Bipolar disorder in adults: Overview of neuromodulation procedures

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INTRODUCTION

Many patients with acute bipolar major depression or mania do not respond to pharmacotherapy; in addition, maintenance treatment with medications and psychotherapy often fails to prevent recurrent mood episodes [1,2]. Patients unresponsive to standard treatment may be candidates for neuromodulation therapies [3].

Neuromodulation interventions include noninvasive and invasive approaches. Noninvasive therapies comprise convulsive (eg, electroconvulsive therapy) and nonconvulsive therapies (eg, repetitive transcranial magnetic stimulation), which stimulate focal areas of the brain with an electric current or magnetic field [4]. Invasive interventions require surgery and are used in more treatment-refractory patients; examples include vagus nerve stimulation and deep brain stimulation.

This topic reviews neuromodulation therapies for different phases of bipolar disorder. Choosing a treatment regimen for acute bipolar depression, acute mania and hypomania, and maintenance treatment is discussed separately, as is an overview of neuromodulation therapies for unipolar depression. (See "Bipolar major depression in adults: Choosing treatment" and "Bipolar mania and hypomania in adults: Choosing pharmacotherapy" and "Bipolar disorder in adults: Choosing maintenance treatment" and "Unipolar depression in adults: Overview of neuromodulation procedures".)

NONINVASIVE NEUROMODULATION THERAPIES

Noninvasive neuromodulation procedures include convulsive and nonconvulsive therapies that use an electric current or magnetic field to stimulate the brain [4]:

- Convulsive therapies:
  - Electroconvulsive therapy (ECT) – Clinically available
  - Magnetic seizure therapy (MST) – Investigational procedure
- Nonconvulsive therapies:
  - Repetitive transcranial magnetic stimulation (TMS) – Clinically available
  - Transcranial direct current stimulation (tDCS) – Investigational procedure
  - Low field magnetic stimulation (LFMS) – Investigational procedure
  - Cranial electrical stimulation – Clinically available

Electroconvulsive therapy (ECT) — ECT is a noninvasive, clinically available procedure in which an electric current is passed between two electrodes placed against the scalp to induce a generalized cerebral seizure while the patient is under general anesthesia. An acute course of ECT includes several treatments and may last days or weeks. A separate topic provides an overview of ECT and addresses the potential mechanisms of action, use of ECT in patients with general medical conditions, administering ECT with concurrent medications, the number and frequency of treatments, safety and adverse effects of ECT, information for patients, and informed consent; other topics discuss medical consultation for ECT, the technique for performing ECT, and the indications and efficacy of ECT for unipolar major depression. (See "Overview of electroconvulsive therapy (ECT) for adults" and "Medical evaluation for electroconvulsive therapy" and "Technique for performing electroconvulsive therapy (ECT) in adults" and "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)".)

Efficacy and adverse effects — The efficacy and adverse effects of ECT for patients with bipolar disorder are discussed separately. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy".)

Magnetic seizure therapy (MST) — MST is a noninvasive, experimental intervention that uses TMS at relatively high intensity and frequency (number of magnetic pulses per second) to induce seizures [2]. A separate topic provides a general description of MST and discusses its

efficacy and adverse effects in unipolar depression. (See "Unipolar depression in adults: Overview of neuromodulation procedures", section on 'Magnetic seizure therapy'.)

Efficacy and adverse effects — Little is known about the efficacy and adverse effects of MST in bipolar disorder because so few studies have been conducted; most of what is known is thus derived from studies of patients with unipolar depression. As an example, a review of MST for unipolar depression and bipolar depression identified eight studies in which a total of 121 patients were treated; only 5 patients had bipolar disorder [5].

Repetitive transcranial magnetic stimulation (TMS) — Repetitive TMS 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 induces an electric current that depolarizes neurons in focal areas of the brain. The US Food and Drug Administration has approved repetitive TMS devices that can administer different types of stimulation:

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

Among these standard types of stimulation, the most widely used and studied type is surface cortical stimulation, which utilizes a figure eight coil, as does theta burst TMS. Deep TMS utilizes H coils, which theoretically stimulate brain structures beneath the surface prefrontal cortex.

The stimulation parameters required to optimize efficacy TMS for bipolar disorder are not known and administration of TMS is thus not standardized. In addition, it is not known if the optimal TMS stimulation parameters vary for different bipolar mood states, nor is it known how TMS should be administered in conjunction with pharmacotherapy for depression, mania, and mixed states. For bipolar depression, some studies have used high frequency, surface cortical TMS to activate the left prefrontal cortex or low frequency, surface cortical TMS to inhibit the right prefrontal cortex [2]. In mania, high frequency TMS has been used to excite the right prefrontal cortex.

Studies of TMS for treating psychiatric disorders has focused primarily upon depressive disorders, and randomized, sham-controlled trials have demonstrated that TMS can be efficacious for treating major depression [6,7]. Although the large majority of patients in these trials had unipolar major depression, some had bipolar major depression, and a few studies have focused solely on patients with bipolar disorder. TMS has also been studied for other neuropsychiatric disorders, including depersonalization/derealization disorder, generalized

anxiety disorder, obsessive-compulsive disorder, chronic pain, Parkinson disease, posttraumatic stress disorder, schizophrenia, smoking cessation, stroke rehabilitation, and tinnitus [6-19]. In addition, TMS has been studied as a diagnostic tool [20].

Due to the lack of high quality evidence, there is no consensus on using TMS for bipolar disorder. Some practice guidelines and clinicians take the position that TMS is a reasonable treatment option [21-25], whereas others either recommend not using TMS for these patients [6,26,27] or take no position [28,29].

Separate topics describe administration of TMS in greater detail and address its indications, efficacy, and adverse effects in patients with unipolar major depression. (See "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)" and "Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)".)

Efficacy of acute treatment — There are more studies of TMS for unipolar major depression than bipolar disorder [6,30]. In bipolar disorder, there are more studies in patients with depression than mania or mixed features. Most studies of TMS in bipolar disorder have relatively small samples and are thus underpowered [6].

Bipolar major depression — Multiple randomized trials suggest that surface cortical and theta burst TMS can be efficacious for bipolar major depression:

- A pooled analysis compared active TMS with sham stimulation in 181 patients with bipolar major depression; these patients were drawn from 19 randomized trials in which the large majority of patients had unipolar major depression [31]. The studies targeted the left dorsal lateral prefrontal cortex, right dorsal lateral prefrontal cortex, or both. The large majority of studies used either high frequency or low frequency surface cortical stimulation; other studies used theta burst stimulation. The use of pharmacotherapy was not reported. Response occurred in more bipolar patients who received active TMS than sham TMS (44 versus 25 percent).

- A two-week randomized trial (not included in the pooled analysis) compared 10 sessions of active TMS with sham TMS in 20 patients; improvement was greater with active stimulation [32]. Although the study did not identify the type of TMS that was administered, presumably it was surface cortical TMS.

One randomized trial found that surface cortical TMS was not beneficial for bipolar depression, but the sample was small and the treatment parameters were insufficient [6]. A four-week trial randomly assigned patients with bipolar II depression to 20 daily sessions of left high frequency TMS, right low frequency TMS, or sham stimulation [33]. In addition, all patients received

quetiapine; mean daily doses in the three groups ranged from 325 to 375 mg. The analysis of patients who completed the study (n = 35) found that improvement of depression and cognitive functioning was no better with active TMS than sham TMS. However, the intensity of active TMS was set at only 80 percent of motor threshold and the number of pulses per session was only 1200. Information about administering TMS, including standard treatment parameters, is described separately. (See "Unipolar major depression: Administering transcranial magnetic stimulation (TMS)".)

Although a prospective observational study suggests that bipolar depression may also be amenable to deep TMS [34], its efficacy is not known due to the dearth of high quality studies. One small, four-week randomized trial compared 20 sessions of active deep TMS with sham stimulation as add-on therapy in patients who continued stable, unsuccessful pharmacotherapy regimens (n = 50; bipolar I = 25 and bipolar II = 25) [35]. Response occurred in twice as many patients who received active than sham stimulation (48 versus 24 percent). However, follow-up assessments one-month posttreatment indicated that the benefits of active TMS had dissipated.

Patients with bipolar major depression have also been treated with investigational TMS protocols. As an example, one small randomized trial compared active bilateral TMS and with sham stimulation in 46 patients [36]. During each treatment session, patients initially received low frequency stimulation of the right dorsolateral prefrontal cortex, followed by high frequency stimulation of the left dorsolateral prefrontal cortex. Improvement was comparable with active and sham TMS.

For patients with bipolar major depression who are treated with TMS, we typically administer adequate doses of mood stabilizing medication (eg, lithium or valproate) to prevent switching to mania, even though the risk of switching appears to be low or nonexistent (see 'Adverse effects' below). In addition, we typically cease TMS in patients who switch to mania because there is no compelling evidence that TMS is effective for mania.

Mania — For patients with mania who are treated with medications, it is not clear whether add-on therapy with surface cortical TMS administered over the right dorsolateral prefrontal cortex is efficacious, due to conflicting results across low quality studies [6]:

- A small, two-week trial randomly assigned patients with mania (n = 16, including four with psychotic symptoms) to receive high frequency TMS that targeted either the right prefrontal cortex or the left prefrontal cortex [37]. TMS was added onto pharmacotherapy initiated prior to study entry, and all patients received 10 sessions of TMS on consecutive weekdays. Improvement was greater with right-sided TMS than left-sided TMS. The study was terminated after 16 patients were enrolled because those who received left-sided

stimulation were clinically worse compared with baseline, despite adequate antimanic pharmacotherapy.

- A two-week, prospective observational study alternatively assigned patients (n = 41, including 40 with psychotic mania) to receive either active TMS plus pharmacotherapy or sham TMS plus pharmacotherapy; the patients were blind to their treatment assignment [38]. High frequency TMS was administered daily for 10 days over the right dorsolateral prefrontal cortex. Remission of mania occurred in more patients who received active TMS than sham TMS (100 versus 65 percent).

- Another small, two-week randomized trial compared active TMS with sham TMS in patients receiving pharmacotherapy initiated prior to study entry (n = 19, including 16 with psychotic mania); 10 sessions of high frequency TMS were administered, targeting the right prefrontal cortex [39]. Improvement was comparable for the two groups [39].

Mixed features — Augmentation of medications with surface cortical TMS may perhaps improve bipolar mood episodes with mixed features. In a prospective observational study, 40 patients with bipolar mood episodes with mixed features who did not respond to pharmacotherapy were treated with 15 sessions of add-on right low frequency TMS for three weeks [40]. Remission of depressive symptoms occurred in 29 percent of patients and remission of manic symptoms occurred in 15 percent.

Neurocognition — In patients with bipolar disorder, it is not known whether TMS improves neuropsychological function, which is often impaired during euthymic states as well as mood episodes. Two randomized trials yielded conflicting results:

- One randomized trial compared left, high frequency, surface cortical TMS with sham stimulation in remitted patients (n = 52) receiving maintenance pharmacotherapy; study treatments were administered for 10 consecutive days [41]. Among the 10 neuropsychological tests that were administered at baseline and posttreatment, improvement on two tests (working memory and processing speed) was greater with active TMS than sham TMS and adverse effects were comparable in the two groups.

- A four-week randomized trial compared 20 sessions of active deep TMS with sham stimulation as add-on therapy in patients with bipolar depression (n = 50) who continued stable, unsuccessful pharmacotherapy regimens [42]. Neuropsychological tests assessed cognitive domains such as verbal memory, working memory, and processing speed. Follow-up assessments one-month posttreatment showed that the benefits of add-on active and sham TMS for neurocognitive functioning (and depressive symptoms) were comparable.

Information about neurocognitive deficits in patients with bipolar disorder are discussed separately. (See "Bipolar disorder in adults: Clinical features", section on 'Cognition'.)

Efficacy of maintenance treatment — For patients with bipolar mood episodes who respond to acute TMS, augmentation of pharmacotherapy with maintenance TMS may possibly be beneficial [43,44]. As an example, a one-year prospective observational study enrolled seven patients with bipolar major depression who responded to left high frequency surface cortical TMS, and administered maintenance treatment with weekly TMS using the same stimulation parameters given during acute treatment [45]. Response to maintenance treatment occurred in three (43 percent) of the patients, such that two patients had no relapses and one patient had a single relapse that resolved with reintroduction of acute TMS each weekday for two weeks.

Adverse effects — The adverse effects of TMS in patients with bipolar disorder are generally similar to those seen in patients with unipolar major depression; the most serious is a generalized tonic-clonic seizure. (See "Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)", section on 'Safety and adverse effects'.)

TMS does not appear to cause switching from bipolar major depression to mania or hypomania [21,46]. Pooled analyses of randomized trials suggest that treatment-emergent mania or hypomania occurs in approximately 1 percent of patients who receive either active or sham TMS:

- One pooled analysis of 19 trials in 181 patients with bipolar major depression found that treatment-emergent mania with active TMS and with sham stimulation occurred in 0.9 and 1.3 percent [31].
- A pooled analysis of 10 trials compared active with sham TMS in 520 patients with major depression (unipolar 455, bipolar 65); switching to mania/hypomania with active TMS and sham TMS occurred in 0.8 and 0.7 percent of patients [46].

Transcranial direct current stimulation (tDCS) — tDCS is a noninvasive, investigational approach that uses two scalp electrodes to deliver a constant, low intensity direct current to specific cortical regions. A separate topic provides a more detailed description of tDCS and discusses its efficacy and adverse effects in unipolar depression. (See "Unipolar depression in adults: Overview of neuromodulation procedures", section on 'Transcranial direct current stimulation'.)

Efficacy of acute treatment — There are more studies of tDCS for unipolar major depression than bipolar disorder. In bipolar disorder, tDCS has been studied in more patients with depression than mania or mixed features.

Bipolar depression — The efficacy of tDCS for bipolar major depression is not clear due to the limited evidence from high quality studies. Although low quality data suggest that tDCS may be effective [47], two relatively small randomized trials that compared active with sham tDCS yielded conflicting results:

- A six-week randomized trial compared add-on active tDCS with sham tDCS in patients who continued to receive stable pharmacologic regimens (n = 59, bipolar I in 36 and bipolar II in 23) [48]. Ten daily sessions were administered on weekdays during weeks 1 and 2, followed by one session at week 4 and one session at week 6. Response, defined as reduction of baseline symptoms ≥50 percent, occurred in more patients who received active tDCS than sham (68 versus 30 percent). In addition, adverse effects, including switching to mania or hypomania, were comparable in the two groups, except for skin redness at the stimulation site, which occurred more frequently with active tDCS (54 versus 19 percent of patients).

- A four-week randomized trial compared active with sham tDCS in 36 patients; 20 daily sessions were administered on weekdays, and most continued to receive stable pharmacologic regimens. Improvement in the two groups was comparable [49].

Neurocognition — Neuropsychological function in bipolar patients is often impaired during euthymic states as well as mood episodes, and adjunctive tDCS may improve neurocognitive functioning. A three-week randomized trial compared active tDCS with sham tDCS in euthymic patients (n = 42) receiving maintenance pharmacotherapy; tDCS was administered daily on each weekday [50]. Improvement of executive functioning (eg, planning, cognitive flexibility, and response inhibition) and visuospatial memory was greater with active stimulation.

Information about neurocognitive deficits in patients with bipolar disorder are discussed separately. (See "Bipolar disorder in adults: Clinical features", section on 'Cognition'.)

Efficacy of maintenance treatment — Following response to acute treatment with tDCS for bipolar major depression, maintenance treatment may perhaps be effective. A small, prospective observational study included 24 patients with major depression (unipolar 16, bipolar 8) who responded to an acute course of treatment with tDCS and then received the intervention twice weekly for six months; pharmacotherapy was permitted as clinically indicated [51]. The estimated probability of remaining well was approximately 75 percent and treatment was well tolerated.

Adverse effects — The side effects of tDCS in patients with bipolar disorder are thought to be generally similar to the adverse effects seen in patients with unipolar major depression. (See

"Unipolar depression in adults: Overview of neuromodulation procedures", section on 'Safety and side effects'.)

It is not known whether tDCS causes treatment-emergent mania or hypomania in patients with bipolar depression, given the paucity of randomized trials comparing active with sham tDCS and that patients can switch to mania/hypomania in the absence of or despite treatment. Nevertheless, limited evidence suggests that tDCS does not cause switching to mania or hypomania in patients with bipolar depression:

- A meta-analysis of 10 randomized trials compared active with sham tDCS as monotherapy or add-on therapy in 416 patients with unipolar or bipolar major depression [52]. The rate of treatment-emergent mania or hypomania was comparable in the two groups (odds ratio 1.8, 95% CI 0.6-5.3).

- In a subsequent trial, which enrolled patients with bipolar major depression on stable pharmacologic regimens (n = 52) and randomly assigned them to add-on active or sham tDCS, switching to mania/hypomania was comparable in the two groups (15 and 19 percent of patients) [48].

Low field magnetic stimulation (LFMS) — LFMS is a noninvasive, investigational intervention that uses a device to generate a magnetic field, which in turn induces a low voltage electric field. A separate topic provides a more detailed description of the intervention, and discusses its efficacy and adverse effects in unipolar depression. (See "Unipolar depression in adults: Overview of neuromodulation procedures", section on 'Low field magnetic stimulation'.)

Bipolar depression — A randomized trial compared active LFMS with sham LFMS as add-on therapy in patients with bipolar depression (n = 41) who were treated with pharmacotherapy; patients received a single treatment session lasting 20 minutes [53]. Improvement in the two groups was comparable and no side effects were reported.

Cranial electrical stimulation — Cranial electrical stimulation is a noninvasive, clinically available approach that uses a battery operated device to deliver low voltage alternating current to the brain via electrodes attached to the scalp or infra- or supra-auricular structures. A separate topic provides a more detailed description of the intervention, and discusses its efficacy and adverse effects in unipolar depression. (See "Unipolar depression in adults: Overview of neuromodulation procedures", section on 'Cranial electrical stimulation'.)

It is not known whether cranial electrical stimulation is an effective adjunctive treatment for bipolar major depression. A small, two-week randomized trial compared active cranial electrical stimulation with sham stimulation as add-on therapy in patients with bipolar depression (n =

16); study treatments were administered each weekday for 20 minutes [54]. Scores on a self-administered depression rating scale improved more with active than sham stimulation. However, improvement on the clinician-administered scale was comparable for the two groups, and improvement of functioning also appeared to be comparable for the two groups. The incidence of adverse effects, including manic symptoms, did not differ between the two groups.

INVASIVE AND SURGICAL THERAPIES

These interventions are generally reserved for treatment-refractory patients due to their invasive nature.

- Vagus nerve stimulation (VNS) – Clinically available
- Deep brain stimulation (DBS) – Investigational procedure
- Ablative neurosurgery – Clinically available

Vagus nerve stimulation (VNS) — VNS is an invasive, clinically available approach in which a pulse generator is implanted in the chest wall and connected to an electrode that extends superiorly and wraps around one vagus nerve to deliver stimulation. A separate topic provides a general description of VNS, and discusses its efficacy and adverse effects in unipolar depression. (See "Unipolar depression in adults: Treatment with surgical approaches", section on 'Vagus nerve stimulation'.)

Efficacy — It is not known if VNS is efficacious as adjunctive treatment for bipolar disorder due to the limited and low quality data that are available:

- A 10-week randomized trial compared VNS with sham stimulation (no stimulation following implantation) in patients with treatment-resistant major depression [55,56]. In the subgroup with bipolar depression (n = 23), response (reduction of baseline symptoms ≥50 percent) was comparable for active and sham treatment. This was consistent with the finding in the total sample that active and sham VNS were comparable.

- A five-year, prospective observational study included patients with treatment-resistant major depression who received usual care plus VNS or usual care alone [57]. In the subgroup with bipolar major depression (n = 134), remission occurred in more patients who received adjunctive VNS; the benefit was evident starting at month 12 and persisted throughout the remaining follow-up. This was consistent with the finding that remission occurred more often with adjunctive VNS in the total sample.

- In a one-year, prospective observational study of nine patients with rapid-cycling bipolar disorder, baseline depressive and manic symptoms improved on average by 38 percent [58].

Safety and side effects — The safety and adverse effects of VNS in patients with bipolar disorder are thought to be generally similar to the adverse effects seen in patients with unipolar major depression. (See "Unipolar depression in adults: Treatment with surgical approaches", section on 'Safety'.)

It is not known whether VNS causes treatment-emergent mania or hypomania in patients with bipolar depression, given the paucity of randomized trials comparing active with sham VNS and that patients can switch to mania/hypomania in the absence of or despite treatment. In a 10-week randomized trial that included 23 patients with bipolar major depression, one patient receiving active VNS switched to mania [55,56]. An observational study also reported a case in which a patient with bipolar major depression developed treatment-emergent mania [59].

Deep brain stimulation (DBS) — DBS is an invasive, experimental intervention in which a pulse generator is surgically implanted in the chest and connected by subcutaneous wires to stimulating electrodes that are implanted in specific areas of the brain. A separate topic provides a general description of DBS, and discusses its efficacy and adverse effects in unipolar depression. (See "Unipolar depression in adults: Treatment with surgical approaches", section on 'Deep brain stimulation'.)

Efficacy — It is not known if DBS is efficacious as adjunctive treatment for bipolar disorder due to the limited and low quality data that are available [60]. One review identified six studies with a total of 12 patients who were treated for bipolar major depression with DBS; the depressive symptoms generally improved [61]. The largest study was a 24-week, prospective observational trial, in which seven patients with bipolar major depression received add-on treatment with DBS that targeted the subcallosal cingulate gyrus (electrodes were implanted bilaterally) [62]. Enrollment criteria included at least four failed antidepressant trials during the current episode, and failure of, intolerance of, or inability to receive electroconvulsive therapy. Baseline depressive symptoms improved on average by approximately 45 percent, and functioning improved as well. In addition, assessments two years after baseline showed that the benefits of ongoing DBS persisted.

Safety and side effects — The safety and adverse effects of DBS in patients with bipolar disorder are thought to be generally similar to the adverse effects seen in patients with unipolar major depression. (See "Unipolar depression in adults: Treatment with surgical approaches", section on 'Safety'.)

It is not known whether DBS causes treatment-emergent mania or hypomania in patients with bipolar depression, given the lack of randomized trials comparing active with sham DBS, and that patients can switch to mania/hypomania in the absence of or despite treatment. The limited evidence includes a two-year, prospective observational study of seven patients with bipolar major depression who received add-on treatment with DBS that targeted the subcallosal cingulate gyrus; no episodes of mania/hypomania occurred [62]. In addition, a review identified five case reports of patients with bipolar depression who were treated with DBS, and found that hypomanic symptoms occurred in one patient; the symptoms resolved after stimulation ceased [61]. These results may be specific to the target for DBS (eg, subcallosal cingulate white matter versus ventral capsule/ventral striatum). In some patients with other neuropsychiatric diseases, such as Parkinson disease or obsessive-compulsive disorder, DBS was associated with manic symptoms [2].

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. Little information is available about the procedure in bipolar disorder [63]. One seven-year, prospective observational study followed 16 patients with bipolar disorder who underwent bilateral subcaudate tractotomy and cingulotomy (limbic leucotomy) [64]. Symptoms of depression and anxiety decreased, whereas manic symptoms did not; a global measure of psychiatric status suggested that improvement occurred in 11 patients (69 percent). Complications included a scalp wound infection, extrapyramidal symptoms, and hallucinations, all of which resolved.

A separate topic provides a general description of ablative neurosurgery, and discusses its indications, efficacy, risks, and adverse effects in unipolar depression. (See "Unipolar depression in adults: Treatment with surgical approaches", section on 'Ablative neurosurgery'.)

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: Bipolar disorder".)

SUMMARY

- **Overview** – Neuromodulation interventions include noninvasive and invasive approaches. Noninvasive therapies stimulate focal areas of the brain with an electric current or a magnetic field, whereas invasive interventions require surgery. (See 'Introduction' above.)

- **Noninvasive neuromodulation therapies** – Noninvasive neuromodulation comprises both convulsive and nonconvulsive therapies. Convulsive therapies include electroconvulsive therapy (ECT) and magnetic seizure therapy; nonconvulsive therapies include repetitive transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), low field magnetic stimulation, and cranial electrical stimulation. (See 'Noninvasive neuromodulation therapies' above.)

  - **ECT** – ECT is a clinically available procedure that induces a generalized cerebral seizure with an electric current that passes between two electrodes placed against the scalp. ECT can be effective for patients with bipolar disorder but can cause multiple adverse effects. (See 'Electroconvulsive therapy (ECT)' above and "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy".)

  - **TMS** – Repetitive TMS is a clinically available treatment that uses a metal coil placed against the scalp to generate a magnetic field, which induces an electric current that depolarizes neurons in focal areas of the brain. TMS is well established for treating unipolar major depression and appears to be efficacious for bipolar major depression. The adverse effects of TMS in patients with bipolar disorder are thought to be generally similar to those seen in patients with unipolar major depression; the most serious is a generalized tonic-clonic seizure. TMS does not appear to cause switching from bipolar major depression to mania or hypomania. (See 'Repetitive transcranial magnetic stimulation (TMS)' above.)

  - **tDCS** – tDCS is an investigational approach that uses two scalp electrodes to deliver a constant, low intensity current to specific cortical regions. It is not clear if adjunctive tDCS is effective for treating bipolar major depression. The side effects of tDCS in patients with bipolar disorder are generally similar to those in patients with unipolar major depression. tDCS does not appear to cause treatment-emergent mania or hypomania in patients with bipolar depression. (See 'Transcranial direct current stimulation (tDCS)' above.)

- **Invasive neuromodulation therapies** – Invasive interventions are reserved for more treatment-refractory patients and include vagus nerve stimulation (VNS), deep brain stimulation (DBS), and ablative neurosurgery.

  - **VNS** – VNS is a clinically available approach in which a pulse generator is implanted in the chest wall and connected to an electrode that extends superiorly and wraps around one vagus nerve to deliver stimulation. It is not known if VNS is efficacious as adjunctive treatment for bipolar disorder. (See 'Vagus nerve stimulation (VNS)' above.)

- **DBS** – DBS is an experimental intervention in which a pulse generator is surgically implanted in the chest and connected by subcutaneous wires to stimulating electrodes that are implanted in specific areas of the brain. It is not known if DBS is efficacious as adjunctive treatment for bipolar disorder. (See 'Deep brain stimulation (DBS)' above.)

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