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March 28, 2016

Division of Dockets Management (HFA–305)
US Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: [Docket ID: FDA-2014-N-1210] "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"

Re: [Docket No. FDA– 2014–D–1318] "Electroconvulsive Therapy (ECT) Devices for Class II Intended Uses: Draft Guidance for Industry, Clinicians and FDA Staff: Availability"

Dear Commissioner Robert Califf, MD and Staff:

On behalf of the American Academy of Child and Adolescent Psychiatry (AACAP), please accept our comments to the Food and Drug Administration (FDA) pursuant to the public notice for comment of the Proposed Order [Docket ID: FDA-2014-N-1210] "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Date of Requirement for Premarket Approval for Electroconvulsive Therapy for Certain Specified Intended Uses" and Draft Guidance [Docket No. FDA– 2014–D–1318] "Electroconvulsive Therapy (ECT) Devices for Class II Intended Uses: Draft Guidance for Industry, Clinicians and FDA Staff: Availability" (hereafter referred to as the Proposed Order and Draft Guidance, respectively).

AACAP is a nearly 9,000 member-strong, professional medical organization comprised of child and adolescent psychiatrists. These uniquely trained physicians promote healthy human development by their evaluation, diagnosis, and treatment of children, adolescents and their families who are affected by disorders of feeling, thinking, learning, and behavior.

AACAP supports FDA's recommendation for reclassification of ECT devices from Class III to Class II for use in treating Major Depressive Disorder (MDD) and Bipolar Disorder (BPD) in patients 18 years of age or older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric medical condition. In addition, AACAP would also submit for consideration: (1) the inclusion of patients under the age of 18, and (2) the inclusion of additional disorders that have demonstrated efficacy in the treatment of youth. In the following, we

provide evidence in support of these critical considerations for the effective reclassification of ECT devices and their ability to serve this vulnerable population.

Inclusion of patients under the age of 18

While AACAP supports the reclassification of ECT devices to Class II, regulating reclassification solely for those 18 years of age or older neglects the adolescent population that, evidence demonstrates, greatly benefit from this treatment intervention. The utilization of ECT in minors is impeded by the lack of randomized control trials (RCTs). There are, however, numerous case series and literature reviews that demonstrate the usefulness and safety of the device, in both typically-developing as well as developmentally-disabled youth. There has not been a single report of death or disability directly associated with ECT, whereas death by suicide is a leading cause of mortality in adolescents who frequently have serious mental illness.

Adolescents receiving ECT are generally 13-17 years of age. Published data from the 1980-90s demonstrate that of all patients treated with ECT, only 1-1.5% are under the age of 18.[1,2] Should the Proposed Rule and Draft Guidance not consider including this vulnerable population, it would make accessing ECT difficult in pediatric cases that do not readily respond to other standard therapies and interventions.

Children and adolescents with similarly treatment-resistant and/or life-threatening disorders as adults respond to ECT equally well and there has been no evidence of brain damage or different response/side effects compared to adults. Generally younger patients require smaller amounts of energy than adults, however the devices are capable of delivering such stimuli and do not need additional modifications.

Inclusion of additional disorders that have demonstrated efficacy in the treatment of youth

ECT in Adolescents with Mood Disorders
Findings uniformly include high response and remission rates and the absence of any lasting side-effects when ECT is properly administered in adolescents with mood disorders. The response and remission identified in these reports far exceed benefit of any currently available medication or psychotherapeutic treatment, although, there are no head-to-head comparisons. In a review of the literature from 1947 to 1990, Bertagnoli and Borchardt[3] reported 148 published cases and reported that with the exception of 4 cases[4], all reports had consistently found marked improvement following ECT. Similarly, Rey and Walter (1997) reviewed all publications (n = 60; participant n = 396) until 1996, which found that the short-term efficacy of ECT ranged from 80-100% for mania, 60-80% for bipolar and unipolar depression and 75% for catatonia.[5] Another report found considerable improvement following ECT in approximately 90% of adolescents with depression resistant to pharmacotherapy.[6] An epidemiological survey based on data spanning five years, found significant response to ECT in 42 adolescents who had

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[1] Thompson, J. W. and J. D. Blaine (1987). "Use of ECT in the United States in 1975 and 1980." American Journal of Psychiatry 144(5): 557-562.
[2] Walter, G. and J. M. Rey (1997). "An epidemiological study of the use of ECT in adolescents." Journal of the American Academy of Child & Adolescent Psychiatry 36(6): 809-815.
[3] Bertagnoli, M. W. and C. M. Borchardt (1990). "A review of ECT for children and adolescents." Journal of the American Academy of Child & Adolescent Psychiatry 29(2): 302-307.
[4] Guttmacher, L. B. and H. Cretella (1988). "Electroconvulsive therapy in one child and three adolescents." Journal of Clinical Psychiatry 49(1): 20.
[5] Rey, J. M. and G. Walter (1997). "Half a century of ECT use in young people." American Journal of Psychiatry 154(5): 595-602.
[6] Rey, J. M. and G. Walter (1997). "Half a century of ECT use in young people." American Journal of Psychiatry 154(5): 595-602.

received ECT as a treatment of "last resort" after failure of pharmacotherapy.[7] Several other publications have found similarly high response and remission rates which range from 60% to 100% for the treatment of depression and 75% to 100% in mania.[8,9,10,11,12,13,14,15] Maintenance or continuation of ECT were also found to be safe and highly effective; remission was achieved in 5 out of 6 adolescents among a group with highly resistant mood disorders and a trend towards improved auditory and verbal memory was noted following the treatment.[16]

ECT in adolescents with schizophrenia spectrum disorders (SSD)

Schizophrenia spectrum disorders (schizophrenia, schizoaffective disorder, psychosis Not Otherwise Specified (NOS)) are disabling disorders with a particularly pernicious outcome associated with adolescent onset. Relatively early onset is associated with greater decline in areas of overall function, socio-economic well-being, and cognition.[17,18] ECT is used in SSD when illness is deemed resistant to standard treatment, when there is inability to tolerate pharmacotherapy, or when there is risk to life due to severe symptoms. Response to ECT in adolescents with SSD has reportedly ranged from 28 to 77%[19,20,21] with higher rates reported in more recent studies and when a SSD diagnosis is associated with affective or catatonic symptoms. Compared with studies involving adolescents with mood disorders treated with

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[7] Walter, G. and J. M. Rey (1997). "An epidemiological study of the use of ECT in adolescents." Journal of the American Academy of Child & Adolescent Psychiatry 36(6): 809-815.

[8] Kutcher, S. and H. Robertson (1995). "Electroconvulsive therapy in treatment-resistant bipolar youth." Journal of Child & Adolescent Psychopharmacology. 5(3): 167-175.

[9] Ghaziuddin, N., C. A. King, M. W. Naylor, M. Ghaziuddin, N. Chaudhary, B. Giordani, J. R. Dequardo, R. Tandon and J. Greden (1996). "Electroconvulsive treatment in adolescents with pharmacotherapy-refractory depression." Journal of Child & Adolescent Psychopharmacology 6(4): 259.

[10] Cohen, D., M. L. Paillere-Martinot and M. Basquin (1997). "Use of electroconvulsive therapy in adolescents." Convulsive Therapy 13(1): 25-31.

[11] Hill, M. A., H. Courvoisie, K. Dawkins, P. Nofal and B. Thomas (1997). "ECT for the treatment of intractable mania in two prepubertal male children." Convulsive therapy 13(2): 74.

[12] Strober, M., U. Rao, M. DeAntonio, E. Liston, M. State, L. Amaya-Jackson and S. Latz (1998). "Effects of electroconvulsive therapy in adolescents with severe endogenous depression resistant to pharmacotherapy." Biological psychiatry 43(5): 335.

[13] Bloch, Y., Y. Levcovitch, A. M. Bloch, S. Mendlovic and G. Ratzoni (2001). "Electroconvulsive therapy in adolescents: similarities to and differences from adults." Journal of the American Academy of Child & Adolescent Psychiatry 40(11): 1332.

[14] Russell, P. S., P. Tharyan, K. Arun Kumar and A. Cherian (2002). "Electro convulsive therapy in a pre-pubertal child with severe depression." Journal of Postgraduate Medicine 48(4): 290-291.

[15] Stein, D., A. Weizman and Y. Bloch (2006). "Electroconvulsive therapy and transcranial magnetic stimulation: can they be considered valid modalities in the treatment of pediatric mood disorders?" Child & Adolescent Psychiatric Clinics of North America 15(4): 1035.

[16] Ghaziuddin, N., S. Dumas and E. Hodges (2011). "Use of continuation or maintenance electroconvulsive therapy in adolescents with severe treatment-resistant depression." Journal of ECT 27(2): 168-174.

[17] Lay, B., Bernd, B. Hartman, M. Schmidt, MH (2000). The psychosocial outcome of Adolescent-onset schizophrenia: a 12-year follow-up. Schizophrenia Bulletin.

[18] White, T., Ho, BC., Ward, J., O'Leary, D., Andreasen NC (2006). Neuropsychological performance in first episode adolescent schizophrenia: A comparison of first-episode adults and adolescent control subjects.

[19] Bloch, Y., et al., *Electroconvulsive therapy in adolescents: similarities to and differences from adults.* J Am Acad Child Adolesc Psychiatry, 2001. 40(11): p. 1332-6.

[20] Stein, D., et al., *Electroconvulsive therapy in adolescent and adult psychiatric inpatients--a retrospective chart design.* J Affect Disorder, 2004. 82(3): p. 335-42.

[21] Bloch, Y., et al., *Reasons for referral for electroconvulsive therapy: a comparison between adolescents and adults.* Australas Psychiatry, 2008. 16(3): p. 191-4.

ECT, there are relatively few studies about adolescents with SSD. However, ECT appears to be highly effective when used in adolescents who have SSD with concomitant mood and/or catatonic symptoms.[22,23]

Earlier literature reviews, such as one by Rey and Walter found a 42% response rate among 36 adolescents diagnosed with SSD; this rate was lower than the response rate identified for adolescents with mood disorders.[24] Walter and Rey (1997) found a variable response rate among 18 patients with SSD; a 28% overall response rate was noted.[25] However, the response rate was 77% when the SSD diagnosis was associated with affective symptoms.

More recent studies have included a report by Baeza and colleagues (2009), who found marked improvement in 3, 13-year old patients following ECT.[26] In 2010, they reported a 54% response rate at 6 months in 13 adolescents ranging in age from 13-17 years who were diagnosed with SSD and were treated with ECT; no serious adverse effects were note.[27] In another study, ECT was found to be safe and effective in 28 adolescents (13-17 years) with an approximate 68% response rate when treated with ECT in combination with an antipsychotic agent.[28] De la Serna (2011) followed two groups of 9 adolescents in each group who were diagnosed with SSD; one group received ECT, while the second group received an antipsychotic agent.[29] They found no differences in the clinical improvement level (both groups had improved) or in cognitive functions.[30]

In the largest study conducted involving adolescents with first episode psychosis, a randomly assigned group was treated with ECT (n = 112) and was compared with a control group that received antipsychotic agents (n= 74); a 74% clinical response rate was noted for the group treated with ECT, versus 54% rate in controls. The ECT group also experienced a significantly greater improvement in positive symptoms associated with the syndrome and had greater improvement in their sleep measured by polysomnography. The authors concluded that ECT is a safe and an effective treatment of first episode psychosis.[31]

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[22] Zhang, Z.-J., Y.-C. Chen, H.-N. Wang, H.-H. Wang, Y.-Y. Xue, S.-F. Feng and Q.-R. Tan (2012). "Electroconvulsive therapy improves antipsychotic and somnographic responses in adolescents with first-episode psychosis--a case-control study." Schizophrenia Research 137(1-3): 97-103.

[23] Flamarique, I., J. Castro-Fornieles, J. Garrido, E. de la Serna, A. Pons, M. Bernardo and I. Baeza (2012). "Electroconvulsive therapy and clozapine in adolescents with schizophrenia spectrum disorders: is it safe and effective combination?" Journal of Clinical Psychopharmacology 32(6): 756-766.

[24] Rey, J. M. and G. Walter (1997). "Half a century of ECT use in young people." American Journal of Psychiatry 154(5): 595-602.

[25] Walter, G. and J. M. Rey (1997). "An epidemiological study of the use of ECT in adolescents." Journal of the American Academy of Child & Adolescent Psychiatry 36(6): 809-815.

[26] Baeza, I., A. Pons, G. Horga, M. Bernardo, M. Lazaro and J. Castro-Fornieles (2009). "Electroconvulsive therapy in early adolescents with schizophrenia spectrum disorders." Journal of ECT 25(4): 278-279.

[27] Baeza, I., I. Flamarique, J. M. Garrido, G. Horga, A. Pons, M. Bernardo, A. Morer, M. L. Lazaro and J. Castro-Fornieles (2010). "Clinical experience using electroconvulsive therapy in adolescents with schizophrenia spectrum disorders." Journal of Child & Adolescent Psychopharmacology 20(3): 205-209.

[28] Flamarique, I., J. Castro-Fornieles, J. Garrido, E. de la Serna, A. Pons, M. Bernardo and I. Baeza (2012). "Electroconvulsive therapy and clozapine in adolescents with schizophrenia spectrum disorders: is it safe and effective combination?" Journal of Clinical Psychopharmacology 32(6): 756-766.

[29] de la Serna, E. (2011). "Two-year follow-up of cognitive functions in schizophrenia spectrum disorders of adolescent patients treated with electroconvulsive therapy. ." J Child Adolesc Psychopharmacol 21(6): 611-619.

[30] de la Serna, E. (2011). "Two-year follow-up of cognitive functions in schizophrenia spectrum disorders of adolescent patients treated with electroconvulsive therapy. ." J Child Adolesc Psychopharmacol 21(6): 611-619.

[31] Zhang, Z.-J., Y.-C. Chen, H.-N. Wang, H.-H. Wang, Y.-Y. Xue, S.-F. Feng and Q.-R. Tan (2012). "Electroconvulsive therapy improves antipsychotic and somnographic responses in adolescents with first-episode psychosis--a case-control study." Schizophrenia Research 137(1-3): 97-103.

ECT in Youth with Catatonia

Catatonia is a devastating neuropsychiatric syndrome consisting of motor, vocal and behavioral symptoms that may have catastrophic, and sometimes lethal, results. Catatonia can occur in minors as well as in adults. One study documented a 5% prevalence of catatonia among 198 child and adolescent psychiatry outpatients, with a higher prevalence of 17% amongst the subset with psychotic illness.[32] Another recent study found catatonia to occur in 17.8% of 101 children and adolescents with "at-risk" diagnoses that are associated with a higher risk for catatonia, including pervasive developmental disability, mental retardation, psychosis and intermittent explosive disorder. Lack of recognition of the syndrome was highlighted, given that only 2 of the patients had been correctly diagnosed with catatonia prior to the retrospective chart review, with obvious implications for delayed treatment.[33] Catatonia has also been regularly reported in patients with autism spectrum disorders; indeed, two large population-based studies reported that 12-17% of autistic adolescents and young adults meet criteria for catatonia,[34,35] and multiple case reports and series offer further delineation of the psychomotor retarded and agitated presentations of catatonia in ASDs, with symptom remission achieved with ECT. Catatonia has been reported in other developmental disorders including Down, Cornelia de Lange, Fragile X and velo-cardio-facial syndromes.[36,37,38,39] Neuroleptic malignant syndrome (NMS) is a form of catatonia that has also demonstrated improvement after ECT treatment.[40,41,42]

There are no randomized controlled trials of ECT for catatonia in youth. However, multiple retrospective studies, case reports and series have documented the safety and efficacy of acute and maintenance ECT in the resolution of catatonia in children and adolescents both with and without developmental disability. The aforementioned 50-year literature survey by Rey & Walter of 60 manuscripts encompassing 396 pediatric ECT patients confirmed a 75% efficacy rate for ECT in catatonia. Consoli et al. (2010) reviewed retrospective studies of ECT in youth from 1993, and found an 86% efficacy rate for catatonia across 10 studies including at least 10 patients each.[43] Three of these 10 studies were controlled trials,

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[32] Thakur, A., K. Jagadheesan, S. Dutta and V. Sinha (2003). "Incidence of catatonia in children and adolescents in a pediatric psychiatric clinic." Australian and New Zealand Journal of Psychiatry 37: 200-203.

[33] Ghaziuddin, N., D. Dhossche and K. Marcotte. (2012). "Retrospective chart review of catatonia in child and adolescent psychiatric patients." Acta Psychiatr Scand 125(1): 33-38.

[34] Wing, L. and A. Shah (2000). "Catatonia in autistic spectrum disorders." British Journal of Psychiatry 176: 357-362.

[35] Billstedt, E., C. Gilberg and C. Gilberg (2005). "Autism after adolescence: population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood." Journal of Autism and Developmental Disorders 35: 351-360.

[36] Chen, Y., P. Hung and C. Wu (2015). "Severe complications of catatonia in a young patient with Hashimoto's encephalopathy comorbid with Cornelia de Lange syndrome." Kaohsiung Journal of Medical Sciences 31: 60-61.

[37] Dykens, E., B. Shah, B. Davis, C. Baker, T. Fife and F. J (2015). "Psychiatric disorders in adolescents and young adults with Down syndrome and other intellectual disabilities." Journal of Neurodevelopmental Disorders 7(9).

[38] Winarni, T., A. Schneider, N. Ghaziuddin, A. Seritan and R. Hagerman (2015). "Psychosis and catatonia in fragile X: Case report and literature review." Intractable & Rare Diseases Research 4(5): 139-146.

[39] Faedda, GL, Wachtel, LE, Higgins, AM, Shprintzen, RJ. 2015. Catatonia in an adolescent with velo-cardio-facial syndrome. Am J Med Genet Part A 167A:2150–2153.

[40] Wachtel L, Commins E, Park M, et al. Neuroleptic malignant syndrome and delirious mania as malignant catatonia in autism: prompt relief with electroconvulsive therapy. Acta Psychiatr Scand 2015;132: 319-320.

[41] San Gabriel M, Eddula-Chnagala B, Tan Y, et al. Electroconvulsive therapy in a Schizophrenic Patient With Neuroleptic Malignant Syndrome and Rhabdomyolysis. J ECT 2015;31: 197-200.

[42] Hashim H, Zeb-un-Nisa, Alkrukn S, et al. Drug resistant neuroleptic malignant syndrome and the role of electroconvulsive therapy. J Pak Med Assoc 2014;64: 471-473.

[43] Consoli, A., Benmiloud, M., Wachtel, L., Dhossche, D., Cohen, D., and Bonnot, O. (2010). "Electroconvulsive Therapy in Adolescents With the Catatonia Syndrome: Efficacy and Ethics." The Journal of ECT 26(4):259-265.

from three separate countries.[44,45] In many of the reported cases of pediatric catatonia, patients were severely compromised due to inability to move, speak, eat, void or maintain stable vital signs, with others having suffered horrendous bodily injury from repetitive self-injurious behaviors, including acute retinal detachment and related loss of vision, painful ossifications, face and head trauma and extensive soft tissue injury requiring ongoing use of chemical and physical restraint and associated with marked disfigurement. In these cases, ECT is presented as a truly life-saving intervention, as it is used when other treatment interventions have failed and no proven alternatives remain for this most compromised patient population in child psychiatry.

Recommendations to ensure safe administration of ECT to children and adolescents

Based on successful outcomes in adolescents treated with ECT, we propose that ECT should be classified as a Class II procedure for all major psychiatric disorders which have known positive response to ECT, (i.e. major depression, bipolar disorder, SSD, catatonia and neuroleptic malignant syndrome (NMS)) while imposing special precautions.

The following are suggested to ensure safe administration:

- ECT should be administered by psychiatrists, with involvement of child and adolescent psychiatrists, anesthesiologists and nursing staff who are experienced in the use of ECT, and have additional familiarity with its usage in youth;
- ECT should be used for disorders, which are known to respond to this treatment (i.e. severe mood disorders, schizophrenia and schizoaffective disorders, catatonia and NMS);
- ECT should be used either for treatment-refractory disorders (failure to respond to 3 medications with/without psychotherapy, if indicated) or when the severity of illness precludes waiting due to imminent danger to the life of the adolescent;
- Standardized evaluation should be used to diagnose, monitor response and side effects. These should be conducted prior to, during and following the treatment;
- Laboratory work up and brain imaging should be routinely completed; and
- Pre and post treatment neuropsychological functions should be completed to detect cognitive changes. Cognitive functions should also be monitored during treatment using standardized rating scales. It is important to note, however, that due to patient condition, assessment would be contingent upon and vary by baseline cognitive functions and some patients may not be able to participate.

Conclusion

Overall, AACAP supports the reclassification of ECT devices to Class II, with the extension of the inclusion of patients under the age of 18 and the inclusion of additional conditions that have demonstrated to be safe and effective, (i.e. severe mood disorders, schizophrenia and schizoaffective disorders, catatonia, NMS). AACAP thanks FDA for requesting comments, so as to increase accessibility to this life-saving treatment for those suffering from severe psychiatric and medical conditions. It is imperative that those under 18 years of age be included in the reclassification to readily access such necessary treatment.

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[44] Kutcher, S. and H. Robertson (1995). "Electroconvulsive therapy in treatment-resistant bipolar youth." Journal of Child & Adolescent Psychopharmacology. 5(3): 167-175.

[45] Bloch, Y., Y. Levcovitch, A. M. Bloch, S. Mendlovic and G. Ratzoni (2001). "Electroconvulsive therapy in adolescents: similarities to and differences from adults." Journal of the American Academy of Child & Adolescent Psychiatry 40(11): 1332.

On behalf of the children and adolescents our members serve, AACAP thanks FDA for considering our comments and stands ready and willing to assist in efforts to improve access, treatment, and delivery of mental health care. Please direct any questions you may have to AACAP's Director of Government Affairs & Clinical Practice, Ronald Szabat, JD, LLM, at (202)587-9666, or by email at rszabat@aacap.org or AACAP's Assistant Director of Quality and Regulatory Affairs, Stephanie M. Demian, MPH, CPH, at (202)587-9670 or by email at sdemian@aacap.org.

Sincerely,

Gregory K. Fritz, MD
President, American Academy of Child and Adolescent Psychiatry