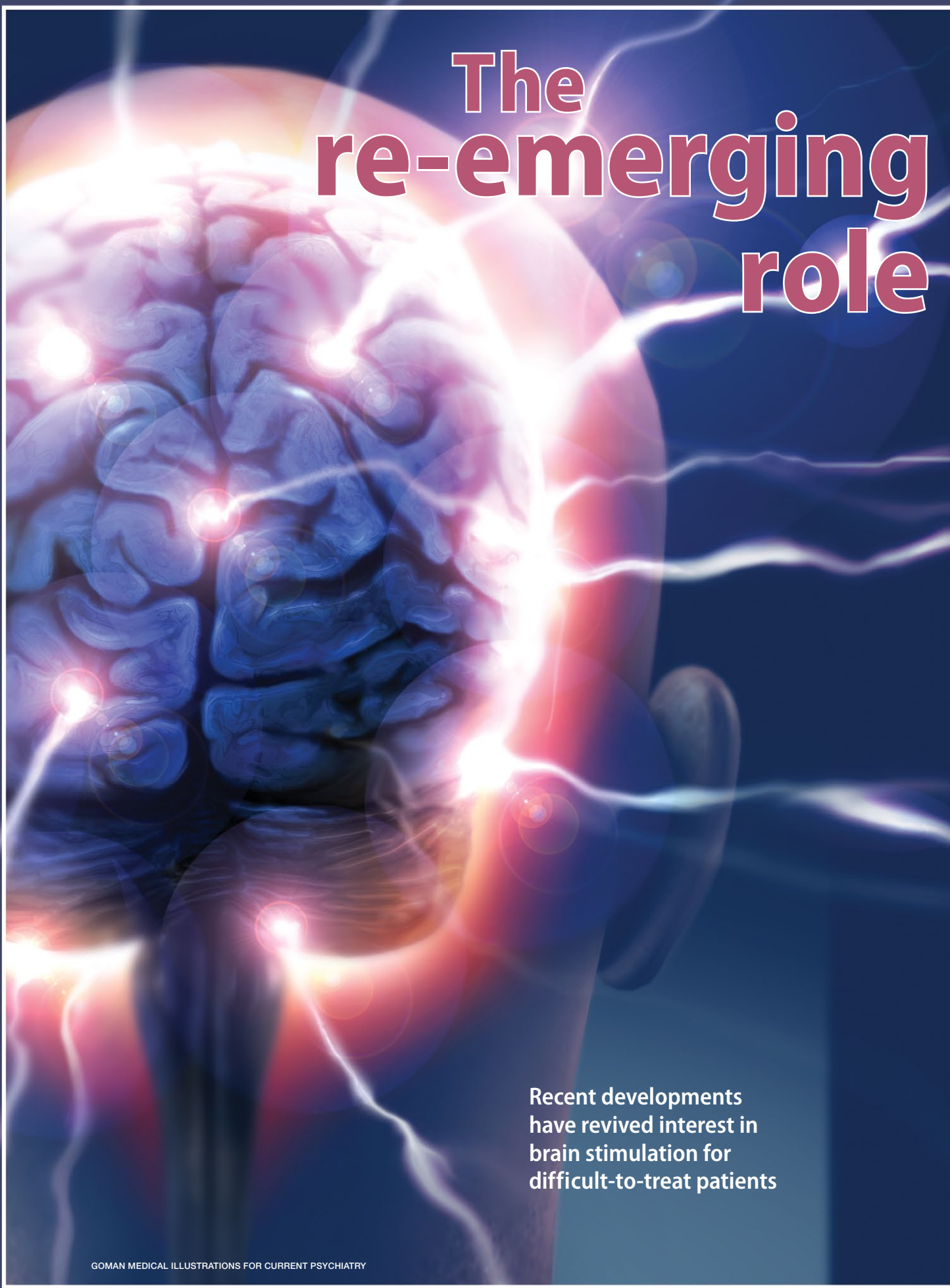

The re-emerging role

Recent developments have revived interest in brain stimulation for difficult-to-treat patients

GOMAN MEDICAL ILLUSTRATIONS FOR CURRENT PSYCHIATRY

# of therapeutic neuromodulation

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The brain is an electrochemical organ, and its activity can be modulated for therapeutic purposes by electrical, pharmacologic, or combined approaches. In general, neuromodulation induces electrical current in peripheral or central nervous tissue, which is accomplished by various techniques, including:

- electroconvulsive therapy (ECT)
- vagus nerve stimulation (VNS)
- transcranial magnetic stimulation (TMS)
- deep brain stimulation (DBS).

It is thought that therapeutic benefit occurs by regulating functional disturbances in relevant distributed neural circuits.[1] Depending on the stimulation method, the frequencies chosen may excite or inhibit different or the same areas of the brain in varying patterns. Unlike medication, neuromodulation impacts the brain episodically, which may mitigate adaptation to the therapy's beneficial effects and avoid systemic adverse effects.

Neuromodulation techniques are categorized based on their risk level as invasive or noninvasive and seizurogenic or nonseizurogenic ***(Table 1, page 68)***. Although these and other approaches are being considered for various neuropsychiatric disorders ***(Table 2, page 69)***, the most common application is for severe, treatment-resistant depression. Therefore, this article focuses on FDA-approved neuromodulation treatments for depression, with limited discussion of other indications.

continued

Therapeutic neuromodulation

Clinical Point

ECT is effective for severe depressive episodes but relapse rates are high and public perception often is negative

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Table 1

Therapeutic neuromodulation: Categorization based on risk

Noninvasive, nonseizurogenic
TMS, tDCS, CES
Noninvasive, seizurogenic
ECT, MST, FEAST
Invasive, nonseizurogenic
VNS, DBS, EpCS

CES: cranial electrotherapy stimulation; DBS: deep brain stimulation; ECT: electroconvulsive therapy; EpCS: epidural prefrontal cortical stimulation; FEAST: focal electrically administered seizure therapy; MST: magnetic seizure therapy; tDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation; VNS: vagus nerve stimulation

ECT: Oldest and most effective

ECT has remained the most effective therapeutic neuromodulation technique for more than 7 decades. It is indicated primarily for severe depressive episodes (eg, psychotic, melancholic), particularly in older patients.

ECT delivers electrical current to the CNS that is sufficient to produce a seizure. Under modified conditions, a typical course of 6 to 12 sessions can resolve severe depressive episodes and may also benefit other disorders, such as bipolar mania and acute psychosis. Although ECT is potentially life-saving, its use was markedly curtailed with the advent of effective antidepressants in the 1950s. Multiple factors impede its use, including:

- access and expertise are limited in many areas
- cognition is at least temporarily adversely affected
- relapse rates after acute benefit are high
- cost
- public perception often is negative.

Studies are addressing several of these concerns. For example, the National Institute of Mental Health-sponsored Consortium on Research with ECT (CORE) group is considering how to more effectively maintain acute benefits of ECT. They compared the potential merits of maintenance ECT with maintenance pharmacotherapy (nortriptyline plus lithium) over 6 months. Although the 2 strategies had comparable results, retention rates were <50% and about one-third relapsed in both groups.[2,3] Potential alternative strategies include a more frequent ECT maintenance schedule and/or combining maintenance ECT with medication(s).

Magnetic seizure therapy (MST) and focal electrically administered seizure therapy (FEAST) are attempts to produce similar efficacy and less cognitive disruption compared with ECT.[4,5] Work also continues on electrode placement (eg, bifrontal) and alteration of waveform characteristics (eg, ultra-brief) to maintain or enhance efficacy while minimizing adverse effects.[6,7]

Stimulating the vagus nerve

VNS was introduced for treating refractory epilepsy in 1997. In 2005, it became the first FDA-approved implantable device for managing chronic or recurrent treatment-resistant depression.

The vagus nerve is the principal parasympathetic, efferent tract regulating heart rate, intestinal motility, and gastric acid secretion. Information about pain, hunger, and satiety is conveyed by these fibers to the median raphe nucleus and locus coeruleus, brain regions with significant serotonergic and noradrenergic innervation. These neurotransmitters also are believed to play a pivotal role in major depression.

With VNS, a pacemaker-like pulse generator is surgically implanted subcutaneously in the patient's upper left chest. Wires extend from this device to the left vagus nerve (80% of whose fibers are afferent) located in the neck, to which the pulse generator sends electrical signals every few seconds ***(Table 3, page 70)***. The right vagus nerve is not used because it provides parasympathetic innervation to the heart. A clinician adjusts stimulation parameters using a computer and a noninvasive handheld device. Common adverse effects include voice alteration or hoarseness, cough, and shortness of breath, which occur during active stimulation because of the proximity of the electrodes to the laryngeal and pharyngeal branches of the vagus nerve. These effects may improve by adjusting stimulation intensity. The device permits a wide range of duty cycles, but preclinical animal studies indicate that >50% activation periods may damage the vagus

Table 2

Approved and investigational indications of neuromodulation

Approach	Description	Clinical application
CES	Uses small pulses of electrical current delivered across the head focused on the hypothalamic region with electrodes usually placed on the ear at the mastoid near the face	Depression Anxiety Sleep disorders
DBS	'Functional neurosurgical' procedure that uses electrical current to directly modulate specific areas of the CNS	Depression OCD* Parkinson's disease* Dystonia*
ECT	Short-term electrical stimulation sufficient to induce a seizure	Depression* Schizophrenia Mania
EpCS	Uses implantable stimulating paddles that do not come in contact with the brain and target the anterior frontal poles and the lateral prefrontal cortex	Depression Pain
FEAST	An alternate form of ECT that involves passage of electrical current unidirectionally from a small anode to a larger cathode electrode	Depression
MST	Intense, high-frequency magnetic pulses sufficient to induce a seizure	Depression
tDCS	Sustained, low-intensity constant current flow usually passing from anode to cathode electrodes placed on the scalp	Depression
TMS	Use of intense high- or low-frequency magnetic pulses to produce neuronal excitation or inhibition	Depression* PTSD OCD Schizophrenia Substance use disorders Tinnitus
VNS	Use of intermittent mild electrical pulses to the left vagus nerve, whose afferent fibers impact structures such as the locus ceruleus and the raphe nucleus	Epilepsy* Depression*

*FDA-approved indications

CES: cranial electrotherapy stimulation; DBS: deep brain stimulation; ECT: electroconvulsive therapy; EpCS: epidural prefrontal cortical stimulation; FEAST: focal electrically administered seizure therapy; MST: magnetic seizure therapy; OCD: obsessive-compulsive disorder; PTSD: posttraumatic stress disorder; tDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation; VNS: vagus nerve stimulation

nerve. If patients become too uncomfortable, they may deactivate the device with a magnet held over the implantation area.

Two open-label studies evaluated VNS to treat major depression. The first involved 10 weeks of stimulation in 59 subjects with chronic or recurrent, nonpsychotic, unipolar or bipolar depression who failed at least 2 adequate antidepressant trials in the current episode.[8] Stable doses of concomitant antidepressants or mood stabilizers were allowed. After 3 months, 18 (31%) patients responded within an average of 45.5 days, and nearly 15% achieved remission. Response was defined as 50% reduction in baseline Hamilton Depression Rating Scale-28 (HDRS-28) score; remission was defined as HDRS-28 score ≤10. Further, clinical response did not differ between unipolar and bipolar depression patients.

In the second trial, 74 patients with treatment-resistant depression received fixed dose antidepressants and VNS for 3 months, followed by 9 months of flexibly dosed VNS and antidepressants.[9] At 3 months, response (≥50% reduction in HDRS-28 score) and remission (HDRS-28 score <10) rates were 37% and 17%, respectively, and increased to 53% and 33% at 1 year.

A sham-controlled trial of VNS in 235 depressed patients used similar inclusion and exclusion criteria as in the open-label study by Sackeim et al.[8,10] Two weeks after device implantation, patients were ran-

Clinical Point

Magnetic seizure therapy and FEAST are attempts to provide the efficacy of ECT with less cognitive disruption

Table 3

Vagus nerve stimulation treatment parameters

Parameter	Units	Range	Median value at 12 months in pivotal study
Output current	Milliamps (mA)	0 to 3.5	1
Signal frequency	Hertz (Hz)	1.30	20
Pulse width	Microseconds (μsec)	130 to 1,000	500
Duty cycle: ON time*	Seconds	7 to 60	30
Duty cycle: OFF time*	Minutes	0.2 to 180	5

*Stimulation cycle is 24 hours per day

Source: Epilepsy patient's manual for vagus nerve stimulation with the VNS Therapy™ system. Houston, TX: Cyberonics, Inc.; 2002, 2004. Depression physician's manual. Houston, TX: Cyberonics, Inc.; 2005

Clinical Point

VNS is indicated for treating depression in patients who have not responded to ≥4 adequate trials of pharmacotherapy or ECT

domized to active treatment (stimulator turned on) or sham control (stimulator left off). At 3 months, the primary outcome measure—response rate based on HDRS-24 score—did not differ significantly between the active and control groups (15% vs 10%, respectively). There was, however, a significantly greater improvement in Inventory of Depressive Symptomatology-Self Report Scale scores with active VNS vs sham VNS.

Patients on sham treatment then were switched to active treatment and both groups were followed for 12 additional months, at which time response and remission rates nearly doubled for both groups.[11] In a post-hoc analysis, the same investigators found significant improvement with VNS compared with a naturalistic, matched control group with similar treatment-resistant depression.[12] The FDA considered this adequate to support efficacy and approved the device for chronic or recurrent treatment-resistant depression in an episode not responsive to at least 4 adequate treatment trials with pharmacotherapy or ECT. Perhaps because post-hoc analyses typically are not sufficient to gain FDA approval, most insurance companies do not reimburse for VNS treatment of depression, and VNS is not frequently used for refractory depression.

A newer option: TMS

TMS is the most recently FDA-approved therapeutic neuromodulation technique for treating depression. In October 2008, a TMS device became available for patients failing to respond to 1 adequate antidepressant trial during the current episode.

TMS delivers intense, intermittent magnetic pulses produced by an electrical charge into a ferromagnetic coil. The pulse intensity is similar to that produced by MRI. The coil usually is placed on the scalp over the left dorsolateral prefrontal cortex (DLPFC) and pulses are delivered in a rapid, repetitive train, causing neuronal depolarization in a small area of the adjacent cerebral cortex, as well as distal effects in other relevant neural circuits (***Table 4, page 72***). TMS typically is administered on an outpatient basis. A standard treatment course for depression consists of 5 treatment sessions per week for 4 to 8 weeks, depending on symptom severity and how quickly patients respond.

TMS initially was examined in several small, open-label studies that looked at various treatment parameters and stimulation sites. Several sham-controlled studies generally found TMS efficacious and further refined treatment administration. Its role in treating depression—and possibly other psychiatric disorders—has been supported by 2 recent meta-analyses.[13,14]

O'Reardon et al[15] conducted the largest double-blind trial of active vs sham TMS (N=301) for moderately treatment-resistant major depression. This study began with a 4- to 6-week, blinded, randomized phase followed by 6 weeks of open-label TMS for initial nonresponders. The third phase reintroduced TMS over 6 months as needed to augment maintenance antidepressants. This trial utilized the most aggressive treatment parameters to date (ie, 10 Hz; 75 4-second

continued on page 72

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Table 4

Treatment parameters of transcranial magnetic stimulation

Parameter	Comment
Motor threshold	Lowest intensity over primary motor cortex to produce contraction of the first dorsal interosseous or abductor pollicis brevis muscle; visual or electromyographically monitored
Stimulus coil location	Most common: Left dorsolateral prefrontal cortex (DLPFC) Less common: Right DLPFC, vertex
Stimulus pulse(s) or train	
Intensity	80% to 120% of MT
Frequency	≤1 to 20 Hz
Duration	≤1 millisecond
Interpulse interval	50 to 100 milliseconds
Stimulus train duration	3 to 6 seconds
Inter-train interval	20 to 60 seconds

Source: Janicak PG, Krasuski J, Beedle D, et al. Transcranial magnetic stimulation for neuropsychiatric disorders. Psychiatr Times. 1999;16:56-63

Clinical Point

In clinical trials, TMS was significantly better than sham treatment in achieving remission from treatment-resistant depression

trains; 26-second inter-train interval; 120% motor threshold) delivering 3,000 pulses per treatment over an average of 24 sessions. Compared with the sham procedure, patients who received active TMS showed significantly higher response rates on the Montgomery-Åsberg Depression Rating Scale (MADRS) at weeks 4 and 6. Similar results were found for the 17- and 24-item HDRS. At 6 weeks, remission rate—defined as a MADRS score <10—was significantly higher in the active treatment group (14%) compared with the sham procedure (6%). A post-hoc analysis found that the most robust benefit occurred in patients with only 1 failed adequate antidepressant trial (effect size=0.83).[16] This administration protocol was well tolerated, with no deaths or seizures and a low rate of discontinuation because of adverse events (5%).[17] The most common adverse effects were application site pain or discomfort and headaches.

Recently, the second largest (N=190) sham-controlled trial of TMS for treatment-resistant major depression was published.[18] This National Institute of Mental Health-sponsored, multiphase study included an initial 2-week, treatment-free period; 3 weeks of daily treatments over the left DLPFC using the same device and parameters as in the O'Reardon study; and an additional 3 weeks of treatment in patients who were improving. Those not responding to initial treatment were crossed over to open-label active TMS. This study advanced TMS development by:

- using a novel somatosensory system that produced similar sensations with sham and active TMS
- assessing the success of maintaining the blind
- establishing a rigorous clinical rating system
- utilizing MRI-guided adjustment of coil placement in a subset of patients.

The authors concluded that active TMS was significantly better than sham treatment in achieving remission (14% vs 5%). In addition, the raters, treaters, and patients were effectively blinded to the treatment condition. MRI-assisted coil placement found that in 33% of the sample, site placement determined by standardized assessment was over the premotor cortex rather than the prefrontal cortex, so the coil was moved 1 additional cm anteriorly in these patients. Similar to those observed by O'Reardon et al, adverse effects of active TMS were generally mild to moderate, did not differ by treatment condition, and led to a low discontinuation rate (5.5%).

Deep brain stimulation

DBS is a "functional neurosurgical" procedure that delivers electrical current directly to specific areas within the brain.[19] Its mechanism of action remains uncertain; depolar-

ization blockade, synaptic inhibition, and "neural jamming" are leading hypotheses. In contrast to conventional ablative surgeries, DBS is reversible and adjustable. Implantation involves positioning pacemaker-like battery devices subcutaneously in the left and right upper chest. Electrodes attached to wires are run subcutaneously behind the ears and, with stereotactic guidance, placed through burr holes in the skull into specific CNS areas implicated in the pathophysiology of conditions such as Parkinson's disease, refractory depression, and severe obsessive-compulsive disorder (OCD).

Antidepressant effects. The FDA recently approved DBS under its humanitarian device exemption program for intractable, severe, disabling OCD based on promising results from open and blind trials that stimulated areas such as the internal capsule and adjacent ventral striatum.[20-22] These studies reported that DBS of the caudate nucleus for OCD and subthalamic nucleus for Parkinson's disease also produced antidepressant effects. Subsequently, trials targeting the subgenual region (Brodmann's area 25), the ventral capsule/ventral striatum, and nucleus accumbens demonstrated antidepressant effects.[23-27] Pending the results of ongoing pilot trials, large, multi-center studies using different devices and target areas are being planned to clarify the role of DBS for patients with severe, disabling, refractory depression.

Adverse effects of DBS can be:

- surgical-related (eg, seizure, bleeding, infection)
- device-related (eg, lead breakage, malfunction)
- stimulation-related (eg, paresthesia, dysarthria, memory disruption, cognitive changes, psychiatric symptoms).

The most serious risk is intracranial bleeding, which occurs in 2% to 3% of patients. Clearly, the risk-benefit ratio must be carefully considered.

Cost and reimbursement

Cost of treatment and potential for third-party reimbursement are important considerations for any risk-benefit analysis. Many patients who seek neuromodulation treatments will not have insurance or other coverage entitlements.[28-30] Further, newer treatments are not routinely covered by insurance; however, individual case coverage may be allowed and some device manufacturers have programs to assist providers and patients obtain coverage.[28-30] Even ECT, which has long been a covered treatment for major depression, is still considered investigational for other disorders. Thus, it is important to pre-certify with the patient's health insurance provider before initiating treatment.

Coverage, however, is not the only consideration when weighing cost effectiveness. Economic studies can assist with clinical and ethical decisions relating to treatment choice.[31] These studies, however, need to be critically evaluated (eg, what costs were included in the analysis). Although direct costs are easier to evaluate, indirect costs—such as the patient's ability to continue to work while receiving the treatment, caretaker availability during treatment, and whether treatment is an inpatient or outpatient procedure—are more difficult to evaluate and should be discussed with the patient. Because these specialized options have the potential to further benefit patients with depression and other neuropsychiatric disorders, it is essential to balance the pressures of cost containment with the need for more effective and better tolerated treatments.[32-34]

References

1. Janicak PG, Pavuluri M, Marder S. Principles and practice of psychopharmacotherapy. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 323-359. In press.
2. Kellner CH, Knapp RG, Petrides G, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression. A multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). Arch Gen Psychiatry. 2006;63:1337-1344.
3. Rasmussen KG, Mueller M, Rummans TA, et al. Is baseline medication resistance associated with potential for relapse after successful remission of a depressive episode with ECT? Data from the Consortium for Research on Electroconvulsive Therapy (CORE). J Clin Psychiatry. 2009;70(2):232-237.
4. Spellman T, McClintock SM, Terrace H, et al. Differential effects of high-dose magnetic seizure therapy and electroconvulsive shock on cognitive function. Biol Psychiatry. 2008;63:1163-1170.
5. Spellman T, Peterchev AV, Lisanby SH. Focal electrically administered seizure therapy: a novel form of ECT illustrates the roles of current directionality, polarity, and electrode configuration in seizure induction. Neuropsychopharmacology. 2009;34(8):2002-2010.
6. Kellner CH, Knapp R, Husain MM, et al. Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. Br J Psychiatry. 2010;196:226-234.
7. Sackeim HA, Prudic J, Nobler MS, et al. Effects of pulse

Clinical Point

Deep brain stimulation is a 'functional neurosurgery' that is reversible and adjustable

Therapeutic neuromodulation

Clinical Point

Because newer neuromodulation therapies are not always covered by insurance, pre-certify with the patient's insurance provider

Related Resource

- Brunoni AR, Teng CT, Correa C, et al. Neuromodulation approaches for the treatment of major depression: challenges and recommendations from a working group meeting. Arq Neuropsiquiatr. 2010;68(3):433-451.

Drug Brand Names

Lithium • Eskalith, Lithobid

Nortriptyline • Aventyl, Pamelor

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width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. Brain Stimulat. 2008;1:71-83.

8. Sackeim HA, Rush JA, George MS, et al. Vagus nerve stimulation (VNSTM) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. Neuropsychopharmacology. 2001;25(5):713-728.
9. Schlaepfer TE, Frick C, Zobel A, et al. Vagus nerve stimulation for depression: efficacy and safety in a European study. Psychol Med. 2008;38(5):651-661.
10. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized controlled acute phase trial. Biol Psychiatry. 2005;58:347-354.
11. Rush AJ, Sackeim HA, Marangell LB, et al. Effects of 12 months of vagus nerve stimulation in treatment resistant depression: a naturalistic study. Biol Psychiatry. 2005;58(5):355-363.
12. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry. 2005;58:364-373.
13. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dordolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol Med. 2009;39:65-75.
14. Slotema CW, Blom JD, Hoek HW, et al. Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry. 2010;71(7):873-884.
15. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry. 2007;62:1208-1216.
16. Lisanby SH, Husain MM, Rosenquist PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. Neuropsychopharmacology. 2009;34(2):522-534.
17. Janicak PG, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J Clin Psychiatry. 2008;69:222-232.
18. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham controlled randomized trial. Arch Gen Psychiatry. 2010;67(5):507-516.
19. Pilitsis JG, Bakay RAE. Deep brain stimulation for psychiatric disorders. Psychopharm Rev. 2007;42(9):67-74.
20. Greenberg BD, Gabriels LA, Malone DA, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry. 2010;15(1):64-79.
21. Mallet L, Plolsan M, Jaafari N, et al. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med. 2008;359:2121-2134.
22. Goodman WK, Foote KD, Greenberg BD, et al. Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. Biol Psychiatry. 2010;67:535-542.
23. Mayberg HS, Lozano AM, McNeely HE, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45(5):651-660.
24. Lozano AM, Mayberg HS, Giacobbe P, et al. Subcallosal cingulated gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry. 2008;64:461-467.
25. McNeely HE, Mayberg HS, Lozano AM, et al. Neuropsychological impact of Cg25 deep brain stimulation for treatment-resistant depression: preliminary results over 12 months. J Nerv Ment Dis. 2008;196(5):405-410.
26. Malone DA, Dougherty DD, Rezai AR, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. Biol Psychiatry. 2009;65(4):267-275.
27. Schlaepfer TE, Cohen MX, Frick C, et al. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology. 2008;33(2):368-377.
28. Health insurance coverage. NeuroStar TMS Therapy® Web site. Available at: http://www.neurostartms.com/TMSHealthInsurance/Health-Insurance-Coverage.aspx. Accessed June 2, 2010.
29. VNS insurance information. Vagus nerve stimulation therapy for treatment-resistant depression Web site. Available at: http://www.vnstherapy.com/depression/insuranceinformation/coverage.asp. Accessed June 2, 2010.
30. Insurance coverage—DBS therapy for OCD. Available at: http://www.medtronic.com/your-health/obsessive-compulsive-disorder-ocd/getting-therapy/insurance-coverage/index.htm. Accessed June 2, 2010.
31. Simpson KN, Welch MJ, Kozel FA, et al. Cost-effectiveness of transcranial magnetic stimulation in the treatment of major depression: a health economics analysis. Adv Ther. 2009;26(3):346-368.
32. Rado J, Dowd SM, Janicak PG. The emerging role of transcranial magnetic stimulation (TMS) for treatment of psychiatric disorders. Dir Psychiatry. 2008;28(25):215-331.
33. Dougherty DD, Rauch SL. Somatic therapies for treatment-resistant depression: new neurotherapeutic interventions. Psychiatr Clin N Am. 2007;30:31-37.
34. Olfson M, Marcus S, Sackeim HA, et al. Use of ECT for the inpatient treatment of recurrent major depression. Am J Psychiatry. 1998;155:22-29.

Bottom Line

Therapeutic neuromodulation techniques such as electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, and deep brain stimulation may fill an important gap for patients with major depression and other psychiatric disorders who do not benefit from or are unable to tolerate existing treatments. Risk-benefit analysis should include cost of treatment and potential for third-party reimbursement.