ECT in Treatment-Resistant Depression

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Electroconvulsive therapy (ECT), which has been in use for 75 years, is an important treatment for severe and treatment-resistant depression. Although it is acknowledged as the most effective acute treatment for severe mood and psychotic disorders, it remains controversial because of misperceptions about its use and lack of familiarity among health care professionals about modern ECT technique. The authors present an illustrative case of a patient for whom ECT is indicated. They review the basic and clinical science related to ECT's mechanism of action and discuss clinical issues in the administration of a course of ECT, including the consent process.

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ECT is a standard treatment in the modern psychiatric armamentarium, used mainly when antidepressant medications fail to adequately treat severe depression (1). Despite its unparalleled record of safety and efficacy, it is regarded as controversial outside of psychiatric circles, largely because of concerns about cognitive impairment and misunderstandings about the informed consent process. There have also been frequent misrepresentations of ECT in the media, and individuals and groups with particular social and political agendas have continued to convey distorted information about ECT (2). Uneasiness about our incomplete knowledge of ECT's mechanism of action is also offered as reason for discrediting the procedure. In this article, we present a case with illustrative clinical features, review clinical indications for ECT, present an overview of the neuroscience of ECT's effects on the brain, and consider ethical issues in the delivery of the treatment, with a focus on the consent process.

Indications

ECT is indicated primarily for the treatment of severe major depression, in the context of either unipolar or bipolar disorders (3). It is also indicated for the treatment of mania, schizophrenia, and catatonia (4). The U.S. Food and Drug Administration lists six "cleared indications for use" (analogous to "on-label" indications for a drug) of ECT devices: depression (unipolar and bipolar), schizophrenia, bipolar manic (and mixed) states, schizoaffective disorder, schizophreniform disorder, and catatonia.

In the United States, the vast majority of ECT is used for the treatment of unipolar depression, largely as a secondary treatment, after one or more trials of psychotropic medications have failed. ECT is indicated as a primary treatment when the urgency of the clinical situation (suicide risk, malnutrition, agitated psychosis) demands rapid symptomatic improvement (3). The use of ECT for mania is uncommon, reserved for severely treatment-resistant cases (5). In many countries, ECT is used much more commonly for the treatment of schizophrenia than it is in the United States (6). This discrepancy is likely a result of different medical cultures rather than any fundamental disagreement about the data supporting ECT's efficacy in certain phases or symptomatic presentations of schizophrenia. While relevant for a much smaller number of patients, there has been a resurgence of interest in the use of ECT to treat catatonia (7).

There has been little agreement in the field about when to refer a patient with moderately to severely treatment-resistant depression for ECT. Many practitioners do not consider referral for ECT before multiple medications have been tried, a process that may span many months or even years and leave the patient seriously ill, suffering, and dysfunctional, for a prolonged period (8). Longer duration of depressive episode has been associated with greater treatment resistance, another reason such delay may be inadvisable (9). There is greater agreement on use of ECT when the patient is at the high end of the severity spectrum, clearly urgently or emergently ill; in such cases, ECT should be considered early on, perhaps before any medication trials. Situations that compel this "primary" use of ECT are active suicidal ideation and behavior; severe weight loss, malnutrition, or dehydration from loss of appetite due to depression,

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A 72-year-old woman with treatment-resistant major depression is considered for ECT.

"Ms. A," a 72-year-old recently retired professional, presents for outpatient psychiatric treatment of an ongoing episode of major depression with psychotic features. She reports a history of mild postpartum depression 40 years previously; her mother had committed suicide in her thirties after a "nervous breakdown." Ms. A's current episode started 2 years ago, with onset of sad mood, loss of interest in her usual activities, and suspiciousness that soon progressed to frank paranoia. An initial trial of escitalopram, augmented with olanzapine, in conjunction with weekly psychotherapy, was only modestly helpful. A suicide attempt by ingestion of a large amount of her medications resulted in a 5-week involuntary hospitalization. Over the next 18 months, multiple antidepressants, atypical antipsychotics, and augmenting strategies (lithium and triiodothyronine) were tried, still in conjunction with weekly psychotherapy. Ms. A remains depressed and barely able to function. An ECT consultation results in the recommendation of a trial of outpatient ECT. The patient's relevant medical conditions are hypertension and gastroesophageal reflux disease, for which preprocedure antihypertensive and antireflux medications are prescribed. A course of eight right unilateral ultrabrief pulse treatments results in nearly complete symptom resolution (the patient's score on the 24-item Hamilton Depression Rating Scale went from 38 to 6) and very modest recent memory impairment. Ms. A is continued on venlafaxine and as-needed lorazepam, as well as weekly psychotherapy. She has been able to resume all of her usual activities and remains well at follow-up 1 year later.

with accompanying worsening of medical status; and psychosis accompanied by agitation (10).

Mechanism of Action

A wealth of preclinical and clinical data attest to ECT's potent effects on the CNS (11). Ottosson's classic research with lidocaine-modified ECT seizures (12) established the seizure as the crucial component of ECT. Later, Sackeim and colleagues' (13) finding that low-dose right unilateral ECT may produce suboptimal clinical outcomes confirmed that ECT seizures are not all equivalent. It appears that both the anatomic site of seizure initiation and the type and intensity of the electrical stimulus affect both efficacy and cognitive effects (14). The four main theories of ECT's mechanism of action are the classical monoamine neurotransmitter theory, the neuroendocrine theory, the anticonvulsant theory, and the neurotrophic theory (10, 15).

The consent process should not be limited to the provision of written materials. There should be ample opportunity for discussions between consentor and physician.

The classical monoamine neurotransmitter theory suggests that ECT works by increasing neurotransmitter availability or changing receptor sensitivity. ECT is known to enhance dopaminergic, serotonergic, and adrenergic neurotransmission (16), and GABA and glutamate have been implicated as well (17, 18). The neuroendocrine theory suggests that ECT induces a release of hypothalamic or pituitary hormones, including prolactin, thyroid-stimulating hormone, adrenocorticotropic hormone, and endorphins (19); it is theorized that the release of these hormones results in the treatment's antidepressant effect. Further evidence for this theory lies in the dysregulation of the hypothalamic-pituitary-adrenal axis in melancholic depression, an abnormality that is corrected with successful ECT (20). The anticonvulsant theory posits that ECT's efficacy is a result of the anticonvulsant nature of the treatment. Evidence for this mechanism includes the observations that seizure threshold rises (and seizure duration decreases) over a course of ECT (21, 22). Neurohormones and GABA have been postulated to mediate this anticonvulsant effect (22). The neurotrophic theory suggests that ECT may have a positive effect by inducing neurogenesis and increasing neurotrophic signaling in the brain. Animal studies have demonstrated increased neurogenesis and synaptogenesis within the rat hippocampus after electroconvulsive shock (ECS), an animal model of ECT (23, 24). Neurotrophic factors, such as brain-derived neurotrophic factor, have been shown to be increased after ECS in animals and ECT in humans (25). Functional neuroimaging studies have suggested that ECT paradoxically further decreases the "hypofrontality" demonstrated in depressed populations (26). Further neuroimaging research is needed to more fully elucidate the effects of ECT on regional brain function.

Clinical Issues

The ECT Consultation

An ECT consultation by an ECT specialist is typically the first step in prescribing the treatment for a patient (27). It is generally agreed that psychiatrists, and to a more limited extent other mental health practitioners, should be knowledgeable about when to seek an ECT consultation. The consultation, performed on either an inpatient or outpatient basis, serves three main functions: 1) to verify

that the patient has an ECT-responsive diagnosis of adequate severity to warrant the treatment; 2) to assess the patient's general medical history and current general medical status in order to maximize safety during the treatment; and 3) to begin the consent process (10). The presence of a family member is often critical, for several reasons: the family member can corroborate the patient's history, help the patient understand information about ECT, and learn how best to care for the patient during the ECT process. The consultation is also often an important opportunity to educate family members and correct misperceptions about ECT.

Clinical Decision Making

Based on the individual's condition as assessed at the consultation, planning for the upcoming course of ECT can begin. This includes decisions about whether to use inpatient or outpatient treatment, the elements of the pre-ECT general medical evaluation, the choice of electrode placement, the frequency of treatment, and concomitant medications. In determining whether to use an inpatient or outpatient course of ECT, one must consider the severity of the patient's illness, including presence of active suicidal ideation and the nature of any comorbid medical illness, and the family's availability to supervise and care for the patient after treatment. A recent trend in the United States has been to perform ECT increasingly on an outpatient basis (28).

Pre-ECT Medical Evaluation

The process of medical optimization prior to ECT begins with taking a full general medical history during the ECT consultation. The cardiovascular, pulmonary, and central nervous systems are the organ systems of most relevance. Depending on the severity and complexity of medical problems, specialty consultations may be considered, most commonly with internal medicine and cardiology (29, 30). Each patient will have a consultation by an anesthesiologist, either in advance or on the day of the first ECT treatment. The pre-ECT laboratory evaluation varies among institutions but typically includes an ECG, a CBC, a chemistry panel, and a pregnancy test for women of childbearing age. Pre-ECT X-rays (chest X-ray, spine films) and brain imaging are no longer routinely ordered. They may be appropriate when there is particular concern about the possibility of an abnormality in a patient. Dental evaluation should be performed prior to ECT; loose teeth may need to be extracted to avoid risk of aspiration.

Decisions about which medications, both psychotropic and general medical, to continue or withhold during the course of ECT are made by the ECT psychiatrist in collaboration with the anesthesiologist and other consultants. Whereas in the past most psychotropic medications were discontinued during ECT, current practice is much more permissive, particularly with regard to antidepressants. There is growing evidence that certain antidepressants may augment the acute ECT response (31), and clinicians are increasingly aware of the need for a carefully planned continuation treatment strategy immediately following an ECT series to help lower high relapse rates. Medications with anticonvulsant properties are generally decreased or discontinued (32). Commonly, if a patient is taking antihypertensive, other cardiac, or antigastroesophageal reflux medications, these are given on the morning of the procedure; otherwise, the patient is instructed not to eat or drink for 8 hours.

Physiological Monitoring During ECT

The comprehensive physiological monitoring that is part of modern ECT contributes to its remarkable safety. ECT is performed under general anesthesia with muscle paralysis; the standards for basic anesthesia monitoring outlined by the American Society of Anesthesiologists must be observed (33).

Vital signs (heart rate, blood pressure, temperature), blood oxygen saturation, end-tidal carbon dioxide levels, ECG, EEG, and electromyogram (to record the duration of the motor component of the seizure) are monitored during ECT. A nerve stimulator may also be used to assess the effects of the paralytic agent.

Blood pressure must be monitored throughout the procedure. Usually this is done with an automatic cuff set to cycle at regular intervals. Sympathetically mediated increases in blood pressure to 20%–30% above baseline are common, and in some patients a mean arterial pressure twice that of pretreatment levels has been recorded (34). At the very least, a blood pressure reading should be taken prior to induction of anesthesia, during the seizure or immediately after cessation of seizure activity, and when the patient has regained consciousness.

ECG is monitored as well, and the five-lead setup that allows for simultaneous monitoring of channels II and V5 is preferred. Initial activation of central parasympathetic centers by the electrical stimulus will result in bradycardia in up to 30% of patients, and short periods of asystole are not uncommon. Subsequent activation of the sympathetic nervous system during seizure activity will result in tachycardia in most patients. While these dysrhythmias are almost always benign and self-limited, close observation for signs of ischemia in patients at risk is warranted.

The use of pulse oximetry is also mandatory and should be employed continuously throughout the patient's stay in the treatment area until the use of supplementary oxygen is no longer necessary to maintain a saturation above 93%. Measurement of end-tidal CO_2 levels via capnometry is required. When coupled with a device capable of graphically displaying a wave form (capnography), it can be used to monitor respiration continuously. This is especially important during the brief period of paralysis while the patient is receiving positive-pressure ventilation, but it may also be helpful in ensuring adequate ventilation once spontaneous respiration resumes. Temperature should be measured prior to treatment, and equipment for repeated

measurement should remain immediately available in the treatment area. A nerve stimulator should be used to monitor the onset of paralysis, ensuring that the electrical stimulus is administered under optimal muscle relaxation.

Choice of Electrode Placement

In contemporary ECT practice, three electrode placements are commonly used: right unilateral, bilateral, and bifrontal (35). A substantial and sometimes contradictory literature has examined the efficacy and cognitive adverse effect profile of each placement. The literature's findings, in short, are that bilateral and bifrontal electrode placements may have slightly greater overall efficacy and speed of response, but may cause considerably more retrograde amnesia than right unilateral electrode placement (3). There is large individual variability among patients, both in antidepressant response and in cognitive adverse effects. One common treatment strategy is to start a course with right unilateral ECT; if the patient is not responding after three to six treatments, despite adjustments in stimulus dosing, a switch to bilateral placement may be made (36). In general, the more severely ill (both psychiatrically and medically) a patient is, the more likely he or she will be started with bilateral electrode placement. Patients who wish to participate in the decision-making process regarding electrode placement may be asked to express a preference after the pros and cons of each placement are explained. With right unilateral electrode placement, a newer type of electrical stimulus, ultrabrief pulse, shows promise for further reducing the cognitive adverse effects of ECT (37).

Frequency of Treatment

In the United States, ECT is typically administered three times a week, usually on a Monday, Wednesday, Friday schedule (38, 39). In other countries, a twice-a-week schedule is more common (40). Recent evidence suggests that outcomes are comparable between the two schedules, and that a three-times-per-week schedule may produce results slightly more quickly but cause somewhat more cognitive impairment (41).

Clinical Monitoring

It is important to monitor resolution of depressive symptoms as well as adverse effects during a course of ECT. Depressive symptoms are best monitored using a structured rating scale, such as the Hamilton Depression Rating Scale (42) or the Montgomery-Åsberg Depression Rating Scale (43). The scale should be administered at baseline and then at least weekly thereafter to document treatment response. A self-report scale, such as the Quick Inventory of Depressive Symptomatology–Self Report (44) may also be useful. Similarly, a cognitive assessment tool, such as the Mini-Mental State Examination (45) or the Montreal Cognitive Assessment (46), should be administered at baseline and at the end of the treatment course, or more frequently if there are concerns about cognitive adverse effects. However, well-documented clinical evaluations of mood change and cognitive status are also acceptable.

Consent for ECT

The informed consent process for ECT, compared with that for most other medical or surgical procedures, is unusual in several ways. First, whether used to treat an acute episode of illness or to prevent relapse, ECT involves a series of treatments. Therefore, consent should be obtained for a series of treatments, not for each procedure (unless otherwise mandated by local law or regulation). Next, the underlying illness as well as the treatment itself (in the event of significant memory impairment), may affect a patient's capacity for consent. It is likely that the consent process for ECT is among the most comprehensive and detailed in all of medicine and surgery: two sets of risk factors, medical and cognitive, are outlined; electrode placement and stimulus dosing are discussed, along with a detailed description of the treatment procedure, recovery, and behavioral restrictions during the treatment course. The typical consent form is three pages long; a separate, equally detailed, consent form is used for maintenance (as opposed to acute) ECT, and family members, when available, are virtually always involved (3, 47).

ECT consent requires an ongoing interaction between physician and consentor, with the physician providing the consentor with updates on the progress of treatment and any adverse effects, involving the consentor in decision making regarding any changes in treatment procedure or technique or changes in the risk-benefit ratio, and incorporating the consentor's concerns and wishes regarding these decisions.

The basic requirements for determining the adequacy of informed consent (3) include provision of adequate information about ECT; documentation that the patient (or proxy consentor) is capable of understanding and acting reasonably on this information; and the absence of coercion.

Information provided as part of the consent process should contain sufficient detail to allow a reasonable person to understand the nature of ECT and why it is being recommended and to evaluate its risks and benefits compared with alternative treatments. The language should be compatible with the consentor's education level, background, and intelligence to help ensure adequate comprehension. Too much technical detail, however, may be counterproductive (48).

The consent process should not be limited to the provision of written materials. There should be ample opportunity for discussions between consentor and physician in which the physician can summarize the relevant information in the consent form, provide additional information specific to the patient for whom ECT is being considered, and allow for discussion of questions and individual concerns. The use of supplemental video material describing and demonstrating ECT may be useful for some patients.

The patient should provide informed consent unless he or she lacks the capacity, or unless otherwise specified by law. Patients should be encouraged to involve significant others in the consent process. Capacity for

informed consent reflects the judgment that a patient is capable of understanding and acting reasonably on information provided about the procedure (3). In general, capacity to consent should be presumed to be present unless there is compelling evidence to the contrary. The presence of psychosis, thought disorder, or involuntary hospitalization does not automatically imply lack of consent capacity. Determination of consent capacity is usually made by the patient's attending physician, although consultation with another physician not directly involved with the patient's care may be sought if there is doubt.

Patients who have been adjudicated as legally incompetent for medical decision-making usually have consent for ECT provided by a legal guardian (substituted consent), although this may vary by jurisdiction. For patients with capacity to consent, ECT should be administered only with their agreement.

Coercion, which may be subtle or overt, plays no part in the ECT consent process. Competent patients who refuse ECT should never be threatened with discharge from a hospital or physician's practice, or with commitment, simply because they refuse ECT. On the other hand, as pointed out by McCall in a thoughtful editorial (49), there is a difference between coercion and persuasion. Patients referred for ECT often have profound ambivalence and indecisiveness as part of their illness and may need firm encouragement from their physician and significant others to agree to or continue with ECT. An appropriate balance must be struck between respecting a patient's autonomy and his or her need to receive effective treatment.

Consent should be reobtained if an unusually large number of treatments are administered in a series. This determination is made locally by each institution, but usually it would apply to a series involving more than 12–15 treatments. Consent should also be reobtained if there are changes in general medical risk factors or the risk-benefit equation.

Continuation and maintenance ECT differs from an acute ECT series in its purpose (prevention of relapse or recurrence, instead of treating acute symptoms). At the time continuation and maintenance ECT is started, the patient's condition is, by definition, improved, and intertreatment intervals are greater and more variable and endpoints of treatment less clearly defined. Since the purpose, risks, and benefits differ from those of an acute series, a different consent form should be signed for continuation and maintenance ECT (and repeated at least every 6 months).

Informed consent for ECT is mandated both ethically and by regulation. However, ECT should be considered no different from other medical procedures with comparable risks and benefits. Although practitioners are legally obligated to follow state and local regulatory requirements regarding ECT consent, efforts should be made to correct attempts at overregulation that may unduly obstruct a patient's access to treatment.

A number of states have passed legislative and administrative codes regulating aspects of ECT practice. These vary from minimal regulation to efforts to control almost every aspect of the treatment (reviewed recently by Harris [50]). Three states—California, Texas, and New York—have legislative requirements that are more stringent and restrictive than the APA recommendations. California requires that even for voluntary patients consenting to ECT, *three* physicians must agree that ECT is indicated and that the patient has capacity to consent to the treatment. In addition, the patient must be provided with written information stating that there is a difference of opinion within the medical profession on the use of ECT. Texas has extensive reporting requirements for all facilities providing ECT and requires registration of all ECT devices. Two physicians must testify to the medical necessity of ECT in all patients over age 65, even though current data suggest that ECT is most often indicated in this group and that older age is a positive predictor of ECT response (51). New York has detailed guidelines for voluntary ECT, issued by the Office of Mental Health. A court must determine that a patient is incompetent to consent to ECT before involuntary ECT can be considered.

Consent issues and regulations governing the use of ECT in children and adolescents are even more complex and varied among jurisdictions, and at times they seem more influenced by emotional and political concerns than by the scientific literature.

As Winslade et al. (52) have pointed out, regulation is most appropriate in areas where basic legal questions exist, such as standards for informed consent, competency to consent, and involuntary treatment. It is least appropriate, and potentially harmful to good patient care, when legal regulations attempt to control medical indications for treatment and access to treatment for specific patient populations, treatment techniques, and details of medical record keeping.

Clinical Guidance

The illustrative case presented above serves to make important points about the management of a patient with severe treatment-resistant depression who is referred for ECT. The diagnosis of psychotic depression, a strong family history of mood disorder, a long episode duration, and multiple medication trial failures make this patient an excellent candidate for ECT. Review of her general medical condition indicated that she had hypertension and gastroesophageal reflux disease. Medications for these conditions should be given before each ECT treatment in order to increase the safety of the procedure. Right unilateral ultrabrief pulse ECT was chosen, in consultation with the patient, to minimize cognitive adverse effects. Current practice is to empirically determine, or estimate, the patient's seizure threshold at the initial treatment, with subsequent treatments administered at a multiple of approximately six times seizure threshold for right unilateral electrode placement and approximately 1.5–2.5 times seizure threshold for bilateral electrode placement (14). If the

patient in the vignette had not begun to respond after three to six treatments, switching to bilateral electrode placement with brief pulse stimuli would have been the next treatment option. Continuation pharmacotherapy with an antidepressant was prescribed; continuation therapy is necessary for virtually all patients after ECT, to maximize the likelihood of prolonged remission (53, 54). For many patients, continuation post-ECT pharmacotherapy should be even more aggressive, using a combination of medications from different classes (antidepressants, antipsychotics, and anticonvulsants).

For a subset of patients with demonstrated severe and highly recurrent illness, continuation and maintenance ECT should be prescribed; for some patients, this may be in addition to combination pharmacotherapy. There is no single schedule for continuation and maintenance ECT that applies to all patients; some degree of individualization and clinical judgment is required. The acute course (three times per week) can be followed by a taper to twice or once a week, then once a week for several weeks. The interval between treatments should then be gradually extended, the goal being to determine the maximal interval that results in maintenance of full remission. Most patients will end up on a schedule of a single treatment every 3–6 weeks, although some will require more frequent treatment. For patients with a clearly demonstrated need for ongoing maintenance ECT, there is no evidence that a limit should be imposed on the lifetime number of treatments (55).

Finally, consent issues are always central to the administration of ECT; psychotic symptoms do not ordinarily affect the patient's capacity to provide fully informed consent. Since regulations vary by state, practitioners should be knowledgeable about local legal requirements. Referral for ECT consultation should be considered for the severely depressed patient who either is urgently ill or has had inadequate response to other treatments.

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Clinical Guidance: ECT in Treatment-Resistant Depression

Electroconvulsive therapy (ECT) is often effective for severely depressed patients who have not responded to multiple medication trials or who are at imminent risk of suicide or other acute clinical condition. Kellner et al. highlight the safety and efficacy of ECT while stressing the importance of the pre-ECT medical evaluation and consent process. A common strategy is to start with right unilateral ECT, which produces less retrograde amnesia, and if it is ineffective, switch to bilateral electrode placement. Antidepressants may be continued during ECT and may augment the response. Psychotic or other severe symptoms do not ordinarily affect the capacity to provide fully informed consent, but a family member can often corroborate the patient's history, help the patient understand information about ECT, and care for the patient during treatment. ECT practitioners should know the local legal requirements, which vary by state and are more complex for children and adolescents.