position. According to current guidelines, the sessions were scheduled daily, 5 days a week for at least 4 weeks (20 sessions), and the course may be extended for two more weeks (10 more supplementary sessions) in patients who showed improvement from baseline but did not reach remission in primary outcome measure (McClintock *et al.,* 2018).

Study parameters

The primary efficacy outcome was improvement in scores of depression as measured by change in HDRS-17 score before, after each week, and after end of sessions among the three study groups (10-Hz rTMS, iTBS, and sham).

Secondary outcome measures were improvement in anxiety and QOL scores as measured by Hamilton Anxiety Rating Scale (HAM-A) and quality-of-life scale (QOLS), respectively, which have been recorded at baseline and after end of sessions.

HAM-A (Hamilton, 1959) was developed as a rating scale for assessing the severity of anxiety neurosis. It is a 14-item rating scale that is designed to assess and quantify the severity of psychological as well as physical symptoms of anxiety (Hamilton, 1959).

The QOLS was originally a 15-item scale that conceptually measures five domains of QOL: social, community and civic activities, material and physical well-being, relationships with other people, recreation and personal development, and fulfillment (Burckhardt and Anderson, 2003).

Statistical Analysis

Data analysis was done using the Statistical Package for the Social Sciences (SPSS), version 25, for Windows (IBM Corporation, New York, USA). Regarding descriptive statistics, means and SDs were calculated for continuous variables, whereas frequencies and percentages were calculated for categorical variables. Analytical statistics were used to compare outcome variables within the three study groups (e.g. *t* tests). Comparison of the three study groups for categorical variables was based on χ^2 tests. Kruskal–Wallis test was used for comparing two or more independent samples with nonparametric distribution and of equal sample size.

RESULTS

Sample characteristics

The three study groups were comparable regarding demographic and clinical characteristics: study participants did not show significant differences regarding age, sex, and duration of illness. Moreover, baseline scores of depression, anxiety, and QOLS were also comparable and balanced within the three groups.

Randomization was successful with respect to the distribution of participants across groups regarding previous treatment failure. The three groups were balanced regarding the level of resistance to medications (more than one versus one or less adequate trials with no response).

Efficacy outcome measures

The improvement in depression symptoms as measured by change in scores of 17-item Hamilton Depression Rating Scale between baseline and after 4 weeks of sessions was in favor of active groups (10-Hz rTMS and iTBS) over the sham group (presented in detail in our other manuscript).

The improvement of anxiety symptoms as measured by the change in scores of HAM-A between baseline and after 4 weeks was in favor of the 10-Hz rTMS over sham. The 10-Hz rTMS group showed a mean improvement in anxiety scores of 11.6±5.9 points in comparison with 2.2±2.7 points in the sham group, with a mean improvement percent of 48.9% in the 10-Hz rTMS group against only 8.4% in the sham group, with a highly significant difference between both groups, with P value less than 0.001 (Tables 1 and 2 and Fig. 1).

QOLS in the conventional (10-Hz rTMS) group showed a mean score of improvement of 20±11.4 points in comparison with 2.2±2.33 points in the sham group, with a mean improvement percent of 54.9% in 10-Hz rTMS group against only 5.8% in the sham group, with a highly significant difference in the outcome of QOL in favor of active 10-Hz rTMS (P<0.001) (Table 2 and Fig. 1).

The iTBS group showed a mean score of improvement of anxiety of 13.2±5.32 points on HAM-A in comparison with 2.2±2.75 points in the sham group, with a mean of improvement percent of 54.3% against 8.4% in the sham group, with a highly significant difference in outcome on anxiety in favor of active iTBS (P<0.001) (Table 3 and Fig. 1).

Table 1: Sociodemographic and clinical characteristics of the three study groups:

	10-Hz rTMS (*N*=15)	iTBS (*N*=15)	Sham (*N*=15)	*P* value	Significance
Age (years)					
Mean±SD	33.20±10.073	39.07±11.145	34.07±9.640	0.254	NS
Range	22–51	18–51	19–55		
Sex [*n* (%)]					
Male	8 (53.3)	5 (33.3)	7 (46.7)	0.533	NS
Female	7 (46.7)	10 (66.7)	8 (53.3)		
Duration of illness (years)					
Mean±SD	7.13±7.170	8.27±5.946	5.47±3.871	0.423	NS
Range	1–28	1–20	1–11		
Hamilton depression score17					
Mean±SD	27.47±5.668	28.20±5.519	24.47±6.081	0.159	NS
Range	18–39	18–37	18–35		
Hamilton anxiety score					
Mean±SD	24.00±4.488	24.27±6.419	26.53 ±3.852	0.229	NS
Range	16–32	16–37	20–32		
Quality of life score					
Mean±SD	39.20±6.428	35.67±7.345	38.27±4.906	0.198	NS
Range	28–49	24–54	33–50		

iTBS, intermittent theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation.

Furthermore, the iTBS group showed a mean improvement of 20.7±9.55 points on QOLS, in comparison with 2.2±2.33 points in the sham group, with a mean improvement percent of 63.18% against only 5.83% in the sham group, with a highly significant difference in favor of active iTBS, with P value less than 0.001 (Table 3 and Fig. 1).

Finally, the comparison between the two active groups (10-Hz rTMS and iTBS) regarding anxiety and QOL score changes before and after interventions showed statistically nonsignificant differences between the two groups (Table 4).

Table 2: Comparison between 10-Hz repetitive transcranial magnetic stimulation and sham groups regarding improvement in anxiety and quality of life at primary end point (4 weeks):

Improvement after 4 weeks	10-Hz rTMS	Sham	*P* value	Significance
HAMA improvement (mean±SD)	11.60±5.92	2.20±2.75	<0.001	HS
HAMA improvement (mean±SD)	48.99±24.59	8.4051±11.27	<0.001	HS
QOLs score improvement (mean±SD)	20.00±11.42	2.20±2.33	<0.001	HS
QOLs improvement (mean±SD)	54.97±36.02	5.83±6.43	<0.001	HS

QOL, quality of life; rTMS, repetitive transcranial magnetic stimulation.

Table 3: Comparison between intermittent theta-burst stimulation and sham group regarding improvement in anxiety and quality of life at primary end point (4 weeks):

Improvement after 4 weeks	iTBS	SHAM	*P* value	Significance
HAMA improvement (mean±SD)	13.20±5.32	2.20±2.75	<0.001	HS
HAMA improvement percentage (%) (mean±SD)	54.37±18.57	8.41±11.27	<0.001	HS
QOLs score improvement (mean±SD)	20.73±9.55	2.20±2.34	<0.001	HS
QOLs improvement percentage (%) (mean±SD)	63.18±36.94	5.83±6.44	<0.001	HS

iTBS, intermittent theta-burst stimulation; QOL, quality of life.

Table 4: Comparison between 10-Hz repetitive transcranial magnetic stimulation and intermittent theta-burst stimulation groups regarding improvement in anxiety and quality of life after 4 weeks of treatment:

Improvement after 4 weeks	10-Hz rTMS	iTBS	*P* value	Significance
HAMA improvement (mean±SD)	11.60±5.92	13.20±5.32	0.371	NS
HAMA improvement percentage (%) (mean±SD)	48.99±24.59	54.36±18.56	0.329	NS
QOL score improvement (mean±SD)	20.00±11.42	20.73±9.55	0.771	NS
QOL improvement percentage (%) (mean±SD)	54.97±36.02	63.18±36.94	0.330	NS

iTBS, intermittent theta-burst stimulation; QOL, quality of life; rTMS, repetitive transcranial magnetic stimulation.

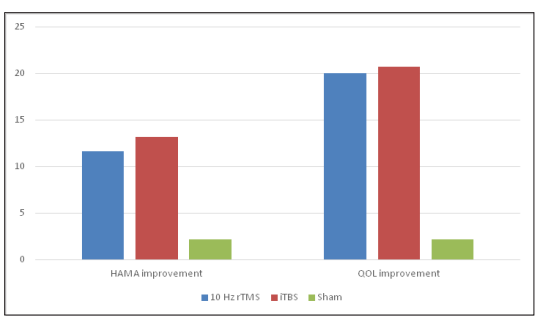

Figure 1: Improvement in anxiety and quality-of-life scores among study groups after 4 weeks of treatment.

DISCUSSION

The sample size was calculated using G*Power 3.0 program (Faul *et al.,* 2007). With an effect size of 0.4 and power of 85%, we needed 48 patients to show a meaningful difference. The number of patients recruited in our study was 51, and the dropouts included six patients.

To make sure that TMS effect was not affected by other confounding factors, we only included patients with stable antidepressant regimens for 4 weeks before treatment, and these regimens continued unchanged throughout TMS courses.

Participants who were unable tolerating two previous antidepressant trials before TMS (n=12 patients) were allowed to receive intervention course without concomitant medications and that helped to ensure that the effect on patients is solely caused by TMS.

The contraindications to rTMS according to consensus guidelines were considered as exclusion criteria in the current study, which included patients who have sensitive magnetic or ferromagnetic metal object implantation in their head or neck close to magnetic field and TMS coil,

surgically implanted medical devices (as pacemakers, metal plates, electrodes, clips, chips, stimulators, pumps, or cochlear implants), past exposure to ferromagnetic-containing ink tattoos, permanent piercings of metal fragments, or any other metal source in the region of head and neck (McClintock *et al.,* 2018).

As most patients with depression suffer from anxiety symptoms, from a therapeutic point of view, proper evaluation of anxiety in depressed patients is of particular importance and interest as patients with both depressive and anxiety symptoms are susceptible to poorer outcomes than patients with depression not reporting comorbid anxiety (Zimmerman *et al.,* 2000).

In the current study, we used the HAM-A to assess the efficacy TMS in improving comorbid anxiety in patients with MDD: HAM-A is a 14-item rating scale designed to assess and quantify severity of psychological as well as physical symptoms of anxiety (Hamilton, 1959).

As depression affects QOL, treatments of depression may lead to an improvement of depressive symptoms and psychosocial functioning as well as improved QOL (Katschnig, 2006).

The treatment effects on QOL have not received much attention as clinical measures of depression. We also used the QOLS to study the effect of intervention on QOL as secondary outcome measure.

Although depression severity is obviously correlated with impairment in QOL (Judd *et al.,* 2000), QOL changes are not fully explained by changes in depression (Hirschfeld *et al.,* 2002), and changes in QOL occur more slowly than depressive symptoms (Trivedi *et al.,* 2006).

Furthermore, treatments that improve depressive symptoms do not necessarily result in QOL improvement. Spielmans *et al.,* (2013) in their meta-analysis on adjunct use of atypical antipsychotics in the management of depression showed that although pharmacotherapy was associated with decreased depression ratings, there was little evidence of improvement of patients' QOL. Moreover, a meta-analysis studying the efficacy of antidepressants in youths revealed that despite depressive symptoms improvement with antidepressant use, patients did not exhibit overall well-being and QOL improvement (Spielmans and Gerwig, 2014).

In the current study, we used the FDA-approved site for 10-Hz rTMS or iTBS stimulation that is the left DLPFC. The conventional 10-Hz rTMS was used according to FDA-approved protocol and parameters (stimulation intensity: 120% RMT, frequency: 10-Hz, 4 s on and 26 s off, 3000 pulses per session, and total duration: 37.5 min). iTBS was delivered at the same site and intensity (120% RMT), differing only in the total number of pulses and stimulation pattern (triplet 50 Hz bursts, 600 pulses/session, repeated at 5 Hz, 2 s on and 8 s off, and total duration: 3 min 9 s).

Obviously, we did not match the number of pulses of iTBS intervention with the 10-Hz rTMS intervention (3000 pulses/session). Previous preclinical data revealed that doubling the number of pulses of iTBS does not enhance the excitatory effect and may in fact have an inhibitory effect following intervention (Gamboa *et al.,* 2010).

Sham stimulation was delivered using the 'two-wing 90°' method through tilting the coil in a double-wing tilting position 90° off the scalp (Lisanby *et al.,* 2001).

The pattern of symptom improvement was consistent in all study outcome measures (depression, anxiety, and QOL). The improvement of anxiety symptoms measured by the score change of HAM-A showed statistically significant difference in outcome on anxiety in favor of active techniques 10-Hz rTMS and iTBS each in comparison with sham ($P<0.001$ for each). These findings are consistent with the general conclusions (significant methodological differences) of Cirillo *et al.,* (2019) in their meta-analysis that confirmed the safety and therapeutic potential of TMS for generalized anxiety disorder and posttraumatic stress disorder.

Moreover, in agreement with results of our study, Bystritsky *et al.,* (2008) reported a significant reduction of scores of HAM-A with rTMS, but in patients with generalized anxiety disorder, the remission rate was 60%.

Moreover, Diefenbach *et al.,* (2013) reported improvement in both anxiety and depressive symptoms from before to after rTMS treatment with moderate to large effects.

This is consistent with Solvason *et al.,* (2014), who reported a statistically significant improvement in QOL of patients with treatment-resistant depression treated by rTMS in comparison with those who received sham. QOLS in our study showed a highly significant difference in favor of active groups (rTMS and iTBS) versus sham ($P<0.001$).

Although the differences between the 10-Hz rTMS and iTBS groups regarding scores of HAM-A and QOLS were statistically nonsignificant ($P=0.371$ and 0.771, respectively), it was in favor of the newer iTBS modality.

In this RCT of active 10-Hz rTMS, iTBS versus sham, active TMS resulted in a significant decrease in HDRS-17, HAM-A, and QOLS scores compared with sham.

Improvement was shown in continuous as well as categorical outcomes in both active groups (10-Hz rTMS and iTBS) in comparison with sham (i.e. change in depression, anxiety, and QOL scores as well as rates of response and remission).

To the best of our knowledge, this is the first double-blinded randomized controlled trial comparing the effectiveness of the 10-Hz rTMS and iTBS with sham in the same setting in patients with MDD, with outcome measures including anxiety and QOL.

In conclusion, we have found that both conventional 10-Hz rTMS and iTBS are effective, efficacious, and tolerable not only in the management of treatment-resistant MDD but also for comorbid anxiety and QOL.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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