National Network of Depression Centers

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Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
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RE: Docket FDA-2014-N-1210: Neurological Devices; Reclassification of Electroconvulsive Therapy (ECT) 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 ECT for Certain Specified Intended Uses

Dear Commissioner Califf,

The National Network of Depression Centers (NNDC), a consortium of major academic centers with interest and expertise in mood disorders, wishes to comment on FDA's proposed order "Neurological Devices; Reclassification of Electroconvulsive Therapy (ECT) 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 ECT for Certain Specified Intended Uses". To the extent possible, NNDC's comments draw upon new data that was not available to FDA at the time of its January, 2011 public hearing on ECT device reclassification, and on a series of discussions among experts of the 24 NNDC Centers of Excellence.

NNDC is aware of the compelling evidence supporting the safe and effective use of ECT for individuals with certain severe psychiatric disorders, and supports FDA's proposal to reclassify ECT devices from Class III to Class II for the indication of severe major depression episodes that are either treatment resistant or require a rapid response. However, NNDC also believes that the reclassification to Class II should be extended to other disorders where there is substantial evidence supporting efficacy and safety, including catatonia, mania, and acute episodes of schizophrenia associated with severe psychotic, affective, or catatonic symptoms where such episodes are either treatment resistant or require rapid response. In addition, because of the demonstrated high relapse rates during the months following a successful acute ECT series, as well as the growing body of evidence supporting safe and effective use of subsequent intermittent ECT for prophylactic purposes, NNDC experts affirm without reservation that reclassification to Class II should also extend to the use of maintenance ECT for the diagnoses mentioned above.

Because there is no evidence that ECT treatment of acute episodes of the above disorders differs in effectiveness or safety as a function of age, NNDC experts believe that reclassification to Class II should not be limited to the treatment of individuals who are 18 or older. Rather, NNDC believes that any concerns regarding the use of ECT in adolescents and children can and should be handled via the special controls mechanism. Finally, NNDC wishes to comment on the methods by which cognitive functions should be monitored prior to and during an acute ECT course. In that regard, NNDC agrees with FDA that ongoing attention to the presence and severity of cognitive adverse effects represents an important part of the overall treatment process for those receiving ECT.

Efficacy and safety of ECT in disorders other than major depression.

Catatonia. Catatonia is most commonly found in the context of severe major depressive episodes, although it may also occur in conjunction with mania, schizophrenia, or even medical etiologies. It is well-known that ECT has a powerful anti-catatonic therapeutic effect regardless of the underlying diagnosis, with extremely high response rates[1-4]. For this reason, ECT is considered the preferred treatment for patients whose response to benzodiazepines, which constitute the first line treatment for these conditions, is inadequate. Catatonia is often a life-threatening condition, and NNDC experts believe that preventing access to the only effective treatment alternative in such cases would be unethical. NNDC experts also believe that because catatonia is uncommon and is typically associated with mutism and inability to respond to questions, it would be impossible to carry out prospective controlled trials in this country. For this reason, NNDC experts believe that it would be inappropriate to withhold reclassification of ECT device use from Class III to Class II for treatment of catatonia because of the absence of such studies.

Mania: In its proposed rule, FDA noted much of the compelling data supporting the efficacy and safety of ECT in the treatment of unipolar and bipolar depression. However, because bipolar disorder is a single disorder, which may present as depression, mania, or as a mixed state, it is not surprising that ECT is as effective in the treatment of acute manic presentations as it is with depressive presentations[5-8]. In this regard, a role for ECT is noted in both national and international guidelines for the treatment of acute manic episodes[9,10]. There is also evidence supporting the use of maintenance ECT for patients who have had a positive response to an acute ECT course but cannot be effectively managed with maintenance medications alone[11-13]. Present practice of ECT for acute mania is largely reserved for use in severely ill patients who are either treatment resistant to anti-manic psychotropic agents or require urgent response because of potentially life-threatening manic excitement or catatonic presentations. As with catatonia, NNDC experts believe that it would be unethical to withhold access to an effective treatment in these latter situations where no effective treatment alternatives exist.

Schizophrenia. A large body of literature since 1980 supports the efficacy of ECT combined with antipsychotic medications for patients with severe positive symptom (psychotic) schizophrenia and schizoaffective disorder who have not responded to antipsychotic medication alone[14]. On the strength of these findings, both national and international treatment guidelines for treatment of acute schizophrenic episodes include ECT combined with antipsychotic medication for management of treatment resistant cases[15,16], Of particular interest is a recent study which randomly assigned clozapine nonresponders to either combined ECT and clozapine or clozapine alone[17]. Not only did this study find a 50% responder rate in the ECT/clozapine group vs 0% responder rate in the clozapine alone group, but when the research patients in the clozapine alone group then received a course of combined ECT plus clozapine, 47% of them became responders. In addition, a recent meta-analysis of studies administering combined ECT and clozapine to schizophrenics who had failed to respond to clozapine alone reported an overall 66% responder rate[18]. Together, these response rates are extraordinarily high for a patient population who have no effective treatment alternatives. For this reason, NNDC experts believe that reclassification of ECT devices to Class II is indicated for severely ill individuals with positive symptom schizophrenia or schizoaffective disorder who have failed a clozapine trial.

Because acute improvement with combined ECT and clozapine is difficult to maintain with continuation of clozapine alone, it is understood that it is generally necessary to enroll such patients in a maintenance ECT program to supplement psychotropic management, with an ECT frequency of 1-2 per month typically needed[19-23]. If that is not done, there is a substantial likelihood that frequent acute courses of ECT combined with clozapine will be necessary.

Safety. With respect to safety, FDA itself notes in its proposed rule that there is no evidence that ECT is any less safe when used to treat any of these disorders than it is for treatment of severe depressive episodes.

Efficacy and safety of maintenance ECT.

Major depression is a prevalent and recurring illness, impacting 17% of all individuals within their lifetime, with ages of onset peaking between 15-24 years of age, and when untreated has a strong propensity to become a chronic illness with extremely high lifetime morbidity and mortality. It is universally accepted that maintenance treatment is important to sustain remission after a successful course of acute ECT. Relapse rates are high, e.g., Sackeim and colleagues reported that 84% of patients who responded to acute ECT relapsed within six months of discontinuation of an acute ECT series unless active maintenance treatment is utilized[24]. In a recently reported multi-center follow-up study, funded by the National Institute of Mental Health (NIMH), the same group reported a six-month relapse rate of at least 50% even with aggressive pharmacotherapy with a combination of antidepressant and Lithium[25]. In another large multicenter trial funded by NIMH and carried out by the Consortium on Research in ECT (CORE), 201 patient participants with major depressive episodes who had remitted following an acute series of ECT were randomized to six months of either maintenance ECT or maintenance pharmacotherapy with combined antidepressant medication and Lithium[26]. Study results show that maintenance ECT alone (i.e. without concomitant pharmacotherapy) is a safe and effective treatment alternative to aggressive pharmacotherapy in decreasing relapse following an acute ECT series, although relapse was still present in a sizable minority of subjects.

The hypothesis of further lowering relapse rates by combining maintenance ECT and pharmacotherapy was then tested in a recently concluded NIMH funded multicenter trial by the CORE group[27], as well as in a separate Swedish trial[28]. In both studies combined maintenance ECT and pharmacotherapy was more effective than pharmacotherapy alone. In the larger and more methodologically rigorous CORE trial, 120 patient research participants with major depressive disorder who had remitted after an acute ECT series were randomized to six-month treatment trials of either venlafaxine plus Lithium alone or maintenance ECT plus the venlafaxine/Lithium combination. At six-month follow-up, subjects receiving the maintenance ECT/pharmacotherapy combination not only had significantly lower Hamilton Depression Rating Scale (HDRS) scores than patients in the pharmacotherapy alone group, but, in addition, relapse was 1.7 times greater for subjects in the maintenance pharmacotherapy alone group. Additionally, investigators found a tendency toward shorter time to relapse for that group compared to the combined maintenance ECT/pharmacotherapy group. This study also corroborated earlier findings[28,29] that cognitive functioning in research patients receiving maintenance ECT treatment did not differ from that of research patients receiving maintenance pharmacotherapy alone. *Collectively, these findings clearly establish that combined maintenance ECT and pharmacotherapy offers patients a better chance to avoid relapse following ECT then does aggressive maintenance pharmacotherapy alone, and does so without impairing cognitive function.*

Efficacy and safety of ECT in individuals under the age of 18.

Mood disorders, catatonia, and schizophrenia can all have onset during childhood or adolescence and although these disorders may present differently in childhood, there is no evidence that the underlying disease differs in these age groups compared with an adult population. Because ECT has been uncommonly utilized in this children or adolescents under 18, there have not been controlled research trials. However, there has been a significant growth of peer-reviewed publications focused on acute and maintenance ECT use in young patients with mood disorders, as well as other serious neuropsychiatric conditions like catatonia and psychotic disorders such as schizophrenia. In particular, retrospective case series have reported similar positive clinical response, as well as tolerability and cognitive side effects to that reported in adult ECT patients. Much of the applicable literature was summarized in 2013 by Ghaziuddin and Walter in an entire textbook titled “Electroconvulsive Therapy in Children and Adolescents”[30]. In addition, guidelines for patient selection and use of ECT in young patients have been published by both the American Psychiatric Association[31] and the American Association of Child and Adolescent Psychiatry[32]. In this regard, the special controls mechanism can be used by FDA to ensure that appropriate, safe, and effective ECT treatment can be provided to individuals in this age group. Specifically, in addition to the national guidelines mentioned above, concurrence by additional independent psychiatrists

experienced in treating children and adolescents, involvement of anesthesia providers experienced with the use of general anesthesia in this age group, and use of age-appropriate ongoing cognitive assessment would represent reasonable special controls. In addition, it should also be noted that at present, utilization of ECT in children and adolescents under 18 is held to higher level of indication from a treatment resistance and need for rapid response standpoint than is the case with adults. For these reasons, *NNDC experts believe that FDA should include ECT for children and adolescents in its proposal to reclassify ECT devices from Class III to Class II, with the imposition of appropriate special controls to ensure adequate efficacy and safety.*

Assessment and monitoring of cognitive functions with ECT.

NNDC agrees with FDA that memory impairment has been the most worrisome side effect from ECT. This concern arose predominantly from the use of unmodified ECT, which was also associated with the use of sinusoidal stimulus waveform, bitemporal electrode placement, and non-individualized stimulus dosing. With present-day evidence-based ECT practice, memory impairment has been substantially reduced. As such, this particular risk is outweighed by the treatment's compelling and sometimes life-saving benefit.

ECT is associated with both anterograde and retrograde amnesia. Studies utilizing objective measures of assessing anterograde amnesia have consistently demonstrated that any such abnormalities disappear within several months following completion of an acute ECT course[33]. Several recent studies have even demonstrated improvement in cognitive function, compared to baseline, several weeks to months after successful treatment with ECT[34-38]. An even more recently published study that reviewed 10 years of cognitive performance data in relation to ECT concluded that there is no evidence of cumulative cognitive deficits associated with repeated ECT courses[39]. Studies investigating the existence, severity, and persistence of retrograde amnesia have focused on autobiographic memory function. Objective measures, although nonstandardized due to the challenges involved in autobiographic memory assessment, have proven sensitive to ECT type, e.g., stimulus electrode placement and stimulus waveform, and have sometimes demonstrated even persistent deficits with some ECT types[40]. Regardless of objective testing results, some patients receiving ECT report persistent anterograde amnesia and/or persistent retrograde amnesia that is greater than what might be expected from the results of studies utilizing objective test measures, although attempts to investigate such reports on a scientific basis have not met with success, perhaps due to the complexity of factors known to affect such self-ratings[41,42].

Early detection of emerging cognitive side effects during the ECT course is important so that providers can adjust the treatment approach to minimize further side-effects. Therefore, NNDC experts agree with the FDA rule that 1) cognitive function should be evaluated before beginning ECT, 2) cognitive function should be monitored throughout the course of treatment, and 3) the results of cognitive testing should be routinely reviewed during the course of treatment and influence appropriate clinical decision-making (e.g., holding or ending treatment, changing ECT treatment parameters). However, NNDC experts also believe that many patients with the most severe illnesses (e.g., catatonia, NMS, or profound depression) will likely be unable to participate in cognitive testing. Therefore, *we recommend that no patient be denied ECT treatment due to the inability to complete cognitive testing.*

With respect to formal memory testing, NNDC experts believe that simple bedside cognitive testing is adequate for the vast majority of patients undergoing ECT. Routine requirement of extensive neuropsychological testing for all ECT patients, on the other hand, would prove counterproductive, create an undue burden, and would commonly be infeasible due to lack of timely availability of clinical neuropsychologist assessment in many clinical settings[43], thus limiting access to a potentially life-saving treatment. An optimal testing instrument for use with ECT would be brief, easy to administer, simple enough for patients with limited ability to focus and complete, and sensitive to the known effects of ECT, particularly in terms of both objective anterograde and retrograde amnesia. The instrument should also provide

an opportunity for memory self-rating by the patient. At present there are no validated ECT-sensitive instruments of this type, however, research in this area is underway. As part of this effort, NNDC investigators at multiple prominent U.S. academic locations are in process of developing a reliable, valid, brief (less than 10 min.), stand-alone cognitive screening tool meeting the above requirements that can be administered at bedside[44].

NNDC believes that highly selective and careful use of ECT remains a major treatment alternative for individuals with treatment resistance and/or a need for rapid response, and appreciates the opportunity to comment on FDA's proposed reclassification rule. As the major National group of experts on the management of depressive, bipolar, and related disorders, NNDC would also welcome the opportunity to meet with FDA to provide further input during the process of developing a final reclassification rule. In this regard, NNDC experts have, as noted above, been developing a practical, sensitive cognitive assessment measure for use with individuals being treated with ECT across a broad range of clinical situations and environments.

Thank you for your consideration of our input to the ECT device reclassification rule.

Sincerely yours,

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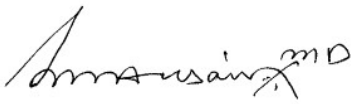

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Citations to the scientific literature

1. Luchini, F, et al. Electroconvulsive therapy in catatonic patients: efficacy and predictors of response. World J Psychiatry 5, 182-192, 2015
2. Medda P, et al. Catatonia in 26 patients with bipolar disorder: clinical features and response to electroconvulsive therapy. Bipolar Disord. 17:892-901, 2015
3. Raveendranathan D, et al. Response rates of catatonia to electroconvulsive therapy and its clinical correlates. European Archives Psychiatry Clinical Neurosci 262, 425-430, 2012
4. Sienaert P, et al. A clinical review of the treatment of catatonia. Frontiers in Psychiatry 5:181, 2014
5. Small JG, et al. Electroconvulsive treatment compared with lithium in the management of manic states. Arch Gen Psychiatry. 45:727-732; 1988.
6. Mukherjee S, et al. Unilateral ECT in the treatment of manic episodes. Convuls Ther. 4:74-80, 1988.
7. Sikdar S, Kulhara P, Avasthi A, Singh H: Combined chlorpromazine and electroconvulsive therapy in mania. British Journal of Psychiatry 164: 806-810, 1994.
8. Mukherjee S, et al. Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. Am J Psychiatry. 151:169-176, 1994
9. American Psychiatric Association: Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry 159 (Suppl), 2002
10. Grunze H, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. World J Biol Psychiatry. 10:85-116, 2009
11. Minnai GP, et al. Effectiveness of maintenance electroconvulsive therapy in rapid-cycling bipolar disorder. J ECT. 27:123-126, 2011
12. Petrides G, et al. Continuation and maintenance electroconvulsive therapy for mood disorders: review of the literature. Neuropsychobiology. 64:129-140, 2011
13. Vanelle JM, et al. Maintenance ECT in intractable manic-depressive disorders. Convuls Ther. 10:195-205, 1994
14. Tharyan P, Adams CE. Electroconvulsive therapy for schizophrenia. Cochrane Database Syst Rev. 2005:CD000076
15. Hasan A, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. World J Biol Psychiatry. 13:318-378, 2012
16. Lehman AF, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 161:1-56, 2004
17. Petrides G, et al. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. Am J Psychiatry. 172:52-58, 2015
18. Lally J, et al. Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: A systematic review and meta-analysis. Schizophr Res. 171:215-224, 2016
19. Chanpattana W, et al. Continuation ECT in treatment-resistant schizophrenia: a controlled study. J ECT. 15:178-192, 1999
20. Levy-Rueff M, et al. Maintenance electroconvulsive therapy: an alternative treatment for refractory schizophrenia and schizoaffective disorders. Psychiatry Res. 175:280-283, 2010
21. Suzuki K, et al. Continuation electroconvulsive therapy to prevent relapse of schizophrenia in relapse-prone patients. J ECT. 23:204-205, 2007
22. Zervas IM, et al. Using ECT in schizophrenia: a review from a clinical perspective. World J Biol Psychiatry. 13:96-105, 2012.
23. Chanpattana W, et al. The use of the stabilization period in electroconvulsive therapy research in schizophrenia: II. Implementation. J Med Assoc Thai. 82:558-568, 1999

24. Sackeim et al., Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy. JAMA. 285:1299, 2001
25. Prudic et al., Pharmacologincal strategies in the prevention of relapse after electroconvulsive therapy. J. ECT. 29:3-12, 2013
26. M3. Kellner et al., Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression (CORE Study). Arch Gen Psych. 63:1337, 2006
27. Kellner et al., A randomized controlled trial of continuation electroconvulsive therapy and medication vs medication alone in geriatric depression; Phase 2 of the PRIDE study. [presented at multiple scientific meetings in 2015 and Manuscript submitted for publication]
28. Nordenskjöld A, et al. Continuation electroconvulsive therapy with pharmacotherapy versus pharmacotherapy alone for prevention of relapse of depression: A randomized controlled trial. J ECT. 29:89-92, 2013
29. Smith GE, et al. A randomized controlled trial comparing the memory effects of continuation electroconvulsive therapy versus continuation pharmacotherapy: results from the Consortium for Research in ECT (CORE) study. J Clin Psychiatry. 71:185-193, 2010
30. Ghaziuddin and Walter (Eds). Electroconvulsive Therapy in Children and Adolescents. New York. Oxford Univ. Press. 2013
31. American Psychiatric Association. The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging. 2nd ed. Washington, DC: American Psychiatric Association; 2001.
32. Ghaziuddin et.al. Practice parameter for use of electroconvulsive therapy with adolescents. J. Am. Acad. Child Adolesc. Psychiatry, 43:1521–1539, 2004
33. Semkovska, M. and D.M. McLoughlin, Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. Biol Psychiatry, 68:568-77, 2010
34. Verwijk, E., et al., Short- and long-term neurocognitive functioning after electroconvulsive therapy in depressed elderly: a prospective naturalistic study. Int Psychogeriatr, 26:315-24, 2014
35. Dybedal, G.S., et al., The Role of Baseline Cognitive Function in the Neurocognitive Effects of Electroconvulsive Therapy in Depressed Elderly Patients. Clin Neuropsychol, 29:487-508, 2015
36. Bodnar, A., et al., Electroconvulsive therapy and cognitive functions in treatment-resistant depression. World J Biol Psychiatry, 17:159-164, 2015
37. Kalogerakou, S., et al., Episodic Visual Learning/Memory and Attentional Flexibility in Patients With Major Depressive Disorder After Clinically Effective Electroconvulsive Therapy. J ECT, 31:246-52, 2015
38. Fernie, G., et al., Detecting objective and subjective cognitive effects of electroconvulsive therapy: intensity, duration and test utility in a large clinical sample. Psychol Med, 44:2985-94, 2014
39. Kirov, G.G., et al., Evaluation of cumulative cognitive deficits from electroconvulsive therapy. Br J Psychiatry, 208:266-70, 2016
40. Semkovska, M. and D.M. McLoughlin. Measuring retrograde autobiographical amnesia following electroconvulsive therapy: Historical perspective and current issues. J ECT, 29:127-133, 2013
41. Rose et al. Patients' perspectives on electroconvulsive therapy: systematic review. British Med. J. 326:1363-1367, 2003
42. Bergsholm P. Patients' perspectives on electroconvulsive therapy: a reevaluation of the review by Rose et al on memory loss after electroconvulsive therapy. J ECT. 28:27-30, 2012
43. Weiner, R., et al., Electroconvulsive therapy device classification: response to FDA advisory panel hearing and recommendations. J Clin Psychiatry, 74:38-42, 2013
44. Hermida, A.P., et al., Validation of a Brief Cognitive Tool (ECA) Designed Specifically for Use During and After Electroconvulsive Therapy ISEN abstracts. J ECT 31: e32-e39, 2015