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## The FDA and ECT

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The practice of electroconvulsive therapy (ECT) in the United States has come to a very important juncture, and we believe this is a critical period that will have a long-term impact on ECT practice in the United States and potentially in other countries. On December 29, 2015, the Food and Drug Administration (FDA) Office of Device Management proposed new rules for the reclassification of ECT devices in the United States. The proposal includes limitations on the indications for use of ECT devices and warnings that will need to be given to patients and their families who are considering ECT (the full texts of the proposed rule [<https://www.gpo.gov/fdsys/pkg/FR-2015-12-29/pdf/2015-32592.pdf>] and guidance document [<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM478942.pdf>] are available for review).

Some key features of the proposed device labeling requirements include reclassifying the use of the devices into the less restrictive category II for the treatment of “severe major depressive episode (MDE) associated with major depressive disorder (MDD) or 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 or medical condition” (albeit with warnings or “special controls”). While this is a positive step forward, the FDA labeling proposes that ECT devices remain in a more restrictive category (i.e., class III) for patients who are diagnosed with catatonia, schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar mania, or mixed states and for patients who are younger than 18 years. Electroconvulsive therapy device labeling would also be required to have special controls

that include “a precaution that describes the limitations of available information on the safety and effectiveness of long-term treatment with the ECT device, also known as maintenance ECT.”

Even if the proposed FDA device classification and labeling is finalized, a physician could presumably use the device “off-label” to treat other disorders such as schizophrenia and catatonia or to administer maintenance ECT. However, we are concerned that the labeling as written may have an adverse effect on the availability of ECT. Insurance companies may well deny coverage for treatments that are not in line with an FDA-approved labeling of the device. In addition, with ever present concerns about malpractice in the United States, practitioners may be reluctant to use ECT devices for an off-label indication.

No doubt the proposed US FDA labeling could also be a model for government oversight groups in other countries, so we would encourage commentary and scientific discussion from clinicians and researchers outside of the United States. To this end, the *Journal of ECT* editorial board has welcomed submissions from investigators worldwide for over 30 years. The initial issue of *Journal of ECT* (then titled *Convulsive Therapy*) had only 1 article from an author outside the United States (from Israel). In comparison, the first issue in 2016 included papers from China, Belgium, Ireland, Australia, Spain, the Netherlands, Norway, Scotland, Canada, and the United States. This international perspective has been essential in discussing best practices in the clinical administration of ECT based on evidence from researchers and practitioners around the world. For example, in 2006, the same year that articles were published on ECT practice in Australia,<sup>1</sup> Belgium,<sup>2</sup> and Spain,<sup>3</sup> a series of articles in the journal critiqued the clinical guidelines on the practice of ECT in England and Wales by the National Institute for Clinical Excellence (NICE).<sup>4-8</sup>

National Institute for Clinical Excellence is the governmental body established to develop clinical guidelines and standardize treatment throughout the National Health Service. The NICE guidelines were in response to a mental health white paper in the United Kingdom on “Reforming the Mental Health Act” amid concerns that the clinical practice of ECT was less than optimal and not in line with evidence-based practices.<sup>9,10</sup> The United Kingdom Department of Health commissioned reviews on the practice of ECT and a Cochrane review on the efficacy and safety of ECT in schizophrenia<sup>9</sup> including both a scientific review of the safety and efficacy of ECT<sup>10</sup> and a “descriptive systematic review” of “26 studies carried out by clinicians and 9 reports of work undertaken by patients.”<sup>11</sup> Both reviews were considered in the final NICE guidelines despite the disclaimer in the systematic review that the results “might be attributed to a selection bias, with patient studies only selecting people who were antagonistic to treatment.”<sup>11</sup> The systematic review found that almost one third of patients who received ECT had persistent memory loss, a statistic that is not in line with the now published research in ECT.<sup>6,12</sup> Consequently, the NICE guidelines were intended to address a concern about the practice of ECT by physicians in the National Health Service and some of the solutions included voluntary certification of practitioners and facilities and updating of practice standards.<sup>5</sup> The NICE guidelines recommended limiting the use of ECT only to cases in which it will be used to achieve rapid and short-term improvement of severe symptoms, after an adequate trial of other treatments has proven ineffective or when the

condition is considered to be potentially life threatening, in individuals with severe depressive disorders, catatonia, and a prolonged or severe manic episode.<sup>13</sup>

Now almost a decade later, the landscape for ECT in the United States may be undergoing a similar, dramatic change with the recently proposed FDA labeling changes for ECT devices. To understand the evolution of the FDA proposed labeling, it is important to appreciate the history of the FDA's regulation of ECT devices. Electroconvulsive therapy was already an established treatment for psychiatric disorders when the FDA began to regulate medical devices (e.g., pacemakers and orthopedic devices) via the Medical Device Amendment Act of 1976. The process outlined in the Act was to put all devices into separate categories or classes. Class I devices were assessed to be low risk (e.g., tongue depressors), and class II devices require greater regulatory controls to ensure safety and effectiveness (e.g., condoms). Class III devices posed the highest risk (e.g., replacement heart valves) and required more rigorous clinical trials and premarket approval (PMA) by the FDA before they were marketed. The PMA process is scientifically rigorous and generally includes prospective randomized controlled trials. In 1976, the FDA gave "grandfathered" approval of ECT devices, classifying them as class III devices, on the basis of long-standing prior experience with the devices.

In 1978, the FDA recommended placing ECT devices in the less rigorous class II designation, which is reserved for devices where sufficient evidence exists to ensure safety and efficacy. Premarket approvals are not required for class II devices. However, in 1979, after a public hearing on the matter, the FDA reversed itself and changed the classification of ECT devices to class III at the same time encouraging the American Psychiatric Association and other groups to provide a reclassification petition to the FDA with new information about the safety and efficacy of ECT. In 1982, the American Psychiatric Association submitted such a petition. In addition, after another public hearing later that year, the FDA published a notice of intent to reclassify ECT devices to class II, but the reclassification to class II was not finalized by the FDA.

Fast forward to 2009 when the Government Accountability Office recommended that the FDA require all grandfathered class III devices (including ECT devices) to either submit data to support a PMA or be reclassified into class I or class II. In January of 2011, the FDA held a public hearing of the FDA Neurological Devices Review Panel to make recommendations on the classification of ECT devices and determine whether there were data to support moving the devices to class II with special controls. The alternative was to leave ECT devices in class III and require the device manufacturers to submit an application to the FDA, which could include preclinical and clinical studies of the device demonstrating the safety and efficacy of the devices in clinical practice (i.e., a PMA application). In the recently proposed rule and draft guidance document, the FDA is responding to the Government Accountability Office recommendation.

In the proposed FDA labeling for ECT devices, the indications are in fact more restrictive than the NICE guidelines as the FDA labeling does not include patients with catatonia or severe manic episodes in class II. Some of the other restrictions in the NICE guidelines are also repeated in the FDA proposal. For example, the emphasis on the short-term efficacy of

ECT (i.e., greater than 3 months) is echoed in the FDA proposed special control for ECT devices 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.” Of course there have been clinical trials in the United States evaluating the safety and efficacy of continuation ECT for up to 6 months (e.g., Kellner et al.<sup>12</sup>). Furthermore, the durability of ECT’s effects are really no different than what would be expected if treatment with antidepressant medication were discontinued after an acute depressive episode or if medication used to treat diabetes, hypertension, or another chronic medical condition was stopped.

Although the impact of the NICE guidelines and the proposed FDA reclassification may be similar for the practice of ECT, it is crucial to understand that the aims of the NICE guidelines differ from the role the FDA has in regulating devices. Specific aspects of the training, qualifications, and clinical practices of the physicians and medical staff administering ECT are of crucial importance but are best determined through development of clinical practice guidelines. The ongoing evaluation of patients receiving ECT and the assessment and management of ECT-related adverse effects would be important elements of such guidelines.

For the FDA, the agency’s regulatory role entails weighing the benefits and risks of a particular device and determining if special controls are needed to optimize safety. In addition to considering the evidence in the published literature on ECT, the FDA should weigh the potential benefits and risks of ECT against those of appropriate alternative treatments. The FDA has done a thorough analysis of these factors for major depressive episodes in individuals aged 18 years or older who are treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition. As a result of this analysis and with appropriate special controls, the FDA has determined that ECT is a safe and effective treatment. For patients with catatonia, treatment-resistant mania, schizophrenia, or adolescents and children with severe treatment-resistant psychiatric disorders, no specific evidence suggests that safety risks or cognitive effects are any different than in major depressive episodes.

In terms of ECT benefits, the available scientific literature on ECT efficacy should be viewed in the context of available evidence on other applicable treatments. For example, in catatonia, evidence suggesting benefits for benzodiazepines is also limited and antipsychotic treatment may have an increased risk of extra-pyramidal syndromes. Thus, in a patient with catatonia whose symptoms have not responded to benzodiazepines, there is no evidence base for other treatments that is more robust than the evidence base for ECT. The same is true for evidence on ECT use in treatment-resistant mania or schizophrenia and in youth with severe treatment-resistant psychiatric disorders.

Finally, there is clear and convincing evidence that severe psychiatric illnesses have substantial associated functional impairments, morbidity and mortality, including that due to suicide.<sup>14-16</sup> When patients have severe treatment-resistant or life-threatening symptoms, inadequate treatment or delays in needed care can result in serious negative and even fatal outcomes. Because restrictions on ECT access may place our patients at risk of these poor

outcomes, we would argue against unwarranted limitations on the use of ECT for these specific severe treatment-resistant diagnoses.

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