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Unipolar major depression: Administering 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 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.

Modern TMS was developed in 1985 and the US Food and Drug Administration approved TMS 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 [8-21]. In addition, TMS has been studied as a diagnostic tool [22].

This topic reviews standard techniques for performing TMS to treat unipolar major depression in adults and briefly describes experimental techniques. The indications, efficacy, and safety of standard TMS for unipolar depression are discussed 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:

- (See ["Unipolar depression in adults: Indications, efficacy, and safety of 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 and other illnesses by modulating activity in cortical regions and associated neural circuits [23]. 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 [8,24-26]. 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 [25,27].

Commercially available TMS devices can administer different types of stimulation, including surface cortical stimulation, deep stimulation, and theta burst stimulation. The efficacy, safety, and adverse effects of these standard TMS protocols are discussed separately. (See ["Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation \(TMS\)".](#))

TMS is the subject of ongoing research to evaluate indications and optimize administration, including the amount of electricity to use and the length of time the electric current passes through the coil, as well as placement of the coil and the number of treatment sessions (see ["Treatment parameters"](#) below and ["Stimulation site"](#) below). Experimental techniques for administering TMS include an accelerated schedule (multiple sessions per day) as well as high dose stimulation and bilateral stimulation. (See ["Experimental techniques"](#) below.)

PRETREATMENT ASSESSMENT

Prior to prescribing repetitive transcranial magnetic stimulation (TMS), clinicians should evaluate patients to confirm the primary diagnosis of treatment-resistant depression and whether the intervention can be used safely [20]. The assessment includes a psychiatric history and mental status examination, with emphasis upon depressive symptoms ([table 1](#)), 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. Evaluations should also include the patient's current use of alcohol and risk of withdrawal, as well as use of other substances that may provoke seizures, such as cocaine, inhalants, phencyclidine, and psychostimulants.

In addition, a general medical history and a screening physical examination is performed; more detailed physical examination should be pursued as guided by the history and review of systems [20,28]. Laboratory tests and neuroimaging studies are obtained as guided by the history and examination [29-31]. The general medical work-up should emphasize risk factors for seizures and preexisting neurologic disease, including history of seizures, loss of consciousness, or traumatic brain injury ([table 2](#)) [20]:

- Personal and family (parent, sibling, or child) history of seizures and epilepsy.
- Intracranial masses and brain disorder/trauma (eg, brain surgery, congenital brain malformation, increased intracranial pressure, stroke, traumatic brain injury, tumor, or vascular abnormalities in the brain).
- Electrolyte disturbance.
- Medications that can lower seizure threshold (eg, antipsychotics, [bupropion](#), stimulants, tricyclic antidepressants, and [theophylline](#)) ([table 3](#)).
- Recent (eg, in the past few days) dose reduction or discontinuation of benzodiazepines or other anticonvulsants.
- Metal in the head or neck.
- Sleep deprivation.
- Other conditions that might affect seizure threshold (eg, caffeine overuse or alcohol withdrawal) ([table 4](#)). (See "[Evaluation and management of the first seizure in adults](#)", [section on 'Acute symptomatic seizures'](#).)

Referral to neurology or internal medicine is warranted if there are questions about the risk of seizures or other adverse effects. (See "[Unipolar depression in adults: Indications, efficacy, and](#)

[safety of transcranial magnetic stimulation \(TMS\)", section on 'Safety and adverse effects'.\)](#)

Additional information about the initial assessment of patients undergoing repetitive TMS is discussed separately in the context of assessing patients for a diagnosis of unipolar depression. (See "[Unipolar depression in adults: Assessment and diagnosis", section on 'Assessment'.](#)")

Some clinicians have questioned recommendations to physically examine candidates for repetitive TMS due to its relative safety [32]. Nevertheless, we recommend a screening physical examination to identify general medical disorders that may contribute to the depressive syndrome or complicate use of TMS [28]. This approach is consistent with treatment guidelines from the National Network of Depression Centers and American Psychiatric Association [3,5,20].

TREATMENT TEAM

A psychiatrist or other qualified clinician should prescribe and supervise treatment of major depression with repetitive transcranial magnetic stimulation (TMS), although individual treatments are often administered by a nurse, physician assistant, or medical assistant [20,25,27,28,33,34]. For most practice settings in which someone other than the psychiatrist is operating the TMS device, the psychiatrist is immediately available [25]. We recommend that all providers receive training through a formal university affiliated or industry independent certification course, or through peer-to-peer training, as well as industry sponsored training on the specific repetitive TMS device to be used. In addition, all personnel should be trained to recognize and initially manage generalized seizures. (See "[Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation \(TMS\)", section on 'Seizure'.](#)")

SETTING

Repetitive transcranial magnetic stimulation (TMS) is generally an outpatient procedure, with patients awake and seated in a reclining chair during treatment. Anesthesia is not used and patients can thus drive themselves to and from sessions, which typically last approximately 30 to 40 minutes [35]. The equipment used to administer TMS is displayed in the graphic ([picture 1](#)).

MONITORING DURING TREATMENT

During a course of repetitive transcranial magnetic stimulation, patients are evaluated at each session for adverse effects [20,25]. In addition, depressive symptoms are monitored with a clinician-administered or patient self-report standardized instrument that is administered weekly or every two weeks. Suitable self-report scales include the Patient Health Questionnaire – Nine Item (PHQ-9) ([table 5](#)) [25]. Additional information about measurement-based care, including the PHQ-9, is discussed separately. (See "[Using scales to monitor symptoms and treat depression \(measurement based care\)](#)".)

STANDARD TECHNIQUES

The US Food and Drug Administration has approved repetitive transcranial magnetic stimulation (TMS) devices that can administer different types of stimulation; these standard types of stimulation include:

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

Surface cortical TMS — Repetitive TMS that stimulates the surface cortex is called surface cortical TMS or superficial TMS. Surface cortical TMS is the most widely used and studied form of TMS.

The efficacy of surface cortical TMS is discussed separately. (See "[Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation \(TMS\)](#)", section on 'Surface cortical TMS'.)

Treatment parameters — TMS can be delivered either as a single pulse (stimulus) or as a series of pulses called a train; stimulation with a train is called repetitive TMS [25,27]. The depth of stimulation is approximately 2 to 3 cm beneath the coil (shaped like a figure-of-eight), and most repetitive TMS devices depolarize cortical neurons in a circular area with a diameter of approximately 2 to 3 cm. Parameters of repetitive TMS include [8,20,25,36]:

- Frequency – Number of magnetic pulses per second (hertz).
 - High (fast) frequency refers to stimulation delivered at >1 pulse per second (typically 10 to 20 pulses per second). High frequency TMS is administered over the left dorsolateral prefrontal cortex and enhances cortical activity.

- Low (slow) frequency denotes stimulation delivered at ≤ 1 pulse per second. Low frequency TMS is administered over the right dorsolateral prefrontal cortex and inhibits cortical activity.

Indications for low frequency TMS include high risk of seizures, and initial treatment with high frequency TMS that is poorly tolerated (eg, stimulation site pain) or is ineffective [20].

- Intensity – Expressed as a percentage of the resting motor threshold, which is established before the first TMS treatment by stimulating the motor cortex and determining the minimum amount of energy that is required to evoke a motor response in a specific muscle group (generally the contralateral small hand muscles such as abductor pollicis brevis). The motor response is assessed visually or with electromyography. Intensity is generally set at 100 to 120 percent of resting motor threshold.

During a course of treatment, the resting motor threshold is reassessed if there are changes in the patient's clinical status that may increase cortical excitability and lower seizure threshold, including:

- Adjustment of concurrent pharmacotherapy
 - Sleep deprivation
 - Changes in substance use
- Train duration (on time; eg, 4 seconds).
 - Intertrain interval – Time between successive trains (off time, eg, 26 seconds).
 - Number of trains per session (eg, 75 trains).

Most studies report the number of pulses per session (eg, 3000), which is calculated from the frequency, train duration, and number of trains per session. The number of pulses given during a specific time period, such as a treatment session, day, week, or treatment course, can be conceptualized as the dose of TMS.

Stimulation site — Most clinical trials of repetitive TMS for unipolar major depression have stimulated a single cortical site [23]. Generally, the left dorsal lateral prefrontal cortex is targeted, and neuroimaging of depressed patients has found hypoactivity in the dorsal lateral prefrontal cortex [37]. However, some trials have stimulated the right dorsal lateral prefrontal cortex, and other trials have sequentially or simultaneously stimulated two cortical sites [38]. TMS of the dorsomedial prefrontal cortex has also been studied [39].

Several methods have been developed to position the magnetic coil for stimulating the left dorsal lateral prefrontal cortex [20]:

- Perhaps the most common technique, which is relatively inexpensive and easy to implement, is performed by first identifying the optimal spot on the scalp for evoking a motor evoked potential in the hand muscles, and then advancing the coil 5 cm anteriorly in a parasagittal plane along the skull surface (some authorities measure 5.5 to 7 cm) [25,36,40]. Although this approach has been widely studied, its utility is limited because patients have varying brain sizes and morphology.
- The preferred coil positioning technique, based upon multiple studies and expert consensus opinion, is another relatively inexpensive approach called the "Beam F3" location system [20,41,42]. This method uses three skull measurements based upon techniques used to place electroencephalography electrodes, and is more precise than using a set distance from the motor cortex because the Beam F3 method accounts for differences in skull size.
- Neuronavigation guided by magnetic resonance imaging scans has been used in some research protocols to localize the prefrontal cortex [26,43,44].
- Another method for coil positioning uses a stereotactic frame with mechanical arms to hold the coil in place with respect to the head [20].

Acute treatment — For acute treatment of unipolar major depression, repetitive TMS is usually administered by stimulating the left dorsal lateral prefrontal cortex daily (Monday through Friday) over four to six weeks, using the following parameters [4,23,25,26,45]:

- 10 magnetic pulses per second (10 hertz)
- 3000 pulses per session
- 100 to 120 percent of motor threshold (ie, the magnetic field intensity relative to the patient's resting motor threshold)

However, the stimulation parameters required to optimize efficacy are not known, and administration of TMS is thus not standardized. As an example, meta-analyses have found that low frequency (≤ 1 pulse per second) and high frequency (≥ 5 pulses per second) TMS are each more effective than sham treatment, and that the benefits of low frequency and high frequency repetitive TMS are comparable. (See "[Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation \(TMS\)](#)", section on 'Compared with sham treatment (placebo)').

The number of treatments necessary for patients with acute major depression is not clear. Some authorities suggest that a trial of repetitive TMS should last a minimum of three to four weeks before determining whether the treatment is beneficial [36]. In addition, it is reasonable to extend treatment to six weeks and beyond six weeks for an additional two to six weeks for patients who have achieved a partial response that has not plateaued and for patients with a prior history of late response (eg, after 10 weeks) to antidepressant medications [25]. Evidence supporting treatment beyond six weeks includes the following:

- In an observational study, 73 patients with unipolar major depression who did not respond to daily repetitive TMS for four to six weeks were treated for an additional six weeks; response (improvement from baseline on the depression rating scale \geq 50 percent) occurred in 26 percent [46].
- Another observational study enrolled 61 patients who did not initially respond satisfactorily to acute TMS and then administered additional acute TMS, such that patients received a total of up to 12 weeks of acute TMS; remission occurred in 31 percent [47].

Treatments can be spaced rather than administered on a daily basis [48]. In a randomized trial, repetitive TMS given three days per week for six weeks (18 sessions) was compared with repetitive TMS given five days per week for four weeks (20 sessions) in 77 patients with major depression; improvement and tolerability were similar [49].

Safety measures for repetitive TMS include use of hearing protection (eg, ear plugs) and keeping oxygen and anticonvulsant medications available for treatment of seizures; these procedures are consistent with TMS guidelines [20,33,50]. The risk of hearing loss and seizures is discussed elsewhere. (See "[Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation \(TMS\)](#)", section on 'Safety and adverse effects'.)

Acute repetitive TMS can be used with or without concurrent medications [25]. Concomitant psychotropic (eg, antidepressants) and nonpsychotropic medications are generally safe to use during a course of repetitive TMS for major depression [51,52], and most clinicians continue currently prescribed antidepressant drugs [8,25]. The pharmacotherapy regimen should be stable (eg, for four weeks) prior to adding TMS, which enables the treatment team to determine that clinical changes are due to the new treatment. Some clinicians taper and discontinue proconvulsant medications (eg, [bupropion](#), tricyclics, and [theophylline](#)). However, given the potential benefit of maintaining even partially effective medications, continuing these medications is reasonable, provided that clinicians carefully monitor the motor threshold to ensure that stimulation intensity does not exceed the recommended safety range [53]. Intensity is discussed elsewhere in this topic. (See '[Treatment parameters](#)' above.)

Although questions have been raised as to whether benzodiazepines reduce the antidepressant efficacy of TMS [8]. It is reasonable to prescribe these medications during a course of repetitive TMS. (See "[Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation \(TMS\)](#)", section on 'Predictors of response'.)

For patients who complete acute treatment with repetitive TMS and are not receiving maintenance TMS (see '[Maintenance treatment](#)' below), we typically discontinue TMS without a taper. However, it is reasonable for clinicians to taper TMS over two to three weeks before stopping it [25]. As an example, during a three-week taper, clinicians can administer three sessions in week 1, two sessions in week 2, and one session in the final week.

Maintenance treatment — For patients with unipolar major depression who respond to acute repetitive TMS and are at risk for recurrence, it is reasonable to use TMS for maintenance treatment; TMS is usually given in conjunction with antidepressant medications but can be used as monotherapy [25]. Maintenance TMS typically uses the same stimulation parameters and neuronavigation that were used during acute treatment, unless side effects necessitate changes [50,54-56]. However, the frequency of sessions for maintenance TMS has not been standardized, and it is not known whether any specific schedule is superior to another [4].

The most common maintenance TMS schedule appears to be one in which the number of sessions is gradually tapered over several months [54], and many clinicians determine the schedule based upon patient response [25]. Examples of specific, reasonable maintenance schedules that have been studied include the following:

- In a retrospective study of 42 patients, daily treatments were reduced to three sessions in week 1 of maintenance treatment, two sessions in week 2, and one session in week 3 [50]. After one session per week for four weeks, the schedule was tapered further to two sessions per month for two months and then to one session per month. The frequency of sessions was intermittently increased or decreased depending upon the patient's clinical status.
- A prospective observational study enrolled 35 patients who initially responded to acute TMS, then relapsed, and subsequently responded to a second course of acute TMS [55]. The maintenance TMS schedule was such that every month, patients received five sessions administered over three days.
- In an 11-month randomized trial that compared active with sham maintenance TMS in 17 patients, maintenance TMS was delivered by gradually tapering treatment over three months from daily sessions to one session every two weeks [56].

It is not known how long patients should receive maintenance TMS. Across different studies, the duration has ranged from approximately six months to six years [50,54,55,57]. Based upon indirect evidence from studies of maintenance pharmacotherapy, patients with unipolar major depression who are at risk for recurrence of major depressive episodes are candidates for maintenance TMS lasting at least one year to three years. (See ["Unipolar depression in adults: Continuation and maintenance treatment", section on 'Duration'](#).)

Deep TMS — Deep TMS is administered by commercially available repetitive TMS devices that theoretically stimulate brain structures beneath the superficial prefrontal cortex using magnetic coils (H coils); these H coils can induce a magnetic field with a deeper and wider distribution than the standard (figure eight) coils used for surface cortical TMS [58-60]. The depth of stimulation beneath with H coils is approximately 4 cm; H coils also stimulate surface cortical structures. It is not clear that stimulation of deeper brain structures with the H coils results in clinically or physiologically meaningful effects. Deep TMS is used to treat multiple neuropsychiatric disorders, including unipolar major depression, as well as obsessive-compulsive disorder, chronic pain, Parkinson disease, and stroke rehabilitation [9-11,17].

In randomized trials that treated unipolar major depression with deep TMS, treatment was administered as follows [20,60,61]:

- Frequency – 18 hertz
- Intensity – 120 percent of resting motor threshold
- Train duration (on time) – 2 seconds
- Intertrain interval (off time) – 20 seconds
- Number of magnetic pulses – 1980 pulses/session
- Stimulation site – Left dorsal lateral prefrontal cortex or prefrontal cortex

General information about repetitive TMS treatment parameters is discussed elsewhere in the context of surface cortical TMS. (See ["Treatment parameters"](#) above.)

One session of deep TMS requires 20 to 30 minutes of stimulation, comparable to that for conventional surface cortical TMS [60,61]. Sessions occur each weekday for four weeks. Thus, the total number of daily sessions for an acute course of treatment with deep TMS is 20, comparable to that for surface cortical repetitive TMS. (See ["Acute treatment"](#) above.)

The efficacy of deep TMS for unipolar major depression is discussed separately. (See ["Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation \(TMS\)", section on 'Deep TMS'](#).)

Theta burst TMS — Theta burst (or intermittent theta burst) repetitive TMS utilizes magnetic pulses that are intended to mimic endogenous theta rhythms; this approach has been studied for unipolar major depression and other neuropsychiatric conditions, including chronic pain, posttraumatic stress disorder, stroke rehabilitation, and tinnitus [12-14,16,62].

In randomized trials that treated unipolar major depression with theta burst TMS, treatment was administered as follows [62,63]:

- Frequency – 5 hertz (five bursts/second; each burst consists of three 50 hertz stimulations)
- Intensity – 120 percent of resting motor threshold
- Train duration (on time) – Two seconds
- Intertrain interval (off time) – Eight seconds
- Number of magnetic pulses – 600 pulses/session
- Stimulation site – Left dorsal lateral prefrontal cortex

General information about repetitive TMS treatment parameters is discussed elsewhere in the context of surface cortical TMS. (See '[Treatment parameters](#)' above.)

One session of theta burst TMS typically requires 3 to 10 minutes of stimulation, which is less than the 30 to 40 minutes required for conventional surface cortical repetitive TMS [64].

Sessions occur each weekday for four to six weeks. Thus, the total number of daily sessions for an acute course of treatment with theta burst TMS is 20 to 30, comparable to that for surface cortical TMS. (See '[Acute treatment](#)' above.)

Multiple studies suggest that theta burst stimulation decreases the amplitude of motor-evoked potentials and also exerts longer lasting effects upon motor cortex excitability than surface cortical repetitive TMS [65,66].

The efficacy of theta burst TMS for unipolar major depression is discussed separately. (See "[Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation \(TMS\)](#)", section on '[Theta burst TMS](#)'.)

EXPERIMENTAL TECHNIQUES

Investigators are studying variations in administering repetitive transcranial magnetic stimulation (TMS) to patients with major depression [67], including an accelerated schedule (multiple sessions per day), high dose stimulation, and bilateral stimulation, which are described in the subsections below.

Accelerated TMS — To address the logistical constraint of repetitive TMS protocols that call for five sessions per week for four to six weeks, investigators have administered multiple (eg, two or three) sessions per day for less than four weeks [68-73]. Evidence supporting accelerated (intensive) TMS includes a three-week trial that enrolled 52 patients with treatment-resistant depression and randomly assigned them to surface cortical TMS delivered either twice/day or once/day (1600 pulses per session) [74]. The study found that the likelihood of remission was greater with twice daily TMS (odds ratio 1.5). In addition, adverse effects were comparable for the two groups.

Other randomized trials in patients with treatment-resistant depression suggest that the benefit of accelerated TMS protocols, given on fewer treatment days, may be comparable to once daily protocols that involve more treatment days:

- A four-week trial compared an accelerated schedule of surface cortical TMS with a once daily schedule in 115 patients [75]. The schedule for accelerated TMS included 18 treatment sessions administered on six treatment days as follows:
 - Week 1 – Three sessions/day on three treatment days
 - Week 2 – Three sessions/day on two treatment days
 - Week 3 – Three sessions/day on one treatment day

Once daily TMS consisted of 20 treatment sessions given each weekday, for a total of 20 treatment days. Each treatment group received a total of 63,000 magnetic pulses. Remission with accelerated TMS and once daily TMS was comparable (15 and 12 percent of patients). However, pain at the stimulation site occurred in more patients who received accelerated TMS than once daily TMS (19 versus 4 percent).

- The same research group conducted a four-week randomized trial that compared an accelerated schedule of theta burst TMS with a once daily schedule of surface cortical TMS in 74 patients [63]. The schedule for accelerated TMS included 21 treatment sessions administered on seven treatment days as follows:
 - Week 1 – Three sessions/day on three treatment days
 - Week 2 – Three sessions/day on two treatment days
 - Week 3 and 4 – Three sessions/day on one treatment day

Once daily TMS consisted of 20 treatment sessions given each weekday, for a total of 20 treatment days. The total number of magnetic pulses over the course of treatment with the accelerated schedule of theta burst TMS was 12,600 and with once daily surface

cortical TMS was 63,000. Remission with accelerated TMS and once daily TMS was comparable (8 and 13 percent of patients), as were adverse effects.

One prospective observational study examined accelerated, high dose, theta burst repetitive TMS in 22 patients with treatment-resistant major depression [44]. After the investigators administered 10 sessions/day, with 1800 pulses/session for five consecutive days, remission occurred in 19 patients (86 percent).

High dose TMS — The dose of repetitive TMS is the number of pulses given during a particular time period, such as a treatment session, day, week, or treatment course [8] (see '[Treatment parameters](#)' above). Delivering more pulses than usual over the same treatment time frame (eg, 6000 pulses per session rather than 3000 pulses) has been tested as a means of improving response.

Randomized trials suggest that the efficacy of high dose and standard dose surface cortical TMS are comparable:

A four-week trial randomly assigned patients with treatment-resistant depression (n = 300) to one of four treatment arms utilizing surface cortical repetitive TMS [76]. Patients and clinical raters were blind to treatment, but clinicians administering TMS were not blind:

- High frequency TMS over the left dorsolateral prefrontal cortex was administered at a high dose (5625 pulses/session) or a standard dose (2250 pulses/session). Response (reduction of baseline symptoms ≥ 50 percent) with high dose and standard dose was comparable (47 and 53 percent of patients).
- Low frequency TMS over the right dorsolateral prefrontal cortex was administered at a high dose (3600 pulses/session) or standard dose (1200 pulses/session). Response with high dose and standard dose was comparable (48 and 49 percent of patients).

One prospective observational study examined high dose, accelerated, theta burst repetitive TMS in 22 patients with treatment-resistant major depression [44]. After the investigators administered 1800 pulses/session during 10 sessions each day, for five consecutive days, remission occurred in 19 patients (86 percent).

Bilateral TMS — Investigators have combined high frequency, surface cortical stimulation of the left dorsolateral prefrontal cortex (conventional TMS) with low frequency, surface cortical stimulation of the right dorsolateral prefrontal cortex to test the hypothesis that stimulation of both sides may activate complementary mechanisms that enhance efficacy. Patients receive conventional TMS plus low frequency TMS during each session, either simultaneously or

sequentially. Although randomized trials have demonstrated that bilateral repetitive TMS is efficacious for unipolar treatment-resistant depression, it is not clear if bilateral TMS provides any advantage over conventional TMS:

- Multiple trials indicate that bilateral repetitive TMS is superior to sham TMS [77-80]. As an example, a meta-analysis of 10 trials in 533 depressed patients found that response (eg, improvement of baseline symptoms ≥ 50 percent) was nearly five times more likely with bilateral TMS than sham TMS (odds ratio 4.9, 95% CI 2.8-8.8) [81]. In addition, all-cause discontinuation of treatment was comparable in the two groups.
- However, the relative efficacy and acceptability of bilateral TMS and conventional TMS is not clear due to conflicting results across studies:
 - Some studies indicate bilateral TMS is no better than conventional TMS:
 - A meta-analysis of four randomized trials (sample size not reported) found that response and all-cause discontinuation of treatment were comparable with bilateral TMS and conventional TMS [77].
 - A meta-analysis of seven randomized trials (n >500 patients) compared bilateral TMS with unilateral surface cortical TMS (either conventional TMS or low frequency stimulation of the right dorsolateral prefrontal cortex); efficacy and all-cause discontinuation of treatment were each comparable in the two groups [82].
 - Other studies indicate that bilateral TMS is more efficacious than conventional TMS. As an example, a meta-analysis of four randomized trials compared bilateral TMS with conventional TMS in 196 patients with treatment-resistant depression [81]. Response was more likely to occur with bilateral TMS (odds ratio 2.49, 95% CI 1.003-6.16), and all-cause discontinuation of treatment was comparable in the two groups.

SUMMARY

- **Indications for transcranial magnetic stimulation (TMS)** – Patients with unipolar major depression who do not respond to standard treatment with pharmacotherapy and psychotherapy are candidates for noninvasive neuromodulation procedures, including repetitive TMS. (See "[Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation \(TMS\)](#)".)
- **Overview** – 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; some TMS devices may also stimulate deeper brain structures. (See '[Overview](#)' above.)

- **Pretreatment assessment** – Prior to prescribing TMS, clinicians should evaluate patients to:
 - Confirm the primary diagnosis of treatment-resistant depression and whether the intervention can be used safely ([table 2](#)).
 - The assessment includes a psychiatric history and mental status examination, with emphasis upon depressive symptoms ([table 1](#)) and types and number of failed treatments during the present episode.
 - Evaluations should also include the patient's current use of alcohol and risk of withdrawal, as well as use of other substances that may provoke seizures. In addition, a general medical history and a screening physical examination is performed.
 - The general medical work-up should emphasize risk factors for seizures and preexisting neurologic disease ([table 2](#)). (See '[Pretreatment assessment](#)' above.)
- **Standard types of stimulation** – The US Food and Drug Administration has approved TMS devices that can administer different types of stimulation, including surface cortical stimulation, deep stimulation, and theta burst stimulation. TMS that stimulates the surface cortex is called surface cortical TMS, and is the most widely used and studied form of TMS. Deep TMS devices theoretically stimulate brain structures beneath the superficial prefrontal cortex, as well as surface cortical structures. Theta burst TMS utilizes magnetic pulses that are intended to mimic endogenous theta rhythms. (See '[Standard techniques](#)' above and '[Surface cortical TMS](#)' above and '[Deep TMS](#)' above and '[Theta burst TMS](#)' above.)
- **Stimulation parameters** – 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 '[Treatment parameters](#)' above.)
- **Stimulation site** – TMS generally targets the left dorsal lateral prefrontal cortex. (See '[Stimulation site](#)' above.)
- **Acute treatment schedule** – For acute treatment of unipolar major depression, TMS is usually administered each weekday over four to six weeks. (See '[Acute treatment](#)' above.)

- **Maintenance TMS** – Maintenance TMS typically uses the same stimulation parameters that were used during acute treatment unless side effects intervene. The frequency of maintenance TMS treatments has not been standardized. (See '[Maintenance treatment](#)' above.)
- **Experimental types of stimulation** – Investigational techniques for administering TMS include an accelerated schedule (multiple treatment sessions per day) as well as high dose stimulation and bilateral stimulation. (See '[Experimental techniques](#)' above.)

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