Electroconvulsive Therapy for Depression

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An 82-year-old widowed woman with a history of recurrent unipolar major depression is referred to the electroconvulsive therapy (ECT) service of an academic medical center. During her illness, she has had four episodes of major depression consisting of periods of depressed mood, crying spells, loss of interest in usual activities, insomnia, loss of appetite and weight, difficulty with concentration, feelings of helplessness and hopelessness, and thoughts of suicide. During the current episode, which has lasted for 6 months, she has had typical symptoms of melancholic depression, as well as psychotic symptoms (e.g., a somatic delusion that she has terminal cancer), with suicidal ideation and a plan for taking a drug overdose. Previous treatment during this episode has included citalopram (Celexa), duloxetine (Cymbalta), and the combination of olanzepine (Zyprexa) and duloxetine, but the patient did not have a response to any of these agents. She could not tolerate the anticholinergic side effects of tricyclic antidepressants. Her psychiatrist seeks specialty consultation regarding the appropriateness and safety of ECT for this patient.

THE CLINICAL PROBLEM

Major depressive disorder affects approximately 14 million adults in the United States each year.1 The World Health Organization estimates that, at current rates, depression will be the second most common cause of disability worldwide by 2020.2 Severe depression can impair the quality of life and lead to death by suicide; the lifetime risk of suicide among patients with affective disorders is 6 to 15%. Severe depression also increases the mortality associated with general medical conditions — most notably, heart disease.

Depression in the elderly is a growing public health problem, with an estimated prevalence of 1 to 2% in the general population of elderly persons, 1 to 3% among those living in the community, and 10 to 12% among those in outpatient primary care and inpatient settings.3 Major depression in older adults is a leading cause of disability, and it increases mortality from all causes and the likelihood of placement in a nursing home.4 The risk of suicide is also a serious concern in this population.

Although antidepressant medications are effective for many patients, the rate of response to the first agent administered can be as low as 50%.5 The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial showed that the remission rate decreased from 36.8% to 13.0% as successive treatment steps were required because of nonresponse.6 Outcomes of treatment with antidepressant medications in the elderly may be suboptimal in part because of intolerance of side effects. Also, brain changes in depression in the elderly, especially abnormalities in frontostriatal limbic circuits, can attenuate the response to medications.7-9
PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Depression is a complex and heterogeneous disorder that comprises three broad domains of clinical manifestations: disorders of mood, cognitive function, and neurovegetative functions (i.e., energy, sleep, appetite, and sexual function). The cause of depression is likewise thought to be complex, including various genetic, developmental, and environmental factors.

Most models of the pathophysiology of depression implicate dysregulation in corticolimbic circuits affecting regional brain structure and function, neurotransmitter function, and neuroendocrine regulation. Researchers have described structural abnormalities in the hippocampus (where atrophy is correlated with the duration of depression in days), the subgenual prefrontal cortex (where atrophy is associated with familial depression), and white-matter hyperintensities (notably in depression in the elderly). Functional abnormalities in the prefrontal, temporal, parietal, limbic, paralimbic, striatal, and thalamic regions have been identified. Abnormalities in neurotransmitter function and receptor expression have been described, including presynaptic and postsynaptic abnormalities in serotonin-receptor expression and deficiencies in γ-aminobutyric acid (GABA). Data from neuroendocrine challenge studies (e.g., the dexamethasone suppression test) have provided evidence of impaired negative feedback inhibition in the hypothalamic–pituitary–adrenal axis, resulting in hypercortisolemia, which itself can cause further impairment in brain function.

The pathophysiology of depression in late life appears to have some unique features. Susceptibility to depression in older adults is thought to be in part mediated by frontal–striatal–limbic dysfunction caused by vascular, neurochemical, neurodegenerative, and aging-related factors. The “vascular depression hypothesis” posits that vascular lesions in white matter disrupt key pathways, leading to a “disconnection syndrome” with abnormal functional activation in downstream cortical and limbic regions and resulting in impaired mood regulation, cognition, and neurovegetative function. A “depression–executive dysfunction syndrome” has been described in late-life depression; this syndrome is characterized by impaired executive function, compromised integrity of the prefrontal white matter, dysfunc-
tion in frontolimbic circuits, and a poor response to antidepressant medications.

ECT for the treatment of depression and other psychiatric disorders involves the application of electricity to the scalp in order to induce seizure activity. This form of therapy has a range of effects on the neurobiologic features of depression. ECT increases cortical GABA concentrations and enhances serotonergic function. It also affects the hypothalamic–pituitary–adrenal axis, normalizing the results of the dexamethasone suppression test. Functional brain activation is altered. Neuronal structure and synaptic plasticity also appear to be influenced; animal studies have shown increases in neurotropic factors and cell proliferation.

CLINICAL EVIDENCE

ECT has been reported to result in a prompt improvement in symptoms of depression in the majority of patients treated. The Consortium for Research in ECT (CORE) reported a 75% remission rate among 217 patients who completed a short course of ECT during an acute episode of depression, with 65% of patients having remission by the fourth week of therapy. A systematic review of six trials involving 256 patients by the UK [United Kingdom] ECT Review Group, reported in 2003, showed that the effect size for ECT was 0.91 (significantly more effective than sham ECT), and a review of 18 trials involving 1144 patients showed that the effect size for ECT was 0.80 (more effective than pharmacotherapy). These data have shortcomings, including suboptimal dosage and an inadequate description of the drug treatment.

A meta-analysis showed ECT to be more effective than antidepressant medications alone in treating the psychotic subtype of depression, and it showed a trend for ECT to be better than combination pharmacotherapy. In a study involving 253 patients, the CORE group reported that patients with the psychotic subtype of depression had higher rates of response to ECT than patients without psychosis; this study also showed that response rates were higher among the elderly.

The efficacy of ECT is highly dependent on technique, with remission rates ranging from 20% to more than 80%, depending on how the treatment is performed. Double-blind, random-
ized, controlled trials have shown powerful interactions between electrode placement and dosage (relative to seizure threshold) in the efficacy and side effects of ECT.\textsuperscript{34} In a review of 22 trials involving 1408 patients, the UK ECT Review Group reported that bilateral electrode placement was moderately more effective than right unilateral placement (effect size, 0.32),\textsuperscript{30} but the efficacy of right unilateral ECT is dose-sensitive, and several of the trials in this analysis may have used insufficient doses. Several studies have not shown a difference in efficacy between high-dose right unilateral ECT and bilateral ECT, and these studies have indicated that unilateral electrode placement on the right side is associated with a lower incidence of cognitive side effects, especially at long-term follow-up.\textsuperscript{34,35}

One report suggests success rates of 30 to 47\% for ECT in community hospitals. These rates have been less robust than those in clinical trials.\textsuperscript{36} This discrepancy is related in part to coexisting conditions, but it may also be related to the tendency to discontinue ECT prematurely, often in order to mitigate side effects. In this study, treating psychiatrists often discontinued ECT before complete remission was achieved.\textsuperscript{36}

**Clinical Use**

ECT was first introduced as a treatment for psychiatric disorders in the 1930s. Early experience with the treatment raised concerns about serious side effects, including fractures (before the use of neuromuscular blocking agents) and cognitive impairment (in part related to dose and technique).\textsuperscript{37} With the introduction of pharmacologic therapy for depression and the concerns about the adverse effects of ECT, the use of ECT declined. In recent decades, however, further research and methodologic advances have led to renewed interest in the role of ECT for the treatment of patients with depression.

The second edition of the guidelines of the American Psychiatric Association (APA) Task Force on Electroconvulsive Therapy, which was published in 2001, includes a complete description of the current clinical use of ECT.\textsuperscript{38} Briefly, the primary indications for ECT among patients with depression are lack of a response to or intolerance of antidepressant medications, a good response to previous ECT, and the need for a rapid and definitive response (e.g., because of psychosis or a risk of suicide). ECT can be used in both unipolar and bipolar disorders.

The decision to use ECT depends on several factors, including the severity and chronicity of the patient’s depression, the likelihood that alternative treatments would be effective, the patient’s preference, and a weighing of the risks and benefits. Although ECT is more effective than antidepressant medications, it is typically reserved for use after several medication trials because of its relatively higher risk of side effects.

There are no absolute contraindications to ECT, but factors that have been associated with reduced efficacy include a prolonged episode, lack of response to medication, and coexisting psychiatric diagnoses such as a personality disorder.\textsuperscript{36} Persons with unstable cardiac disease such as ischemia or arrhythmias, cerebrovascular disease such as recent cerebral hemorrhage or stroke, or increased intracranial pressure may be at increased risk for complications. The pre-ECT workup therefore should include a complete medical and neurologic evaluation to detect and manage such conditions. ECT can be used safely in elderly patients and in persons with cardiac pacemakers or implantable cardioverter–defibrillators.\textsuperscript{39} ECT can also be used safely during pregnancy, with proper precautions and in consultation with an obstetrician.

Common electrode positions include bilateral, right unilateral, and bifrontal (Fig. 1). Right unilateral and bifrontal placement may be selected to reduce the burden of side effects, whereas bilateral placement may be selected if the right unilateral or bifrontal positions are unlikely to be effective (e.g., in patients in whom previous ECT treatment with the latter positions has failed).

The ECT dose is measured in millicoulombs of charge delivered; the dose administered must be sufficient to induce seizure activity. One approach, called seizure-threshold titration, involves giving progressively higher doses during the initial ECT session until the seizure threshold is reached, and then selecting a dose at various percentages above the seizure threshold during subsequent treatment sessions. Another accepted approach involves the use of an age-based dosing algorithm, although this technique has some limitations, since age accounts for only a small percentage of the variance in the seizure threshold.\textsuperscript{40}

Some medications (e.g., lithium, theophylline, and medications with anticonvulsant action) can...
interact with ECT, and they should be tapered or discontinued before ECT is initiated. Antidepressant drugs are often discontinued before the initiation of ECT. However, clinical experience suggests that at least some of these agents may be used safely during treatment, and such an approach may reduce the risk of a relapse of depression after treatment is completed.

ECT is performed while the patient is under general anesthesia; therefore, all patients must undergo a full evaluation by an anesthesiologist, including an assessment of the risk associated with anesthesia, before the start of ECT. Patients are not typically intubated, but mask ventilation with supplemental oxygen is used. Neuromuscular blocking agents are administered to prevent skeletal muscle contraction and possible injury during tonic–clonic activity. Atropine or glycopyrrolate may be given to minimize bradycardia and salivation.

The electroencephalogram is monitored during ECT to confirm seizure activity and to document seizure duration. In addition, evidence of seizure motor activity is monitored. This technique involves the placement of a tourniquet around one of the patient’s ankles before the administration of the muscle relaxant so that the potential for muscle contraction in the foot is maintained. Oxygen saturation and cardiac rhythm are monitored during the procedure.

In the United States, ECT treatments are usually administered three times weekly for approximately 6 to 12 treatments, depending on the severity of the patient’s symptoms and the rapidity of the response. Since premature discontinuation of ECT can predispose the patient to relapse, it is important to monitor the efficacy of the treatment in a systematic fashion. Efficacy can be monitored by using standardized rating scales for depression or by keeping track of the severity of selected target symptoms. It is also essential to track side effects that emerge during treatment, such as amnesia, with the use of rating scales of cognitive performance and memory.

After remission, it is important to initiate maintenance therapy with an antidepressant and a mood stabilizer, and in some patients, maintenance ECT is required. The optimal approach to maintenance with ECT or medications requires further study.

ECT can be performed on an inpatient or an outpatient basis. The APA has estimated the cost of ECT to be approximately $800 to $1,000 for each treatment in a series; this cost includes the

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**Figure 1. Standard Electrode Placements for Electroconvulsive Therapy.**

The three standard electrode placements are bifrontotemporal (commonly referred to as “bilateral”), right unilateral, and bifrontal. In bilateral placement, there is one electrode on each side of the head. In right unilateral placement, one electrode is in the right frontotemporal position, and the second electrode is placed to the right of the vertex. In bifrontal placement, there is one electrode on each side of the head, but the placement is more frontal than it is in standard bilateral placement.
professional fees of the psychiatrist and the anesthesiologist, as well as the cost of the use of the facility, equipment, and supplies.\textsuperscript{42}

**ADVERSE EFFECTS**

In the short term, ECT causes anterograde amnesia that typically resolves soon after ECT is completed. In addition, postictal disorientation or even delirium may occur, but these conditions also tend to resolve within 1 hour after the procedure. Prolonged seizures during ECT are rare.

Retrograde amnesia is the most common persistent adverse effect of ECT. Shortly after ECT, most patients have gaps in the memory of events that occurred before the treatment, and retrograde amnesia may extend back several months or years. The memory of autobiographical information is less affected by ECT than the memory of events of an impersonal nature.\textsuperscript{43} Although retrograde amnesia often improves during the first few months after ECT, for many patients, recovery is incomplete, with prolonged amnesia regarding events that occurred close to the time of treatment.\textsuperscript{44} Preexisting cognitive impairment is predictive of amnesia after ECT, and amnesia is more likely in older adults.\textsuperscript{45} Variations in ECT technique (e.g., right unilateral electrode placement or ultrabrief pulse width) can reduce the incidence and severity of retrograde amnesia substantially.\textsuperscript{46,47} For example, persistent loss of autobiographical memories 2 months after treatment is greater with bilateral than with right unilateral ECT.\textsuperscript{43}

Other side effects of ECT include headache, muscle aches, nausea, and fatigue. Despite concerns about structural brain injury with ECT, studies in both humans and nonhuman primates have not shown evidence of anatomical damage.\textsuperscript{48-51}

**AREAS OF UNCERTAINTY**

Perhaps the most pressing issue in the field of ECT is how to prevent relapse after a remission has been induced by a short course of treatment during an acute episode of depression. In one trial, patients who did not receive any form of maintenance therapy had a relapse rate of 84% 6 months after ECT.\textsuperscript{52} Monotherapy with nortriptyline reduced the relapse rate to 60%, and combination therapy with nortriptyline and lithium reduced the relapse rate to 39\%.\textsuperscript{52} The CORE group found that 46% of patients with depression that remits after ECT remain well at 6 months when they receive maintenance treatment with either combination pharmacotherapy or maintenance ECT.\textsuperscript{53} In a report on ECT use in the community setting, only 36% of patients remained well, perhaps because of less aggressive maintenance treatment or premature discontinuation of ECT in the presence of residual symptoms.\textsuperscript{36}

Another concern involves the burden of cognitive side effects of ECT. In addition to changes in electrode placement, a shorter pulse width has been reported to reduce amnesia associated with ECT.\textsuperscript{54} Other approaches have included improving the localization of seizure induction with the use of magnetic fields that can be targeted more precisely than electrical stimulation because of the absence of impedance.\textsuperscript{55} Work to date with magnetic seizure therapy has been encouraging, but it is still in the research phase.

Other studies have examined the efficacy of alternatives to seizure induction for the treatment of depression. Electromagnetic treatments such as subconvulsive dosages of transcranial magnetic stimulation have been used with encouraging results and an excellent safety profile,\textsuperscript{56} but they are associated with a smaller effect size than that seen with ECT. Vagus-nerve stimulation is approved by the Food and Drug Administration as an alternative for the adjunctive management of treatment-resistant depression. This treatment does not have known cognitive side effects and has shown some benefit in long-term management,\textsuperscript{57} but it does not have the speed of action or the large effect size of ECT.

**GUIDELINES**

The APA endorses ECT when it is administered by properly qualified psychiatrists for appropriately selected patients in accordance with the guidelines of the APA's Task Force on Electroconvulsive Therapy.\textsuperscript{36} Most practice guidelines for depression recommend ECT only for difficult-to-treat depression, often as a fifth, sixth, or seventh step after the failure of other therapy. The APA also supports the use of ECT for relapse prevention. In the United Kingdom, the National Institute for Clinical Evidence recommends the restriction of ECT to patients with severe depression, catatonia,
or prolonged or severe mania, and, unlike the APA, this organization does not recommend ECT as maintenance therapy.58

The APA task force guidelines on ECT set forth detailed criteria for patient selection, medical screening, ECT procedures, and training in ECT.78 ECT practitioners must be credentialed by their local hospital, but there is no nationwide quality-assurance program or board certification for ECT practice in the United States. In other countries, more active approaches have been taken to monitor and ensure quality in ECT centers.59

**RECOMMENDATIONS**

I would recommend ECT for the patient described in the vignette for several reasons. ECT would be appropriate given her lack of a response to or intolerance of adequate trials of antidepressant medications and neuroleptic agents. In addition, the presence of suicidal ideation with a plan for suicide underscores the need for a rapidly acting and definitive treatment. The presence of the psychotic subtype in this patient is a good prognostic indicator for a response to ECT, as is her age. It would be appropriate to consider starting with right unilateral ECT at an adequate dosage above the seizure threshold, but if she does not have a response, bilateral ECT could be used. Given the severity of her depression and her history of multiple episodes, I would also recommend combining ECT with an antidepressant medication to prevent a relapse, tapering the ECT rather than abruptly discontinuing it on remission, and adding a mood stabilizer to the antidepressant to prevent a relapse. Maintenance ECT is also a reasonable strategy, and it should be discussed with the patient and her family before the initiation of treatment.

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