35 - 30 Brain Stimulation Methods

01 - 30.1 Electroconvulsive Therapy

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Brain Stimulation Methods 30.1 Electroconvulsive Therapy Convulsive therapies for major psychiatric illnesses predate the modern therapeutic era, with the use of camphor reported as early as the 16th century and the existence of several accounts of camphor convulsive therapies from the late 1700s to the mid-1800s. Unaware of the history of camphor convulsive therapy, the Hungarian neuropsychiatrist Ladislas von Meduna made the observation that the brains of epileptics had greater than normal numbers of glial cells, whereas those of schizophrenics had fewer, and he hypothesized that there might be a biological antagonism between convulsions and schizophrenia. Following animal experimentation, camphor was (again) selected as the appropriate agent to use for the therapeutic induction of seizures. In 1934, the first catatonic psychotic patient was successfully treated using intramuscular injections of camphor in oil to produce therapeutic seizures. Lucio Bini and Ugo Cerletti were interested in the use of electricity to induce seizures, and, after a series of animal experiments and observation of the use of electricity commercially, they were able to safely apply current across the heads of animals for this purpose. In 1938, the first electroconvulsive treatment (ECT) course was administered to a delusional and incoherent patient, who improved with one treatment and remitted after 11 treatments. Electrical induction of convulsive therapy could be made more reliable and shorter acting than chemically induced convulsive therapies, and, by the early 1940s, it had replaced them. In 1940, the first use of ECT occurred in the United States. In an effort to reduce the retrograde memory problems that persisted for some patients after the initial recovery period post-ECT, explorations of nondominant electrode placement and alternative, more efficient waveforms were undertaken in subsequent decades. The practice of ECT also benefited from the introduction of controlled trials methodology, which demonstrated its safety and efficacy, and from refinements made in diagnostic systems and the process of informed consent. In the 1980s and 1990s efforts to ensure uniformly high standards of practice were under way with the publication of recommendations for treatment delivery, education, and training by professional organizations in the United States, England, Scandinavia, and Canada, among others. With the widespread use of pharmacological agents as first-line treatments for major psychiatric disorders, ECT is now more commonly used for patients with resistance to those treatments, except in the case of life-threatening illness due to inanition, severe suicidal symptoms, or catatonia. Although the failure of subconvulsive stimulation to

induce the remission of psychiatric illness and the effectiveness of chemical convulsive therapy suggested that the seizure was necessary and sufficient for therapeutic benefit with ECT, it is now known that there is a dose–response relationship with right unilateral ECT and that bilateral ECT is likely to be ineffective with ultrabrief pulse widths. Work continues to explore the underlying mechanisms and biological characteristics of effective ECT treatments, with interest in having the treatment focus on appropriate neural networks with a more efficient stimulus as a method of reducing cognitive side effects. With the growing understanding that depression is a chronic disease for many patients, more emphasis has been placed on continuation and maintenance treatments following an acute course of ECT. Utilization of ECT has diminished since the middle of the 20th century; but because ECT remains the most effective treatment for major depression and a rapidly effective treatment for lifethreatening psychiatric conditions, ECT, unlike its contemporaneous somatic therapies, such as insulin coma, remains in the active treatment portfolio of modern therapeutics. Its use has shifted from public to private institutions, and it is estimated that approximately 100,000 patients have received ECT annually over the past few decades in the United States (Table 30.1-1). Table 30.1-1 Milestones in the History of Convulsive Therapy

The Nobel Laureate Paul Greengard has suggested that the term electrocortical therapy might be used to replace the current term electroconvulsive therapy. Greengard has acknowledged that if the mechanism of action of ECT, as yet unknown, turns out to be subcortical, then the term might have limited use. Until that time, however, the authors of this text think Greengard's suggestion deserves consideration. It would help diminish the fear associated with the word convulsion and help destigmatize a very effective treatment method. ELECTROPHYSIOLOGY IN ELECTROCONVULSIVE THERAPY Neurons maintain a resting potential across the plasma membrane and may propagate an action potential, which is a transient reversal of the membrane potential. Normal brain activity is desynchronized; that is, neurons fire action potentials asynchronously. A convulsion, or seizure, occurs when a large percentage of neurons fire in unison. Such rhythmical changes in the extracellular potential entrain neighboring neurons, propagate the seizure activity across the cortex and into deeper structures, and eventually engulf the entire brain in high-voltage synchronous neuronal firing. Cellular mechanisms work to contain the seizure activity and to maintain cellular homeostasis,

and the seizure eventually ends. In epilepsy, any of possibly several hundred genetic defects can alter the balance in favor of unrestrained activity. In ECT, seizures are triggered in normal neurons by application through the scalp of pulses of current, under conditions that are carefully controlled to create a seizure of a particular duration over the entire brain. The qualities of the electricity used in ECT can be described by Ohm's law: $E = IR$, or $I = E/R$, in which E is voltage, I is current, and R is resistance. The intensity or dose of electricity in ECT is measured in terms of charge (milliampere-seconds or millicoulombs) or energy (watt-seconds or joules). Resistance is synonymous with impedance and, in the case of ECT, both the electrode's contact with the body and the nature of the bodily tissues are the major determinants of resistance. The skull has a high impedance; the brain has a low impedance. Because scalp tissues are much better conductors of electricity than bone, only about 20 percent of the applied charge actually enters the skull to excite neurons. The ECT machines that are now widely used can be adjusted to administer the electricity under conditions of constant current, voltage, or energy. MECHANISM OF ACTION The induction of a bilateral generalized seizure is necessary for both the beneficial and the adverse effects of ECT.

Although a seizure superficially seems as though it is an allor-none event, some data indicate that not all generalized seizures involve all the neurons in deep brain structures (e.g., the basal ganglia and the thalamus); recruitment of these deep neurons may be necessary for full therapeutic benefit. After the generalized seizure, the electroencephalogram (EEG) shows about 60 to 90 seconds of postictal suppression. This period is followed by the appearance of high-voltage delta and theta waves and a return of the EEG to preseizure appearance in about 30 minutes. During the course of a series of ECT treatments, the interictal EEG is generally slower and of greater amplitude than usual, but the EEG returns to pretreatment appearance 1 month to 1 year after the end of the course of treatment. One research approach to the mechanism of action for ECT has been to study the neurophysiological effects of treatment. Positron emission tomography (PET) studies of both cerebral blood flow and glucose use have shown that, during seizures, cerebral blood flow, use of glucose and oxygen, and permeability of the blood–brain barrier increase. After the seizure, blood flow and glucose metabolism are decreased, perhaps most markedly in the frontal lobes. Some research indicates that the degree of decrease in cerebral metabolism is correlated with therapeutic response. Seizure foci in idiopathic epilepsy are hypometabolic during interictal periods; ECT itself acts as an anticonvulsant because its administration is associated with an increase in the seizure threshold as treatment progresses. Recent data suggest that for 1 to 2 months following a session of ECT, EEGs record a large increase in slow-wave activity located over the prefrontal cortex in patients who responded well to the ECT. Highintensity, bilateral stimulation produced the best response; low-intensity, unilateral stimulation, the weakest. These data are of unclear significance, however, because the

specific EEG correlate disappeared 2 months after ECT, whereas the clinical benefit persisted. ECT affects the cellular mechanisms of memory and mood regulation and raises the seizure threshold. The latter effect may be blocked by the opiate antagonist naloxone (Narcan). Neurochemical research into the mechanisms of action of ECT has focused on changes in neurotransmitter receptors and, recently, changes in second-messenger systems. Virtually every neurotransmitter system is affected by ECT, but a series of ECT sessions results in downregulation of postsynaptic β-adrenergic receptors, the same receptor change observed with virtually all antidepressant treatments. The effects of ECT on serotonergic neurons remain controversial. Various research studies have reported an increase in postsynaptic serotonin receptors, no change in serotonin receptors, and a change in the presynaptic regulation of serotonin release. ECT has also been reported to effect changes in the muscarinic, cholinergic, and dopaminergic neuronal systems. In second-messenger systems, ECT has been reported to affect the coupling of G-proteins to receptors, the activity of adenylyl cyclase and phospholipase C, and the regulation of calcium entry into neurons. Recently, there has been increased interest in structural changes in the brain associated with psychiatric syndromes and response to treatment. This has been particularly so for microscopic changes associated with electroconvulsive stimulation, as well as antidepressant and other medications. In animals, mostly rodents, synaptic plasticity in hippocampus, including mossy fiber sprouting, alterations in cytoskeletal structure, increased connectivity in perforant pathways, promotion of neurogenesis, and suppression of apoptosis have been observed. Many of these structural events are also observed, although to a lesser extent, with antidepressant medications such as fluoxetine (Prozac). These reports have also galvanized controversy over various aspects of the technical validity of the observations. It is unknown whether such changes occur clinically and, if they do, what significance to efficacy and cognitive side effects might be discovered.
INDICATIONS Major Depressive Disorder The most common indication for ECT is major depressive

disorder, for which ECT is the fastest and most effective available therapy. ECT should be considered for use in patients who have failed medication trials, have not tolerated medications, have severe or psychotic symptoms, are acutely suicidal or homicidal, or have marked symptoms of agitation or stupor. Controlled studies have shown that up to 70 percent of patients who fail to respond to antidepressant medications may respond positively to ECT. Table 30.1-2 presents the indications for the use of ECT. Table 30.1-2 Indications for the Use of Electroconvulsive Therapy

ECT is effective for depression in both major depressive disorder and bipolar I disorder. Delusional or psychotic depression has long been considered particularly responsive to ECT; but recent studies have indicated that major depressive episodes with psychotic features are no more responsive to ECT than nonpsychotic depressive disorders. Nevertheless, because major depressive episodes with psychotic features respond poorly to antidepressant pharmacotherapy alone, ECT should be considered much more often as the first-line treatment for patients with the disorder. Major depressive disorder with melancholic features (e.g., markedly severe symptoms, psychomotor retardation, early morning awakening, diurnal variation, decreased appetite and weight, and agitation) is considered likely to respond to ECT. ECT is particularly indicated for persons who are severely depressed, who have psychotic symptoms, who show suicidal intent, or who refuse to eat. Depressed patients less likely to respond to ECT include those with somatization disorder. Elderly patients tend to respond to ECT more slowly than do young patients. ECT is a treatment for major depressive episode and does not provide prophylaxis unless it is administered on a longterm maintenance basis. Manic Episodes ECT is at least equal to lithium (Eskalith) in the treatment of acute manic episodes. The pharmacological treatment of manic episodes, however, is so effective in the short term and for prophylaxis that the use of ECT to treat manic episodes is generally limited to situations with specific contraindications to all available pharmacological approaches. The relative rapidity of the ECT response indicates its usefulness for patients whose manic behavior has produced dangerous levels of exhaustion. ECT should not be used for

a patient who is receiving lithium, because lithium can lower the seizure threshold and cause a prolonged seizure. Schizophrenia Although an effective treatment for the symptoms of acute schizophrenia, ECT is not for those of chronic schizophrenia. Patients with schizophrenia who have marked positive symptoms, catatonia, or affective symptoms are considered most likely to respond to ECT. In such patients, the efficacy of ECT is about equal to that of antipsychotics, but improvement may occur faster. Other Indications Small studies have found ECT effective in the treatment of catatonia, a symptom associated with mood disorders, schizophrenia, and medical and neurological disorders. ECT is also reportedly useful to treat episodic psychoses, atypical psychoses, obsessivecompulsive disorder, and delirium and such medical conditions as neuroleptic malignant syndrome, hypopituitarism, intractable seizure disorders, and the on–off phenomenon of Parkinson’s disease. ECT may also be the treatment of choice for depressed suicidal pregnant women who require treatment and cannot take medication; for geriatric and medically ill patients who cannot take antidepressant drugs safely; and perhaps even for severely depressed and suicidal children and adolescents who may be less likely to respond to antidepressant drugs than are adults. ECT is not effective in somatization disorder (unless accompanied by depression), personality disorders, and anxiety disorders. CLINICAL GUIDELINES Patients and their families are often apprehensive about ECT; therefore, clinicians must explain both beneficial and adverse effects and alternative treatment approaches. The informed-consent process should be documented in the patients’ medical records and should include a discussion of the disorder, its

natural course, and the option of receiving no treatment. Printed literature and videotapes about ECT may be useful in attempting to obtain a truly informed consent. The use of involuntary ECT is rare today and should be reserved for patients who urgently need treatment and who have a legally appointed guardian who has agreed to its use. Clinicians must know local, state, and federal laws about the use of ECT. Pretreatment Evaluation Pretreatment evaluation should include standard physical, neurological, and preanesthesia examinations and a complete medical history. Laboratory evaluations should include blood and urine chemistries, a chest X-ray, and an electrocardiogram (ECG). A dental examination to assess the state of patients' dentition is advisable for elderly patients and patients who have had inadequate dental care. An X-ray of the

spine is needed if other evidence of a spinal disorder is seen. Computed tomography (CT) or magnetic resonance imaging (MRI) should be performed if a clinician suspects the presence of a seizure disorder or a space-occupying lesion. Practitioners of ECT no longer consider even a space-occupying lesion to be an absolute contraindication to ECT, but with such patients the procedure should be performed only by experts. Concomitant Medications. Patients' ongoing medications should be assessed for possible interactions with the induction of a seizure, for effects (both positive and negative) on the seizure threshold, and for drug interactions with the medications used during ECT. The use of tricyclic and tetracyclic drugs, monoamine oxidase inhibitors, and antipsychotics is generally considered acceptable. Benzodiazepines used for anxiety should be withdrawn because of their anticonvulsant activity; lithium should be withdrawn because it can result in increased postictal delirium and can prolong seizure activity; clozapine (Clozaril) and bupropion (Wellbutrin) should be withdrawn because they are associated with the development of late-appearing seizures. Lidocaine (Xylocaine) should not be administered during ECT because it markedly increases the seizure threshold; theophylline (Theo-Dur) is contraindicated because it increases the duration of seizures. Reserpine (Serpasil) is also contraindicated because it is associated with further compromise of the respiratory and cardiovascular systems during ECT. Premedications, Anesthetics, and Muscle Relaxants Patients should not be given anything orally for 6 hours before treatment. Just before the procedure, the patient's mouth should be checked for dentures and other foreign objects, and an intravenous (IV) line should be established. A bite block is inserted in the mouth just before the treatment is administered to protect the patient's teeth and tongue during the seizure. Except for the brief interval of electrical stimulation, 100 percent oxygen is administered at a rate of 5 L a minute during the procedure until spontaneous respiration returns. Emergency equipment for establishing an airway should be immediately available in case it is needed. Muscarinic Anticholinergic Drugs. Muscarinic anticholinergic drugs are administered before ECT to minimize oral and respiratory secretions and to block bradycardias and asystoles, unless the resting heart rate is above 90 beats a minute. Some ECT centers have stopped the routine use of anticholinergics as premedications, although their use is still indicated for patients taking β-adrenergic receptor antagonists and those with ventricular ectopic beats. The most commonly used drug is atropine, which can be administered 0.3 to 0.6 mg intramuscularly (IM) or subcutaneously (SC) 30 to 60 minutes before the anesthetic or 0.4 to 1.0 mg IV 2 or 3 minutes before the anesthetic. An option is to use glycopyrrolate (Robinul) (0.2 to 0.4 mg IM, IV, or SC), which is less likely to cross the blood–brain barrier and less likely to cause cognitive dysfunction and nausea, although it is thought to have less cardiovascular protective activity than does atropine.

Anesthesia. Administration of ECT requires general anesthesia and oxygenation. The depth of anesthesia should be as light as possible, not only to minimize adverse effects but also to avoid elevating the seizure threshold associated with many anesthetics. Methohexital (Brevital) (0.75 to 1.0 mg/kg IV bolus) is the most commonly used anesthetic because of its shorter duration of action and lower association with postictal arrhythmias than thiopental (Pentothal) (usual dose 2 to 3 mg/kg IV), although this difference in cardiac effects is not universally accepted. Four other anesthetic alternatives are etomidate (Amidate), ketamine (Ketalar), alfentanil (Alfenta), and propofol (Diprivan). Etomidate (0.15 to 0.3 mg/kg IV) is sometimes used because it does not increase the seizure threshold; this effect is particularly useful for elderly patients because the seizure threshold increases with age. Ketamine (6 to 10 mg/kg IM) is sometimes used because it does not increase the seizure threshold, although its use is limited by the frequent association of psychotic symptoms with emergence from anesthesia with this drug. Alfentanil (2 to 9 mg/kg IV) is sometimes coadministered with barbiturates to allow the use of low doses of the barbiturate anesthetics and, thus, reduce the seizure threshold less than usual, although its use can be associated with an increased incidence of nausea. Propofol (0.5 to 3.5 mg/kg IV) is less useful because of its strong anticonvulsant properties. Muscle Relaxants. After the onset of the anesthetic effect, usually within a minute, a muscle relaxant is administered to minimize the risk of bone fractures and other injuries resulting from motor activity during the seizure. The goal is to produce profound relaxation of the muscles, not necessarily to paralyze them, unless the patient has a history of osteoporosis or spinal injury or has a pacemaker and, therefore, is at risk for injury related to motor activity during the seizure. Succinylcholine (Anectine), an ultrafast-acting depolarizing blocking agent, has gained virtually universal acceptance for the purpose. Succinylcholine is usually administered in a dose of 0.5 to 1 mg/kg as an IV bolus or drip. Because succinylcholine is a depolarizing agent, its action is marked by the presence of muscle fasciculations, which move in a rostrocaudal progression. The disappearance of these movements in the feet or the absence of muscle contractions after peripheral nerve stimulation indicates maximal muscle relaxation. In some patients, tubocurarine (3 mg IV) is administered to prevent myoclonus and increases in potassium and muscle enzymes; these reactions can be a problem in patients with musculoskeletal or cardiac disease. To monitor the duration of the convulsion, a blood pressure cuff may be inflated at the ankle to a pressure in excess of the systolic pressure before infusion of the muscle relaxant to allow observation of relatively innocuous seizure activity in the foot muscles. If a patient has a known history of pseudocholinesterase deficiency, atracurium (Tracrium) (0.5 to 1 mg/kg IV) or curare can be used instead of succinylcholine. In such a patient, the metabolism of succinylcholine is disrupted, and prolonged apnea may necessitate emergency airway management. In general, however, because of the short half-life of succinylcholine, the duration of apnea after its administration is generally shorter than the delay in regaining consciousness caused by the anesthetic and the

postictal state. Electrode Placement. Historically, most practitioners have used bifrontotemporal electrode placement because of its reliability in producing efficacy and its ease of use. This electrode placement is also associated with more short-term and long-term adverse cognitive effects and is more likely to produce delirium, which may require interrupting a course of ECT and perhaps even terminating it before optimal therapeutic effects have been obtained. Hence, when bifrontotemporal ECT is used, attention should be paid to restricting the dose to a moderately suprathreshold level to attenuate adverse cognitive effects as much as possible. It should be emphasized that the combination of ultrabrief pulse and bifrontotemporal electrode placement has

not been demonstrated to be effective. Treatment with bilateral electrode placements, particularly a bifrontal configuration, is more likely to manifest EEG seizure without motor seizure, and EEG monitoring can be particularly useful in detecting its occurrence. Newer electrode placements include bifrontal configuration and asymmetrical placements. There are limitations to these strategies, imposed by the fact that the high impedance of the skull and scalp causes spreading of the electrical stimulus and restricts possibilities for localization of the stimulus. Bifrontal electrode placement, with positioning far enough laterally to minimize interference with impedance relations, has been investigated, and there have been several demonstrations that bifrontal electrode placements are equally effective to bifrontotemporal and adequately dosed right unilateral electrode configurations. Evidence of advantages in sparing of cognitive effects is quite preliminary, and adequately powered investigations with more extensive and sensitive cognitive batteries are needed. Seizure threshold is likely to be relatively higher with bifrontal ECT. The relatively better cognitive side effect profile of right unilateral ECT should encourage wider use now that the efficacy of this electrode placement can be ensured with adequate dosing strategies. In contrast to bilateral ECT, a dose closer to 500 percent above the seizure threshold is more likely to ensure efficacy. ECT devices in the United States are restricted to an output in the range of 504 to 576 mCi. Approximately 90 percent of patients have seizure thresholds that can accommodate optimal dosing with brief-pulse right unilateral ECT, and the combination of right unilateral electrode placement with ultrabrief pulse width extends the range of US devices so that most patients can be treated within these constraints. Individuals with an exceptionally high seizure threshold may require bilateral electrode placements to remain within the device restrictions. Maximizing interelectrode distance by using the d’Elia placement may also be optimal. Many other right unilateral placements have been described, but there is little work to support their use (Fig. 30.1-1).

FIGURE 30.1-1 Electrode placements. Position 1 represents the frontotemporal position, used for both electrodes, one on each side of the head, in conducting bilateral electroconvulsive therapy (ECT). For right unilateral ECT, one electrode is in the right frontotemporal position, and the other is just to the right of the vertex at position 2. (Courtesy of American Psychiatric Association, with permission.) There has been some concern that left-handed patients may require different electrode placement than right-handed patients, especially if unilateral placement is desired. Even when handedness is lateralized to the left, the anatomic localization of language function in 70 percent of left-handed individuals is the same as in those who are righthanded. Furthermore, there is evidence for independent lateralization of affect, with the right hemisphere involved in sustaining depressed mood regardless of handedness. Because of limited indications that affective function and efficacy of ECT are associated with handedness, handedness is not generally used to guide the choice of electrode placement. Electrical Stimulus The electrical stimulus must be sufficiently strong to reach the seizure threshold (the level of intensity needed to produce a seizure). The electrical stimulus is given in cycles, and each cycle contains a positive and a negative wave. Old machines use a sine wave; however, this type of machine is now considered obsolete because of the inefficiency of that wave shape. When a sine wave is delivered, the electrical stimulus in the sine wave before the seizure threshold is reached and after the seizure is activated is unnecessary and excessive. Modern ECT machines use a brief pulse waveform that administers the

electrical stimulus usually in 1 to 2 milliseconds at a rate of 30 to 100 pulses a second. Machines that use an ultrabrief pulse (0.5 milliseconds) are not as effective as brief pulse machines.

Establishing a patient’s seizure threshold is not straightforward. A 40 times variability in seizure thresholds occurs among patients. In addition, during the course of ECT treatment, a patient’s seizure threshold may increase 25 to 200 percent. The seizure threshold is also higher in men than in women and higher in older than in younger adults. A common technique is to initiate treatment at an electrical stimulus that is thought to be below the seizure threshold for a particular patient and then to increase this intensity by 100 percent for unilateral placement and by 50 percent for bilateral placement until the seizure threshold is reached. A debate in the literature concerns whether a minimally suprathreshold dose, a moderately suprathreshold dose (one and a half times the threshold), or a high suprathreshold dose (three times the threshold) is preferable. The debate about stimulus intensity resembles the debate about electrode placement. Essentially, the data support the conclusion that doses of three times the threshold are the most rapidly effective and that minimal suprathreshold doses are associated with the fewest and least severe cognitive adverse effects. Induced Seizures A brief muscular contraction, usually strongest in a patient’s jaw and facial muscles, is seen concurrently with the flow of stimulus current, regardless of whether a seizure occurs. The first behavioral sign of the seizure is often a plantar extension, which lasts 10 to 20 seconds and marks the tonic phase. This phase is followed by rhythmic (i.e., clonic) contractions that decrease in frequency and finally disappear. The tonic phase is marked by high-frequency, sharp EEG activity on which a higher frequency muscle artifact may be superimposed. During the clonic phase, bursts of polyspike activity occur simultaneously with the muscular contractions but usually persist for at least a few seconds after the clonic movements stop. Monitoring Seizures. A physician must have an objective measure that a bilateral generalized seizure has occurred after the stimulation. The physician should be able to observe either some evidence of tonic-clonic movements or electrophysiological evidence of seizure activity from the EEG or electromyogram (EMG). Seizures with unilateral ECT are asymmetrical, with higher ictal EEG amplitudes over the stimulated hemisphere than over the nonstimulated hemisphere. Occasionally, unilateral seizures are induced; for this reason, at least a single pair of EEG electrodes should be placed over the contralateral hemisphere when using unilateral ECT. For a seizure to be effective in the course of ECT, it should last at least 25 seconds. Failure to Induce Seizures. If a particular stimulus fails to cause a seizure of sufficient duration, up to four attempts at seizure induction can be tried during a course of treatment. The onset of seizure activity is sometimes delayed as long as 20 to 40

seconds after the stimulus administration. If a stimulus fails to result in a seizure, the contact between the electrodes and the skin should be checked, and the intensity of the stimulus should be increased by 25 to 100 percent. The clinician can also change the anesthetic agent to minimize increases in the seizure threshold caused by the anesthetic. Additional procedures to lower the seizure threshold include hyperventilation and administration of 500 to 2,000 mg IV of caffeine sodium benzoate 5 to 10 minutes before the stimulus. Prolonged and Tardive Seizures. Prolonged seizures (seizures lasting more than 180 seconds) and status epilepticus can be terminated either with additional doses of the barbiturate anesthetic agent or with IV diazepam (Valium) (5 to 10 mg). Management of such complications should be accompanied by intubation, because the oral airway is insufficient to maintain adequate ventilation over an extended apneic period. Tardive seizures—that is, additional seizures appearing some time after the ECT treatment—may develop in patients with preexisting seizure disorders. Rarely, ECT precipitates the development of an epileptic disorder in patients. Such situations should be managed clinically as if they were pure epileptic disorders. Number and Spacing of Treatments ECT treatments are usually administered

two to three times a week; twice-weekly treatments are associated with less memory impairment than thrice-weekly treatments. In general, the course of treatment of major depressive disorder can take 6 to 12 treatments (although up to 20 sessions are possible); the treatment of manic episodes can take 8 to 20 treatments; the treatment of schizophrenia can take more than 15 treatments; and the treatment of catatonia and delirium can take as few as 1 to 4 treatments. Treatment should continue until the patient achieves what is considered the maximal therapeutic response. Further treatment does not yield any therapeutic benefit, but increases the severity and duration of the adverse effects. The point of maximal improvement is usually thought to occur when a patient fails to continue to improve after two consecutive treatments. If a patient is not improving after 6 to 10 sessions, bilateral placement and high-density treatment (three times the seizure threshold) should be attempted before ECT is abandoned. Multiple-Monitored Electroconvulsive Therapy. Multiple-monitored ECT (MMECT) involves giving multiple ECT stimuli during a single session, most commonly two bilateral stimuli within 2 minutes. This approach may be warranted in severely ill patients and in those at especially high risk from the anesthetic procedures. MMECT is associated with the most frequent occurrences of serious cognitive adverse effects. Maintenance Treatment A short-term course of ECT induces a remission in symptoms but does not, of itself, prevent a relapse. Post-ECT maintenance treatment should always be considered.

Maintenance therapy is generally pharmacological, but maintenance ECT treatments (weekly, biweekly, or monthly) have been reported to be effective relapse prevention treatments, although data from large studies are lacking. Indications for maintenance ECT treatments can include rapid relapse after initial ECT, severe symptoms, psychotic symptoms, and the inability to tolerate medications. If ECT was used because a patient was unresponsive to a specific medication, then, following ECT, the patient should be given a trial of a different medication. Failure of Electroconvulsive Therapy Trial Patients who fail to improve after a trial of ECT should again be treated with the pharmacological agents that failed in the past. Although the data are primarily anecdotal, many reports indicate that patients who had previously failed to improve while taking an antidepressant drug do improve while taking the same drug after receiving a course of ECT treatments, even if the ECT seemed to be a therapeutic failure. Nonetheless, with the increased availability of drugs that act at diverse receptor sites, it is less often necessary to return to a drug that has failed than it was formerly. ADVERSE EFFECTS Contraindications ECT has no absolute contraindications, only situations in which a patient is at increased risk and has an increased need for close monitoring. Pregnancy is not a contraindication for ECT, and fetal monitoring is generally considered unnecessary unless the pregnancy is high risk or complicated. Patients with space-occupying central nervous system lesions are at increased risk for edema and brain herniation after ECT. If the lesion is small, however, pretreatment with dexamethasone (Decadron) is given, and hypertension is controlled during the seizure and the risk of serious complications minimized for these patients. Patients who have increased intracerebral pressure or are at risk for cerebral bleeding (e.g., those with cerebrovascular diseases and aneurysms) are at risk during ECT because of the increased cerebral blood flow during the seizure. This risk can be lessened, although not eliminated, by control of the patient’s blood pressure during the treatment. Patients with recent myocardial infarctions are another high-risk group, although the risk is greatly diminished 2 weeks after the myocardial infarction and is even further reduced 3 months after the infarction. Patients with hypertension should be stabilized on their antihypertensive medications before ECT is administered. Propranolol (Inderal) and sublingual nitroglycerin can also be used to protect such

patients during treatment. Mortality The mortality rate with ECT is about 0.002 percent per treatment and 0.01 percent for each patient. These numbers compare favorably with the risks associated with general

anesthesia and childbirth. ECT death is usually from cardiovascular complications and is most likely to occur in patients whose cardiac status is already compromised. Central Nervous System Effects Common adverse effects associated with ECT are headache, confusion, and delirium shortly after the seizure while the patient is coming out of anesthesia. Marked confusion may occur in up to 10 percent of patients within 30 minutes of the seizure and can be treated with barbiturates and benzodiazepines. Delirium is usually most pronounced after the first few treatments and in patients who receive bilateral ECT or who have coexisting neurological disorders. The delirium characteristically clears within days or a few weeks at the longest. Memory. The greatest concern about ECT is the association between ECT and memory loss. About 75 percent of all patients given ECT say that the memory impairment is the worst adverse effect. Although memory impairment during a course of treatment is almost the rule, follow-up data indicate that almost all patients are back to their cognitive baselines after 6 months. Some patients, however, complain of persistent memory difficulties. For example, a patient may not remember the events leading up to the hospitalization and ECT, and such autobiographical memories may never be recalled. The degree of cognitive impairment during treatment and the time it takes to return to baseline are related, in part, to the amount of electrical stimulation used during treatment. Memory impairment is most often reported by patients who have experienced little improvement with ECT. Despite the memory impairment, which usually resolves, no evidence indicates brain damage caused by ECT. This subject has been the focus of several brain-imaging studies, using a variety of modalities; virtually all concluded that permanent brain damage is not an adverse effect of ECT. Neurologists and epileptologists generally agree that seizures that last less than 30 minutes do not cause permanent neuronal damage. Other Adverse Effects of Electroconvulsive Therapy Fractures often accompanied treatments in the early days of ECT. With routine use of muscle relaxants, fractures of long bones or vertebrae should not occur. Some patients, however, may break teeth or experience back pain because of contractions during the procedure. Muscle soreness can occur in some individuals, but it often results from the effects of muscle depolarization by succinylcholine and is most likely to be particularly troublesome after the first session in a series. This soreness can be treated with mild analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs). A significant minority of patients experience nausea, vomiting, and headaches following an ECT treatment. Nausea and vomiting can be prevented by treatment with antiemetics at the time of ECT (e.g., metoclopramide [Reglan], 10 mg IV, or prochlorperazine [Compazine], 10 mg IV; ondansetron [Zofran] is an acceptable alternative if adverse effects preclude use of dopamine receptor antagonists).

ECT can be associated with headaches, although this effect is usually readily manageable. Headaches often respond to NSAIDs given in the ECT recovery period. In patients with severe headaches, pretreatment with ketorolac (Toradol) (30 to 60 mg IV), an NSAID approved for brief parenteral use, can be helpful. Acetaminophen (Tylenol), tramadol (Ultram), propoxyphene (Darvon), and more potent analgesia provided by opioids can be used individually or in various combinations (e.g., pretreatment with ketorolac and postseizure management with acetaminophen-propoxyphene) to manage more intractable headache. ECT can induce migrainous headache and related symptoms; sumatriptan (Imitrex) (6 mg SC or 25 mg orally) may be a useful

addition to the agents described above. Ergot compounds can exacerbate cardiovascular changes observed during ECT and probably should not be a component of ECT pretreatment. INVESTIGATIONS IN ELECTRICAL BRAIN STIMULATION TREATMENT There is interest in continued refinements of ECT techniques. Common themes in these approaches are focusing the treatment spatially to optimize dosing in brain areas associated with putative neural networks involved in depression and other psychopathologies that are indications for ECT, diminishing dosing in areas associated with adverse cognitive effects, and improving the efficiency of a noninvasive electrical stimulus in direction and amplitude, even to a subconvulsive level. This research is parallel to investigations in magnetic stimulation (e.g., repetitive transcranial magnetic stimulation) and to the renaissance of invasive electrical techniques (e.g., vagal nerve stimulation and deep brain stimulation). REFERENCES Byrne P, Cassidy B, Higgins P. Knowledge and attitudes towards electroconvulsive therapy among health care professionals and students. J ECT. 2006;22(2):133. Cristancho MA, Alici Y, Augoustides JG, O'Reardon JP. Uncommon but serious complications associated with electroconvulsive therapy: Recognition and management for the clinician. Curr Psychiatry Rep. 2008;10:474. Hooten WM, Rasmussen KG Jr. Effects of general anesthetic agents in adults receiving electroconvulsive therapy: A systematic review. J ECT. 2008;24:208. Ingram A, Saling MM, Schweitzer I. Cognitive side effects of brief pulse electroconvulsive therapy: A review. J ECT. 2008;24:3. Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM. 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. Lapidus KA, Shin JS, Pasculli RM, Briggs MC, Popeo DM, Kellner CH. Low-dose right unilateral electroconvulsive therapy (ECT): Effectiveness of the first treatment. J ECT. 2013;29(2):83–85. Munk-Olsen T, Laursen TM, Videbech P, Rosenberg R, Mortensen PB. Electroconvulsive therapy: Predictors and trends in utilization from 1976 to 2000. J ECT. 2006;22(2):127. Painuly N, Chakrabarti S. Combined use of electroconvulsive therapy and antipsychotics in schizophrenia: The Indian evidence. A review and a meta-analysis. J ECT. 2006;22:59. Prudic J. Electroconvulsive therapy. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of

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Psychiatry. 9th ed. Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2009:3285. Prudic J. Strategies to minimize cognitive side effects with ECT: Aspects of ECT technique. J ECT. 2008;24:46. Rapinesi C, Serata D, Casale AD, Carbonetti P, Fensore C, Scatena P, Caccia F, Di Pietro S, Angeletti G, Tatarelli R, Kotzalidis GD, Giradi P. Effectiveness of electroconvulsive therapy in a patient with a treatment-resistant major depressive episode and comorbid body dysmorphic disorder. J ECT. 2013;29(2):145–146. Sackeim HA, Prudic J, Nobler MS, Fitzsimons L, Lisanby SH. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. Brain Stimul. 2008;1:71. Schmidt EZ, Reininghaus B, Enzinger C, Ebner C, Hofmann P. Changes in brain metabolism after ECT-positron emission tomography in the assessment of changes in glucose metabolism subsequent to electroconvulsive therapy—lessons, limitations and future applications. J Affect Disord. 2008;106:203. Shorter E, Healy D. Shock Therapy: The History of Electroconvulsive Therapy in Mental Illness. Piscataway, NJ: Rutgers University Press; 2007. Weiner R, Lisanby SH, Husain MM, Morales OG, Maixner DF, Hall SE, Beeghly J, Greden JF, National Network of Depression Centers. Electroconvulsive therapy device classification: Response to FDA Advisory Panel hearing and recommendations. J Clin Psychiatry. 2013;74(1):38–42. 30.2 Other Brain Stimulation Methods Brain stimulation in psychiatric practice and research uses electrical currents or magnetic fields to alter neuronal firing. There is a growing list of tools capable of eliciting such neuromodulation, each with a different spectrum of action. These tools either apply electrical or magnetic fields transcranially or involve the surgical implantation of electrodes to deliver electrical currents to a cranial nerve or to the brain directly. The transcranial techniques include cranial electrical stimulation (CES), electroconvulsive therapy (ECT), transcranial direct current stimulation (tDCS, also called direct current polarization), transcranial magnetic stimulation (TMS), and magnetic seizure therapy (MST). The surgical techniques include cortical brain stimulation (CBS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS). In 1985, nearly 50 years after the first use of ECT, Anthony Barker and colleagues published on the first use of pulsed magnetic fields to stimulate the brain with a procedure called transcranial magnetic stimulation. TMS was initially used in neurology for studies of nerve conduction, but it quickly caught the attention of psychiatrists eager to explore other, less invasive alternatives to ECT. This nonconvulsive stimulation method through TMS is under active

study, with some promising results in the treatment of various psychiatric disorders, including depression, anxiety, and schizophrenia, as described by Sarah H. Lisanby, Leann H. Kinnunen, and colleagues in 2002. In the past decade, a convulsive treatment derived from the application of more powerful magnetic stimulation has been under investigation in nonhuman primates and in human studies in both the United States and Europe. The first MST procedure was performed in an animal in 1998 and in a human in 2000. MST is under development as a more focal means of inducing seizures in an attempt to retain the thus-far-unparalleled efficacy of ECT with fewer cognitive side effects. Two more recent additions to brain stimulation methods, DBS and VNS, were introduced about a decade following the first trials of TMS. Both were first approved by the U.S. Food and Drug Administration (FDA) in 1997 in the realm of treating sequelae of neurological syndromes. DBS was initially approved for the treatment of essential tremor and Parkinson's tremor, whereas VNS was approved for the treatment of epilepsy. Five years later, in 2002, indications for DBS

were expanded to include treatment of all symptoms of Parkinson's disease, including tremor, slowness, and stiffness, as well as involuntary movements induced by medications. TMS, DBS, and VNS originated in the field of neurology. Psychiatrists quickly saw the potential for those tools in the treatment of psychiatric conditions, however, and as a result of clinical trials in depression, VNS subsequently received FDA approval for the adjunctive long-term treatment of chronic or recurrent depression in adults. In addition, human studies are under way to validate the efficacy of DBS in the treatment of depression and obsessive-compulsive disorder. THERAPEUTIC NEUROMODULATION: TREATING PSYCHIATRIC DISORDERS THROUGH BRAIN STIMULATION Mechanism of Action Electrical Stimulation—Common Pathway. The brain stimulation modalities just reviewed generate either electrical or magnetic pulses. However, both of these share a common final pathway—they affect the neurons electrically. That electrical effect may either be through the direct application of electricity or through the indirect induction of electricity via magnetic stimulation. The direct forms of electrical stimulation are exemplified in either transcranial delivery, as with ECT, CES, and tDCS, or intracerebral delivery, as in the case of DBS or direct cortical stimulation (epidural or subdural). The indirect forms of electrical stimulation include TMS and MST, which induce electrical fields in the brain through the application of alternating magnetic fields. Of note, both the epidural and intracerebral modalities are more focal than the transcranial application of electricity because electrodes are placed directly in the neuronal tissue, bypassing the impedance of the scalp and skull. The relatively more contemporary magnetic stimulation methods (TMS and MST) also bypass the impedance of the scalp and skull and are thus likewise more focal. However, magnetic stimulation is in fact an example of an indirect method of electrical brain stimulation, in that the changing magnetic fields from these devices induce electricity in the brain, the latter acting as a conductor, according to the principle first described by Michael Faraday in a law that bears his name and later incorporated into James Clerk Maxwell's equations, which unify all of electromagnetism. The magnetic modalities achieve their enhanced focality noninvasively, in contrast to the intracerebral and epidural methods, and are thus at the center of intensive research in that they offer the promise of an unparalleled degree of spatial specificity without the need for surgery. All but one of the brain stimulation modalities described here act by stimulating neurons. The one exception is tDCS, which does not stimulate but rather polarizes. In this sense, the "S" of tDCS is a misnomer. It is more accurate to conceptualize tDCS as exerting a polarizing effect that may alter the likelihood of neuronal firing. The action of the subconvulsive modalities of stimulation relies on the effects of the repeated stimulation of the

targeted neural circuitry. However, in the case of the convulsive modalities (ECT and MST), the action depends on the seizure induced by the stimulation and the effects of repeated seizure induction on brain processes. This is not to say that the form of stimulation that triggers the seizure has no effect on outcome. Indeed, it is well replicated that electrode placement and electrical stimulus parameters have a profound effect on the efficacy and side effects of ECT. Whether the same will be true for MST is under active investigation.

Acute versus Prolonged Effects. Brain stimulation can have immediate or lasting effects. A single electrical pulse delivered at sufficient intensity can induce depolarization, trigger an action potential, release neurotransmitters at the synapse, and result in transsynaptic propagation with subsequent activation of a functional circuit. For example, brain stimulation applied to the hand area of the primary motor cortex may activate the corticospinal tract and induce a muscle twitch in the contralateral hand. Such stimulation can result acutely in the induction of either a positive effect, as in the case of a muscle twitch or visualization of phosphenes, or a disruptive effect, as in the case of visual masking. Repetitive pulses delivered at fixed frequencies can exert even more powerful effects. Epstein and colleagues described in 1999 how repetitive TMS (rTMS) applied to the language-dominant hemisphere induced an arrest of speech. After termination of the stimulation, speech returned to normal. Some more invasive brain stimulation modalities, such as DBS or VNS, are programmed to operate chronically, thus extending the acute action for as long as the stimulation is turned on. In the case of DBS, the pulses are typically given continuously at a high frequency, whereas in the case of VNS the pulses are given in trains lasting up to 30 seconds and typically repeated every 5 minutes. The less invasive modalities, such as rTMS, tDCS, CES, and even ECT, presumably require the induction of some form of neuroplasticity for their effect to become lasting. TRANSCRANIAL MAGNETIC STIMULATION Definition TMS is the application of a rapidly changing magnetic field to the superficial layers of the cerebral cortex, which locally induces small electric currents, also referred to as eddy currents. This induction was originally discovered by Faraday through his experiments in 1831 and later quantified in Maxwell’s equations of electromagnetism. Thus, TMS may be referred to as electrical stimulation without an electrode, in that it uses magnetic fields to indirectly induce electrical pulses. TMS devices deliver strong magnetic pulses via a coil that is held on the scalp. Because magnetic fields are unaffected by the electrical impedance of the scalp and skull, this method of stimulation enables the focal stimulation of smaller areas of the brain than is possible with other noninvasive devices that use either alternating (ECT, CES) or direct (tDCS) electrical current for primary stimulation. TMS is an example of noninvasive stimulation of focal regions of the brain and, as such, can be used for research or therapeutically without the need for anesthesia. Mechanisms of Action At sufficient intensity, electrical currents will stimulate neuronal depolarization, which can result in an action potential. For example, when the TMS coil is positioned over the hand area of the cerebral cortex’s motor strip, the changing magnetic field generated by

the repetitive pulses induces local currents immediately below the site of stimulation that cause the neurons in area M1 to fire. In turn, this action potential propagates through the polysynaptic corticospinal tract and results in a twitch in the contralateral hand muscle. In summary, TMS uses magnetic fields to indirectly induce focal electrical currents in the brain, thereby triggering the firing of functional neuronal circuits that can lead to observable behavioral effects. This effect can be easily demonstrated by single TMS pulses that can be used to map the homunculus simply by moving the TMS coil across the cortical representation of neighboring muscle groups and

simultaneously to study the excitability of the corticospinal system. Single TMS pulses can exert other effects when moved to different cortical areas. When positioned over the primary visual cortex (V1), scotomas, or “blind spots,” are often elicited. This illustrates that TMS can transiently disrupt functions. Activation of motor neurons resulting in a muscle twitch and disruption of visual perception with a single-pulse TMS represent examples of the acute effects of TMS-induced neuronal depolarization, as shown in Table 30.2-1. The effects of single TMS pulses are believed to be immediate and short lived. The muscle twitch as induced by TMS to area M1 is nearly instantaneous, with the hand movement occurring approximately 20 milliseconds after the TMS pulse is applied. The visual masking likewise operates on a similar time scale measured in milliseconds. TMS can, however, exert longer-lasting effects when the pulses are repeated at regular intervals in a process of rTMS or when they are paired with other forms of stimulation in which TMS pulses are coupled with electrical stimulation of a peripheral nerve (as in paired associative stimulation [PAS]) or when TMS is paired with audiovisual stimuli, as in the example of classical conditioning of the brain response to TMS. The mechanisms underlying these lasting effects of TMS have been described by various researchers and are thought to be related to neuroplasticity and alterations in synaptic efficacy. Table 30.2-1 Acute and Prolonged Mechanisms of Action Treatment of psychiatric disorders with rTMS has been informed by attempts to focally alter pathological cortical excitability, believed to be linked to a specific illness. Reduced activity in the left dorsolateral prefrontal cortex has been implicated in several studies as a physiological correlate of affective disorders. To correct this, numerous studies have applied high frequencies of rTMS, which have been reported to increase excitability, to the left dorsolateral prefrontal cortex (DLPFC) in an attempt to normalize activity in this region. In a related approach, some investigators who implicated abnormal interhemispheric balance in activation between the right and left DLPFC applied low-frequency rTMS, which has been reported to be inhibitory, to the right DLPFC in an attempt to normalize this balance. Side Effects, Interactions with Medications, and Other Risks

Administration of TMS is a noninvasive, relatively benign procedure when applied by a knowledgeable professional to a subject who has been properly evaluated. However, it is not entirely without risk. The most serious known risk of TMS is an unintended seizure. There are several factors that may contribute to seizure risk. Primarily, these include the form of TMS, with single-pulse stimulation less likely to result in a seizure than rTMS, and, in an equally important manner, the dose, which is the combination of treatment parameters including frequency, power, train duration, and intertrain interval. In addition, subject factors can be important, such as the presence of a neurological disorder (epilepsy or a focal brain lesion) or use of seizure-lowering medications. Single-pulse TMS is generally considered to be of minimal risk when administered to appropriately screened adults without seizure risk factors. On the other hand, rTMS can induce seizures in individuals without predisposing conditions when given at sufficiently high doses. Patient Selection Patients who have failed a trial of one or more antidepressant medications or have untoward side effects to medications may be good candidates for TMS. However, given the lower effect size of TMS, for urgent or severely refractory cases, ECT would remain the ultimate gold standard treatment. Future Directions and Controllable Pulse Shape TMS TMS and other forms of magnetic stimulation hold a tremendous promise in psychiatric treatment due to their focality and noninvasiveness. However, much research is needed to replicate preliminary findings, improve optimal dosing, establish the patient characteristics that predict response, and examine the influence of concomitant medications on TMS effect. Posttreatment relapse prevention is one of many areas that have to be properly explored. Other vigorously pursued directions are attempts to

develop stimulation coils that will allow deeper brain penetration and work on pulse shapes that may be more physiologically optimal for human stimulation. TRANSCRANIAL DIRECT CURRENT STIMULATION Definition Transcranial direct current stimulation is a noninvasive form of treatment that uses very weak (1 to 3 mA) direct electrical current applied to the scalp. Because direct current (DC) polarizes rather than stimulates with discrete pulses, its action does not appear directly to result in action potential firing in cortical neurons. It is also this DC form of electrical stimulation that distinguishes it from devices that use alternating currents (AC) as found in CES, ECT, VNS, and DBS, which produce discrete pulse stimulation. In addition, because tDCS works via polarization and does not affect action potential firing

in cortical neurons, the term transcranial direct current polarization is favored by some modern investigators, and both terms appear interchangeably in the literature today. The small device is very portable and usually operated by readily available DC batteries. Side Effects There are no known serious adverse effects of tDCS. It is well tolerated, with reported common side effects in the literature listing mostly minimal tingling at the site of stimulation, with a few reported cases of skin irritation. Mechanism of Action Direct current polarizes current, and tDCS is believed to act via the alteration of neuronal membrane polarization, but little is known about the actual mechanism of action of tDCS. Polarization may affect the firing and conductance of neurons by either lowering or raising the threshold of activation. Because tDCS involves the application of low currents to the scalp via cathodal and anodal electrodes, depending on the direction of current flow, polarization can either inhibit (cathodal) or facilitate (anodal) function. Clinical Studies Preliminary research suggests that tDCS may enhance certain brain functions independent of mood; however, tDCS technology and its use in psychiatry are in the early stages of exploration. Research is focusing on its potential effectiveness in facilitating recovery from stroke and from certain forms of dementia. Future Directions Most of the current tDCS devices use large, saline solution–soaked electrodes. Future device development will most likely investigate electrode shape and contact material to optimize the intended clinical effects and further improve ease of use. However, basic questions of efficacy, indications, and dose–response relationships, as well as predictors of response, will need to be explored first. CRANIAL ELECTRICAL STIMULATION Definition CES, like tDCS, uses a weak (1 to 4 mA) current. However, with CES the current is alternating. It is traditionally applied via saline-soaked, felt-covered electrodes clipped onto the earlobes. Other placement strategies are also being investigated. Mechanism of Action The exact mechanism of action has not been elicited, and there is no agreement among researchers on the predominant mode of action. Previous hypotheses proposed that the

stimulation with the alternating microcurrent affects the thalamic and hypothalamic brain tissue and facilitates the release of neurotransmitters. Claims have been made that through interaction with cell membranes, the stimulation produces changes in signal transduction associated with classical second-messenger pathways, including calcium channels and cyclic adenosine monophosphate (AMP). There are summary reports that CES causes increases in plasma serotonin, norepinephrine, dopamine, and monoamine oxidase type B (MAOB) in blood platelets and cerebrospinal fluid (CSF), as well as release of 5-hydroxy-indol-acetic acid (DHEA) and enkephalins and reduction of cortisol and tryptophan. However, most of these reports have not been validated through modern research. Side Effects It is believed that the CES stimulation is not harmful, primarily due to its low voltage power supply (9-V battery) and lack of any reported adverse event by the FDA. Local skin effects, as well as a general feeling of dizziness, have been reported,

however, and the use of the device during pregnancy, in those with low blood pressure, or in people who have arrhythmias or pacemakers is not advised by device manufacturers. Clinical Studies In a meta-analysis by the Harvard School of Public Health, 18 human clinical trials were examined that used CES to treat depression, anxiety, drug addiction, insomnia, headache, and pain. The overall pooled result showed CES to be better than sham treatment for anxiety at a statistically significant level. Current Status in Treatment Algorithms, Patient Selection, and Dosing The use of CES has not been studied sufficiently in the United States, and it does not have a specific place in any algorithm of standard US psychiatric practice. Future Directions As with tDCS, basic issues of indications, patient selection, dose–response relationship, and efficacy are under active research and remain to be optimized. MAGNETIC SEIZURE THERAPY Definition MST is a novel form of a convulsive treatment that is under development in several research institutions in the United States and Europe. The treatment uses an alternating magnetic field that crosses the scalp and the calvarium bone unaffected by their high electrical impedance, to in turn induce a more-localized electrical current in the targeted regions of the cerebral cortex than is possible with ECT. The aim is to produce a seizure

whose focus and patterns of spread may be controlled. MST is a convulsive treatment, in many ways similar to ECT. It is performed under general anesthesia. It requires approximately the same preparation and infrastructure as ECT. However, MST is given using a modified TMS device, one that can administer higher output than the conventional TMS devices and thus relies on magnetic stimulation, unlike electric stimulation in ECT. The MST procedure is performed under general anesthesia with a muscle relaxant. MST is at the stage of clinical trials and is not FDA approved. Mechanism of Action Induction of a seizure is hypothesized to be the underlying event responsible for the likely multiple specific mechanisms of action of MST treatment. As in ECT, these are not fully understood. However, due to its focality, MST appears to represent a tool better suited than ECT to study the mechanisms of action of convulsive therapy through its potential of inducing seizures initiated in different regions of the brain. Side Effects Adverse effects from MST, like those of ECT, are largely connected to the risks associated with anesthesia and generalized seizure. In addition, the MST magnetic coil produces a clicking noise that may potentially affect hearing. To mitigate that risk and prevent any cumulative damage, earplugs should be worn by both the patient and members of the treating team. Studies suggest that MST results in less retrograde and anterograde amnesia than ECT, although this result should be replicated in a larger trial. Current Status in Treatment Algorithms No clinical algorithms exist for MST, given that it is still an investigational protocol and treatments outside of research are not FDA approved. Assuming that the hypothesis that MST can approach the efficacy of ECT (but with fewer side effects) is correct, this magnetically induced convulsive treatment will play an important role prior to referral for ECT. Future Directions MST is a novel treatment in early phases of clinical testing. Clinical treatment variables, including dosing, optimal coil placement, patient selection, and mechanisms of action, are the topics of ongoing and future studies. VAGUS NERVE STIMULATION Definition

VNS is the direct, intermittent electrical stimulation of the left cervical vagus nerve via an implanted pulse generator, usually in the left chest wall. The electrode is wrapped around the left vagus nerve in the neck and is connected to the generator subcutaneously. Mechanisms of Action The majority of the fibers contained in the left vagus are afferents. It is estimated that as many as 80 percent of these fibers are up-going afferents, and thus chronic stimulation of these nerve fibers predominantly changes activity in the brainstem nuclei such as the nucleus of the tractus solitarius

and other neighboring nuclei (e.g., Raphe) that alter serotonergic activity in cortical and limbic structures. In addition, persistent stimulation of the vagal afferents is anticonvulsant, an effect that appears to depend on the norepinephrine-producing locus ceruleus. Side Effects and Contraindications To date, reasonably comprehensive literature confirms that VNS is generally well tolerated. The adverse events that are most frequently reported are voice alteration, dyspnea, and neck pain. Besides the risk of perioperative infection, the surgical implantation carries a small risk of vocal cord paralysis, bradycardia, or asystole. Current Status in Treatment Algorithms The FDA indicated VNS for the adjunctive long-term treatment of chronic or recurrent depression in patients 18 years or older experiencing a major depressive episode in the setting of unipolar or bipolar disease who have not had an adequate response to four or more adequate antidepressant treatments. Consultation with another clinician experienced with treatment-resistant depression and VNS is recommended. VNS treatment success rates are lower than those with ECT. Its onset of action is also comparatively slow—typically an approximately 30 percent response rate is observed after 1 year. VNS may be worth considering, therefore, when patients have failed to respond to less invasive treatments, ECT was ineffective, or post-ECT relapse cannot be prevented with less invasive means. VNS might be helpful with longer-term relapse prevention, but results of controlled trials would be useful to guide practice. Patient Selection VNS is approved as an adjunctive long-term treatment for chronic or recurrent depressive episodes in adults with a major depressive episode who have not had a satisfactory response to four or more adequate antidepressant trials. The efficacy of VNS in other disorders is unknown. ECT can be safely used in patients with an implant as long as the VNS generator is turned off during the convulsive treatment. This is needed because of the anticonvulsant effects of VNS. It remains to be studied whether VNS could be useful in relapse

prevention post-ECT. Dosing The optimal dosing for psychiatric applications of VNS is still largely an area of investigation. The published studies do not identify optimal dosing parameters like time on, time off, frequency, current, or pulse width. However, the epilepsy literature suggests that there is a threshold current for efficacy. Given current knowledge of VNS dosing, electrical current is typically increased up to greater than 1 mA and clinical benefit is assessed over several months. Because the adverse effects of VNS are known to be dose dependent, treatment parameters are often chosen to mitigate specific side effects. For example, lowering pulse width reduces neck pain, allowing patients to tolerate higher currents. Future Directions More research is required to establish the dose–response relationships for VNS. Future studies may explore optimal medication strategies to augment responses, test the potential role of VNS for long-term relapse prevention (e.g., after ECT), and study its mechanisms of action. IMPLANTED CORTICAL STIMULATION Definition CBS is a novel neurosurgical approach in which electrodes are implanted over the surface of the cortex to provide electrical brain stimulation in a targeted superficial region. This approach is being studied for treatment of conditions like stroke, tinnitus, and treatment-resistant depression. REFERENCES Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol. 2008;11(2):249. Englot DJ. Vagus nerve stimulation versus “best drug therapy” in epilepsy patients who have failed best drug therapy. Seizure. 2013;22(5):409–410. Esser SK, Huber R, Massimini M, Peterson MJ, Ferrarelli F. A direct demonstration of cortical LTP in humans: A combined TMS/EEG study. Brain Res Bull. 2006;69(1):86. Fitzgerald PB, Brown TL, Marston NAU, Oxley T, de Castella A. Reduced plastic brain responses in schizophrenia: A transcranial magnetic stimulation study. Schizophren Res.

2004;71(1):17. Fregni F, Boggio PS, Nitsche M, Pascual-Leone A. Transcranial direct current stimulation. Br J Psychiatry. 2005;186(5):446. Lisanby SH, Kinnunen LH, Crupain MJ. Applications of TMS to therapy in psychiatry. J Clin Neurophysiol. 2002;19(4):344. Lisanby SH, Luber B, Schlaepfer TE, Sackeim HA. Safety and feasibility of magnetic seizure therapy (MST) in major depression: Randomized within-subject comparison with electroconvulsive therapy. Neuropsychopharmacology. 2003;28(10):1852.

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Luber B, Kinnunen LH, Rakitin BC, Ellsasser R, Stern Y. Facilitation of performance in a working memory task with rTMS stimulation of the precuneus: Frequency- and time-dependent effects. Brain Res. 2007;1128:120. Luber B, Stanford AD, Malaspina D, Lisanby SH. Revisiting the backward masking deficit in schizophrenia: Individual differences in performance and modeling with transcranial magnetic stimulation. Biol Psychiatry. 2007;62(7):793. Mall V, Berweck S, Fietzek UM, Glocker FX, Oberhuber U. Low level of intracortical inhibition in children shown by transcranial magnetic stimulation. Neuropediatrics. 2004;35(2):120. Peterchev AV, Kirov G, Ebmeier K, Scott A, Husain M. Frontiers in TMS technology development: Controllable pulse shape TMS (cTMS) and magnetic seizure therapy (MST) at 100 Hz. Biol Psychiatry. 2007;61:107S. Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK. Vagus nerve stimulation for treatment-resistant depression: A randomized, controlled acute phase trial. Biol Psychiatry. 2005;58(5):347. Schestatsky P, Simis M, Freeman R, Pascual-Leone A, Fregni F. Non-invasive brain stimulation and the autonomic nervous system. Clin Neurophysiol. 2013; 124(9):1716–1728. Schlaepfer TE, Lancaster E, Heidbreder R, Strain EC, Kosel M. Decreased frontal white-matter volume in chronic substance abuse. Int J Neuropsychopharmacol. 2006;9(2):147. Tomlinson SP, Davis NJ, Bracewell R. Brain stimulation studies of non-motor cerebellar function: A systematic review. Neurosci Biobehav Rev. 2013;37(5):766–789. 30.3 Neurosurgical Treatments and Deep Brain Stimulation After a long and checkered history, neurosurgical treatments for psychiatric illness have reemerged as a focus of great interest. Many still associate psychiatric neurosurgery with the bygone era of crude freehand “psychosurgery,” when prefrontal lobotomy saw wide and indiscriminate use. Those primitive operations, which predated modern psychopharmacology, yielded modest reductions in symptoms but were accompanied by unacceptable adverse effects. Over nearly five decades, techniques, and importantly, procedures and practices have evolved tremendously. First, ablative lesions are now accurately, precisely, and reproducibly placed in specific brain targets stereotactically guided by magnetic resonance imaging (MRI) and specialized software. Alternative methods include

radiosurgery, which allows stereotactic lesion placement without craniotomy. Deep brain stimulation (DBS), while requiring craniotomy to implant stimulating electrodes in specific brain targets, is intentionally nonablative and allows flexible and reversible modulation of brain function. Second, strict criteria for patient selection are observed, and the process of determining appropriate candidacy has been formalized. Currently, surgical intervention is predominantly reserved for patients with severe, incapacitating major depression or obsessive-compulsive disorder (OCD) who have failed an exhaustive array of standard treatments. Surgery is not approved unless a multidisciplinary committee reaches consensus regarding its appropriateness for a given candidate and the patient renders informed consent. Although a large body of clinical data has already been collected that indicates the effectiveness and safety of modern neurosurgical interventions, major centers providing these treatments continue to gather information prospectively, and controlled trials are under way or planned. With these advances in neurosurgical techniques and better-

established selection criteria and long-term follow-up procedures, available data suggest that psychiatric neurosurgery yields substantial improvement in symptoms and functioning in approximately 40 to 70 percent of cases, with morbidity and mortality drastically lower than for earlier procedures. Although lesion procedures have been influenced by theories implicating corticolimbic systems in disordered behavior, they were initially developed largely empirically. Although psychiatric neurosurgery is sometimes criticized for this reason, as for any clinical therapy, the relevant issues are safety and efficacy, not correction of pathophysiological processes that are not yet fully understood. However, in addition to the promise of modern lesion procedures and DBS as clinical treatments, clinicians permit testing of hypotheses derived from the results of lesions or from systematic human neuroimaging. Thus, psychiatric neurosurgery is now developing in a scientific context where translation of data between clinical results to cross-species anatomical, neuroimaging, and physiological studies of neural networks involved a promise to illuminate mechanisms of therapeutic action. HISTORY Trephination performed by ancient civilizations probably represents the earliest form of surgical intervention for psychopathology. In 1891 the first formal report of neurosurgical treatment in psychiatry was published, describing bilateral cortical excisions in demented and depressed patients, which yielded mixed results. After four decades in which little progress was made, in 1935 John Fulton and Charles Jacobsen presented their research on primate behavior following frontal cortical ablation. They observed that lobectomized chimpanzees showed reduction in “experimental neurosis” and were less fearful, while retaining an ability to perform complex tasks. Egaz Moniz, a renowned Portuguese neurologist, pioneered prefrontal leukotomy in collaboration with his neurosurgical colleague Almeida Lima. First by using absolute alcohol injections and subsequently by mechanical means with a leukotome, Moniz and Lima performed “psychosurgery” on 20 severely ill institutionalized patients; 14 were said to have exhibited worthwhile improvement. In an era of overflowing asylums and few effective treatments for chronic debilitating psychiatric illness, this mode of therapy was initially enthusiastically embraced, and Moniz won the 1949 Nobel Prize in Medicine or Physiology for this contribution. From the mid-1930s until the emergence of the phenothiazines in the mid-1950s, these techniques proliferated globally. Walter Freeman, a neuropsychiatrist, was perhaps the most zealous promoter of psychosurgery in the United States. Pioneering a series of freehand procedures to achieve prefrontal lobotomy (i.e., severing the white matter connections between the prefrontal cortex and the rest of the brain), Freeman together with neurosurgeon James Watts reported on their first 200 cases by 1942. Although the benefits of the surgery were highlighted,

others acknowledged a significant complication rate, including frontal lobe syndrome, seizures, and even deaths. At its peak, lobotomy was being performed on approximately 5,000 patients per year in the United States alone. A review of the results of 10,365 prefrontal lobotomies performed from 1942 to 1954 in Britain concluded that while 70 percent showed improvement, adverse effects included 6 percent mortality, seizures in 1 percent, and disinhibition syndromes in 1.5 percent. There were widespread reports of blunted personality and socially inappropriate behavior. In the late 1940s and early 1950s, recognition of these risks prompted attempts to develop modified stereotactic surgical procedures that might yield better results. For example, Ernest Spiegel and Henry Wycis, who began stereotactic neurosurgery in humans, reported in the 1940s that dorsomedial thalamotomies improved obsessive-compulsive symptoms. However, with the introduction of chlorpromazine

(Thorazine) in 1954, medical management of psychiatric illness became newly possible. Thus, despite the advent of stereotactic neurosurgical techniques and a continued high prevalence of severe, treatment-refractory psychiatric illness, psychiatric neurosurgery was all but abandoned in favor of nonsurgical therapies. PATIENT SELECTION: INDICATIONS AND CONTRAINDICATIONS Although limited reports have suggested efficacy across a broad range of psychiatric conditions and research is expanding rapidly, as of this writing the best established indications for psychiatric neurosurgery remain major depression and OCD. In evaluating candidates, several factors are considered:

1. Primary diagnosis: The patient must meet clinical criteria for the diagnostic indication, and this disorder should be a primary cause of the patient’s debility and suffering.
2. Severity: The patient must have chronic, severe, and debilitating illness; duration of the primary illness must exceed 1 year and typically exceeds 5 years. Severity is gauged on standardized instruments (e.g., patients with OCD typically have YaleBrown Obsessive-Compulsive Scale scores of 25 to 30; patients with major depression typically have Beck Depression Inventory scores of 30 or higher), while debility should be indicated by a low level of functioning (e.g., a Global Assessment of Functioning score of 50 or less) and a poor quality of life.
3. Adequacy of previous treatment: Patients must have already undergone an exhaustive array of other available established treatments, which are documented in detail.
4. Psychiatric comorbidity: Appropriate treatment must have been rendered for any comorbid psychiatric disorder; the presence of psychoactive substance use or severe personality disorders are considered strong relative contraindications.
5. Medical comorbidity and surgical fitness: Structural brain lesions or significant central nervous system injuries are strong contraindications. Medical conditions that increase neurosurgical risks (e.g., cardiopulmonary disease) and age 65 years are relative contraindications for lesion procedures, while for DBS the relative age restriction might be older. A history of past seizures is a risk factor for perioperative seizures after lesion procedures and must be weighed in the overall risk–benefit assessment (again, data are currently less clear in this regard for psychiatric DBS).
6. Access to postoperative care: The psychiatric neurosurgery procedures themselves represent the beginning of a new episode of care. It is crucial that patients have access to adequate postoperative treatment, including a psychiatrist (typically the referring physician) who will accept responsibility for managing the case after discharge.

> Arrangements for postoperative care (e.g., intensive behavior therapy) should be confirmed ahead of time. Importantly, after lesion procedures, care can generally be delivered in standard treatment settings without the need for highly specialized psychiatric neurosurgery teams. For deep brain stimulation, access to such teams is essential over the long term. Once implanted, patients require clinical monitoring and device adjustment, which can be intensive and time-consuming, especially early in treatment. Device monitoring and replacements may need to occur

on a relatively urgent basis. The continuing costs incurred can be substantial, and adequacy of third-party reimbursement needs to be ensured in advance to the extent possible. After either lesion procedures or DBS, family or significant others may be needed to support and accompany patients to follow-up care, similar to the level of support that is usually necessary during the intensive evaluation process. 7. Informed consent: Under no circumstances should psychiatric neurosurgery be performed on patients against their will. The patient must be able and willing to render an informed consent. Formal consent monitoring may be used to ensure that the consent process is adequate. In rare instances, these procedures are performed with assent of the patient and formal consent from a legal guardian. In this context, age less than 18 years also represents a relative contraindication. POSTOPERATIVE CARE Immediate postoperative care includes the standard medical and surgical considerations following any stereotactic neurosurgical procedure. Special attention is paid to signs or symptoms of potential surgical complications, including infection, hemorrhage, seizures, or altered mental status. A postoperative MRI should be obtained to document the placement and extent of lesions. Intensive postoperative psychiatric treatment is recommended since the efficacy of the surgery may rely on some synergy between the neurosurgical intervention itself and enhanced response to pharmacological or behavioral therapies. Although dosages of psychotropic medications may be reduced during the immediate perioperative period, the medication regimen should be readjusted as tolerated postoperatively. Moreover, in the case of OCD, intensive behavior therapy should be initiated as soon as possible, preferably within the first month postoperatively. For DBS, electrode implantation is usually followed by a several-week delay to enable resolution of local edema and stabilization of other factors that might influence the response to stimulation. Then, systematic outpatient adjustment of stimulation parameters is performed before initial settings are determined. This is often a timeconsuming process, lasting hours over 1 or more days. Ongoing protocols for DBS entail frequent follow-up, especially during the approximate 6 months after implantation, to enable optimization of stimulation parameters, monitoring of the patient, and coordination of other pharmacological and behavioral therapies. LESION PROCEDURES Although numerous approaches have been tried, four lesion procedures have evolved as the safest and most effective for treating psychiatric disorders. All four entail bilateral lesions and are performed using modern stereotactic methods. Subcaudate Tractotomy Subcaudate tractotomy was introduced by Geoffrey Knight in Great Britain in 1964 as one of the first attempts to limit

adverse effects by restricting lesion size. By targeting the substantia innominata (just inferior to the head of the caudate nucleus), the goal was to interrupt white matter tracts connecting orbitofrontal cortex and subcortical structures. The surgery involved placement of radioactive yttrium-90 seeds at the desired centroid, yielding lesion volumes of approximately 2 cc on each side. Indications for subcaudate tractotomy are major depression, OCD, and other severe anxiety disorders. ANTERIOR CINGULOTOMY Anterior cingulotomy remains the most commonly employed

neurosurgical treatment for psychiatric disease in North America. The surgery is conducted under local anesthesia and two or three approximately 1-cc lesions are made on each side by thermocoagulation through bilateral burr holes. The target is within the anterior cingulate cortex (Brodmann areas 24 and 32), at the margin of the white matter bundle known as the cingulum. Originally, the placement of lesions was determined by ventriculography; however, since 1991, anterior cingulotomy has been conducted via MRI guidance. Approximately 40 percent of patients return several months following the first operation for a second procedure to extend the first set of lesions. The indications for anterior cingulotomy include major depression and OCD. Limbic Leukotomy Limbic leukotomy was introduced by Desmond Kelly and colleagues in England in 1973. The procedure combines the targets of subcaudate tractotomy and anterior cingulotomy. The lesions have typically been made via thermocoagulation or with a cryoprobe. Historically, the precise placement of the lesions was guided by intraoperative stimulation; pronounced autonomic responses were believed to designate the optimal lesion site. The indications for limbic leukotomy include major depression, OCD, and other severe anxiety disorders. More recently, there is also some evidence that this procedure might be beneficial for repetitive self-injurious behaviors or in the context of severe tic disorders. ANTERIOR CAPSULOTOMY Anterior capsulotomy or its newer variant, Gamma Knife (Elekta, Stockholm) capsulotomy, are used in Scandinavia, the United States, Belgium, Brazil, and elsewhere. The procedure places lesions within the anterior limb of the internal capsule, which impinges on the adjacent ventral striatum, thereby interrupting fibers of passage between prefrontal cortex and subcortical nuclei including the dorsomedial thalamus. Although the original anterior capsulotomy procedure is performed using thermocoagulation via burr holes in the skull, over the past 15 years capsulotomy has also been performed using the Gamma Knife as an alternative. This radiosurgical instrument makes craniotomy unnecessary. Typically, gamma capsulotomy lesions are smaller than those induced by thermocapsulotomy, remaining within the ventral portion of the anterior capsule. Hence, the term gamma ventral capsulotomy is coming into use to describe this procedure. In contrast to thermocapsulotomy, gamma ventral capsulotomy may be performed as an outpatient procedure, with an overnight hospital stay usually the most that is required. The relative advantages and disadvantages of this radiosurgical approach are the focus of ongoing research, including a current controlled study of gamma ventral capsulotomy for OCD, the first of its kind for a lesion procedure in psychiatry. Some data suggest, unsurprisingly, that the rates of neuropsychiatric adverse effects may be considerably lower for gamma ventral capsulotomy than for earlier procedures in which much larger tissue volumes were lesioned. Indications for anterior capsulotomy include major depression, OCD, and other severe anxiety disorders.

Deep Brain Stimulation DBS for psychiatric illness is not a new idea, although the devices, surgical techniques, and theoretical models of relevant neurocircuitry have all advanced. The procedure involves placement of small-diameter brain “leads” (e.g., approximately 1.3 mm) with multiple electrode contacts into subcortical nuclei or specific white matter tracts. The surgeon drills burr holes in skull bone under local anesthesia and then places the leads, guided by multimodal imaging and precise stereotactic landmarking. Usually this is done bilaterally. The patient is typically sedated but awake during surgery. Later, the “pacemaker” (also known as an implantable neurostimulator or pulse generator) is implanted subdermally (e.g., in the upper chest wall) and connects it, via extension wires tunneled under the skin, to the brain leads. The goals of DBS are to achieve improved efficacy and more favorable adverse effect profiles in comparison with ablation. Because various combinations of electrodes can be activated, at adjustable polarity, intensity, and

frequency, DBS allows more flexible modulation of brain function, referred to as neuromodulation. Thus, parameters can be optimized for individual patients, but the process, typically performed by a specially trained psychiatrist in the outpatient setting, can be quite time-consuming and requires attentive, long-term follow-up. In cases where no beneficial settings can be identified despite extensive efforts, the electrodes can be inactivated, and devices may be removed. In that event, devices are usually only partly explanted, with the brain electrodes left in place given the small risk of hemorrhage upon removal. The relative advantages and disadvantages of DBS are the focus of very active research. TREATMENT OUTCOME For all four contemporary ablative procedures, outcome cannot be fairly assessed for a considerable period postoperatively, which could extend from 6 months to 2 years. In the first two or three decades of this work, clinical reports usually employed measures of global improvement, such as the Pippard Postoperative Rating Scale, which rates outcomes as follows: (1) symptom free, (2) much improved, (3) slightly improved, (4) unchanged, and (5) worse. Most studies have operationalized significant improvement as categories 1 and 2. In addition, many of the reports employ a measure of symptom severity that is specific to the indication for the procedure (e.g., the Yale-Brown Obsessive-Compulsive Scale for OCD and the Beck Depression Inventory for major depression). The majority of studies focus on one or another of the procedures and are best reviewed according to surgical approach. Outcome with Subcaudate Tractotomy Significant improvement was seen in 68 percent of patients with major depression, 50 percent of patients with OCD, and 62.5 percent of patients with other anxiety disorders. Patients with schizophrenia, substance abuse, or personality disorders did poorly. Shortterm side effects include transient headache and confusion or somnolence, which

typically resolve in less than 1 week. Patients are usually ambulatory by the third postoperative day. Transient disinhibition syndromes were common. In 1994, a largescale review of 1,300 cases was conducted and concluded that the procedure enables 40 to 60 percent of patients to lead normal or near normal lives, with a reduction in suicide rate to 1 percent versus 15 percent in a similarly affected control group with major affective disorders. Outcome with Anterior Cingulotomy Significant improvement occurred in 62 percent of patients with affective disorders, 56 percent with OCD, and 79 percent with other anxiety disorders. Among patients with unipolar depression, 60 percent responded favorably; among patients with bipolar disorder, 40 percent responded favorably; and among patients with OCD, 27 percent were classified as responders with another 27 percent categorized as possible responders. Short-term side effects include headache, nausea, or difficulty with urination; however, these typically resolve within a few days. Patients are usually ambulatory within 12 hours following the operation and discharged on the third to fifth postoperative day. Over the past 10 years the practice of treating patients who experience perioperative seizures with chronic anticonvulsant therapy has been discontinued, and no cases of new onset recurrent seizures have been seen. Although patients have occasionally (5 percent or less) noted transient problems with memory, an independent analysis of 34 patients was performed and demonstrated no significant intellectual or behavioral impairments attributable to anterior cingulotomy; a subsequent study of 57 patients likewise found no evidence for lasting neurological or behavioral adverse effects. Outcome with Limbic Leukotomy Significant improvement occurred in 89 percent of patients with OCD, 78 percent with major depression, and 66 percent with other anxiety conditions. Short-term side effects include headache, lethargy or apathy, confusion, and lack of sphincter control, which may last from a few days to a few weeks. In particular, it is common for postoperative confusion to last at least several days, and patients are often not discharged in less than 1 week. There were no seizures and no deaths; however, one

patient suffered severe memory loss due to improper lesion placement, and enduring lethargy was present in 12 percent of cases. Outcome with Anterior Capsulotomy Thermocapsulotomy. A favorable response occurred in 50 percent of those with OCD and 48 percent of those with major depression. Short-term side effects can include transient headache or incontinence. Postoperative confusion often lasts for up to 1 week. Recovery from gamma capsulotomy is swifter and characterized by less discomfort and virtually no confusion, but side effects from radiation exposure,

principally cerebral edema, may be delayed for up to 8 to 12 months. For the open capsulotomy, patients are typically ambulatory in a matter of hours to days following the operation, although the length of hospital stay may be influenced by the duration of confusion. Weight gain has been noted to be a common enduring side effect with a mean increase in mass of 10 percent. Gamma Ventral Capsulotomy. Gamma capsulotomy was generally well tolerated and effective for patients with otherwise intractable OCD. Adverse events included cerebral edema and headache, small asymptomatic caudate infarctions, and possible exacerbation of preexisting bipolar mania. A therapeutic response, defined conservatively, was seen in 60 percent of over 50 patients receiving the most recent gamma capsulotomy procedure, in which pairs of lesions in the ventral capsule are made bilaterally, impinging on the ventral striatum. Therapeutic benefit was achieved over 1 to 2 years and was essentially stable by 3 years. Adverse effects of gamma ventral capsulotomy include significant radiation-induced edema, appearing months after the procedure, apparently due to a differential sensitivity to radiation that remains poorly understood. Long-term follow-up will be necessary to clarify risks and benefits of gamma ventral capsulotomy. The same applies to any neurosurgery, including lesion procedures and deep brain stimulation. Outcomes with DBS Obsessive-Compulsive Disorder. Over the past 10 years, four groups have collaborated closely on development of DBS at the ventral anterior limb of the internal capsule and adjacent ventral striatum (the VC/VS) for otherwise intractable OCD: Leuven/Antwerp, Butler Hospital/Brown University, the Cleveland Clinic, and the University of Florida. Long-term outcomes of open stimulation in 26 patients showed clinically significant symptom reductions and functional improvement in about two thirds of patients overall. Conservatively defined responses (35 percent or greater reductions on the Yale-Brown Obsessive-Compulsive Scale) were seen in one third of patients in the initial group, irrespective of study center, while the response rate was over 70 percent in the second and third patient cohorts treated. Development of psychiatric DBS is following the path of stimulation for movement disorders, where several targets have been pursued with therapeutic benefit. As in movement disorders, overlapping or converging effects of DBS at different anatomical sites on the neurocircuitry involved are likely and are a focus of active research. The same reasoning applies to DBS for depression. Major Depression. A body of functional neuroimaging research implicates the subgenual cingulate cortex as a node in circuits involved in the normal experience of sadness, symptoms of depressive illness, and responses to depression treatments. Chronic DBS for up to 6 months was associated with sustained remission of depression in four of the six patients studied. Another line of research on DBS for depression was

prompted by the OCD research discussed above and also by the reported antidepressant effects of anterior capsulotomy on which the VC/VC stimulation target was initially based. The OCD patients, who had very high rates of comorbid depression, characteristically responded to stimulation onset with mood enhancement and reductions in nonspecific as well as OCD-related anxiety. Such effects were accompanied, or even preceded, by improvements in social interaction and daily functioning.

Worsening in these same clinical domains was noted in some patients with cessation of VC/VS stimulation. Moreover, DBS-induced changes in mood and nonspecific anxiety often seemed to precede reductions in core OCD symptoms. Outcome Across Contemporary Neurosurgical Procedures Although the field is developing rapidly, the conclusion reached is that 40 to 70 percent of carefully selected psychiatric patients should meaningfully benefit from contemporary neurosurgical treatment. Twenty-five percent or more might be expected to show outstanding improvement. Responses to ablative procedures have appeared marginally superior for major depression than for OCD generally. The adverse-effect profiles of this group of procedures are influenced by lesion size, the surgical approach, and whether radiosurgical methods (in which the tempo of lesion development is very slow versus thermocoagulation) are used. But adverse effects are greatly minimized in comparison with procedures of the past. Although minor short-term side effects may be common after some modern ablative procedures, severe or enduring adverse consequences are relatively rare. These can include seizures in about 1 to 5 percent of cases. Although frontal syndromes, confusion, or subtle cognitive deficits can still be seen, overall cognitive function, as indicated by the standard intelligence quotient, is generally enhanced, a finding that has been attributed to the overriding beneficial effects of symptomatic improvement. Psychiatric neurosurgery likely reduces mortality, as evidenced by data on comparative suicide rates. Nonetheless, patients who undergo and fail to benefit from these procedures are at particularly high risk for completed suicide. Therefore, as with any therapy, the potential risks and benefits of psychiatric neurosurgery must be weighed against the potential risks and benefits of undergoing this brand of treatment. The advent of DBS in psychiatry has created tremendous interest and considerable research activity. This therapy is intentionally nonablative, can be optimized for individual patients, is reversible, and is based on devices that are (to varying degrees) removable. DBS may therefore be accepted by patients who would not choose to undergo lesion procedures (although the reverse is also true). With all of its advantages, DBS requires that patients be treated by highly specialized teams willing and able to provide long-term care. The logistics and expenses involved can represent significant barriers. In contrast, psychiatric care can be delivered in standard treatment settings after lesion procedures. However, although the relative risks of enduring adverse effects after psychiatric DBS remain to be clearly established, at this stage ablative methods appear to carry a greater potential for them. Because rates of adverse outcomes are low

when modern lesion procedures are performed at highly experienced centers, there may be a particularly strong rationale for referral of appropriate patients to such expert centers.
REFERENCES Belmaker R, Agam G. Deep brain drug delivery. Brain Stimulation. 2013;6(3):455–456. deSouza R-M, Moro E, Lang AE, Schapira AH. Timing of deep brain stimulation in Parkinson disease: A need for reappraisal? Ann Neurol. 2013;73(5):565–575. Dougherty DD, Baer L, Cosgrove GR, Cassem EH, Price BH. Update on cingulotomy for intractable obsessive-compulsive disorder: Prospective long-term follow-up of 44 patients. Am J Psychiatry. 2002;159:269. Fins JJ, Rezai AR, Greenberg BD. Psychosurgery: Avoiding an ethical redux while advancing a therapeutic future. Neurosurgery. 2006;59(4):713. Gabriels L, Nuttin B, Cosyns P. Applicants for stereotactic neurosurgery for psychiatric disorders: The role of the Flemish Advisory Board. Acta Psychiatr Scand. 2008;17(5):381. Greenberg BD, Gabriels LA, Malone DA, Rezai AR, Friehs GM, Okun MS, Shapira NA, Foote KD, Cosyns PR, Kubu CS, Malloy PF, Salloway SP, Giftakis JE, Rise MT, Machado AG, Baker KB, Stypulkowski PH, Goodman WK, Rasmussen SA, Nuttin BJ. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: Worldwide experience. Mol Psychiatry. 2010;15(1):64–79. Greenberg BD, Price LH, Rauch SL, Jenike MA,

Malone D. Neurosurgery for intractable obsessive-compulsive disorder and depression: Critical issues. Neurosurg Clin North Am. 2003;14:199. Heeramun-Aubeeluck A, Lu Z. Neurosurgery for mental disorders: A review. Afr J Psychiatry. 2013;16(3):177–181. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45:651. Montoya A, Weiss AP, Price BH, Cassem EH, Dougherty DD. Magnetic resonance imaging-guided stereotactic limbic leukotomy for treatment of intractable psychiatric disease. Neurosurgery. 2002;50(5):1043. OCD-DBS Collaborative Group. Deep brain stimulation for psychiatric disorders. Neurosurgery. 2002;51(2):519. Rauch SL. Neuroimaging and neurocircuitry models pertaining to the neurosurgical treatment of psychiatric disorders. Neurosurg Clin North Am. 2003;14(2):213. Rauch SL, Dougherty DD, Malone D, Rezai A, Friehs G. A functional neuroimaging investigation of deep brain stimulation in patients with obsessive-compulsive disorder. J Neurosurg. 2006;104:558. Van Laere K, Nuttin B, Gabriels L, Dupont P, Rasmussen SA. Metabolic imaging of anterior capsular stimulation in refractory obsessive compulsive disorder: A key role for the subgenual anterior cingulate and ventral striatum. J Nucl Med. 2006;47:740.