Unipolar depression in adults: Overview of neuromodulation procedures

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INTRODUCTION

Many patients with unipolar major depression do not respond to standard treatment with pharmacotherapy and/or psychotherapy [1,2], and are thus candidates for neuromodulation procedures [3-8]. These procedures are often classified as either noninvasive (eg, electroconvulsive therapy and repetitive transcranial magnetic stimulation) or invasive (requiring surgery, such as vagus nerve stimulation and deep brain stimulation). Several neuromodulation interventions are clinically available, whereas others remain investigational.

This topic describes noninvasive and invasive neuromodulation therapies for unipolar major depression. Choosing a specific treatment for unipolar depression is discussed separately. (See "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

OVERVIEW

Neuromodulation procedures for unipolar major depression are often classified as either noninvasive or invasive [3-8].

- **Noninvasive therapies** – Noninvasive neuromodulation procedures vary in their clinical availability:

- Clinically available
  - Electroconvulsive therapy (ECT) – ECT is the oldest neurostimulation procedure (it also predates all currently used antidepressant drugs) and is the most rapid and effective intervention for severe unipolar major depression
  - Repetitive transcranial magnetic stimulation (rTMS)
  - Cranial electrical stimulation
- Investigational
  - Magnetic seizure therapy
  - Focal electrically administered seizure therapy
  - Transcranial direct current stimulation (tDCS)
  - Transcranial low voltage pulsed electromagnetic fields
  - Trigeminal nerve stimulation
  - Low field magnetic stimulation
  - Transcutaneous vagus nerve stimulation

The most widely available noninvasive neuromodulation procedures, with well-established efficacy for treatment-resistant depression, are ECT and rTMS. A network meta-analysis of 113 randomized trials evaluated the efficacy of noninvasive brain stimulation in more than 6700 patients with depressive syndromes [9]. The large majority of patients had treatment-resistant depression; the vast majority had unipolar major depression and only a few had bipolar depression. Response rates (reduction of baseline symptoms was ≥50 percent) were determined from direct comparisons of treatments in head-to-head trials, as well as indirectly comparing treatments through their relative effect with a common comparator (typically sham stimulation). The likelihood of response was greater for each of the following active treatments, compared with sham stimulation:

- Bitemporal ECT (odds ratio 9, 95% CI 3-31)
- High-dose right unilateral ECT (odds ratio 7, 95% CI 2-28)
- High-frequency left rTMS (odds ratio 3, 95% CI 2-4)
- tDCS (odds ratio 3, 95% CI 2-5)

Each of the noninvasive neuromodulation procedures is discussed below. (See 'Noninvasive neuromodulation therapies' below.)

- **Invasive neuromodulation interventions** – Invasive procedures require surgery and have generally been studied in more treatment-refractory patients:

  - Vagus nerve stimulation – Clinically available
  - Deep brain stimulation – Investigational approach
  - Direct cortical stimulation – Investigational approach
  - Ablative neurosurgery – Clinically available

  Each of these therapies is discussed below. (See 'Invasive/surgical neuromodulation therapies' below.)

NONINVASIVE NEUROMODULATION THERAPIES

Noninvasive neuromodulation procedures use an electric current or magnetic field to stimulate the central nervous system [6].

Convulsive therapies — Noninvasive neurostimulation treatments for major depression include convulsive therapies:

- Electroconvulsive therapy (ECT)
- Magnetic seizure therapy (MST)
- Focal electrically administered seizure therapy (FEAST)

Electroconvulsive therapy — ECT is a noninvasive, clinically available approach that uses an electric current that passes between two electrodes placed against the scalp to induce a generalized cerebral seizure while the patient is under general anesthesia. A course of ECT involves a series of treatments that are delivered over several days to weeks. ECT is superior to pharmacotherapy for unipolar major depression based upon meta-analyses of randomized trials and is generally considered the most efficacious treatment for depression [10]. However, ECT is associated with safety risks, adverse effects, logistical constraints, and patient refusal, and recurrence following remission is common, especially in patients with treatment-resistant depression.

Separate topics provide an overview of ECT (including adverse effects, number and frequency of treatments, use of ECT in patients with general medical conditions, information for patients, and informed consent) and discuss indications for and efficacy of ECT in unipolar major depression, medical consultation for ECT, and the technique for performing ECT. (See "Overview

of electroconvulsive therapy (ECT) for adults" and "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)" and "Medical evaluation for electroconvulsive therapy" and "Technique for performing electroconvulsive therapy (ECT) in adults".)

Magnetic seizure therapy — MST is a noninvasive, investigational approach that uses a transcranial magnetic stimulation (TMS) device to induce a generalized seizure; a larger dose of magnetic stimulation is used in MST (eg, frequency of 100 hertz) than repetitive transcranial magnetic stimulation (rTMS; eg, 10 hertz) [11]. It is hypothesized that MST causes fewer adverse cognitive effects than ECT because MST initially stimulates a more focal (smaller) portion of the brain to induce a seizure; the procedure targets the prefrontal cortex and spares medial temporal structures that may be most involved in the adverse cognitive effects incurred by ECT.

As with ECT, a treatment course with MST involves a series of seizures are that induced under general anesthesia [11]. A muscle relaxant is administered to prevent muscle contractions and seizure duration is monitored. As with TMS, hearing protection (eg, ear plugs) is used because the TMS device repeatedly emits a loud clicking noise. Patients typically receive 8 to 12 sessions over three to four weeks. In the United States, MST is available to patients with unipolar major depression only through a research protocol.

Efficacy — Evidence supporting the efficacy of MST for treatment-resistant unipolar major depression is relatively weak. No randomized trials have compared active MST with sham MST. In one prospective observational study, which included 38 patients (unipolar 28, bipolar 10) who did not respond to pharmacotherapy and received add-on MST (8 to 12 sessions), response (reduction of baseline symptoms ≥50 percent) occurred in nearly 70 percent [12]. Another prospective observational study included 27 patients with unipolar major depression and found that MST (mean number of treatments = 17) was associated with a reduction in suicidal ideation [13].

Although small head-to-head randomized trials suggest that MST may be as efficacious as right unilateral ECT for treatment-resistant depression, methodologic problems limit the conclusions that can be drawn:

- One open-label trial compared MST with ECT as add-on therapy in 20 patients with major depression (unipolar 16, bipolar 4) receiving pharmacotherapy; all patients received 12 treatments of convulsive therapy [14]. Symptomatic improvement was comparable for the two groups.

- Another open-label trial compared MST with ECT in 37 patients with major depression (unipolar 31, bipolar 6), who continued baseline pharmacotherapy deemed clinically

appropriate; each treatment group received approximately 12 treatments of convulsive therapy [15]. Improvement with MST and ECT was comparable.

- A third trial compared MST with ECT in 20 patients with major depression (unipolar 17, bipolar 3) receiving pharmacotherapy who completed the study; patients received approximately 8 to 12 treatments [16]. Improvement with MST and ECT was comparable.

Interpreting the results of these three trials is difficult because of the small samples that included patients with bipolar disorder, the lack of blinding, and lack of placebo (sham) control groups.

The evidence that best supports the benefit of MST comes from a network meta-analysis of 113 randomized trials that studied the efficacy of noninvasive brain stimulation in more than 6700 patients with depressive syndromes [9]. Response rates were determined from direct comparisons of treatments in head-to-head trials, as well as indirectly comparing treatments through their relative effect with a common comparator (typically sham stimulation). The likelihood of response was greater for MST than sham stimulation (odds ratio 5.6, 95% CI 1.1-29.0). However, this result rests heavily upon the indirect comparison of patients who received active MST (total n = 44) with patients in other randomized trials who received sham ECT stimulation, sham TMS, or sham transcranial direct current stimulation (tDCS).

Continuation MST appears to be effective in preventing depression relapse in individuals who have responded to MST. In one prospective study, individuals who had responded to 24 sessions of MST for treatment-resistant depression were treated with continuation MST (tapering from once per week to once per month over six months) [17]. Most of the participants (67 percent) showed sustained improvements and no adverse cognitive effects were reported. Additionally, all individuals who had resolution of suicidal thoughts during the acute treatment had sustained resolution of suicidality during continuation MST.

Safety and side effects — MST is usually well tolerated [14,18] and may cause fewer physical side effects (eg, headaches and myalgias) compared with ECT [19]. In addition, magnetic seizure stimulation appears to cause relatively few cognitive side effects and in that regard may perhaps be better tolerated than ECT [11,18,20-22]:

- An open-label, randomized trial compared MST with ECT in 20 patients with major depression (unipolar 16, bipolar 4) who were also treated with pharmacotherapy; postprocedure time to recovery of full orientation was shorter in patients who received MST than ECT (mean of two versus eight minutes) [14]. Neuropsychological tests, which assessed 15 different domains of cognition, showed that functioning on one of the

measures was better in the group that received MST, compared with the group who received ECT; functioning on the other 14 measures was comparable for the two groups.

- Another open-label trial compared MST with ECT in 37 patients with major depression (31 unipolar, 6 bipolar), who continued baseline pharmacotherapy deemed clinically appropriate; each treatment group received approximately 12 treatments of convulsive therapy [15]. Among 20 neuropsychological test results, the two groups were comparable on 19; on one measure, functioning was better in the group that received MST, compared with ECT.

- A prospective study examined the neuropsychological functioning of 10 patients with major depression who were treated with convulsive therapy [19]. MST was given in two of the first four sessions and ECT in the remaining sessions; the order of treatment was randomly assigned, cognition was evaluated for the first four sessions, and raters and patients were blind to treatment. Performance on tests measuring attention, retrograde amnesia, category fluency, and recovery of orientation was significantly better after MST than ECT.

Mechanism of action — The mechanism by which MST may treat unipolar major depression is unknown but is probably comparable to that of ECT. (See "Overview of electroconvulsive therapy (ECT) for adults", section on 'Mechanism of action'.)

Focal electrically administered seizure therapy — FEAST is a noninvasive, investigational approach that combines unidirectional current, control of polarity, and an asymmetric electrode arrangement (with one electrode much larger than the other) in an attempt to induce generalized seizures more efficiently than ECT [23,24]. Like MST, FEAST is hypothesized to cause fewer adverse cognitive effects than ECT by initially stimulating a more focal portion of the brain (prefrontal cortex) to induce a seizure and avoiding the temporal lobes. As with ECT, a treatment course with FEAST involves a series of seizures [11]. Patients receive general anesthesia, a muscle relaxant is administered to prevent muscle contractions, and seizure duration is monitored. In the United States, the intervention is available to patients with unipolar major depression only through a research protocol.

Efficacy, safety, and side effects — Two small, prospective observational studies by the same research group suggest that for treatment-resistant depression, response to FEAST occurs in approximately 50 to 65 percent of patients, and that the procedure is safe and well tolerated:

- One study enrolled 17 patients with major depression (unipolar 14, bipolar 3) who discontinued pharmacotherapy and received a course of FEAST, with a median of 10 sessions [24]. Response (reduction of baseline symptoms ≥50 percent) occurred in 8

patients (47 percent). Following each session, the mean time to recovery of full orientation was six minutes. Baseline and posttreatment cognitive functioning were comparable.

- A second study enrolled 20 patients with major depression (unipolar 17, bipolar 3), including 16 who discontinued pharmacotherapy [25]. Following a mean of nine FEAST treatments, response occurred in 13 patients (65 percent). Following each session, the mean time to recovery of full orientation was four minutes. Baseline and posttreatment cognitive functioning were comparable.

Repetitive transcranial magnetic stimulation — rTMS is a noninvasive, clinically available approach that uses an alternating current passed through a metal coil placed against the scalp to generate a magnetic field, which in turn induces an electric current that depolarizes neurons in a focal area of the surface cortex. The intervention involves a series of daily treatments that are administered over several days to weeks without anesthesia and with the patient fully awake. Meta-analyses of randomized trials indicate that the intervention is beneficial for treating unipolar major depression that has not responded to pharmacotherapy. TMS is discussed separately. (See "Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)" and "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)".)

Transcranial direct current stimulation — tDCS is a noninvasive, investigational approach that uses two scalp electrodes to deliver a constant, low-amplitude (weak) direct current to specific superficial cortical regions [9,26]. Either cathodal or anodal stimulation is used; the choice determines the direction of the current through the target neurons, and each type is associated with different neurophysiologic effects [27]. The target of stimulation is typically the left dorsolateral prefrontal cortex (as with most studies of TMS for depression), but other montages have been used in tDCS [27-29]. A series of treatment sessions are generally administered over consecutive days for one or more weeks. In the United States, tDCS is available to patients with unipolar major depression only through a research protocol.

Efficacy — Meta-analyses of randomized trials suggest that tDCS can be beneficial for acute treatment of unipolar major depression, but the overall database is mixed [30-32].

Positive results using tDCS include the following:

- A meta-analysis of patient-level data from six trials compared active tDCS with sham stimulation in 289 patients with major depression (n = 278 unipolar and 11 bipolar); patients received 5 to 15 sessions [33]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received active treatment than sham treatment (34 versus 19 percent). After adjusting for potential confounding factors, the analyses

found that a higher dose (total charge) of tDCS was associated with increased tDCS efficacy, whereas patients with treatment-resistant depression during the current depressive episode had a poorer response to tDCS than patients without treatment-resistant depression.

- A subsequent meta-analysis of 12 trials compared active tDCS with sham tDCS in patients with depressive syndromes (n = 657, primarily unipolar major depression) [9]. The likelihood of response was three times greater with active tDCS than sham tDCS (odds ratio 3.0, 95% CI 1.5-6.3). However, heterogeneity across studies was moderate to large.

- A network meta-analysis also found that tDCS was efficacious. (See 'Overview' above.)

Also, tDCS may be efficacious for poststroke depression [34].

However, other trials have found that tDCS was not beneficial for unipolar major depression. As an example, a relatively large, six-week trial compared active with sham tDCS as add-on treatment in 150 patients who had not responded to a selective serotonin reuptake inhibitor; patients received 24 study treatments [35]. The number of patients who responded to active or sham tDCS was comparable (33 and 44 percent of patients). The discrepancy of these negative results with those from previous trials may be due to heterogeneity of the study patients with regard to treatment resistance or other clinical factors [36].

In addition, antidepressant drugs appear to be more efficacious than tDCS. A 10-week randomized trial compared escitalopram (20 mg/day) plus sham tDCS with oral placebo plus active tDCS (22 sessions) in patients with unipolar depression (n = 185) [37]. Improvement was greater with escitalopram than tDCS.

It is not known whether adding tDCS to psychotherapy is beneficial, due to conflicting results across small randomized trials [27,38-41].

Safety and side effects — tDCS is generally safe and well tolerated [42-46]. Randomized trials indicate that side effects are usually transient and have found that active and sham treatment are associated with comparable rates of adverse effects, including uncomfortable scalp sensations (described as tingling or itchiness), fatigue, dizziness, nausea, concentration difficulties, and visual phenomena [47-50]. As an example, a meta-analysis of patient-level data from six trials compared active tDCS with sham tDCS in 289 patients with major depression and found that the number of patients who reported any adverse effect was comparable for active and sham stimulation (73 and 68 percent) [46]. In addition, a subsequent randomized trial, which compared active tDCS with sham tDCS in 154 patients with unipolar depression, found

that the incidence of severe adverse effects in the two groups was comparable, as was the incidence of moderate adverse effects and mild adverse effects [37].

Although tDCS can cause skin burns and lesions if excessive energy is used [51,52], more recent studies conducted by experienced clinicians using devices with proper safety features have avoided these adverse effects [27]. Monitoring skin pain and redness during treatment sessions can help prevent skin burns.

It appears that tDCS generally does not adversely affect neuropsychological functioning. A meta-analysis of patient-level data from seven randomized trials compared active tDCS with sham tDCS in 478 patients with major depression (nearly all with unipolar depression) [53]. Patients received 5 to 22 sessions, and cognitive functioning was assessed at baseline and posttreatment in 12 different domains. Neuropsychological functioning in both groups improved or did not change; however, functioning in one domain (processing speed) improved more in the sham group than the active treatment group.

It is not clear if tDCS causes treatment-emergent mania/hypomania [27]. A pooled analysis of 10 randomized trials compared active tDCS with sham tDCS in depressed patients (n = 416) and found that switching from depression to mania/hypomania was comparable with active and sham tDCS (3.5 and 0.5 percent) [54]. However, a subsequent randomized trial, which compared active with sham tDCS in 154 patients, reported that two patients treated with active tDCS switched from depression to new-onset mania, whereas no switching occurred with sham tDCS [37]. One aspect that may confound this issue is that some trials included patients with bipolar depression [27].

Mechanism of action — tDCS does not directly cause neuronal depolarization, but rather, is associated with changes that affect the probability of neuronal firing [27,55]. Thus, it is hypothesized that the primary mechanism of action involves modulation of cortical excitatory tone. One model hypothesizes that cathodal stimulation is generally associated with a decrease of spontaneous cell firing, and that anodal stimulation is typically associated with an increase in spontaneous firing [55]; however, the validity of this model is disputed [27]. Comparable with other brain stimulation interventions, tDCS is thought to exert its antidepressant effects via functional changes within a neural network of brain regions involved in mood regulation. The left dorsolateral prefrontal cortex is often targeted for stimulation [27].

Transcranial low voltage pulsed electromagnetic fields stimulation — Transcranial low voltage pulsed electromagnetic fields stimulation (T-PEMF) is a noninvasive, investigational approach that uses a generator to provide electrical pulses to a set of coils (placed around the head), which produce low-intensity electromagnetic fields. These give rise to low voltage

alternating currents within the underlying brain tissue [56]. The intensity of stimulation is less than that generated by TMS equipment and is insufficient to depolarize cortical neurons. A series of treatment sessions are generally administered over consecutive days for several weeks. In the United States, T-PEMF is available to patients with unipolar major depression only through a research protocol.

Efficacy — Evidence for the efficacy of T-PEMF includes a five-week randomized trial that compared active with sham treatment in 50 patients with major depression [56]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received active stimulation compared with sham (61 versus 13 percent).

Safety and side effects — Based upon limited data, there is no noticeable sensation with T-PEMF, and it appears to be well-tolerated. A randomized trial that compared active with sham treatment found that the incidence of specific adverse effects was comparable for the two groups [56].

Mechanism of action — The mechanism by which T-PEMF treats unipolar major depression is unknown. Neurostimulation techniques analogous to T-PEMF have been shown to increase cortical excitability in healthy controls [57]. In addition, T-PEMF may increase angiogenesis [58] and alter intracellular signaling [59].

Trigeminal nerve stimulation — Trigeminal nerve stimulation is a noninvasive, investigational procedure for treatment-resistant depression [27]. An external pulse generator delivers an electrical current via bilateral cutaneous electrodes that are placed on the forehead to stimulate the supraorbital and supratrochlear nerves of the V1 branch of the trigeminal nerve (cranial nerve V). Although the intervention is an investigational procedure for depression, the US Food and Drug Administration (FDA) has approved a trigeminal nerve stimulation device for attention deficit hyperactivity disorder [60].

Efficacy — A two-week randomized trial compared active trigeminal nerve stimulation (administered each weekday for 30 minutes) with sham stimulation in 40 patients with treatment-resistant unipolar major depression [61]. Improvement was greater with active treatment, and the benefit persisted for two weeks after the end of treatment.

Safety and side effects — In one randomized trial [61] and two observational studies [62,63], in which a total of 36 patients were treated with trigeminal nerve stimulation, no serious adverse events occurred and the intervention was well tolerated. Transient and mild paresthesias occurred during the first few seconds of stimulation [61].

Mechanism of action — It is hypothesized that the procedure acts upon afferent fibers in the trigeminal nerve, which project to central nervous system structures that may be involved in depression, such as the locus coeruleus and the nucleus tractus solitarius [62,63].

Low field magnetic stimulation — Low field magnetic stimulation (LFMS) is a noninvasive, investigational procedure for treatment-resistant depression. The device includes a magnetic coil, power source, and amplifier that generates a magnetic field, which induces a rapidly oscillating, low voltage electric field (<1 V/m, 1 kHz) in the brain [64,65]. The patient lies supine and the head is inserted into one end of the cylindrical coil. LFMS has also been administered using a system referred to as synchronized TMS, which provides stimulation synchronized to the patient's baseline electroencephalogram-determined alpha rhythm [66].

Efficacy — Based upon results from four randomized trials, LFMS does not appear to be useful for unipolar major depression. Although two relatively short and small trials found that active LFMS was superior to sham stimulation, two longer trials with larger samples found otherwise.

- Two relatively long and large randomized trials found that LFMS was not beneficial. A six-week trial compared 30 sessions of active LFMS with sham stimulation in patients (n = 202) with unipolar major depression who were medication free [66]. Improvement in the two groups was comparable. Another trial, lasting five days, compared four sessions of add-on active LFMS with sham LFMS in 84 patients with treatment-resistant unipolar major depression; all patients were receiving antidepressants [67]. Improvement in the two groups was comparable.

- Evidence supporting the benefit of LFMS includes one trial that found that a single session of active LFMS was superior to sham stimulation in 22 patients with unipolar major depression [64]. A second trial lasting one week compared three sessions of active LFMS with sham LFMS in 30 patients with treatment-resistant unipolar major depression, most of whom were receiving pharmacotherapy [65]. Improvement was greater with active treatment.

Safety and side effects — The FDA has declared that the device poses a nonsignificant risk [64]. Randomized trials have found that LFMS caused no significant adverse effects [64-67].

Mechanism of action — It is hypothesized that the low-strength electromagnetic field (which is too low to depolarize neurons) affects the electrical activity of cortical neurons, which project to subcortical regions that are involved in mood regulation [64,67]. Positron emission tomography indicates that LFMS reduces glucose metabolism in the cerebral cortex (and thus affects brain activity).

Transcutaneous vagus nerve stimulation — Transcutaneous vagus nerve stimulation (tVNS) is a noninvasive, investigational procedure for unipolar major depression that uses a device to generate an electric current that stimulates afferent vagus nerve fibers through electrodes attached to the ear [68]. This approach is distinguished from vagus nerve stimulation (VNS), an invasive procedure that involves surgically attaching an electrode to the vagus nerve. (See 'Vagus nerve stimulation' below.)

tVNS may possibly be efficacious for major depression [68]. In a pooled analysis of two small randomized trials (total n = 37), active tVNS was compared with sham stimulation as add-on therapy in patients hospitalized for major depression and treated with antidepressants and cognitive-behavioral therapy [69]. Each trial lasted two weeks. Patient self-report assessments suggested that improvement of depression was greater with adjunctive active tVNS than sham stimulation. However, clinician assessments found that improvement was comparable in the two groups. No adverse effects occurred. The mechanism of action is presumed to be similar to that for VNS. (See "Unipolar depression in adults: Treatment with surgical approaches", section on 'Mechanism'.)

Cranial electrical stimulation — Cranial electrical stimulation (CES) is a noninvasive, clinically available approach that uses a battery-operated device to deliver low-voltage (low energy) alternating current to the brain via electrodes attached to the scalp or infra- or supra-auricular structures (eg, earlobes, mastoid processes, zygomatic arches, or maxilla-occipital junctions) [70,71]. There are numerous methods for delivering the electrical current, though the basic intervention remains the same.

Although the FDA has approved the use of cranial electrotherapy stimulation for “depression” [27,72], we do not use the device for patients with major depression. Multiple reviews indicate that no high-quality studies have demonstrated that CES is efficacious for unipolar major depression [27,71,73]. As an example, a review identified three randomized trials lasting two or three weeks, which compared active with sham CES in patients with unipolar or bipolar depressive syndromes (total n = 66) [74]. All of the studies were of low-quality, and heterogeneity across studies precluded a meta-analysis. None of the three studies found that active treatment was beneficial.

INVASIVE/SURGICAL NEUROMODULATION THERAPIES

Invasive neuromodulation therapies for treating unipolar major depression include:

- Vagus nerve stimulation (VNS)

- Deep brain stimulation (DBS)
- Direct cortical stimulation (DCS)
- Ablative neurosurgery

Invasive neuromodulation interventions require surgery and have generally been studied in patients with chronic, treatment-refractory, debilitating depression, because most clinicians view invasive interventions as riskier than the noninvasive techniques described above.

Among the surgical approaches, VNS, DBS, and DCS are generally:

- Reversible – Hardware can be removed
- Revisable – Stimulating electrodes can be moved to optimize response
- Adjustable – Stimulation parameters can be modified to optimize response

By contrast, ablative surgery does not involve:

- Indwelling metal hardware and contraindications to magnetic resonance imaging (MRI) and metal detectors
- Surgical follow-up to replace batteries or pulse generators every few years or to revise dysfunctional systems

Vagus nerve stimulation — VNS is a clinically available treatment in which a battery-powered pulse generator is implanted in the chest wall and connected to an electrode that is attached around one vagus nerve (typically the left). Although stimulating the vagus nerve with electrical impulses is an established option for medication refractory epilepsy, acute efficacy for treatment-resistant major depression has not been demonstrated in rigorous studies. Additional information about VNS is discussed separately. (See "Unipolar depression in adults: Treatment with surgical approaches", section on 'Vagus nerve stimulation' and "Vagus nerve stimulation therapy for the treatment of epilepsy".)

Deep brain stimulation — DBS is an investigational procedure for treatment-resistant depression, in which one or more electrodes is implanted into specific brain regions using a stereotactic frame and MRI. The electrodes are connected to a subcutaneously implanted pulse generator that controls stimulation parameters, comparable to VNS. Stimulating deep brain centers with electrical impulses is an established treatment for treatment-resistant Parkinson disease, essential tremor, and dystonia, and an experimental treatment for incapacitating and treatment-refractory obsessive-compulsive disorder.

Additional information about DBS for major depression and other disorders is discussed separately. (See "Unipolar depression in adults: Treatment with surgical approaches", section on

'Deep brain stimulation' and "Deep brain stimulation for treatment of obsessive-compulsive disorder" and "Device-assisted and lesioning procedures for Parkinson disease", section on 'Deep brain stimulation' and "Surgical treatment of essential tremor", section on 'Deep brain stimulation' and "Treatment of dystonia in children and adults", section on 'Deep brain stimulation'.)

Direct cortical stimulation — DCS is an investigational approach for treating refractory unipolar major depression, in which electrodes are implanted outside, upon, or beneath the dura mater to directly stimulate the cortex. Stimulation parameters are controlled by a subcutaneously implanted pulse generator, comparable to VNS and DBS. Additional information about DCS is discussed separately. (See "Unipolar depression in adults: Treatment with surgical approaches", section on 'Direct cortical stimulation'.)

Ablative neurosurgery — Ablative neurosurgery for intractable major depression is a clinically available but rarely used approach in which a lesion is made in limbic or paralimbic structures. Early ablative procedures for psychiatric illness, such as the prefrontal leucotomy [75], have been supplanted by stereotactic neurosurgical techniques that allow for more focal lesions with fewer side effects, including [76-78]:

- Anterior capsulotomy – Lesion in the anterior limb of the internal capsule
- Anterior cingulotomy – Lesion in the dorsal anterior cingulate
- Subcaudate tractotomy – Lesion in thalamocortical white matter tracts inferior to the anterior striatum
- Limbic leucotomy – Combines cingulotomy with subcaudate tractotomy

Additional information about ablative surgery is discussed separately. (See "Unipolar depression in adults: Treatment with surgical approaches", section on 'Ablative neurosurgery'.)

EXTERNAL SOURCES OF PATIENT EDUCATION

Educational material explaining electroconvulsive therapy, transcranial magnetic stimulation, magnetic seizure therapy, vagus nerve stimulation, and deep brain stimulation is available in a document entitled “Brain Stimulation Therapies” that is published by the National Institute of Mental Health. This publication can be obtained through a toll-free number, 866-615-6464, or online at the National Institute of Mental Health website. The website also provides information about depression in language intended for the lay public.

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

- Different therapies, including neuromodulation procedures, are available in choosing a specific treatment for unipolar depression. (See "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

- Many patients with unipolar major depression do not respond to standard treatment with pharmacotherapy and psychotherapy and are thus candidates for noninvasive and invasive neuromodulation procedures. The most widely available noninvasive neuromodulation procedures, with well-established efficacy for treatment-resistant depression, are electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation. (See 'Overview' above.)

- Noninvasive neuromodulation interventions include convulsive therapies that induce therapeutic generalized seizures. Convulsive therapies include ECT, which is clinically available and is the most efficacious treatment for major depression. However, ECT is associated with safety risks, adverse effects, logistical constraints, patient refusal, and high relapse rates. Other convulsive therapies include magnetic seizure therapy and focal electrically administered seizure therapy, both of which are investigational treatments that are hypothesized to cause fewer adverse cognitive effects than ECT. (See 'Electroconvulsive therapy' above and 'Magnetic seizure therapy' above and 'Focal electrically administered seizure therapy' above.)

- Another noninvasive brain stimulation procedure is transcranial magnetic stimulation (TMS), which is a clinically available treatment with demonstrated efficacy. TMS devices generate magnetic fields that induce electric currents, which depolarize neurons in the surface cortex. (See 'Repetitive transcranial magnetic stimulation' above.)

- Transcranial direct current stimulation is a noninvasive, investigational approach that delivers an electric current to specific cortical regions. Multiple randomized trials indicate that the treatment can be beneficial for acute treatment of major depression and is generally safe and well tolerated. However, other trials have found that tDCS was not beneficial for unipolar major depression. (See 'Transcranial direct current stimulation' above.)

- Other noninvasive, investigational neuromodulation procedures include transcranial low voltage pulsed electromagnetic fields stimulation, trigeminal nerve stimulation, low field magnetic stimulation, and transcutaneous vagus nerve stimulation. (See 'Transcranial low voltage pulsed electromagnetic fields stimulation' above and 'Trigeminal nerve stimulation' above and 'Low field magnetic stimulation' above and 'Transcutaneous vagus nerve stimulation' above.)

- Cranial electrical stimulation is an available approach that uses a battery-operated device to deliver low-voltage current to the brain via electrodes attached to the scalp or infra- or supra-auricular structures. There are no high-quality data supporting its use for major depression. (See 'Cranial electrical stimulation' above.)

- Invasive neuromodulation therapies for major depression require surgery and have generally been studied in patients with chronic, treatment-refractory, debilitating depression. Clinically available invasive procedures include vagus nerve stimulation and ablative neurosurgery; investigational procedures include deep brain stimulation and direct cortical stimulation. (See 'Invasive/surgical neuromodulation therapies' above and "Unipolar depression in adults: Treatment with surgical approaches".)

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