AMERICAN PSYCHIATRIC ASSOCIATION

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March 10th, 2016

Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Neurological Devices; Reclassification of Electroconvulsive Therapy Devices Intended for Use in Treating Severe Major Depressive Episode in Patients 18 Years of Age and Older Who Are Treatment Resistant or Require a Rapid Response; Effective Date of Requirement for Premarket Approval for Electroconvulsive Therapy for Certain Specified Intended Uses [Docket No. FDA–2014–N–1210]

Electroconvulsive Therapy Devices for Class II Intended Uses: Draft Guidance for Industry, Clinicians, and FDA Staff; Availability [Docket No. FDA–2014–D–1318]

Dear Commissioner Califf,

The American Psychiatric Association (APA), the national medical specialty society representing more than 36,000 psychiatric physicians and their patients, appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) concerning the proposed order (2014-N-1210) and draft guidance for industry, clinicians and FDA staff (2014-D-1318) related to electroconvulsive therapy (ECT) devices.

Given the importance of ECT as a lifesaving treatment for the severely mentally ill and the long established history of ECT safety and efficacy, the APA strongly supports the FDA proposal to reclassify ECT devices into class II (special controls) for use in treating severe major depressive episode (MDE) associated with major depressive disorder or bipolar disorder in patients who are treatment resistant or who require a rapid response due to the severity of their psychiatric or medical condition.

The extensive body of evidence for safe and effective use of ECT in the treatment of major depressive episodes is well described in the FDA proposed order.[1] Reports published since the FDA public hearing in 2011 include randomized trials that compare different ECT electrode placements or stimulus parameters. This research consistently shows substantial rates of response and remission of treatment-resistant major depressive episodes to ECT,[2] particularly when compared to response of treatment-resistant depression to additional trials of pharmacotherapy.[3] In addition, analyses show rates of remission and response in individuals with bipolar depressive episodes that are generally comparable to that observed with major depressive disorder.[4] These data

provide further support for the proposed reclassification of ECT devices to class II for major depressive episodes.

The APA recommends that a class II designation also be given for catatonia, manic episodes (in bipolar disorder), schizophrenia, and schizoaffective disorder and that the patient population in each of these illnesses be limited to individuals with treatment-resistant psychiatric disorders and/or patients with life-threatening conditions related to their underlying psychiatric condition. We also recommend that the class II designation include ECT treatment for children and adolescents meeting the criteria for treatment resistance and in need of a potentially life-saving intervention for the conditions previously indicated and for MDE associated with major depressive disorder or bipolar disorder.

From a safety standpoint, as the FDA notes, ECT-related risks for these conditions are comparable for major depressive episodes.[5] Evidence from peer-reviewed scientific literature, which meets the FDA definition of valid scientific evidence, supports the benefits of ECT in these conditions.[6] This research is summarized below and includes reports published since the FDA public hearing in 2011, although these comments should not be construed as a complete review of all available scientific evidence. Consequently, in individuals with treatment-resistant psychiatric conditions, or in which the patient's symptoms are life-threatening, the probable benefit to health from use of ECT outweighs the probable injury or illness. Any reclassification should not have the unintended consequence of unfairly reducing access for such life-saving treatment.

The following includes a more detailed discussion of our recommendations, as well as our specific suggestions for how to safely and effectively deliver ECT to emergently ill patients.

Evidence for use of ECT in Catatonia

In patients with catatonia, ECT provides relief in most instances in which there is no significant response to benzodiazepines, which represent the recommended first-line treatment.[7] In a randomized controlled trial (RCT) comparing ECT to risperidone in patients who did not respond to lorazepam, ECT response was found to be superior.[8] Overall, response to ECT is routinely reported in 80-100 percent of catatonic patients[9] with a similarly robust response rate of 75 percent in patients with catatonia who are under the age of 18 years.[10] Furthermore, when insufficiently treated, catatonia is associated with significant mortality and morbidity due to complications such as dehydration,[11] rhabdomyolysis with associated kidney injury, deep vein thrombosis (DVT) and subsequent pulmonary embolism (PE),[12] decubitus ulcers with the possibility of infection and disseminated sepsis,[13] or aspiration pneumonia.[14] For these reasons, ECT is already the "gold standard" of treatment for catatonia when pharmacological approaches, such as use of benzodiazepines, are ineffective.[15]

Evidence for use of ECT in Mania

ECT also has demonstrated efficacy in individuals with acute manic episodes on the basis of a large case series,[16] retrospective studies,[17] and prospective comparison studies.[18] One prospective trial compared ECT with lithium treatment;[19] another compared ECT with combined treatment with lithium and haloperidol;[20] a third study compared real and sham ECT in patients receiving neuroleptic treatment.[21] Each of these studies found that ECT was efficacious and resulted in better short-term outcomes than the comparison treatments. In addition, a comprehensive review of the English-language literature

found that response to ECT in acute mania was equivalent or superior to treatment with lithium carbonate or chlorpromazine.[22] Furthermore, ECT was associated with remission or marked clinical improvement in 80 percent of 589 patients with acute mania despite the fact that a substantial number had not responded to other treatments[23] and response to placebo in such patients is low.[24] Case reports have also supported the efficacy of continuation ECT in patients with rapid cycling or following improvement of manic or mixed episodes to an acute course of ECT.[25] Given these benefits, both national and international practice guidelines suggest ECT as an option in patients with severe, treatment-resistant mania.[26]

Evidence for use of ECT in Schizophrenia and Schizoaffective Disorder

In individuals with schizophrenia and schizoaffective disorder, ECT is typically administered in combination with an antipsychotic medication. In studies since 1980 that include individuals with either schizophrenia or schizoaffective disorder, therapeutic benefits are seen for ECT combined with antipsychotic medication as compared with antipsychotic medication alone or antipsychotic plus sham treatment.[27] A Cochrane meta-analysis of these studies concludes that "ECT, combined with treatment with antipsychotic drugs, may be considered an option for people with schizophrenia, particularly when rapid global improvement and reduction of symptoms is desired" or "for those with schizophrenia who show limited response to medication alone."[28] In patients with schizophrenia who had not responded to clozapine, a recent randomized prospective trial found improved outcomes with a combination of clozapine and ECT as compared with continued clozapine treatment alone.[29] Specifically, an acute series of ECT plus clozapine showed a 50 percent responder rate (using rigorous response criteria) compared to 0 percent for clozapine alone. In addition, when the clozapine alone subjects were then crossed over to receive combination treatment, 47 percent responded. In addition, a recent meta-analysis of the applicable published literature shows a response rate of 66 percent to clozapine in combination with ECT among patients with schizophrenia who have not responded to clozapine previously.[30] When individuals with treatment-resistant schizophrenia have responded to an acute course of ECT in combination with antipsychotic medication, persistent response can often be achieved with continuation and maintenance ECT.[31] In a randomized control trial of patients with treatment-resistant schizophrenia, the combination of an antipsychotic with ECT was significantly superior to ECT alone or antipsychotic alone in preventing relapse at 6 months.[32] Given these benefits of ECT, practice guidelines suggest ECT as an option in patients with schizophrenia whose symptoms have not responded to antipsychotic medications particularly when symptoms include catatonia, severe and persistent psychosis, or suicidal ideation and behavior.[33]

Evidence for use of ECT in children and adolescents with severe and potentially life-threatening symptoms

Children and adolescents are treated infrequently with ECT. When a decision is made to use ECT in a child or adolescent, it is virtually always related to significant functional disability with a lack of response to other treatments and/or the existence of severe and potentially life-threatening symptoms such as inadequate oral intake due to catatonia, significant suicide risk, or extreme and repeated self-injury.[34] Having access to a rapid and effective treatment such as ECT is especially meaningful in children and adolescents because suicide is a leading cause of death in this age group; it is the third leading cause of death in children ages 10 to 14 and the second leading cause in children ages 15 to 18.[35] It is noteworthy that no death has ever been reported in a child or an adolescent that was directly related to ECT.

Information on the efficacy of ECT in youth comes primarily from retrospective studies, case series and reviews that summarize large numbers of cases.[36] These peer reviewed studies provide strong clinical evidence for ECT as an effective treatment in severe and/or treatment refractory depressive episodes, mania, psychotic disorders, catatonia and neuroleptic malignant syndrome in children and adolescents. ECT is also effective in catatonia, mood and psychotic disorders when individuals have intellectual disability, autism or another developmental syndrome.[37]

In terms of possible cognitive effects of ECT, the available literature does not suggest a greater level of cognitive dysfunction in children and adolescents following ECT as compared to other therapeutic options.[38] In addition, the very severe psychiatric illnesses that lead to referral for ECT in younger individuals are themselves associated with a high level of cognitive dysfunction. Furthermore, the prompt response of symptoms with ECT reduces the risk of suicide and minimizes disruptions to schooling and other critical areas of psychosocial functioning for children and adolescents.[39]

Use of ECT in individuals who are treatment resistant or require a rapid response

The FDA specifically requested comment on the clarity of the term "treatment resistant" and the phrase "require rapid response" in defining the population for which ECT benefits outweigh risks.[40] The APA believes that the current wording is appropriate since there is no consensus on a "gold standard" rating scale to assess treatment resistance[41] or on the most valid ways to identify treatment resistance in clinical contexts.[42]

In terms of a definition for “the need for a rapid response,” many factors could contribute to such a determination. A working definition is that the health and well-being of the individual is in acute danger of being compromised without an immediate intervention to treat their psychiatric disorder. A clinical decision about the use of ECT would need to consider the presence, magnitude and importance of relevant factors for the individual patient.

Special controls to assure safety and efficacy of ECT

The APA concurs with the FDA on the role of special controls to assure safe and effective use of ECT. More specifically, we agree with the appropriateness of:

- Safety tests, software validation and electrical and mechanical performance data, using established technical parameters[43]
- Specific device use instructions, including pre-ECT assessment and monitoring during the procedure[44]
- Training of clinicians who will be administering ECT[45]
- Information on the intended patient population and typical course of treatment[46]
- Disclosure of contraindications, precautions, warnings and potential adverse effects/complications in physician and patient labelling[47]

Special controls related to potential cognitive effects of ECT

The FDA proposes a number of special controls related to potential cognitive effects of ECT. For some patients, cognitive function may be no worse, or even improved, when assessed across several cognitive domains at least two weeks after the end of ECT.[48] However, in other individuals, demonstrable

cognitive impairment occurs with ECT treatment. Thus, the APA concurs with the inclusion of information on assessing the possible cognitive effects of ECT as part of the device labelling and as an element of informed consent. The APA also agrees with the importance of using validated screening instruments to monitor cognitive status prior to and during the ECT course, with more detailed cognitive testing obtained if clinically indicated. We suggest a particular focus on memory function, because memory deficits are most reported by patients and represent the primary form of cognitive deficit that is observed in research on cognition and ECT. At the same time, some patients with severe psychiatric illness (e.g., major depressive episodes with psychosis, catatonia) may not be able to undertake even brief cognitive testing, especially before beginning ECT. Although every effort should be made to conduct some assessment of cognition in all patients, no patient should be denied ECT treatment due to an inability to complete cognitive testing.

The APA does suggest several modifications to the wording in the proposed labelling. Detailed formal neuropsychological assessment[49] is not necessary in all patients treated with ECT and will not be possible in many treatment centers, resulting in a barrier to ECT treatment if this is required. Thus, the APA suggests that the phrase “formal neuropsychological assessment” be deleted from the labelling. Instead, we recommend a staged approach to cognitive testing similar to what is used in other disorders in health care. Screening assessments covering orientation, attention, and memory in all patients prior to and during ECT would permit identification of those individuals who may require more detailed testing. Asking patients and family members about subjective concerns about cognition during the ECT course can also identify individuals who may require more detailed testing or adjustments in ECT treatment parameters.

The APA also proposes a change in the wording of the patient labeling[50] so that it would read “The use of controlled electrical stimuli in modern ECT devices and adjustments in the way that ECT is given (such as alternative electrode placements and pulse parameters) can minimize but not completely eliminate these risks”. We advise against including a table (such as the one shown in the draft guidance[51]) that delineates the relationship between stimulation parameters and memory effects in the actual labelling. Adjustments in parameters such as treatment frequency and stimulus intensity often need to consider effects on cognition as well as effects of efficacy. In addition, recommendations on preferred treatment modalities may change as research evidence on ECT accrues.

Special controls related to ECT contraindications

In the discussion of labelling recommendations in the draft guidance, a number of conditions are listed as contraindications to ECT. The APA suggests that these conditions be described as "associated with substantially increased risk"[52] rather than as a contraindication, per se. As with all medical decisions, clinical decisions about initiating treatment with ECT require weighing the possible benefits and risks of treatment against the possible benefits and risks of other treatment options or foregoing treatment. In some circumstances, when a psychiatric condition is life-threatening, the potential benefits of ECT may still outweigh the risks of ECT in the presence of one of these conditions. Describing these conditions as contraindications is likely to restrict access to needed ECT in very rare but life-threatening situations.

Special controls for indications other than major depressive episodes

From a safety standpoint, as the FDA notes, ECT-related risks for major depressive episodes are comparable for catatonia, manic episodes (in bipolar disorder), schizophrenia, and schizoaffective

disorder.[53] Special controls as described for individuals with major depressive episodes would be able to mitigate the risks of ECT in these conditions.

For individuals under the age of 18, the APA suggests additional special controls that would support a change to a class II designation. Before proceeding with ECT, the APA recommends that the child or adolescent be evaluated by two independent psychiatrists with experience in treating youth of that age range as well as by the psychiatrist who will be performing ECT. The purpose of these evaluations is to determine whether the child or adolescent has a diagnosis for which ECT is clinically indicated and whether additional trials of pharmacotherapy are indicated prior to initiating ECT as well as to determine the benefits and risks of ECT for the individual relative to other treatment options based upon the clinical circumstances. Special controls in youth related to potential cognitive effects should parallel the recommendations in adults for specific assessment of orientation, attention, memory, and executive function using validated screening instruments with more detailed cognitive testing obtained if clinically indicated. Instruments should be designed for use in children or adolescents. As with adults, every effort should be made to conduct some assessment of cognition in all patients. However, this may not be possible due to the severity of psychiatric symptoms or the patient's level of baseline intellectual function, and no patient should be denied ECT treatment due to an inability to complete cognitive testing. To assure safe delivery of anesthesia to children or adolescents who are being treated with ECT, the APA recommends that anesthesia providers be experienced in administering anesthesia to patients of a similar age.

Special controls related to long-term use of ECT

The FDA proposes a warning that "When used as intended this device provides short-term relief of symptoms. The long-term safety and effectiveness of ECT treatment has not been demonstrated."[54] The APA suggests that this warning not be included in the device labelling. ECT is not unique in having a substantial rate of symptom return if active treatment is stopped. However, similar warnings are not required with other devices or pharmacotherapies. In addition, evidence from RCTs shows that symptom remission can be prolonged after an acute course of ECT if patients receive continuation/maintenance treatment with pharmacotherapy and/or ECT.[55] In terms of long-term safety and effectiveness, there is a substantial body of evidence from case series,[56] retrospective studies,[57] clinical trials[58] and systematic reviews[59] on the safety and efficacy of continuation and maintenance ECT. Most recently, in the National Institute of Mental Health (NIMH)-sponsored Prolonging Remission in Depressed Elderly (PRIDE) trial, geriatric depressed patients who had remitted with ECT and venlafaxine in the acute phase were randomly assigned to 6 months of treatment with either 1) venlafaxine and lithium (n=64) or 2) continuation ECT (4 treatments in the first month and additional ECT only if they began to relapse) plus lithium and venlafaxine (n=64).[60] At the 6-month study endpoint, the Hamilton Rating Scale for Depression score (HRSD-24) of patients who received continuation ECT plus medication was significantly lower than that of patients in the medication-only group. In addition, the odds of being rated “not ill at all” on the Clinical Global Impression – Severity scale (CGI-S) were 5.2 times greater for the continuation ECT plus medication group compared with the medication-only group. The odds of relapsing were 1.7 times higher for patients in the medication-only group compared to the continuation ECT plus medication group. These results confirm and extend the evidence for the long-term efficacy of ECT beyond 3 months. In terms of the safety of ECT with longer-term use, well-designed studies that have assessed cognitive effects of continuation and maintenance ECT show no significant differences in cognitive outcomes in comparison with continuation pharmacotherapy.[61]

Thank you for your consideration of these comments on this important regulatory issue. We look forward to working with you in the future to develop and implement any policy changes related to ECT. In addition, we would be pleased to expand on any of the above comments. If you have any further questions, please contact Philip Wang, M.D., Dr.P.H., APA's Director of Research, at pwang@psych.org.

Sincerely,

Renée Binder, M.D.
President

Saul Levin, M.D., M.P.A.
CEO and Medical Director

[1] Federal Register Vol 80(249): 81227-81228

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[5] Federal Register Vol 80(249): 81231, section C Risks to Health.

[6] Federal Register Vol 80(249): 81231

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