Unipolar depression in adults: Treatment with surgical approaches

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INTRODUCTION

Unipolar major depression often does not respond to standard treatment with pharmacotherapy, psychotherapy, and noninvasive neuromodulation interventions such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS). This has led to investigation of surgical/invasive treatments that include vagus nerve stimulation, deep brain stimulation, direct cortical stimulation, and ablative neurosurgery. However, none of these interventions are part of standard treatment.

This topic reviews treatment of resistant unipolar major depression with surgical approaches. Overviews of neuromodulation procedures, ECT, and TMS are discussed separately, as is choosing treatment for resistant and highly resistant depression.

- (See "Unipolar depression in adults: Overview of neuromodulation procedures".)
- (See "Overview of electroconvulsive therapy (ECT) for adults".)
- (See "Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

OVERVIEW AND GENERAL PRINCIPLES

Surgical/invasive approaches for treating unipolar major depression include:

- Surgical implantation of devices
  - Vagus nerve stimulation – Clinically available
  - Deep brain stimulation – Investigational
  - Direct cortical stimulation – Investigational
- Ablative neurosurgery – Clinically available

Among invasive treatments for unipolar major depression, ablative neurosurgery is the "last resort" and its use is heavily restricted. Careful evaluation of patients should be conducted to ensure that multiple courses of other reasonable treatments have either failed or are not suitable; in some cases, an independent review board may be involved to confirm that patients are appropriate candidates for ablative surgery [1-3].

Surgical interventions are reserved for patients with severe and disabling unipolar major depression lasting for at least one to two years that is refractory to multiple trials of standard treatment, including [4-10]:

- Monotherapy with several (eg, at least three) different classes of antidepressants, for an adequate duration (eg, three weeks at the usually recommended dose).
- Sequential trials of an antidepressant plus an augmentation agent (eg, second-generation antipsychotic, lithium, stimulant, or triiodothyronine).
- Psychotherapy (eg, cognitive-behavioral therapy or interpersonal psychotherapy) added onto pharmacotherapy, for an adequate duration (eg, at least 10 sessions).
- At least one course of noninvasive neuromodulation that usually consists of electroconvulsive therapy, but may also include transcranial magnetic stimulation.

Examples of exclusion criteria in studies of surgical interventions include current obsessive-compulsive disorder, posttraumatic stress disorder, psychosis, substance-related and addictive disorder (except tobacco use disorder), severe personality disorder (eg, borderline personality disorder), and imminent risk of suicide, as well as pregnancy and current neurologic disorder [4-8,10,11].

All patients who receive surgical neurostimulation interventions require postoperative care [3]. After surgery, most studies have maintained patients on their presurgical antidepressant

medications and psychotherapies [4,5,10-14]. Patients with refractory depression may require a relatively long time (eg, one year) to respond to surgical interventions [10,15].

Assessment — Candidates for surgical treatment of refractory unipolar major depression should be evaluated by multiple clinicians to confirm the diagnosis and whether surgery is indicated and can be performed safely [3]. The assessment includes a psychiatric history and mental status examination, with emphasis upon current suicide risk, other depressive (table 1) symptoms, psychotic symptoms, comorbid disorders (eg, substance use and personality disorders), neuropsychological functioning, length of the current depressive episode, types and number of failed treatments during the present episode, psychosocial functioning, and the number, length, and treatment history of prior depressive episodes, as well as decision making capacity to provide informed consent. Some clinicians also obtain consent from a caregiver [8].

In addition, a general medical history and physical examination is performed, as well as laboratory tests and neuroimaging studies that are guided by the history, examination, and possibility of surgery [16,17]. The medical work-up should emphasize preexisting neurologic disease (eg, epilepsy, intracranial masses, and vascular abnormalities).

More detailed information about assessing depression is discussed separately. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Assessment'.)

VAGUS NERVE STIMULATION

Overview — Vagus nerve stimulation (VNS) is a clinically available intervention that is not part of standard treatment for resistant or highly resistant depression. VNS involves surgery, typically with general anesthesia, to attach an electrode around one vagus nerve (usually the left because of its limited cardiac effects) in the carotid sheath; the electrode is connected to a pulse generator implanted subcutaneously in the chest wall [5,13,18,19]. The device is turned on after a postsurgical recovery period generally lasting two weeks. Stimulation is intermittent and usually occurs for a 30-second period every five minutes; stimulation parameters (amplitude, pulse width, and frequency) are adjusted using a wireless, hand-held transmitter. VNS is an established treatment for medication-refractory epilepsy, which is discussed separately. (See "Vagus nerve stimulation therapy for the treatment of epilepsy".)

Although a few small studies in patients with major depression have examined transcutaneous VNS, which does not involve surgery, this topic focuses exclusively upon invasive VNS that requires surgical implantation of the electrode and pulse generator.

Outcome studies — The best evidence from relatively short randomized trials indicates that VNS is not efficacious for treatment-resistant unipolar major depression [20]:

- A 10-week trial compared active VNS with sham stimulation (no stimulation following implantation) in 222 patients with treatment-resistant major depression; response (reduction of baseline symptoms ≥50 percent) was comparable in patients who received active or sham treatment (15 and 10 percent) [21].

- A subsequent 22-week trial included 310 patients who all received active VNS and were randomly assigned to low, medium, or high electrical stimulation (dose), as determined by the amplitude and pulse width [5]. Response was comparable across the three groups.

Nevertheless, it is possible that VNS requires more time to exert its effect, based upon prospective observational studies that followed patients for up to one or more years [13,18]. As an example:

- A one-year study found that response occurred more often in 180 patients with treatment-resistant major depression who received VNS plus usual care, compared with 112 comparable patients followed in a separate study who received usual care alone (22 versus 12 percent) [22]. However, many patients who responded to adjunctive VNS subsequently relapsed [23,24].

- A five-year registry study included patients with treatment-resistant major depression who either received VNS or did not (n = 765); remission occurred in more patients treated with usual care plus VNS than usual care alone (43 versus 26 percent) [6]. VNS was also associated with greater improvement of quality of life [25]. Following remission, the median time to recurrence was two times longer with usual care plus VNS than usual care alone (40 compared with 19 months) [6]. In addition, suicidal behavior was less likely to occur with adjunctive VNS (odds ratio 0.49, 95% CI 0.25-0.93), and the rate of suicide deaths and all-cause mortality among those who received VNS were each 50 percent less than the rate in those who received usual care alone.

- A systematic review examined outcomes in patients with treatment-resistant depression who were treated for up to 12 months, either with VNS plus usual care (10 studies, total n = 457 patients) or with usual care alone (two studies, n = 133) [26]. The pooled analyses found that response occurred in four times as many patients who received VNS plus usual care than usual care alone (43 and 10 percent).

Other observational studies also suggest that VNS may be beneficial for treatment-resistant depression [27,28].

Safety — Serious adverse events, such as suicidal behavior, mania, or worsening depression requiring hospitalization, have occurred in studies of VNS for treatment-resistant depression. A meta-analysis of two randomized trials and four observational studies found that among 640 patients who were treated for up to 12 months with VNS plus usual care, at least one serious adverse event occurred in 6 percent [26]. However, heterogeneity across studies was substantial.

Adverse effects — VNS is generally safe and well-tolerated [28,29]. Risks include the following:

- Surgery
  - Bleeding
  - Infection
  - Anesthesia complications
- Stimulation [5,21,27,28]
  - Voice alteration/hoarseness (by far the most common adverse effect)
  - Cough
  - Dizziness
  - Dyspepsia
  - Dysphagia
  - Dyspnea
  - Headache
  - Hypomania or mania
  - Laryngismus
  - Nausea/vomiting
  - Pain (device site, incision site, and/or neck)
  - Paresthesia
  - Pharyngitis

It may be feasible to mitigate stimulation-related side effects by reducing the stimulation intensity. No significant adverse neuropsychologic effects of chronic VNS for treatment-resistant depression have been identified [30].

Batteries for the pulse generator that is implanted subcutaneously in the chest need to be replaced periodically.

Mechanism — The mechanism of action by which VNS may perhaps treat unipolar major depression is unknown. The vagus nerve (cranial nerve X) is a mixed nerve composed of

approximately 80 percent afferent sensory fibers carrying information to the brain and 20 percent efferent fibers sending signals from the brain [31]. The nerve is connected to the nucleus tractus solitarius, which communicates with brainstem nuclei implicated in mood regulation (eg, the locus coeruleus). In addition, neuroimaging data suggest that VNS can modulate activity in several cortical and subcortical brain regions that may be involved in mood regulation [32-34].

External sources of patient education — Educational material explaining VNS for patients and family members is freely available for printing at the United States National Institute of Mental Health website.

DEEP BRAIN STIMULATION

Overview — Deep brain stimulation is an investigational treatment for intractable unipolar major depression; it is not part of standard treatment for depression. The intervention involves implanting one or more electrodes into targeted brain regions through burr holes or a craniotomy using a stereotactic frame and magnetic resonance imaging [35,36]. Multiple brain regions have been studied as targets for stimulation (see 'Efficacy' below). Surgery is usually performed under local anesthesia with the patient awake [37]. A second procedure is performed under general anesthesia to tunnel wires beneath the scalp and skin of the neck to connect the electrodes to a pulse generator that controls stimulation parameters and is implanted subcutaneously in the chest, typically below the right clavicle. Stimulation of the surrounding gray or white matter is usually continuous rather than intermittent, and parameters (eg, amplitude, pulse width, and frequency) are adjusted with a wireless handheld transmitter [13,35,37]. In the United States, deep brain stimulation is available to patients with unipolar major depression only through a research protocol.

Deep brain stimulation has displaced ablative neurosurgery (see 'Ablative neurosurgery' below) as the focus of treatment studies for highly resistant (refractory) depression because the lesion involved in deep brain stimulation is less pronounced than that for ablative procedures. In addition, deep brain stimulation parameters are adjustable, and in most cases the intervention is reversible [38,39].

Electrical stimulation of deep brain centers is an established treatment for refractory Parkinson disease, essential tremor, and dystonia, and an investigational treatment for obsessive-compulsive disorder. (See "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' and "Deep brain stimulation for treatment of obsessive-compulsive disorder".)

Efficacy — It is not known if deep brain stimulation is efficacious for treatment-refractory major depression:

- A meta-analysis of three randomized, parallel group trials in 128 patients found that response with active and sham deep brain stimulation was comparable (relative risk 1.0, 95% CI 0.4-2.2) [40].

- A meta-analysis of nine studies in 190 patients, followed for up to 16 weeks, found that response was more likely to occur with active deep brain stimulation than sham stimulation (odds ratio 6, 95% CI 3-11) [41]. Although the index of heterogeneity across studies was low (I^2 = 5), nevertheless, it is questionable whether the studies should be pooled because there were multiple, substantive differences in the study designs. As an example, the underlying studies targeted different brain sites, and the theoretical basis for stimulating each site varies across sites. In addition, not all of the studies randomly assigned patients to active or sham stimulation, and most of the studies used a crossover design; when the analyses were restricted to randomized, parallel group trials, the efficacy of active and sham stimulation were comparable. Further, different definitions of response were used across studies.

Cognitive impairment, one of the symptoms of major depression, may improve with deep brain stimulation. (See 'Cognitive effects' below.)

In patients with refractory depression, gray and white matter regions that have been targeted for deep brain stimulation include the [41-51]:

- Ventral anterior internal capsule and ventral striatum
- Subcallosal cingulate gyrus
- Medial forebrain bundle
- Nucleus accumbens
- Inferior thalamic peduncle
- Bed nucleus of the stria terminalis
- Habenula

Although no compelling data indicate that stimulating a particular site is efficacious, additional research may determine that targeting one region is more efficacious than stimulating the others. Alternatively, different subtypes of treatment-refractory depression may require

different locations for implanted electrodes, because structural, functional, and connectivity abnormalities may differ across patients.

Multiple experts agree that the lack of demonstrated efficacy for the intervention is not cause to abandon the treatment; rather, it indicates the need to continue developing the proper techniques for using the intervention [4,10,11,38]. Response to deep brain stimulation probably depends upon stimulation parameters and the activity state of the stimulated site, and optimal stimulation parameters are not known [35]. Effective administration of deep brain stimulation may also require standardized use of tractography guided surgical placement and intraoperative testing of the electrodes [10,38,52].

In addition, observational studies suggest that some patients with severe treatment-resistant depression do experience sustained benefit from long-term administration of deep brain stimulation [45,53]. For example, in a retrospective study, eight patients with severe treatment-resistant depression (failed trials of electroconvulsive therapy [ECT] plus a minimum of four medication trials) were treated with deep brain stimulation to the ventral capsule/ventral striatum for a mean of 11 years. At the last follow-up, 50 percent of the individuals had achieved a response to treatment (≥50 percent improvement on the Montgomery-Asberg Depression Rating Scale [MADRS]) while 25 percent achieved remission (MADRS score ≤10) [53].

Each of the bulleted sections below describes the efficacy of deep brain stimulation for a specific brain target.

- **Ventral anterior internal capsule and ventral striatum** – Randomized trials of deep brain stimulation of the ventral anterior internal capsule and ventral striatum have yielded conflicting results, and the small sample sizes limit interpretation:

  - A 16-week trial (n = 29 patients) compared active with simulated (sham) deep brain stimulation of electrodes that were implanted in the ventral capsule/ventral striatum [50]. Response (reduction of baseline symptoms ≥50 percent) was comparable for active and sham stimulation (3 of 15 versus 2 of 14 patients [20 versus 14 percent]). Following the randomized trial, all patients received active stimulation and were assessed intermittently for up to two years, during which approximately 20 to 25 percent responded.

  - A second study initially treated 25 patients with open-label deep brain stimulation of the ventral capsule/ventral striatum for an average of 52 weeks, during which 10 patients (40 percent) responded [51]. Subsequently, a crossover trial compared six weeks of active with six weeks of sham stimulation in 16 patients (nine responders and seven nonresponders) who served as their own controls, and were randomly assigned

to the order in which they received active and sham treatment. After correcting for potential confounding factors (the order in which active and sham stimulation were administered, carryover effects, and depression rating scale scores at the end of open-label treatment), the analyses found that depressive symptoms were lower during active stimulation, and the clinical difference was large.

A meta-analysis of the two studies found that the benefit of active and sham stimulation of the ventral/internal capsule was comparable [41].

In addition, a randomized, crossover trial compared stimulation of the internal capsule plus the bed nucleus of the stria terminalis with stimulation of the inferior thalamic peduncle for varying lengths of time in seven patients; improvement was comparable for the two groups [9]. The small sample size and lack of a sham control make it difficult to interpret the results.

- **Subcallosal cingulate gyrus** – For treatment-refractory depression, limited evidence suggests that deep brain stimulation of the subcallosal cingulate gyrus is not efficacious. A meta-analysis of five studies (n = 122 depressed patients), which compared active deep brain stimulation with sham stimulation of the subcallosal cingulate gyrus, found that response was comparable (odds ratio 3.0, 95% CI 0.9-9.8) [41]. Subsequently, an eight-week randomized trial (n = 8) also found that active and sham stimulation of the subcallosal cingulate gyrus were comparable [14].

  In addition, studies have not established optimal stimulation parameters for deep brain stimulation of the subcallosal cingulate gyrus in refractory major depression. A six-month randomized trial (n = 9) that compared high frequency with low frequency subcallosal cingulate stimulation found comparable improvement [54]. Another six-month randomized trial (n = 22), which compared short pulse width with long pulse width stimulation, also found that improvement was comparable [7].

- **Medial forebrain bundle** – The efficacy of deep brain stimulation of the medial forebrain bundle is unknown. Although a meta-analysis of two randomized trials found that response was more likely to occur with active stimulation of the medial forebrain bundle than sham stimulation (odds ratio 8, 95% CI 3-24), the result was based upon two small studies (total n = 20) with a high or unclear risk of bias [41].

  Subsequently, an eight-week randomized trial in 16 patients found that the benefit of active and sham medial forebrain stimulation was comparable [11]. In addition, improvement in the group that received sham stimulation, acutely following insertion of the electrodes, suggested either a placebo effect or micro-lesioning effect.

- **Nucleus accumbens** – Two small prospective observational studies suggest that deep brain stimulation of the nucleus accumbens may perhaps relieve treatment-refractory depression. A one-year study of nucleus accumbens stimulation in 10 patients found that response occurred in 50 percent [8], and a second study in 11 patients treated for one to four years found a response rate of 45 percent [45].

- **Bed nucleus of the stria terminalis** – A prospective observational study of five patients with treatment-refractory depression found that deep brain stimulation of the bed nucleus of the stria terminalis (a brain region connected to the amygdala, hypothalamus, thalamus, and prefrontal cortex) was associated with clinically significant improvement in four patients [46].

Safety — Serious risks of deep brain stimulation include those associated with surgery, such as intracranial bleeding (which can cause permanent neurologic deficits), seizures, anesthesia complications (including death), infections, and problems with wound healing [4,7,11,36]; however, these risks appear to be low [37,55]. More commonly, hardware may malfunction, wires fracture, and electrodes dislodge. In addition, the pulse generator may be deactivated inadvertently by magnetic fields (eg, metal detectors).

Batteries for the pulse generator that is implanted subcutaneously in the chest are eventually depleted, which has necessitated surgical replacement of the pulse generator. In a prospective, eight-year, observational study of 28 patients who were treated with subcallosal cingulate stimulation for refractory depression, the mean life of the generator was 17 months [10]. Battery depletion in some patients was associated with worsening of depressive symptoms, which remitted within one to three months of surgically replacing the hardware and resuming stimulation. Newer devices with longer lasting or wirelessly rechargeable batteries are being developed.

Another safety issue is that attempted and completed suicides have occurred in at least 10 studies of deep brain stimulation that targeted different neuroanatomical sites [4,7,9-11,45,46,54,56,57]. Although it is possible that the intervention was responsible, it seems more likely that suicidality in these patients reflects their severity of illness, including past history of suicide attempts, and indicates the need for close monitoring [58]. As an example, one study included four patients who remitted with deep brain stimulation; two subsequently attempted suicide and two others committed suicide [56]. Three of the patients had attempted suicide prior to surgery, and two had a family history of completed suicide. One patient who killed herself had four maternal relatives who committed suicide; following remission with deep brain stimulation, the patient relapsed and was then successfully treated with ECT three months before death.

Adverse effects — Side effects of deep brain stimulation for treatment-refractory depression include [4,7,8,11,12,37,48,57,59-62]:

- Agitation
- Dysphoria
- Hypomania
- Psychosis
- Diaphoresis
- Diarrhea
- Disequilibrium
- Dizziness
- Dysphagia
- Headache
- Hearing disturbance
- Insomnia
- Muscle cramps, spasms, and stiffness
- Nausea and vomiting
- Pain (eg, at incision sites)
- Paresthesia
- Polyuria
- Pulling sensation along extension site
- Seizure
- Swollen eye
- Syncope
- Tinnitus
- Tremor
- Visual disturbance
- Weight gain

Adverse effects of stimulation may be specific to stimulation location and parameters, and are generally transient or resolve after adjusting stimulus parameters (eg, increasing or decreasing amplitude) [11,14].

Cognitive effects — Deep brain stimulation of different sites does not appear to adversely affect neuropsychological functioning; rather, it is associated with improvement, based upon prospective observational studies [7,11,30,46,54]:

- A one-year study of subcallosal cingulate stimulation in six patients found that attention, executive functioning, memory, psychomotor speed, risk taking/decision making, and

verbal intelligence quotient did not deteriorate, and that performance improved in several areas that were impaired at baseline [63].

- A six-month study of subcallosal cingulate stimulation in 17 patients found that general intellectual ability, executive functioning, memory, risk taking/decision making, and set shifting remained stable or improved [12].

- A one-year study of nucleus accumbens stimulation, and a comparable study of ventral anterior internal capsule and ventral striatum stimulation, each with 10 patients, found no detrimental effects upon executive functioning, general intellectual ability, language, learning, memory, and processing speed [8,60]. In the study that stimulated the nucleus accumbens, improvement occurred on tests of attention, learning and memory, executive functions, and visual perception, which was independent of the antidepressant effects of stimulation or changes in stimulation parameters [64].

Therapeutic mechanism — Deep brain stimulation relies upon our incomplete understanding of the functional neuroanatomy of major depression. Based upon biochemical, postmortem, and functional and structural neuroimaging studies, the most likely hypothesis is that stimulation modulates pathologic activity within a network (circuit) of integrated grey matter brain regions that are involved in mood regulation [8,48,59,65,66]. The neuronal effects of modulation depend upon the location and mix of cell bodies and white matter fibers in the field of stimulation, and whether the neurons are excitatory, inhibitory, or modulatory [35].

External sources of patient education — Educational material explaining deep brain stimulation for patients and family members is freely available for printing at the United States National Institute of Mental Health website.

DIRECT CORTICAL STIMULATION

Overview — Direct cortical stimulation (also called epidural cortical stimulation) is an investigational treatment for refractory unipolar major depression; it is not part of standard treatment for depression. The intervention involves implanting one or more epidural or subdural electrodes through burr holes or a craniotomy to directly stimulate a targeted area of the cortex [67,68]. The electrodes are connected by leads that run beneath the scalp and skin of the neck to a pulse generator, which controls stimulation parameters and is implanted subcutaneously in the chest. In the United States, direct cortical stimulation is available to patients with unipolar major depression only through a research protocol.

Intraoperative direct cortical stimulation has been used during neurosurgery to map motor, language, and other cognitive functions, to help guide resection of lesions [69].

Effectiveness — It is not known if direct cortical stimulation is efficacious for treatment of refractory unipolar major depression, due to the paucity of evidence:

- A two-month, single-blind, randomized trial compared direct cortical stimulation (targeting the left dorsolateral frontal cortex) with sham treatment in 11 patients who were masked to treatment [68]. Improvement of symptoms did not differ significantly between the two groups. Following the randomized phase, the 11 patients received open-label, active treatment for two years, and response (improvement from baseline on the depression rating scale ≥50 percent) occurred in five patients within 1 to 15 months.

- In a seven-month, open-label observational study that implanted epidural electrodes bilaterally at the anterior frontal poles and midlateral prefrontal cortex in five patients, remission occurred in three patients within four to seven months [67].

Safety and adverse effects — Risks of direct cortical stimulation are primarily related to the nonspecific risks of surgery (bleeding, infection, and anesthesia complications), and the pulse generator needs to be replaced periodically. Studies have reported urinary incontinence and worsening of essential tremor, but have not observed seizures, episodes of mania or psychosis, or worsening cognition [67,68].

Mechanism — The mechanism of action by which direct cortical stimulation may treat unipolar major depression is unknown; one hypothesis is that the procedure modulates activity within a network of grey matter brain regions that are involved in mood regulation and depression [70].

ABLATIVE NEUROSURGERY

Overview — Ablative neurosurgery for intractable unipolar major depression is a clinically available but very rarely used approach, in which a lesion is made in limbic or paralimbic structures [1]. Early ablative techniques for psychiatric illness, such as the prefrontal leucotomy (“lobotomy”) [71], were initially used in the 1950s prior to the discovery of the first antidepressant medications [72-74]. However, stereotactic neurosurgical techniques that allow for more focal lesions with fewer side effects have emerged and include [75-77]:

- Anterior capsulotomy – Lesion in the anterior limb of the internal capsule that connects the frontal cortex and thalamus

- Anterior cingulotomy – Bilateral lesions in the dorsal anterior cingulate gyrus

- Subcaudate tractotomy – Bilateral lesions in thalamocortical white matter tracts inferior to the anterior striatum
- Limbic leucotomy – Combines cingulotomy with subcaudate tractotomy

Craniotomy is typically used to perform these procedures, although noninvasive gamma knife surgery can be used for capsulotomy because of its particularly small lesion volume [78].

Cingulotomy has been used most often, with over 500 reported cases [79].

Deep brain stimulation has displaced ablative neurosurgery as a focus of study. (See 'Deep brain stimulation' above.)

Indication — There are no established criteria (including number and type of failed treatments) that need to be met before a patient with unipolar major depression is considered appropriate for ablative surgery; this largely depends upon the clinical judgment of the evaluating psychiatrist and neurosurgeon. Candidates include patients with chronic, severe, and incapacitating symptoms that are refractory to [1,2,80,81]:

- Pharmacotherapy
  - Monotherapy with several (eg, four) different antidepressant classes at therapeutic doses for several weeks (eg, four to eight)
  - Multiple (eg, three) trials of an antidepressant plus an established adjunctive drug (eg, second-generation antipsychotic, lithium, and triiodothyronine)
- Adjunctive psychotherapy such as cognitive-behavioral therapy or interpersonal psychotherapy
- Electroconvulsive therapy

Contraindications to ablative surgery for unipolar major depression include [1,80,81]:

- Severe personality disorders
- Comorbid substance use disorders
- Suicidal ideation or behavior
- Chronic, poorly controlled general medical conditions
- Previously diagnosed intracranial masses

- Intracerebral vascular abnormalities
- Pregnancy

Institutions offering ablative neurosurgery for treatment-refractory depression often have a multidisciplinary committee (eg, including neurosurgery, psychiatry, and neurology) to review referrals and ensure that the procedure is indicated [1-3]. In many countries, use of the procedure is controlled by legislation and overseen by public agencies [2,80,82].

Before undertaking ablative neurosurgery, clinicians and patients with major depression should note that the course of illness is such that recovery can occur after lengthy periods of illness. (See "Unipolar depression in adults: Course of illness", section on 'Chronic major depression'.)

Response — Randomized trials for ablative procedures in treatment-refractory depression have not been conducted. Based upon the following three prospective observational studies of different ablative procedures, response (improvement from baseline on the depression rating scale ≥50 percent) occurs in approximately 30 to 60 percent of patients [77]:

- Anterior cingulotomy or limbic leucotomy – Thirty-three patients were treated and the mean duration of follow-up was 30 months; response occurred in 33 percent [1].
- Anterior cingulotomy – Eight patients were treated and followed for up to 12 months; response occurred in 63 percent [81].
- Anterior capsulotomy – Twenty patients were treated and the mean duration of follow-up was seven years; response occurred in 50 percent [2].

Retrospective studies of patients with treatment-refractory depression have suggest that the rate of response to ablative neurosurgery may be roughly 50 percent or higher:

- Subcaudate tractotomy or limbic leucotomy – In one study with a mean duration of follow-up of 14 years, recovery occurred in 5 of 22 patients (23 percent) and significant improvement in another 11 (50 percent) [80]. However, among 24 patients who were deceased at follow-up, 25 percent had committed suicide.
- Anterior capsulotomy – A second retrospective study identified 24 patients with pre- and postsurgical assessment of depressive symptom severity; follow-up occurred at varying lengths of times [83]. Response occurred in 54 percent (13 of 24).

Improvement of major depression with ablative surgery generally occurs within days to weeks of the procedure [80], but the effect may be delayed for months [1,84]. Insufficient or

impersistent improvement may lead patients to undergo a second operation to extend the lesions created in the first operation or to make lesions in an additional site [1,2,80,83].

Risks and side effects — For patients with treatment-refractory depression, observational studies suggest that ablative surgery is associated with:

- Nonspecific neurosurgical risks [1,80]:
  - Intracranial bleeding
  - Infection
  - Anesthesia complications
  - Delirium
- Risks specific to the lesion [1,2,30,80]:
  - Epilepsy
  - Impaired cognition (including executive functioning, memory, set shifting, and verbal fluency)
  - Personality changes (eg, impulsivity, disinhibition, and amotivation)
  - Urinary incontinence (typically transient)
  - Weight gain

However, some studies found that neurosurgery did not adversely affect neuropsychological function [2,81].

Mechanism of action — The rationale for using ablative procedures is based upon a model that conceptualizes refractory major depression as a problem in neural networks (circuits) that regulate mood, rather than an abnormality in a single neuroanatomical structure or neurotransmitter system [77]. It is hypothesized that abnormal communication between grey matter brain regions involved in the pathophysiology of major depression can be interrupted by severing their white matter connections.

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

- Unipolar major depression often does not respond to standard treatment, which has led to investigation and use of invasive (surgical) treatments. However, none of these interventions are part of standard treatment. Surgical interventions are reserved for patients with major depression who are refractory to multiple courses of pharmacotherapy, psychotherapy, and noninvasive neuromodulation interventions (eg, electroconvulsive therapy and transcranial magnetic stimulation). (See 'Introduction' above and 'Overview and general principles' above.)

- The assessment of candidates for surgical treatment of refractory major depression includes a psychiatric history and mental status examination, with emphasis upon current suicide risk and other depressive (table 1) symptoms, psychotic symptoms, comorbid disorders, neuropsychological functioning, length of the current depressive episode, types and number of failed treatments, psychosocial functioning, and ability to provide informed consent. A general medical history, physical examination, and focused laboratory tests and neuroimaging studies are also performed, with emphasis upon preexisting neurologic disease. (See 'Assessment' above.)

- Specific surgical approaches for unipolar depression include:

  - Vagus nerve stimulation (VNS) – VNS is a clinically available intervention that involves surgery to attach an electrode around one vagus nerve; the electrode is connected by a wire to a pulse generator implanted subcutaneously in the chest wall. Randomized trials lasting 10 and 22 weeks indicate that VNS is not efficacious for treatment-resistant unipolar major depression; however, prospective observational studies suggest that VNS may require more time to exert its effect. The most common side effect is voice alteration. (See 'Vagus nerve stimulation' above.)

  - Deep brain stimulation – Deep brain stimulation is an investigational treatment in which electrodes are implanted into targeted brain regions (eg, ventral anterior internal capsule and ventral striatum, subcallosal cingulate gyrus, or medial forebrain bundle) through burr holes. A second procedure is performed to tunnel wires beneath the skin to connect the electrodes to a pulse generator that controls stimulation parameters and is implanted subcutaneously in the chest. Multiple randomized trials have not clarified whether the intervention is efficacious and whether targeting one region is more efficacious than stimulating other regions. (See 'Deep brain stimulation' above.)

  - Direct cortical stimulation – Direct cortical stimulation is an investigational treatment in which epidural or subdural electrodes are implanted through burr holes to directly

stimulate a targeted area of the cortex. The electrodes are connected by leads that run beneath the skin to a pulse generator, which controls stimulation parameters and is implanted subcutaneously in the chest. It is not known if direct cortical stimulation is efficacious for treatment of refractory unipolar major depression, due to the paucity of evidence. (See 'Direct cortical stimulation' above.)

- Ablative neurosurgery – Ablative neurosurgery for intractable major depression is a clinically available but very rarely used approach, in which a lesion is made in limbic or paralimbic structures. The first ablative procedures that were developed have been supplanted by stereotactic neurosurgical techniques that allow for more focal lesions with fewer side effects. Nevertheless, deep brain stimulation has displaced ablative neurosurgery as a focus of study. (See 'Ablative neurosurgery' above.)

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