Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)

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INTRODUCTION

Many patients with unipolar major depression do not respond to standard treatment with pharmacotherapy and psychotherapy [1,2] and are thus candidates for noninvasive neuromodulation procedures, including repetitive transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT) [3-5]. Although ECT is more efficacious than repetitive TMS [6,7], patients may prefer repetitive TMS because it is better tolerated and unlike ECT, TMS does not require general anesthesia and induction of seizures.

This topic reviews the indications, efficacy, and safety of TMS for treating unipolar major depression in adults; the technique for performing TMS is reviewed elsewhere. Other neuromodulation procedures, including ECT, magnetic seizure therapy, focal electrically administered seizure therapy, transcranial direct current stimulation, transcranial low voltage pulsed electromagnetic fields, cranial electrical stimulation, vagus nerve stimulation, deep brain stimulation, direct cortical stimulation, and ablative neurosurgery, are also discussed separately, as is choosing treatment for treatment resistant depression and treatment refractory depression:

- (See "Technique for performing transcranial magnetic stimulation (TMS)".)
- (See "Unipolar depression in adults: Overview of neuromodulation procedures".)
- (See "Overview of electroconvulsive therapy (ECT) for adults".)
- (See "Unipolar depression in adults: Treatment with surgical approaches".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Unipolar depression in adults: Management of highly resistant (refractory) depression".)

OVERVIEW

Repetitive transcranial magnetic stimulation (TMS) treats major depression by modulating activity in cortical regions and associated neural circuits [8]. The intervention uses an alternating current passed through a metal coil placed against the scalp to generate rapidly alternating magnetic fields, which pass through the skull nearly unimpeded and induce electric currents that depolarize neurons in a focal area of the surface cortex [9-11]. The magnetic field generated by repetitive TMS is comparable to that of a standard magnetic resonance imaging (MRI) device (approximately 1.5 to 3 Tesla); however, the TMS field is focal (beneath the coil), whereas the MRI field is large and fills the room housing the MRI device [10,12]. Repetitive TMS is comparable to electroconvulsive therapy (ECT) in that both are noninvasive neuromodulation therapies. (See "Unipolar depression in adults: Overview of neuromodulation procedures", section on 'Noninvasive neuromodulation therapies'.)

In addition to its use as a therapeutic tool, TMS has been used in attempts to map brain functions and connections between different brain regions, and assess cortical excitability and brain-behavior relationships [8,13].

Mechanism of action — The mechanism of action of repetitive TMS is unknown. One hypothesis is that stimulation of discrete cortical regions alters pathologic activity within a network of grey matter brain regions that are involved in mood regulation and connected to the targeted cortical sites [14,15]. This is supported by functional imaging studies that show repetitive TMS can change activity in brain regions remote from the site of stimulation [16-29].

Repetitive TMS has many molecular effects comparable to ECT, including increased monoamine turnover and normalization of the hypothalamic pituitary axis [12]. In one neuroimaging study of depressed patients, a prefrontal serotonin deficiency at baseline normalized after treatment with repetitive TMS.

The effect of repetitive TMS appears to vary according to the frequency; high frequency stimulation is thought to excite the targeted neurons (and is typically used to activate the left prefrontal cortex), whereas low frequency stimulation appears to inhibit cortical activity (and is usually directed at the right prefrontal cortex) [15]. Consistent with this hypothesis, a review examined 66 studies in depressed patients who were treated with TMS targeting the dorsal lateral prefrontal cortex and found that high frequency TMS generally increased regional cerebral blood flow and that low frequency TMS generally decreased regional cerebral blood flow [29].

MONITORING

We suggest that clinicians using repetitive transcranial magnetic stimulation monitor patient outcomes with a self-report scale, such as the Patient Health Questionnaire – Nine Item (PHQ-9) (table 1) [10]. Additional information about measurement based care, including the PHQ-9, is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

INDICATIONS

The role of repetitive transcranial magnetic stimulation (TMS) in treating patients with unipolar major depression is discussed separately. (See "Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Transcranial magnetic stimulation'.)

Repetitive transcranial magnetic stimulation (TMS) is indicated for patients with unipolar major depression who have failed at least one antidepressant medication; in many studies, patients have failed multiple courses of pharmacotherapy and psychotherapy as well as a trial of electroconvulsive therapy [30], and most patients have suffered prior episodes of major depression [10]. Use of repetitive TMS for treatment resistant/refractory depression is consistent with treatment guidelines from the American Psychiatric Association [3,4], Canadian Network for Mood and Anxiety Treatments [31], and the Royal Australian and New Zealand College of Psychiatrists [32]. In addition, TMS is indicated for patients who responded to a prior course of TMS [10].

Assessment — Prior to repetitive TMS treatment, the patient should be evaluated to confirm the primary diagnosis of treatment resistant depression and whether the intervention can be used safely. The assessment includes a psychiatric history and mental status examination, with emphasis upon depressive symptoms (table 2), length of the current depressive episode, types and number of failed treatments during the present episode, as well as the number, length, and treatment history of prior depressive episodes. In addition, a general medical history and physical examination is performed, as well as laboratory tests and neuroimaging studies that are guided by the history and examination [33-35]. The medical work-up should emphasize risk factors for seizures and preexisting neurologic disease (eg, epilepsy, intracranial masses, and vascular abnormalities).

CONTRAINDICATIONS

To screen patients for contraindications to repetitive transcranial magnetic stimulation (TMS), we use a 13-item, clinician-administered questionnaire (table 3) [36].

Repetitive TMS is contraindicated in patients with [37-39]

- Increased risks for seizures (see 'Safety and adverse effects' below)
- Implanted metallic hardware (eg, aneurysm clips or bullet fragments)
- Cochlear implants
- Implanted electrical devices (eg, pacemakers, intracardiac lines, and medication pumps)
- Unstable general medical disorders

It may be possible to safely use repetitive TMS in depressed patients with a personal or family history of seizures if the stimulation frequency is low (≤1 pulse per second) and the motor threshold is monitored to ensure that stimulation intensity does not exceed the recommended safety range [40]. However, patients at increased risk for seizures should be considered for repetitive TMS only if the potential benefit outweighs the increased risk; as an example, the depressive episode has not responded to multiple (eg, six) courses of pharmacotherapy, including monotherapy and combination treatment, as well as trials of psychotherapy and electroconvulsive therapy. Stimulation frequency and treatment resistant depression are discussed elsewhere. (See 'Overview' above and "Unipolar depression in adults: Choosing treatment for resistant depression".)

Psychotic features (delusions and hallucinations) are not a contraindication for treating major depression with repetitive TMS [41], but most randomized trials have excluded psychotic patients [37,42-46]. Psychosis and treatment of psychotic depression are discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment" and "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation".)

EFFICACY

Multiple reviews have found consistent evidence that repetitive transcranial magnetic stimulation (TMS) provides a clinically relevant benefit to patients with treatment resistant depression [10,11]. The large majority of studies have examined the efficacy of surface cortical TMS. (See "Technique for performing transcranial magnetic stimulation (TMS)", section on 'Surface cortical TMS'.)

Acute TMS — For patients with acute major depression who have not responded to at least one antidepressant medication, numerous meta-analyses of randomized trials have found that repetitive TMS is superior to sham treatment [47-55]; however, TMS is less effective than electroconvulsive therapy. (See "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)", section on 'Compared with transcranial magnetic stimulation'.)

Compared with sham treatment (placebo) — In a meta-analysis of 34 randomized trials that compared repetitive TMS with sham treatment in 1383 patients with major depression

who did not respond to one or more trials of pharmacotherapy, improvement was greater with active treatment [51].

However, absolute rates of remission with repetitive TMS in some studies are modest [56]. As an example, a relatively large and rigorous randomized trial (n = 301) found that remission with active TMS occurred in only 14 percent of patients (compared with 5 percent in the sham TMS group) [37]. It is worth noting that depressed patients who have previously failed pharmacotherapy are generally less responsive to subsequent pharmacotherapy or electroconvulsive therapy [37].

Combined with pharmacotherapy — In most randomized trials that compared active repetitive TMS with sham TMS for treating major depression, the experimental procedure was added onto antidepressant medications that were ineffective for the presenting episodes, but were nevertheless maintained during the trials so that all patients received active treatment. As an example, in a meta-analysis of 34 trials that found active repetitive TMS was superior to sham treatment, patients were free of antidepressant medications in only seven trials [51].

For patients who have not responded to adequate antidepressant therapy, add-on treatment with repetitive TMS is efficacious. A pooled analysis of six randomized trials compared active TMS with sham TMS as augmentation in patients (n = 230) with treatment resistant depression who continued their antidepressant drugs [57]. Patients received 10 to 30 sessions of high frequency TMS. Response (eg, reduction of baseline symptoms ≥50 percent) occurred in more patients who received active than sham TMS (47 versus 22 percent).

In addition, simultaneously starting repetitive TMS plus pharmacotherapy for major depression may be superior to initiating pharmacotherapy alone. A meta-analysis of four randomized trials (213 patients) compared high frequency repetitive TMS plus antidepressants (primarily selective serotonin reuptake inhibitors) with antidepressants alone as initial treatment and found that remission occurred more often with combination treatment (odds ratio 2.4, 95% CI 1.3-4.6) [58]. However, two negative studies did not report enough data for the purposes of the meta-analysis and were thus excluded [45,59].

Predictors of response — Although individual studies of repetitive TMS for major depression have found factors associated with response (eg, number of antidepressant medications that have failed to resolve the presenting episode [60]), no consistent predictors have been identified in meta-analyses. As an example, a meta-analysis of 30 randomized trials (1164 patients) found that improvement was significantly greater with active repetitive TMS than sham treatment; however, the effect of repetitive TMS was comparable in trials with medication resistant depression and trials with nonmedication resistant depression [61]. In addition, a meta-analysis (34 randomized trials, 1383 depressed patients) compared left dorsal lateral prefrontal cortex repetitive TMS with right dorsal lateral prefrontal cortex

stimulation, and found that efficacy was comparable [51]. Other meta-analyses suggest that the efficacy of high frequency (>1 pulse per second) and low frequency (≤1 pulse per second) repetitive TMS are comparable [47,54,61].

In addition, a review of 41 studies found that several neurobiologic factors (eg, genetic polymorphisms and baseline regional cerebral blood flow) may be associated with response to repetitive TMS [62]. However, assessment of these factors to predict response is restricted to research settings and is not part of standard clinical care.

Compared with electroconvulsive therapy (ECT) — For treatment of major depression, repetitive TMS is less efficacious than electroconvulsive therapy. (See "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)", section on 'Compared with transcranial magnetic stimulation'.)

Durability of response — Follow-up studies of patients with major depression who were treated acutely with repetitive TMS in randomized trials indicate that the short-term benefit of TMS is stable. A meta-analysis of 16 trials examined the level of depression in 495 patients who were treated with either active TMS or sham TMS and then followed after acute treatment ceased [63]. TMS consisted of high frequency stimulation of the left dorsolateral prefrontal cortex; the trials included relatively few sessions (5 to 15) and utilized low dosing parameters (eg, 800 to 2000 stimuli per session) compared with standard protocols. Follow-up in most trials lasted one to four weeks; during follow-up, none of the trials administered maintenance TMS, but most trials provided antidepressant medications. Depression rating scale scores during follow-up were lower in patients who received active TMS than sham TMS, and the clinical advantage was moderate. TMS treatment parameters are discussed separately. (See "Technique for performing transcranial magnetic stimulation (TMS)", section on 'Treatment parameters'.)

With regard to longer-term benefits of repetitive TMS, prospective, observational studies lasting at least six months suggest that in patients with major depression who improve with acute repetitive TMS, relapse occurs in about 35 percent [64,65]:

- A group of 76 patients who remitted were followed for up to one year, during which most patients received maintenance medications and/or TMS was reintroduced when patients deteriorated; relapse occurred in 34 percent [66].
- Among 99 patients who partially responded (reduction of baseline symptoms ≥ 25 percent) to repetitive TMS and were treated with maintenance pharmacotherapy for six months, symptomatic deterioration occurred in 38 percent [67].

A one year, prospective observational study of 120 patients who responded or remitted with acute TMS found that durability of response to TMS was not associated with age, sex, severity

of depressive symptoms prior to TMS, and number of failed antidepressant trials prior to TMS [66].

Following relapse — For patients with unipolar major depression who improve with a course of repetitive TMS and subsequently deteriorate or relapse, another course (reintroduction) of repetitive TMS using the same stimulation parameters may be helpful [10,65-72].

Maintenance TMS — It is not known if maintenance treatment with repetitive TMS for unipolar major depression is beneficial because few randomized trials using standard protocols have been conducted. One small randomized trial, which included 49 medication free patients who responded to TMS, found that initially administering maintenance TMS only once per month provided no advantage over watchful waiting [72].

However, in several small observational studies of patients who responded (eg, reduction of baseline symptoms ≥50 percent) to acute TMS, the results suggest that maintenance TMS may perhaps be beneficial [73]. As an example:

- In a prospective study of 59 patients (most had unipolar major depression), 37 agreed to continuation treatment for 20 weeks (15 TMS sessions; most patients received adjunctive pharmacotherapy) [74]. A propensity analysis controlled for baseline patient characteristics that may have influenced the choice to continue TMS, and found that relapse occurred in fewer patients who received continuation TMS, compared with patients who did not (38 versus 82 percent [14 of 37 versus 18 of 22]).
- A prospective, 48-month study of 35 patients found that 29 percent remained euthymic; the mean time to recurrence was 10 months [75].
- A retrospective study of 48 patients found that after six months of maintenance TMS, response persisted in 62 percent [40].

SAFETY AND ADVERSE EFFECTS

Repetitive transcranial magnetic stimulation (TMS) is generally safe and well-tolerated [8,10,12,37]. As an example, a randomized trial of 301 patients found that study discontinuation due to adverse effects was comparable for active and sham repetitive TMS (5 and 3 percent) [37].

Seizure — The most serious adverse effect of repetitive TMS is a generalized tonic-clonic seizure [10,38,39]. However, the risk of seizure appears to be comparable to that for antidepressant medications, and seizures probably occur in less than 0.1 to 0.5 percent of patients when safety guidelines regarding patient selection and stimulation parameters are

followed [10,12,38]. Seizures that have occurred were self-limited, required no medications, and did not recur.

Factors that increase the risk of seizures include:

- Patient factors
  - Personal and family (parent, sibling, or child) history of epilepsy
  - Preexisting neurologic disorder (eg, prior head injury with loss of consciousness, prior brain surgery, or congenital brain malformation)
  - Medications that lower seizure threshold (eg, bupropion, stimulants, tricyclic antidepressants, antipsychotics, and theophylline)
  - Recent discontinuation of alcohol, benzodiazepines, or anticonvulsants
  - Sleep deprivation
- Repetitive TMS stimulation parameters (see "Technique for performing transcranial magnetic stimulation (TMS)", section on 'Treatment parameters'):
  - Higher frequency
  - Increased intensity
  - Shorter intertrain interval

Other side effects — Hypomania and mania have been described in randomized trials [76] as well as case reports of patients with major depression (both unipolar and bipolar) who were treated with repetitive TMS [77-85]. However, the clinical significance is not known because patients with bipolar major depression can switch to mood elevated states in the absence of an antidepressant treatment. A review pooled results from 10 randomized trials (520 patients with major depression) that addressed switching to mania, and found that treatment emergent mania was comparable for active repetitive TMS and sham treatment (0.8 and 0.7 percent) [76].

Treatment of unipolar major depression with repetitive TMS does not appear to increase suicidal ideation or behavior [8]. In a randomized trial that compared active repetitive TMS with sham treatment in 323 patients with unipolar major depression, there were no completed suicides, and self-harm occurred in one patient in the sham group [37]. In addition, increased suicidal ideation occurred in 10 patients who received sham treatment and 1 patient in the active treatment group.

Common side effects of repetitive TMS include [38,39]:

- Headache and scalp pain – A review of randomized trials in patients with major depression found that the incidence of headache with active treatment and sham treatment was 28 and 16 percent, and the incidence of scalp pain with active and sham treatment was 39 and 15 percent. No migraine headaches have been reported. Headache and scalp pain may be more pronounced when higher stimulation frequencies and intensities are used; topical lidocaine may reduce scalp pain [86]. Reducing stimulation intensity can decrease scalp discomfort, but this can also reduce efficacy [68]; thus, for sensitive patients, the dose of TMS can be titrated up during the first week [10]. Headache and scalp pain generally resolve over the first two weeks, although some patients may require an analgesic (eg, acetaminophen or ibuprofen) [10].

- Transient (<4 hours) increase in auditory threshold – Caused by repeated clicks that are produced as current passes through the stimulating magnetic coil and mechanically deforms it; hearing loss is prevented with foam earplugs or noise protection ear coverings [10].

Another potential side effect is vasovagal syncope; management generally consists of reassurance [10].

Tolerability of repetitive TMS may be better with lower stimulation parameters compared with higher parameters [8,87]. (See "Technique for performing transcranial magnetic stimulation (TMS)", section on 'Treatment parameters'.)

Repetitive TMS in patients with major depression does not impair cognition [8,37-39,88-91]. Although many uncontrolled studies suggest that neuropsychological functioning may possibly improve during a course of treatment, randomized trials indicate that improvement of cognitive functioning does not differ significantly between active and sham treatment [39,91].

For clinicians who administer the procedure over years, the safety and long-term adverse effects of repetitive TMS are not known [38].

SPECIAL POPULATIONS

Elderly — For elderly patients with major depression, repetitive transcranial magnetic stimulation (TMS) can be beneficial if the stimulation intensity is sufficient [12]. Prefrontal atrophy in older patients can increase the distance between the coil and cortex to the point that lower intensity stimulation (which typically penetrates to a depth of 2 to 3 cm) does not affect cortical activity [92-94]; increasing the intensity above the motor threshold can overcome the added distance [12]:

- A randomized trial compared active repetitive TMS using an intensity set at 110 percent of the motor threshold with sham treatment in 62 patients (age ≥50 years) with vascular depression (ie, late-life depression accompanied by clinical evidence of cerebrovascular disease); improvement was greater with active treatment [95].

- A randomized trial compared active repetitive TMS using an intensity set at 110 percent of the motor threshold with sham treatment in 20 patients (mean age approximately 64 years) with poststroke depression; improvement was greater with active treatment [96].

- By contrast, a randomized trial in 20 patients (mean age 61 years) with treatment refractory depression found that active repetitive TMS using an intensity set at 80 percent of motor threshold provided no advantage over sham treatment [97].

In addition, a retrospective study of repetitive TMS found no difference in response and remission rates between younger (<60 years; n = 156) and older adults (≥60 years; n = 75) [98].

The clinical features and treatment of late life depression are discussed separately. (See "Diagnosis and management of late-life unipolar depression".)

Poststroke depression — Depression frequently occurs after stroke, and repetitive TMS may help these patients. As an example, a meta-analysis of 22 randomized trials compared TMS with no TMS in patients with poststroke depression (n >1700) [99]. Nearly all of the studies administered active TMS as an adjunctive treatment with usual care, and most studies did not use sham TMS as part of the control intervention. Improvement was greater with active TMS, and response occurred in more patients treated with active TMS, compared with patients who did not (64 versus 40 percent). In addition, impairment caused by stroke and activities of daily living were each superior in patients treated with active TMS, and discontinuation of treatment due to adverse effects was comparable for patients treated with active TMS, compared with patients who were not. However, heterogeneity across studies was substantial.

The clinical features and treatment of poststroke depression are discussed separately. (See "Complications of stroke: An overview", section on 'Depression'.)

Pediatric depression — Although no randomized trials have evaluated repetitive TMS for treatment resistant major depression in youth, perhaps due to the risk of seizures, one review identified 15 observational studies in which a total of 87 adolescents (no children) were treated [100]. The results suggested that TMS may perhaps be beneficial; response occurred in 63 percent, generally within two to eight weeks of starting TMS. However, residual symptoms were present following treatment in many patients. In addition, many patients reported adverse effects such as headache and scalp pain, which was generally tolerated. Seizures occurred in three patients (3 percent).

The clinical features, diagnosis, and treatment of pediatric depression are discussed separately. (See "Pediatric unipolar depression: Epidemiology, clinical features, assessment, and diagnosis" and "Overview of prevention and treatment for pediatric depression".)

Pregnancy and postpartum depression — For pregnant and postpartum patients with major depression, observational studies suggest that repetitive TMS may possibly be safe and effective [101-106]. It appears unlikely that the fetus is directly affected by repetitive TMS because magnetic fields rapidly attenuate with distance [38]. Additional information about treating antenatal depression with TMS is discussed separately. (See "Severe antenatal unipolar major depression: Choosing treatment", section on 'Other options'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

SUMMARY

- Patients with unipolar major depression who do not respond to standard treatment with pharmacotherapy and psychotherapy are candidates for noninvasive neuromodulation procedures, including repetitive transcranial magnetic stimulation (TMS) and electroconvulsive therapy. (See "Unipolar depression in adults: Overview of neuromodulation procedures", section on 'Noninvasive neuromodulation therapies' and "Overview of electroconvulsive therapy (ECT) for adults".)

- TMS modulates activity in cortical regions and associated neural circuits by passing an alternating current through a metal coil placed against the scalp to generate rapidly alternating magnetic fields, which pass through the skull and induce electric currents that depolarize neurons in a focal area of the surface cortex. Repetitive TMS is delivered as a series of pulses called a train; stimulation parameters include frequency, intensity, train duration, intertrain interval, and number of trains per session. (See 'Overview' above.)

- TMS is indicated for patients with unipolar major depression who have failed at least one antidepressant medication; TMS is contraindicated in patients with increased risks for seizures, implanted metallic hardware, cochlear implants, implanted electrical devices (eg, pacemakers, intracardiac lines, and medication pumps), and unstable general medical disorders. (See 'Indications' above and 'Contraindications' above and

"Unipolar depression in adults: Choosing treatment for resistant depression", section on 'Transcranial magnetic stimulation'.)

- For patients with acute unipolar major depression who have not responded to at least one antidepressant medication, meta-analyses of randomized trials have consistently found that TMS is superior to sham treatment. However, TMS is less effective than electroconvulsive therapy. In addition, many patients who respond to acute TMS subsequently suffer a recurrence, and it is not known if maintenance TMS is beneficial. (See 'Efficacy' above.)

- TMS is generally safe and well-tolerated. Serious adverse effects include generalized tonic-clonic seizures, but the risk is low and appears to be comparable to that for antidepressant medications. Factors that increase the risk of seizures include patient factors (history of epilepsy; preexisting neurologic disorder; proconvulsant medications; recent discontinuation of alcohol, benzodiazepines, or anticonvulsants; and sleep deprivation) and stimulation parameters (higher frequency, increased intensity, and shorter intertrain interval). Common side effects include headache, scalp pain, and transient hearing loss. (See 'Safety and adverse effects' above.)

- For elderly patients with major depression, repetitive TMS is beneficial if the stimulation intensity is sufficient to bridge the distance between the coil and cortex, which is increased by prefrontal atrophy. TMS may also be safe and effective for poststroke depression, as well as antenatal and postpartum major depression. The benefit of TMS for pediatric patients is not clear. (See 'Special populations' above.)

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Topic 14641 Version 22.0

GRAPHICS

PHQ-9 depression questionnaire

Name:	**Date:**			
Over the last 2 weeks, how often have you been bothered by any of the following problems?	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Trouble falling or staying asleep, or sleeping too much	0	1	2	3
Feeling tired or having little energy	0	1	2	3
Poor appetite or overeating	0	1	2	3
Feeling bad about yourself, or that you are a failure, or that you have let yourself or your family down	0	1	2	3
Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
Moving or speaking so slowly that other people could have noticed? Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual.	0	1	2	3
Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
Total ___ =	___	**+** ___	**+** ___	**+** ___
PHQ-9 score ≥10: Likely major depression				
Depression score ranges:				
5 to 9: mild				
10 to 14: moderate				
15 to 19: moderately severe				
≥20: severe				
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all ___	Somewhat difficult ___	Very difficult ___	Extremely difficult ___

PHQ: Patient Health Questionnaire.

Graphic 59307 Version 12.0

DSM-IV-TR diagnostic criteria for major depression

A. Five (or more) of the following symptoms have been present during the same 2-week period, and represent a change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest or pleasure.
(Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.)
Depressed mood most of the day, nearly every day (or alternatively can be irritable mood in children and adolescents)
Markedly diminished interest or pleasure in all, or almost all, activities, nearly every day
Significant weight loss while not dieting, weight gain, or decrease or increase in appetite
Insomnia or hypersomnia nearly every day
Psychomotor agitation or retardation nearly every day
Fatigue or loss of energy nearly every day
Feelings of worthlessness or excessive or inappropriate guilt nearly every day
Diminished ability to think or concentrate, or indecisiveness, nearly every day
Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms do not meet criteria for a Mixed Episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of substance or a general medical condition.
E. The symptoms are not better accounted for by Bereavement, ie, after the loss of a loved one, the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Adapted from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision. American Psychiatric Association, Washington, DC 2000.

Graphic 70852 Version 4.0

Screening 13-item questionnaire for rTMS candidates

1. Do you have epilepsy or have you ever had a convulsion or a seizure?
2. Have you ever had a fainting spell or syncope? If yes, please describe on which occasion(s).
3. Have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness?
4. Do you have any hearing problems or ringing in your ears?
5. Do you have cochlear implants?
6. Are you pregnant or is there any chance that you might be?
7. Do you have metal in the brain, skull, or elsewhere in your body (eg, splinters, fragments, clips, etc)? If so, specify the type of metal.
8. Do you have an implanted neurotransmitter (eg, DBS, epidural/subdural, VNS)?
9. Do you have a cardiac pacemaker or intracardiac lines?
10. Do you have a medication infusion device?
11. Are you taking any medications? (please list)
12. Did you ever undergo TMS in the past? If so, were there any problems?
13. Did you ever undergo MRI in the past? If so, were there any problems?

rTMS: repetitive transcranial magnetic stimulation; DBS: deep brain stimulation; VNS: vagus nerve stimulation; TMS: transcranial magnetic stimulation; MRI: magnetic resonance imaging.

Graphic 85964 Version 3.0