Electroconvulsive Therapy Device Classification: Response to FDA Advisory Panel Hearing and Recommendations

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ABSTRACT

Electroconvulsive therapy (ECT) is a safe and highly effective treatment for management of acute episodes of a variety of serious mental disorders, particularly for major depressive episodes that are resistant to multiple interventions with treatment alternatives. As such, the National Network of Depression Centers (NNDC), a consortium of major academic centers with interest and expertise in this area, believes there is an important public health need for ECT to remain available for clinical use. As with all medical devices, ECT is regulated by the US Food and Drug Administration (FDA), which is presently involved in formulating a proposed rule as to how such devices should be classified. Since such classification may have substantial effects on the availability of ECT to patients for whom it is clinically indicated, the NNDC has reviewed the information provided by the FDA to its Advisory Panel, as well as the subsequent deliberations of the Panel itself at a January 2011 public hearing. This review indicates that the FDA may have substantially underestimated the efficacy of ECT as a means to produce large clinical improvements for individuals suffering from severe major depressive disorders and that such an underestimate likely affected the Panel's willingness to recommend reclassification of ECT devices to a less restrictive category. In addition, the NNDC's review generates support for a variety of methods by which the safety of ECT can be ensured, which is an essential requirement for such reclassification.

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On January 27 and 28, 2011, the Neurological Devices Panel of the Medical Devices Advisory Committee to the US Food and Drug Administration (FDA) Center for Devices and Radiologic Health met in open public session to review the issue of electroconvulsive therapy (ECT) device classification and to make recommendations to the FDA regarding device classification for various psychiatric diagnoses.[1–3] In its unofficial voting, the Panel was closely split on reclassification from Class III to Class II for 2 diagnoses: major depression and catatonia. A preponderance of votes against reclassification was present for other diagnoses, including mania and schizophrenia spectrum disorders. At the end of the hearing, the FDA indicated that it would review the Panel's recommendations, along with other information at hand, including its own in-house review, and make a proposed final recommendation.

The National Network of Depression Centers (NNDC) is a consortium of leading depression centers and academic medical centers that have come together to effect a transformation in the field of mood disorders, making diagnosis more standardized and treatments more evidence-based, affordable, accessible, personalized, and precise. The NNDC facilitates large-scale, measurement-based collaborative projects among its 21-member Centers of Excellence.

NNDC members have a substantial interest in the matter of ECT device classification, which will have a major impact on the availability of this treatment modality. NNDC members have carefully reviewed the Panel proceedings, as well as the extensive literature relevant to the efficacy and safety of ECT, and believe strongly that there is ample evidence for reclassification of ECT devices to Class II. It is our hope that the FDA's careful consideration of this information will assist the FDA in the formulation of its proposed final rule regarding ECT device reclassification.

We believe that the following information and clarifications, which we have also provided to the FDA, are of relevance to all practitioners who evaluate and treat those with major depressive disorders, especially treatment-resistant depression.

I. THE NEED FOR ECT IN THE MANAGEMENT OF TREATMENT-RESISTANT MAJOR DEPRESSION

Major depression is a serious illness and a major public health concern. In any given year, over 20 million Americans suffer from clinical depression, according to recent estimates from the Centers for Disease Control and Prevention.[4] Results from the National Comorbidity Survey Replication indicate a lifetime prevalence of 16.5% and a 12-month prevalence of 6.7% in the US adult population.[5]

Treatment approaches for depression include pharmacotherapy, psychological and social therapies, ECT, and other forms of neuromodulation. Recent data from the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) clinical trial indicate that, despite an adequate course of first-line antidepressant treatment, nearly 50% of those who suffer from this condition will experience no response or only a partial response.[6] Furthermore, this large study demonstrated that the likelihood of response

after 2 medication trial failures is less than 20% in a third trial. Failure to achieve response after multiple successive trials is termed *treatment-resistant depression* (TRD).[7] Against this backdrop of great need and lack of effective treatments for patients who have tried all available strategies and who remain severely or chronically ill, ECT often stands as the last best hope. Numerous scientific reviews, meta-analyses, and recent studies document the superior acute efficacy of ECT in major depression, psychotic depression, and catatonia, particularly in those with TRD.[8–12] Given the strong safety record of present ECT devices (see section IV) and the essential need for seriously ill patients to have access to this most efficacious treatment amid a lack of viable alternatives, the continued availability of ECT is essential.

II. ECT IS AN EFFECTIVE TREATMENT

The FDA's systematic review largely demonstrated that ECT was efficacious in its ability to produce an acute beneficial response. However, the Panel deliberations on this issue were particularly focused on the point that FDA's meta-analysis for ECT vs sham ECT, although statistically significant, indicated "only" a 7.1-point advantage for true ECT in the Hamilton Depression Rating Scale (HDRS) score—a difference that was not perceived as being highly clinically significant. Notwithstanding the fact that a 7.1-point difference in HDRS improvement with ECT vs sham ECT is already much greater than what was claimed for both transcranial magnetic stimulation (2.4-point difference) and the newer antidepressant medications desvenlafaxine vs duloxetine vs placebo (2.9-point difference) in their successful FDA submissions, it is our position that this 7.1-point difference, while significant, is itself a gross underestimate of the true effect size between ECT and sham ECT. In its meta-analysis of ECT vs sham ECT randomized controlled trials, the FDA included a study by Lambourn and Gill,[13] which has been widely criticized as using a type of barely suprathreshold unilateral ECT that is known to be ineffective.[14] In addition, the FDA included a study by Jagadeesh and coauthors,[15] a small Indian trial (total of 24 subjects) in which the "sham" group all received 1 true ECT treatment. Finally, the FDA included a study by Wilson and colleagues,[16] which had a largest group size of only 6 subjects.

The remaining studies included in the FDA's meta-analysis were 2 larger recent sham ECT trials. While Johnstone and coworkers[17] reported an ECT vs sham ECT HDRS improvement difference of 12 points, Brandon and colleagues[18] found a 23-point difference. In clinical terms, these differences are huge, and they are also quite consistent with the findings of a comparably sized English study by Gregory and coworkers,[19] who reported a 15-point HDRS difference favoring true ECT. This evidence is also consistent with the high remission and response rates found in recent National Institute of Mental Health–funded ECT trials comparing various ECT modalities, albeit even in highly treatment-resistant subjects.[11,14] In addition, the evidence is consistent with the results of other meta-analyses, including 2 of the most recent, both of which, using rigorous Cochrane-compatible methodology, reported very large standardized effect sizes close to 1.0.[9,20] Together, these findings demonstrate that the efficacy of ECT in the treatment of major depressive episodes is not just clinically significant, but highly clinically significant to a degree exceeding that of all other available treatment alternatives. We believe that had the Panel considered a more accurately formulated meta-analysis of effect size differences between ECT and sham ECT, their advice to the FDA regarding the indication of major depression would have been less closely split and would have been favorable for moving ECT devices to a Class II designation.

III. THE PURPOSE BEHIND AN ACUTE ECT COURSE IS TO TREAT AN EPISODE OF ILLNESS, NOT TO PREVENT EVENTUAL RELAPSE

A second concern expressed by the Panel was that, because there is limited evidence of efficacy of ECT past the acute phase of illness, its clinical importance is marginal. The NNDC believes this argument is based on 2 erroneous understandings. First, the primary treatment goal of an acute index course of ECT is to bring an individual out of a severe episode of illness. This is analogous to the use of a course of antibiotics to treat an episode of infection. The fact that patients susceptible to future infections may get sick again is, of course, no reason to question the effectiveness of the antibiotic as an acute treatment. The same is true of ECT with respect to its ability to induce a clinically meaningful degree of improvement in severely acutely ill and highly treatment-resistant patients with a major depressive episode, particularly given the substantial morbidity and mortality that is associated with such episodes. Second, the common longitudinal course of major depressive illness is episodic and recurrent. Maintenance of wellness is especially difficult for those with treatment resistance. Research investigations are needed to develop improved strategies for maintaining wellness, but that aim is a separate clinical objective.

IV. THE SAFETY OF ECT

One of the most disturbing concerns often expressed in regard to ECT is whether it causes brain damage. Recent evidence, however, suggests that major depression itself is associated with a neurodegenerative process. A loss of gray and white matter in depressed individuals is found in both cortical and subcortical areas and is correlated with a loss of cognitive and memory capacities. The extent of injury due to depression is more marked with the duration of depression, the amount of time the depression is untreated, and the number of prior episodes of depression.[21–24] Therefore, institution of a rapidly and highly effective treatment, ie, ECT, can actually be expected to reduce the risk of neuropathologic changes.

In addition, postmortem studies of patients who have had ECT treatments using modern techniques involving hyperoxygenation, anesthesia, and neuromuscular blockade do not support brain damage as a result of ECT.[25] In fact, animal studies have shown that electroshock stimulation increases brain-derived neurotrophic factor expression,

which enhances cell survival and viability and does not cause neuronal damage or death.[25–27]

Mortality and morbidity due to the ECT procedure have been studied and compared to outcomes with comparable procedures requiring anesthesia. In the 2003 National Healthcare Quality Report,[28] the rate of complication associated with anesthesia was found to be 0.8447% among surgical discharges. This was similar to a study of 3.7 million surgical procedures in The Netherlands that reported a mortality rate of low-risk procedures at 0.07%.[29]

In multiple large database studies, ECT has been consistently shown to have a mortality rate lower than or comparable to those of other anesthetic procedures and equal or decreased morbidity secondary to the treatment. For example, no deaths were reported in the recently published Veterans Affairs National Center for Patient Safety database of 73,440 treatments.[30] These data are consistent with the proper classification of ECT as low risk, as defined by the American College of Cardiology/American Heart Association criteria[31] (less than 1% rate of mortality).

Major depression itself substantially increases the risk of death and is especially implicated in death by unnatural causes and cardiovascular disease.[32] However, ECT has been shown in most studies to reduce overall mortality rates.[33–36] ECT appears to decrease, or does not significantly increase, suicidality.[30,37]

There are fewer deaths associated with ECT compared to other low-risk procedures requiring anesthesia and a comparable or decreased rate of complication as a result of the treatment. The evidence to date weighs heavily against the suggestion that ECT can cause brain damage, but rather, like other antidepressant treatments, ECT may in fact prevent brain damage caused by depression itself. The data are overwhelmingly in favor of ECT's being safe. It remains a procedure that is not only the most effective treatment for depression, but also a treatment that reduces overall morbidity and mortality rates in depressed patients as well.

V. THE EFFECTS OF ECT ON MEMORY FUNCTION

In the Advisory Panel's deliberation of potential adverse effects associated with ECT, by far the major focus was on memory dysfunction. This focus was indeed consistent with the FDA's own in-house systematic review of the literature and meta-analyses as well as much of the public testimony presented to the Panel prior to their deliberations. NNDC Task Group members agree that memory dysfunction is the primary side effect of concern with ECT and that, although it is not invariably present, it is common. The FDA correctly pointed out, in its presentation to the Advisory Panel, that there is little to no evidence, on the basis of controlled studies, that objective test measures of memory function demonstrate persistent amnesia with ECT, with the possible exception of autobiographic memory with bilateral electrode placement. If, however, one considers subjective (ie, self-report) data, a more complex picture is present, in that it is not a rare phenomenon that some individuals who have received ECT believe that persistent memory impairment, particularly in terms of personal autobiographic memory, does occur. The etiology of these impairments is complex and is confounded by a variety of non–ECT-related factors, both neurobiological (eg, medications, preexisting and concurrent cerebral dysfunction, substance abuse) and nosologic (eg, underlying depression).

The American Psychiatric Association (APA), in its recommendations for the practice of ECT,[8] has clearly stated that mention of the possibility of both acute and persistent memory impairment should be conveyed to all individuals for whom ECT is recommended, as part of the informed consent procedure, with specific mention of personal, or autobiographic, memory as being potentially affected. A requirement that ECT device manufacturers include a statement that device users incorporate such information into informed consent discussions with their patients would constitute a useful special control for ECT as a Class II device. Other potential special controls that would serve to provide reasonable assurance for the safety of ECT with respect to memory effects could be established in regard to stimulus characteristics, routine choice of stimulus electrode placement, and recommendations for monitoring of outcome.

VI. MONITORING OF ECT-RELATED COGNITIVE EFFECTS

During its deliberations, the Advisory Panel discussed the value and manner of formal memory testing prior to, during, and following ECT, as well as the credentials for those who would perform such testing. The NNDC believes that the findings in the FDA's review, as well as the overall literature in this area, including 2 recent reviews cited by the FDA,[38,39] indicate that (1) routine formal pre-ECT memory assessment is not indicated, (2) ongoing simple objective and subjective assessment of memory function should be carried out during an acute (index) ECT course, and (3) formal post-ECT memory testing should be required only if acute memory impairment is severe or if there are substantial patient complaints of potentially ECT-related memory impairment lasting several months or more.

With respect to formal pre-ECT memory testing, there is no evidence that doing this would affect treatment choice. While it might be presumed that such testing constitutes a "baseline" in regard to potential subsequent formal testing, the results of any formal pre-ECT testing would frequently be heavily confounded by the presence of severe depression symptoms, as well as the effects of concurrent medications.

Ongoing assessment of memory function during an acute ECT course (also recommended by the APA) is necessary to ensure that appropriate treatment modifications can be instituted if necessary. The use of formal testing for such a purpose would be counterproductive, in that such testing does not focus on the types of memory dysfunction that are most bothersome to individuals receiving ECT and is usually not logistically feasible. Alternative "bedside" means of testing (eg, delayed recall of 3 items [different for each treatment], global self-rating by the patient and rating by any significant other who is available, and evidence of ability to

recall life-relevant material since last treatment) are easy to devise, rapid to administer, and already in place in multiple institutions.

VII. MISCONCEPTIONS ABOUT ECT

Despite ECT's well-documented record of efficacy and safety for severe forms of mental illness, misconceptions persist and help fuel public and professional opposition to its use.[40,41] Present misconceptions about ECT include the following:

- ***ECT is obsolete and rarely used nowadays.*** The facts are that ECT is widely used today and is essential for the management of severe and often treatment-refractory psychiatric disorders. Approximately 100,000 people in the United States and over 1,000,000 worldwide are treated annually.[42,43]
- ***ECT is done to get doctors rich.*** Actually, insurance payments for ECT to psychiatrists are relatively low as compared with other psychiatric services. Hospitals often cannot meet the costs of providing ECT, especially under Medicare and Medicaid reimbursement. For these reasons and others, ECT is not available in some communities in the United States.[42,43]
- ***ECT is administered to patients against their will for behavioral control.*** The vast majority of ECT in the United States is provided to patients who have given informed consent under regulations determined by the individual states, with provision for surrogate decision-making for incapacitated patients.[44,45] The APA Task Force on ECT has clear recommendations for this consent process, which includes provision of adequate information to a competent patient and the absence of coercion.[8] The quality of the interactions between patient and physician is emphasized, especially as consent for ECT is an ongoing process.
- ***ECT is painful and cruel and causes terrible side effects.*** Scientific studies have shown that patients who actually receive ECT are much more favorable about it than are the general public or patients who have not received ECT. They report low levels of side effects, and, in one study, 98% were open to the idea of receiving it if they became depressed again.[46,47]

VIII. WHY ECT DEVICES SHOULD BE RECLASSIFIED

Reclassification of a medical device from Class III to Class II requires that the device be effective and that any major risks can be maintained within a reasonable level through the use of identified special controls. NNDC Task Group members strongly believe that convincing evidence indicates that ECT is highly effective in the treatment of severe major depression; is, in fact, the most effective and rapid treatment available for this disorder in appropriate patients; and, in some cases, is lifesaving. The risks of ECT, as discussed earlier, are definable and can be controlled to a substantial degree by a wide variety of potential special controls, ranging from constraints on who can use the device, to device labeling, to limitations on stimulus parameters and device output, to required elements of informed consent, physiologic monitoring during treatments, and monitoring of outcome, both for efficacy and for adverse effects. Examples for all of these potential special controls have been characterized in published APA recommendations[8] referenced earlier in this article. The NNDC believes that, given that all treatments (and also the failure to effectively treat a patient) are associated with risks, the determination of what constitutes a "reasonable" level of risk must be considered within the context of the severity, mortality, and morbidity of the condition if it were to remain untreated and the relative efficacy and safety of available treatment alternatives at that point in the course of illness. In present circumstances, individuals referred for ECT represent a small, but highly compelling, subset of those with major depression, that is, those who are highly treatment resistant or whose condition is so dire that the need for a definitive response is urgent and, at times, even lifesaving. Usually, there are no other viable choices for these individuals than ECT.

While some FDA Advisory Panel members stated their belief that the efficacy and safety of ECT devices are sufficiently strong to make it highly likely that premarket approval would be granted, others expressed a concern that the lack of specificity in Class III premarket approval requirements raises the possibility that the FDA's evidentiary requirements could be held to a standard so artificially high that it would be impossible for the small companies who manufacture ECT devices to realistically meet.[48] Even if financial resources were available, it is extremely unlikely that any US medical school institutional review board would allow another "sham" ECT–controlled study to be conducted, as it would be considered unethical to deprive such severely ill individuals of a known effective treatment. The NNDC believes that maintenance of ECT devices in Class III for the treatment of major depression would pose a substantial risk to the future availability of ECT in this country and strongly urges the FDA to reclassify ECT devices to Class II.

Drug names: desvenlafaxine (Pristiq), duloxetine (Cymbalta).

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