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

AUTHOR: Paul E Holtzheimer, MD
SECTION EDITOR: Peter P Roy-Byrne, MD
DEPUTY EDITOR: David Solomon, MD

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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 such as 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.

Following the invention of modern TMS in 1985, the US Food and Drug Administration approved it for treatment-resistant depression in 2008 [8]. Other neuropsychiatric disorders that have been treated with TMS include bipolar disorder, depersonalization/derealization disorder, generalized anxiety disorder, obsessive-compulsive disorder, chronic pain, Parkinson disease, posttraumatic stress disorder, schizophrenia, smoking cessation, stroke rehabilitation, and tinnitus [8-19].

This topic reviews the indications, efficacy, and safety of repetitive TMS for treating unipolar major depression in adults; the administration of TMS is reviewed elsewhere. Other neuromodulation procedures, including ECT, vagus nerve stimulation, and deep brain stimulation are also discussed separately, as is choosing treatment for resistant depression:

- (See "Unipolar major depression: Administering 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".)

OVERVIEW

Repetitive transcranial magnetic stimulation (TMS) treats major depression by modulating activity in cortical regions and associated neural circuits [20]. The intervention uses a large alternating electrical 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; some TMS devices may also stimulate deeper brain structures [8,21-23]. The magnetic field generated by 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 [22,24].

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 [20,25]. TMS has also been studied as a diagnostic tool [26].

The US Food and Drug Administration has approved repetitive TMS devices that can administer different types of stimulation, including:

- Surface cortical stimulation
  - High frequency
  - Low frequency
- Theta burst stimulation
- Deep stimulation

Administering these standard types of TMS is discussed separately. (See "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)".)

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 [27,28]. This is supported by functional imaging studies that show TMS can change activity in brain regions remote from the site of stimulation [29-44]. As an example, functional MRI indicates that surface cortical stimulation of the left dorsal lateral prefrontal

cortex increases anterior cingulate cortex connectivity within a meso-cortico-limbic network that may be involved in mood and includes the dorsal cingulate cortex, posterior dorso-medial prefrontal cortex, dorsal lateral prefrontal cortex, inferior parietal lobule, inferior frontal cortex, and posterior temporal lobes [45]. In addition, stimulation of the left dorsal lateral prefrontal cortex with either surface cortical TMS or theta burst TMS may decrease functional connectivity between the default mode network and the anterior cingulate cortex [46].

Repetitive TMS may also act by stimulating neuroplasticity. This may lead to increased expression of brain-derived neurotrophic factor and to structural changes, such as increased hippocampal volume [47,48].

Some molecular effects of repetitive TMS are comparable to those of ECT, including increased monoamine turnover and normalization of the hypothalamic pituitary axis [24]. In one neuroimaging study of depressed patients, a prefrontal serotonin deficiency at baseline normalized after treatment with TMS [24].

The effect of repetitive TMS appears to vary according to the frequency. High frequency surface cortical stimulation is thought to excite the targeted neurons (and is typically used to activate the left prefrontal cortex), whereas low frequency surface cortical stimulation appears to inhibit cortical activity (and is usually directed at the right prefrontal cortex) [28]. Consistent with this hypothesis, multiple reviews of studies in depressed patients who were treated with TMS targeting the dorsal lateral prefrontal cortex have found that high frequency TMS generally increased regional cerebral blood flow and that low frequency TMS generally decreased regional cerebral blood flow [42,49]. In addition, a prospective observational study of 15 patients with treatment-resistant unipolar major depression, who were treated with high frequency TMS of the left dorsal lateral prefrontal cortex, found that increased cerebral blood flow in the frontal cortex was associated with clinical improvement [50].

INDICATIONS

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

Repetitive TMS is indicated for patients with unipolar major depression who have failed at least one antidepressant medication; in some studies, patients have failed multiple courses of pharmacotherapy and psychotherapy as well as a trial of electroconvulsive therapy [51], and most patients have suffered prior episodes of major depression [22]. In addition, TMS is

indicated for patients who responded to a prior course of TMS [22]. TMS may also help depressed patients with general medical comorbidities because the treatment does not cause systemic adverse effects [8]. (See 'Safety and adverse effects' below.)

Use of repetitive TMS for treatment-resistant depression is consistent with treatment guidelines from the American Psychiatric Association [3,5], Canadian Network for Mood and Anxiety Treatments [4], British Association for Psychopharmacology [52], and the Royal Australian and New Zealand College of Psychiatrists [53].

Relatively few patients with unipolar major depression who are medication-naïve have been treated with TMS in a clinical trial [54]. Nevertheless, using TMS is reasonable as first-line treatment if patients decline pharmacotherapy and cannot access psychotherapy, such as patients who are pregnant or breastfeeding, have contraindications such as pre-existing liver damage, or are adolescents.

CONTRAINDICATIONS

To screen patients for contraindications to repetitive transcranial magnetic stimulation (TMS), we use a 13-item, clinician-administered questionnaire (table 1) [55].

Repetitive TMS is contraindicated in patients with [16,56-58]:

- Increased risks for seizures (see 'Seizure' below)
- Implanted metallic hardware, such as clips, electrodes, plates, and stimulators (eg, deep brain stimulators and vagus nerve stimulators)
- Metal fragments (eg, bullets)
- Cochlear implants
- Implanted electrical devices, including cardiac pacemakers, implantable cardioverter-defibrillators, intracardiac lines, and medication pumps
- Tattoos in the head or neck made with ferromagnetic-containing ink
- Unstable general medical disorders

Conversely, TMS is safe in patients with nonferromagnetic orthodontic hardware (eg, braces and fillings) and metal implants below the neck [16].

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 [59]. 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 adequate pharmacotherapy, including monotherapy and combination treatment, as well as trials of psychotherapy and electroconvulsive therapy (ECT). Stimulation frequency and choosing treatment for resistant depression are discussed elsewhere. (See "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)", section on 'Treatment parameters' and "Unipolar depression in adults: Choosing treatment for resistant depression".)

In addition, the contraindication to repetitive TMS in patients with an implanted vagus nerve stimulator is not absolute, provided that the TMS coil is not positioned near the vagus nerve stimulator components [16,60]. Prior to administering TMS to these patients, we suggest consultation with experts in using vagus nerve stimulation.

Psychotic features (eg, delusions and hallucinations) are not a contraindication for treating major depression with repetitive TMS [61], but most randomized trials have excluded psychotic patients [16,56,62-66]. In addition, one practice guideline on using TMS suggested treating psychotic depression with remedies other than TMS, such as ECT [16]. The clinical features and treatment of psychotic depression are discussed separately. (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis", section on 'Clinical features' and "Unipolar major depression with psychotic features: Acute treatment".)

EFFICACY

Based upon randomized trials, multiple reviews have consistently concluded that repetitive transcranial magnetic stimulation (TMS) can be efficacious and is generally safe for patients with treatment-resistant unipolar major depression [8,16,22,23]. More randomized trials have examined the efficacy of surface cortical TMS compared with other standard TMS protocols, such as deep TMS and theta burst TMS [67]. Although it is feasible to blind/mask clinicians administering TMS as well as patients and outcome raters [20], a methodologic limitation of many trials is that clinicians administering TMS were not blinded.

Evidence supporting the use of repetitive TMS includes a network meta-analysis of 31 randomized trials of pharmacologic and somatic interventions in patients with treatment-resistant depression (sample size not reported), including 11 trials that studied TMS [68]. Six

weeks after baseline, response (improvement of symptoms ≥50 percent) was more than eight times as likely with TMS than placebo pill/sham stimulation (odds ratio 8.6, 95% CI 1.2-112.6). However, discontinuation of treatment due to adverse effects was four times more likely with TMS than placebo pill/sham.

Although the relative efficacy and acceptability of different repetitive TMS protocols is not clear because few head-to-head trials have been conducted, it appears that outcomes with surface cortical TMS, theta burst TMS, and deep TMS are generally comparable. Two separate network meta-analyses compared different TMS protocols, including surface cortical TMS, theta burst TMS, and deep TMS, as well as experimental modalities such as an accelerated TMS and bilateral TMS, using results from direct comparisons between the modalities, as well as indirectly comparing modalities through their relative effect with a common comparator (eg, sham stimulation) [67,69]. Each study found that response and all-cause discontinuation were comparable among surface cortical TMS, theta burst TMS, and deep TMS.

Results of head-to-head comparisons between standard TMS protocols are described elsewhere in this topic. (See 'Theta burst TMS' below and 'Deep TMS' below.)

Surface cortical TMS — Repetitive TMS that stimulates the surface cortex is called surface cortical TMS; this is the most widely used and studied form of TMS. The administration of surface cortical TMS is described separately. (See "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)", section on 'Surface cortical TMS'.)

Acute treatment — For patients with acute major depression who have not responded to at least one antidepressant medication, numerous meta-analyses of randomized trials have demonstrated that repetitive surface cortical TMS is superior to sham treatment [67,70-77]. However, the best evidence indicates that TMS is less effective than electroconvulsive therapy (ECT). (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) — Multiple randomized trials have consistently demonstrated that repetitive surface cortical TMS is superior to sham TMS for treatment-resistant unipolar major depression [70-72,74,78,79]. These trials indicate that high frequency surface cortical TMS over the left dorsolateral prefrontal cortex (high frequency left TMS) and low frequency surface cortical TMS over the right dorsolateral prefrontal cortex (low frequency right TMS) are each efficacious and well tolerated. As an example, over 40 trials show that response (reduction of baseline symptoms ≥50 percent) is at least three times more likely with high frequency left TMS than sham TMS. Also, all-cause discontinuation of treatment with high frequency left TMS and low frequency right TMS is comparable to that of sham TMS:

- A systematic review conducted meta-analyses that found high frequency left TMS and low frequency right TMS were each superior to sham TMS [67]:
  - One meta-analysis (50 trials, sample size not reported) found that response was more than three times as likely with high frequency left TMS than sham TMS (odds ratio 3.3, 95% CI 2.3-4.6).
  - A second meta-analysis (12 trials, sample size not reported) found that response was more than twice as likely with low frequency right TMS than sham TMS (odds ratio 2.5, 95% CI 1.2-5.1).
- A subsequent systematic review also found that high frequency left TMS and low frequency right TMS were each superior to sham TMS [69]:
  - A meta-analysis of 43 trials compared high frequency left TMS with sham TMS in 1907 patients with treatment-resistant depression. Response was more likely to occur with active TMS (odds ratio 3.5, 95% CI 2.4-5.2).
  - A second meta-analysis of seven trials compared low frequency right TMS with sham TMS in 234 patients with treatment-resistant depression. Response was more likely to occur with active TMS (odds ratio 3.7, 95% CI 1.3-10.3).
- All-cause discontinuation of treatment in the four meta-analyses was comparable for active and sham treatment.

However, absolute rates of remission with repetitive TMS in some studies are modest [80]. As an example, two relatively large and rigorous randomized trials (n = 301 and 190) both found that remission with active high frequency left TMS occurred in only 14 percent of patients (compared with 5 to 6 percent in the sham TMS groups) [20,56]. One explanation is that some trials required patients to be medication free and to discontinue antidepressants that may have been partially effective. In addition, the low absolute rates of remission are consistent with findings that depressed patients who have previously failed pharmacotherapy are generally less responsive to subsequent pharmacotherapy or ECT [16,56].

Combined with pharmacotherapy — Repetitive TMS for unipolar major depression is typically administered in conjunction with antidepressants [8]. In most randomized trials that compared active TMS with sham TMS, 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 TMS was superior to sham treatment, patients were free of antidepressant medications in only seven trials [74].

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 [81]. Patients received 10 to 30 sessions of high frequency, left surface cortical 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) [82]. However, two negative studies did not report enough data for the purposes of the meta-analysis and were thus excluded [65,83].

No randomized trials have established that simultaneously starting repetitive TMS plus pharmacotherapy is superior to initiating TMS alone for major depression [84,85].

Predictors of response — Randomized trials indicate that treatment protocol (type of stimulation) is not associated with the rate of response in patients treated with surface cortical repetitive TMS. One meta-analysis (34 randomized trials, 1383 depressed patients) compared left dorsal lateral prefrontal cortex TMS with right dorsal lateral prefrontal cortex stimulation and found that efficacy was comparable [74]. Other meta-analyses suggest that the benefits of high frequency (>1 pulse per second) and low frequency (≤1 pulse per second) TMS are comparable [67,70,86,87].

Although individual studies of repetitive TMS for major depression have found clinical factors associated with response (eg, number of antidepressant medications that have failed to resolve the presenting episode [88]), 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 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 [86]. In addition, a subsequent randomized trial found that the number of adequate antidepressant trials prior to onset of TMS was not associated with response [89].

Some studies have suggested that use of benzodiazepines may reduce the antidepressant effect of repetitive TMS:

- A randomized trial compared high frequency, surface cortical TMS with theta burst TMS in 388 patients with treatment-resistant unipolar major depression; TMS was added onto stable pharmacotherapy regimens, which included benzodiazepines in 32 percent of the patients [89]. Among the 388 patients, nonresponse to TMS was more than twice as likely among patients taking benzodiazepines (odds ratio 2.25, 95% CI 0.99-5.11).

- A retrospective study identified patients with unipolar major depression who were treated with high frequency, surface cortical TMS of the left dorsolateral prefrontal cortex, as well as low frequency surface cortical TMS of the right dorsolateral prefrontal cortex if response to left-sided stimulation was inadequate [90]. Concomitant benzodiazepines were present in 72 patients and absent in 109 patients. Response at week 6 occurred in fewer benzodiazepine users than nonusers (16 versus 36 percent).

However, a potential confounding factor in both studies is comorbid anxiety, which may be associated with a poor response to TMS, just as it is associated with a poor response to pharmacotherapy [8,91]. Both studies measured anxiety symptoms and attempted to control for it in the analyses and the randomized trial found that anxiety did not predict response to TMS. Nevertheless, neither study was designed to specifically assess the relationship between anxiety and response to TMS, and the association between benzodiazepines and poor response may have been due to residual confounding.

One proposed predictor of response to repetitive TMS in patients with depression is comorbid posttraumatic stress disorder (PTSD). A randomized trial raised the possibility that add-on, high frequency surface cortical TMS over the left prefrontal cortex was no better than sham TMS for veterans (n = 164) with treatment-resistant unipolar major depression because nearly half of them had PTSD [92]. However, another randomized trial found that in veterans (n = 103) with a primary diagnosis of PTSD, adjunctive, low frequency right dorsal lateral prefrontal cortex stimulation was beneficial for this disorder [18]. Also, in a prospective observational study of veterans with treatment-resistant major depression who were treated with high frequency, left prefrontal TMS, remission was comparable in those without comorbid PTSD (n = 45) and those with PTSD (n = 44) [93].

Other proposed clinical predictors of response to repetitive TMS include relatively less severe episodes of unipolar treatment-resistant major depression, which may be more likely to respond [89]. By contrast, patients who initially respond poorly to TMS (eg, <20 percent improvement after two weeks) may be less likely to respond with additional treatment [94].

Neurobiologic factors such as the functional connectivity of the stimulation target to neural networks involved in depression may predict response to repetitive TMS [95-101]. Genetic polymorphisms, baseline regional cerebral blood flow, and baseline resting electroencephalography measures may also be associated with response to TMS [102]. However, assessing these factors to predict response is restricted to research settings and is not part of standard clinical care.

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

Durability of response — Among patients with major depression who respond to acute treatment with repetitive TMS, the benefit of TMS is often stable in the short-term (eg, four weeks posttreatment). In addition, response to TMS may persist for at least one year:

- **Short-term** – A meta-analysis of 16 trials included 495 patients who were randomly assigned to active TMS or sham TMS and then followed posttreatment for 1 to 16 weeks [103]. 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 patients received 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.

- **Longer-term** – A subsequent meta-analysis examined durability of response in 732 patients who responded to acute treatment with TMS in randomized trials or observational studies and were followed posttreatment for a minimum of three months [104]. During follow-up, patients received maintenance treatment with TMS and/or pharmacotherapy. Among the initial responders, the proportion who sustained response at different time points posttreatment was as follows:

  - 3 months – 67 percent
  - 6 months – 53 percent
  - 12 months – 46 percent

Across different studies, there are no clinical factors that are consistently associated with a durable response to TMS [103,104].

Following relapse — For patients with unipolar major depression who improve with a course of repetitive TMS and subsequently deteriorate or relapse, observational data suggest that another course (reintroduction) of TMS using the same stimulation parameters may be helpful [22,105-112].

Maintenance TMS — Among patients with unipolar major depression who respond to acute repetitive TMS, it is not known if maintenance TMS for is beneficial. Although two randomized trials found that maintenance TMS was not beneficial, both studies were limited by small samples and the frequency of maintenance treatment in these trials may have been inadequate:

- A 12-month, open label trial, which included 49 medication free patients who initially responded to acute TMS (Hamilton Rating Scale for Depression (table 2) score <15), found that administering maintenance TMS only once per month provided no advantage over watchful waiting [112].

- An 11-month trial compared active maintenance TMS plus pharmacotherapy with sham maintenance TMS plus pharmacotherapy in 17 patients who initially responded to acute TMS plus pharmacotherapy; response was defined as at least 50 percent reduction of baseline scores on the Hamilton Rating Scale for Depression [113]. Maintenance TMS was delivered by gradually tapering treatment over a three-month period from daily sessions to one session every two weeks. The benefit of active and sham maintenance TMS was comparable.

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 be beneficial [59,114-116].

In addition, there is evidence that maintenance TMS may be effective in acutely depressed patients who improve after treatment with antidepressant medications. In one study, patients (n = 281) with depressive syndromes who responded to open label antidepressants for at least three months were randomly assigned to one of three treatment regimens for one year: continue the same antidepressant as monotherapy, continue the same antidepressant and add TMS, or switch to TMS as monotherapy [117]. Relapse occurred in fewer patients who received either antidepressant plus TMS or TMS alone, compared with antidepressant alone (16 and 24 versus 44 percent). The difference between antidepressant plus TMS and TMS alone was not statistically significant.

Theta burst TMS — Theta burst (or intermittent theta burst) repetitive TMS involves high frequency magnetic pulses that are administered at 50 hertz five times per second and are

intended to mimic endogenous theta rhythms. (See "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)", section on 'Theta burst TMS'.)

Randomized trials that compared theta burst TMS with sham TMS for unipolar major depression demonstrate that theta burst TMS is efficacious and well tolerated [78,79]:

- In a systematic review, a conventional meta-analysis used direct evidence from four randomized trials in 155 patients with major depression and found that response (reduction of baseline symptoms ≥50 percent) was more likely to occur with theta burst TMS than sham TMS (odds ratio 2.6, 95% CI 1.2-5.6) [67]. In addition, the review included a network meta-analysis that used both direct and indirect evidence; the network meta-analysis also showed that theta burst TMS was more efficacious than sham TMS. In both meta-analyses, discontinuation of treatment for any reason was comparable for active and sham treatment.

- A pooled analysis of five randomized trials compared theta burst TMS with sham TMS in patients with major depression (n = 221) and found that response occurred in more patients who received active treatment (36 versus 17 percent) [118]. In addition, discontinuation of treatment for any reason was comparable for active and sham theta burst TMS (4 and 8 percent).

- A meta-analysis of three randomized trials compared theta burst TMS with sham TMS in 89 patients with treatment-resistant depression [69]. Response was more likely to occur with theta burst TMS (odds ratio 4.3, 95% CI 1.2-14.8).

In addition, randomized trials indicate that the efficacy and acceptability of theta burst TMS are comparable to that of surface cortical TMS and deep TMS:

- In network meta-analyses, response and all-cause discontinuation of theta burst TMS were comparable to that of surface cortical TMS and deep TMS. (See 'Efficacy' above.)

- A four-week, noninferiority randomized trial compared add-on theta burst TMS with surface cortical TMS in 414 patients with unipolar major depression that did not respond to an antidepressant [119]. With theta burst TMS, 600 pulses per session were delivered over three minutes; with surface cortical TMS, 3000 pulses per session were delivered over 37.5 minutes. All patients received up to 30 daily sessions. Both treatments targeted the left dorsolateral prefrontal cortex with a stimulus intensity of 120 percent of resting motor threshold. The trial was open-label, but outcome assessors were masked to treatment. The completer analysis showed that remission with theta burst and conventional TMS was comparable (32 and 27 percent). The most common adverse event was headache, which

occurred in approximately 65 percent of patients in each group. Although average pain scores were modestly greater with theta burst TMS, all-cause discontinuation of treatment in each group was comparable (approximately 7 percent).

Deep TMS — Commercially available repetitive TMS devices have been developed that theoretically stimulate brain structures beneath the superficial prefrontal cortex using magnetic coils (H coils). (See "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)", section on 'Deep TMS'.)

Several studies suggest that deep repetitive TMS is safe and beneficial for unipolar major depression [22,120,121]. As an example, a 16-week randomized trial compared deep TMS with sham TMS in 212 patients with treatment-resistant depression who discontinued all medications [122]. During the first four weeks of the trial, study treatments were administered each weekday and during the next 12 weeks, two days per week. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received active TMS than sham TMS:

- After 4 weeks – 37 versus 28 percent
- After 16 weeks – 41 versus 26 percent

Application site pain occurred in more patients with active TMS than sham TMS (5 versus 0 percent). Other adverse effects such as headache were comparable for the two groups.

Based upon network meta-analyses of randomized trials, the efficacy and acceptability of deep TMS appears to be comparable to that of surface cortical TMS and theta burst TMS (see 'Efficacy' above). Nevertheless, other evidence suggests that deep TMS may perhaps be more efficacious than surface cortical TMS. Subsequent to the network meta-analyses, a four-week randomized trial compared add-on deep TMS (20 sessions) with surface cortical TMS in patients with treatment-resistant depression (n = 147) who continued to receive stable, ongoing pharmacotherapy [123]. Although remission in the two groups was comparable, response occurred in more patients who were treated with adjunctive deep TMS than surface cortical TMS (67 versus 44 percent). In addition, all-cause discontinuation occurred more than twice as often with deep TMS than surface cortical TMS (10 and 4 percent of patients). Adverse effects with deep TMS and surface cortical TMS included the following: headache (29 and 20 percent of patients), muscle twitching/spasms or jaw pain (12 and 0 percent), and application site pain (7 and 0 percent).

SAFETY AND ADVERSE EFFECTS

Repetitive transcranial magnetic stimulation (TMS) is generally safe and well-tolerated [16,20,22,24,56] and does not cause systemic side effects [8]. As an example, a randomized trial in 301 patients found that study discontinuation due to adverse effects was comparable for active and sham surface cortical repetitive TMS (5 and 3 percent) [56]. Among the standard types of TMS stimulation (surface cortical, theta burst, and deep), it is not clear if there are clinically significant differences in the safety and adverse effects because relatively few head-to-head trials have been conducted.

Seizure — The most serious adverse effect of repetitive TMS is a generalized tonic-clonic seizure [22,57,58]. However, seizures are rarely observed and the risk appears to be comparable to that for antidepressant medications. 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, and one review found that the incidence of seizure was 0.003 percent [16,22,24,57]. Seizures that have occurred were self-limited, required no medications, and did not recur [22,57,58].

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

(See "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)", section on 'Pretreatment assessment'.)

- Repetitive TMS stimulation parameters:
  - Higher frequency
  - Increased intensity
  - Shorter intertrain interval

Excessive stimulation intensity can occur if clinicians initially fail to identify the optimal site for motor response and thus incorrectly determine that the resting motor threshold is higher than the true value [16]. During the TMS session, monitoring the contralateral hand for movement or twitching can signal the possibility of a seizure and the need to adjust treatment parameters. TMS stimulation parameters are discussed separately. (See "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)", section on 'Treatment parameters'.)

If a seizure occurs [16]:

- Immediately terminate the procedure
- Assess airway breathing and circulation
- Do not restrain the patient or place anything in the patient's mouth
- After convulsions cease, turn the patient onto one side to help clear the airway and prevent aspiration
- Summon emergency medical services
- Document the event, including ictal behaviors, duration, and postictal features

Most seizures remit spontaneously within two minutes. (See "Evaluation and management of the first seizure in adults", section on 'Early postseizure management'.)

Other side effects — Hypomania and mania have been described in randomized trials [124] as well as case reports of patients with unipolar or bipolar major depression who were treated with different types of repetitive TMS [125-134]. 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 TMS and sham treatment (0.8 and 0.7 percent) [124].

Treatment of unipolar major depression with repetitive TMS does not appear to increase suicidal ideation or behavior [20]. In a randomized trial that compared active 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 [56]. 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 [57,58]:

- Headache and scalp pain – Headache and scalp pain can occur proximal to the site of stimulation. 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 [57]. No migraine headaches have been reported [16].

  Headache and scalp pain may be more pronounced when higher stimulation frequencies and intensities are used; topical lidocaine may reduce scalp pain [135]. Reducing stimulation intensity can also decrease discomfort, but this can reduce efficacy as well [16,105]; thus, for sensitive patients, the dose of TMS can be titrated up during the first week [22]. Headache and scalp pain generally resolve over the first two weeks, although some patients may require an analgesic (eg, acetaminophen or ibuprofen) [16,22].

- 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 [22].

Another potential side effect is vasovagal syncope; management generally consists of reassurance [16,22]. In addition, encourage adequate hydration, assess concurrent pharmacotherapy for potential source of orthostasis, and check blood pressure before and after each TMS session. If syncope occurs during a session, terminate it and lower the patient's head to promote cerebral perfusion.

Tolerability of repetitive TMS may be better with lower stimulation parameters compared with higher parameters [20,136]. (See "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)", section on 'Treatment parameters'.)

Repetitive TMS in patients with major depression does not impair cognition [20,56-58,137-140]. 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 [58,140].

It is not known whether clinicians who administer repetitive TMS for years face any safety issues or long-term adverse effects [57].

SPECIAL POPULATIONS

Older adult — For older adult patients with major depression, repetitive transcranial magnetic stimulation (TMS) can be beneficial if the stimulation intensity is sufficient [24]. 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 [141-143]; increasing the intensity above the motor threshold can overcome the added distance [24].

Evidence supporting the use of TMS for late-life depression includes randomized trials employing increased stimulation intensity as noted above:

- One trial compared high frequency, surface cortical TMS with sham treatment in 62 patients (age ≥50 years) with vascular depression (ie, late-life depression accompanied by clinical evidence of cerebrovascular disease); active TMS used an intensity set at 110 percent of the motor threshold [144]. Remission occurred in more patients treated with active TMS than sham TMS (27 versus 4 percent). However, headache occurred in twice as many patients who received active treatment (21 versus 10 percent).

- A trial of deep TMS in 52 patients (age 60 to 80 years) used an intensity of 120 percent of motor threshold and found that remission occurred in more patients who received active TMS than sham TMS (40 versus 15 percent) [145]. However, pain at the stimulation site occurred in more patients treated with active TMS (16 versus 0 percent).

Across both trials, improvement of cognitive functioning was generally comparable in patients treated with active TMS and sham TMS.

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) [146]. Nearly all the studies administered active TMS as an adjunctive treatment with usual care (eg, antidepressants), and most studies did not use sham TMS as part of the control intervention. Improvement of depression was greater with active TMS, and response (reduction of baseline symptoms ≥50 percent) occurred in more patients treated with active TMS than controls (64 versus 40 percent). In addition, improvement of neurologic function 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.

- A subsequent meta-analysis of 17 randomized trials compared TMS with no TMS in patients with poststroke depression (n >1000) [147]. Nearly all the studies administered active TMS as an adjunctive treatment with usual care (eg, antidepressants) 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 than controls (58 versus 34 percent). In addition, improvement of neurologic function and activities of daily living were each superior in patients treated with active TMS. However, heterogeneity across studies was substantial and headache was more likely to occur in patients who received active TMS (odds ratio, 3.5, 95% CI1.9-8.6).

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 youth with treatment-resistant major depression, perhaps due to the risk of seizures, observational studies suggest that TMS may perhaps be beneficial [148]. As an example, one review identified 15 observational studies in which a total of 87 adolescents (no children) were treated with TMS [149]. 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, small randomized trials and observational studies suggest that repetitive TMS may possibly be safe and effective [150-157]. It appears unlikely that the fetus is directly affected by repetitive TMS because magnetic fields rapidly attenuate with distance [57]. 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

- **Neuromodulation procedures** – 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".)

- **Overview of TMS** – TMS modulates activity in cortical regions and associated neural circuits by passing an alternating electrical 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; some TMS devices may also stimulate deeper brain structures. Standard TMS devices can administer different types of stimulation, including surface cortical stimulation, theta burst stimulation, and deep stimulation. (See 'Overview' above.)

- **Indications** – TMS is indicated for patients with unipolar major depression who have failed at least one antidepressant medication, whereas 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'.)

- **Efficacy** – For patients with treatment-resistant unipolar major depression, multiple randomized trials indicate that surface cortical TMS, theta burst TMS, and deep TMS can each be efficacious and are generally well tolerated. The most widely studied type of TMS is surface cortical TMS. Among patients who respond to acute treatment, the benefit of TMS is often stable in the short-term (eg, four weeks posttreatment) and response to TMS may persist, albeit at a lower frequency, for at least one year. However, it is not known if maintenance treatment with TMS is beneficial. (See 'Efficacy' above.)

- **Safety and adverse effects** – 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. Patient factors that increase the risk of seizures include history of epilepsy; preexisting neurologic disorder; proconvulsant medications; recent discontinuation of alcohol, benzodiazepines, or anticonvulsants; and sleep deprivation. Stimulation parameters associated with seizures include 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.)

- **Special populations** – For older adult patients with major depression, TMS can be beneficial if the stimulation intensity is high enough to bridge the distance between the coil and cortex. 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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