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Is Conduct of Research in Electroconvulsive Therapy Ethical?

Youssef NA* and W. Vaughn McCall

Department of Psychiatry & Health Behavior, The Medical College of Georgia, Augusta University, Augusta, Georgia, USA

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***Corresponding author:** Nagy A. Youssef, Department of Psychiatry and Human Behavior, Medical College of Georgia, Augusta University, 997 St. Sebastian Way, Augusta, GA 30912, USA, Tel: 1706-7216-597; E-mail: nyoussef@gru.edu*

Abstract

Introduction: Controversy surrounding ECT creates skepticism about the ethics of conducting ECT research. This paper discusses the ethical conduct of clinical research and then focus on the ethics as applied to ECT.

Methods: PubMed was searched for articles related to the ethical conduct of research and that of ECT research (published in English).

Results: ECT research is ethically justified and should always to be conducted with the highest ethical standards. ECT research entails few ethical peculiarities such as involving multiple sessions where capacity to consent can change. It would be unethical not to conduct ECT research.

Conclusion: ECT research must be based on sound hypotheses in the presence of clinical equipoise in well-designed studies. ECT studies must select a fair and non-biased sample of participants. It is important that participants represent the broad population of the people that would be receiving ECT for that specific indication. ECT research is ethical; and more research in this field could help decrease stigma and barriers to treatment, and/or reduce side effects and improve efficacy of a potentially life-saving intervention.

Keywords: Electroconvulsive Therapy; Misconceptions; Risk-Benefit Ratio; Equipoise

Introduction

How would research in the field of electroconvulsive therapy (ECT) further improve the efficacy of ECT and reduce its side effects? Is it ethical to conduct ECT research? Controversy surrounding ECT creates an obstacle in the conduct of ECT research. This paper will discuss the ethical conduct of clinical research in general and then focus as on research as applied to ECT. Our intention is not only to discuss the ethics of conducting ECT research, but also to discuss the general ethics of conducting human research, then to mention how that applies to the conduct of ECT clinical research, and to mention the limited differences.

The purpose of clinical research is to develop generalizable knowledge in order to improve health of people. Guidance on the ethical conduct of clinical research has been based for over 50 years on the Nuremberg code [1], Declaration of Helsinki [2], Belmont Report [3], International Ethical Guidelines for Biomedical Research Involving Human Subjects [4], and the like.

There are few fields of medicine that have as much controversy in both the clinical application and clinical research as ECT, and this has been fueled, in part, by misconceptions about the administration and role of clinical ECT.

Misconceptions

As a result of the stigma surrounding ECT, Fink writes "it is hardly available for patients in the most need. The education of medical students and psychiatric residents is so restricted that medical practitioners cannot advise their patients effectively" [5]. It has also been mentioned that the "public sees ECT as controversial, painful, and frightening. The negative attitudes to ECT have roots in misperceptions about the treatment and about psychiatric illness. Some believe that it is still forced on the patient, used by the state to subjugate its unruly citizens, and that memory disturbances are so severe and so persistent that no rational human being would undergo this procedure" [5].

Although ECT is an effective treatment for patients with the most severe and treatment-resistant psychiatric disorders, it is has been regarded by some as controversial or stigmatizing, mainly due to misconceptions about how modern ECT is administered, its efficacy, and an exaggerated view of side effects. Misconceptions regarding the clinical conduct of ECT include that it is not effective, or rather works by inducing forgetfulness, or that it leads to brain damage, or that ECT is administered without informed consent [6-9]. These misconceptions are also reflected in the public opinion [8,10].

The effectiveness of ECT has been proven over 75 years of research and has shown that there is no evidence that ECT leads to brain damage [11]. The memory side effects of ECT are not bothersome to most patients [12].

Modern ECT practice includes informed consent, oxygenation, anesthesia, and muscle relaxation. As a result, ECT is a low-risk procedure that is administered on an outpatient basis in over 80-90% of the cases in major academic medical centers in the US [13,14]. The application of ECT is associated with lower overall mortality, as compared with depressed patients receiving psychotropics alone, or no treatment [15]. This has been replicated again in a study by Ahmadi, et al [16], with a mean duration of eight years showing statistically significant risk reduction for all-cause mortality as well as lower mortality due suicide and lower cardiovascular mortality in the ECT group compared to patients who did not receive ECT.

This paper will discuss the ethical conduct of clinical research and how it applies to the field of ECT research.

Methods

PubMed was searched for articles related to the ethical conduct of research of ECT using the terms "ethics", "conduct of research" and "electroconvulsive therapy" or "ECT". We searched for relevant articles that address ethics of research of ECT in adults using modern ECT techniques that are published in English. None were found that discussed or reviewed the ethical conduct of research in ECT. Thus, this article represents the first effort to address this topic from the vantage point of the codes, regulations, and the general ethical principles of clinical research in medicine, and the few papers dedicated to the ethical clinical practice of ECT [5,17-20].

Results and Discussion

The atrocities of the experimentation of Nazi times stimulated the development of formal written codes of ethical conduct: The Nuremberg Code of 1947. The Code established the first written

guidelines for appropriate ethical treatment and research in humans. The code was later supplemented by other codes, regulations, and guidelines.

The most recent is the 2002 revision provided by the World Medical Association. The Declaration of Hawaii in 1977 by the World Psychiatric Association and the amendments in the Declaration of Madrid in 1996 are especially relevant to psychiatric research in specific and clinical research in general. Thus, with each step, medical research better approximates the ethical principles that are rooted back to the Hippocrates oath [21].

Principles of Ethical Conduct of Clinical Research

The basic principles of ethical conduct of human research include beneficence, nonmaleficence, autonomy, and justice [22,23].

Requirements of Ethical Conduct of Clinical Research, including ECT

Emanuel, et al [22], have nicely characterized "seven requirements" of clinical research that also apply and should always guide the conduct of research in general including ECT research. These seven requirements overlap with the four basic principles of conduct of clinical research in humans: Respect, Justice, Beneficence, and Nonmaleficence.

Value: Ethical research in ECT has and must provide valuable knowledge to the field and the community and lead to better understanding, or treatment of disease or improvement of health and well-being [24,1]. In addition, to contribute to generalizable knowledge, it has to be practical and implementable. Research that leads to generalizable knowledge but has no practical implication does not pass the "so what" test. Also, research that is not implementable would not be valuable or worth the potential risk of the participants, thus has doubtful ethical grounds.

If and only if, clinical research would improve health through the dissemination of generalizable knowledge, then is it ethical to pursue and could justify potential risks to participants. Dissemination of research is required not only to have broad impact on health practice, but also to prevent unnecessary duplication of research and unnecessary exposure of participants to risk.

Scientific rigor: The ethics of clinical trials requires that ECT clinical research be conducted in a methodologically rigorous manner [24]. Poorly conducted clinical research produces invalid results and does not answer the proposed question, due to lack of methodological rigor, biased samples, or statistical problems [25]. Thus, poorly conducted research is unethical [24-27]. The Council for International Organizations of Medical Sciences (CIOMS) guidelines indicates that: "Scientifically unsound research on human subjects is ipso facto unethical in that it may expose subjects to risks or inconvenience to no purpose" [4].

Interventional research, especially, must have a valid "null hypothesis" with equipoise [27,28]. Equipoise means that there is controversy (uncertainty among all or divided opinion) amongst clinicians and researchers of whether the intervention under investigation is better or not than an alternative therapy or placebo (depending on the standard in that field of research) [28]. In addition, in cases where equipoise is absent because a more or less uniform consensus of opinion is present, but the consensus is not based upon rigorous research, it would be justifiable to proceed with research to test the assumptions of the consensus. For example, it was widely believed that hormone-replacement therapy in post-menopausal women decreased the risk of coronary artery disease, until rigorous studies of the question were completed, thus showing the opposite was true [29].

Fair Selection of Participants: Fair selection of participants is an expectation of ethical research [26,27,30]. This will lead to equitable and fair distribution of both benefits and burdens of research. Ethics requires that consideration be given to the need to generalize knowledge to groups that are often excluded from research, such as the elderly or pregnant women. Also, the burden of study participation should not be targeted to only one demographic group (i.e. ethnic, gender etc). Thus, fair participant selection distributes vulnerability and privilege and results in generalization of findings to populations that would benefit from the results of the research.

Favorable Risk-Benefit Ratio: Research inherently entails uncertainty about the degree of risk and benefits. ECT clinical research is only justified if: the potential risks to participants are minimized, and the potential benefits to participants and society outweigh the risks [2,26,27]. Nonmaleficence and beneficence is encompassed in the need for favorable risk-benefit ratio as an ethical foundation of clinical research [21,26,27].

Independent Review of the Study Protocol by the Institutional Review Board: Independent review by a panel from the institutional review board (IRB) should include: (1) a range of expertise, (2) community representatives, and both groups represent a neutral committee uninvolved in the research that is being evaluated, in order to minimize the potential impact of conflicts of interest or personal bias of the investigator(s) [26,31]. Independent review of ECT research is also important for social accountability. Clinical research may impose risks on participants for the benefit of society. Independent review of ECT research also assures society that participants enrolled from this society will be treated with respect, with fair distribution of burdens and benefits, and a favorable risk-benefit ratio.

Informed Consent: The informed consent process requires that research participants in ECT studies must comprehend the purpose, procedure, risks, benefits, and alternatives of the research, and to make a voluntary decision regarding participation in research or pursuit of other clinical usual care or neither [32,33]. Comprehension requires basic capacity to make decisions and should be assessed by the researcher clinically during the interview with more extensive assessment if there is a reason to believe that it is compromised.

Respect: Individuals should be treated with respect and honesty during enrollment and throughout participation in ECT research projects. This includes, as in clinical research in general, but is not limited to the following: 1) privacy must be respected with strict confidentiality; 2) respect of the decision-making process, including respect for withdrawal of consent for any reasons or no reason without penalty; 3) sharing and informing participants about any new information about the intervention under the investigation or if other new treatments or information arise; 4) health and well-being of participants should be carefully followed, and treatment should be provided if adverse reactions or unexpected events occur, and participants should be removed from the study if needed for their safety; 5) lack of deception and transparency as part of the informed consent process; 6) informing participants and the society of what information and benefits were gained from the research [34].

Ethical Principals of Conduct in ECT Research

ECT research must follow the basic principles of clinical research in humans as follows.

Beneficence: Beneficence is to do good, in other words, to provide benefits to participants or to others in the community. A

treatment that provides effective treatment to a substantial number of patients with minimal risk or reasonable favorable risk-benefit ratio is considered beneficial [22]. ECT is an effective treatment for depression (including treatment resistant depression) [35,36], mania [37], psychosis [38], and catatonia [39]. ECT reduces risk of death due to suicide [40,41]. Six months after treatment for depression, ECT patients had 0.8% chance of attempting suicide compared to 4.2% who received pharmacotherapy and 7% of non-treated patients [21]. A meta-analyses found superior effectiveness of ECT compared to psychopharmacology in 1144 participants (18 randomized clinical trials) [36]. It has also been shown to be effective in maintaining remission [42].

Nonmaleficence: It is important in ECT researches to abide by the notion of "do no harm". The use of anesthesia, muscle relaxation, and physiological monitoring in ECT, in clinical practice and hence in clinical research has reduced the risks of harm including death, fractures and status epileptics or tardive seizures [5].

Autonomy: Protection of the patient's autonomy is among the most important aspects of the ethical conduct of ECT research. The misrepresentation of ECT by some groups and movies gives the mistaken impression that most ECT patients do not provide consent [43]. In practice, ECT is a procedure that requires informed consent in the US and most countries, often facilitated with the use of printed material and/or sometimes educational videos about the procedure. As with any clinical research, participants must be able to withdraw consent if needed [22].

Justice: As mentioned, the principle of justice means that research should enroll participants regardless of age, gender, social and financial status, or ethnicity etc. and not exclude certain groups without reason, or overburden others. This leads to fair and equitable distribution of risks and benefits [22]. Thus, fair selection of participants is based on this principle.

Difference of the Standards and the Ethical Consent between ECT Research and Other Clinical Research

There are multiple similarities between the ethics and consent process of conducting clinical research in general, and ECT clinical research. ECT research is (and should be) conducted with the same ethical consideration as other types of clinical research. However, there are some differences in the consent process of ECT research.

ECT involves a course of multiple sessions during which there is gradual improvement of symptoms, and thus the capacity to consent may, at least theoretically, change over the course of ECT as the patient improves or begins to accumulate cognitive side effects. Some studies have found more severely depressed patients to have better capacity to consent for clinical research stating that "subjects who were more depressed demonstrated fewer misconceptions about the nature of the research study" [44]. This was explained by depressive realism [45]. That is to say depressed patients have "more accurate judgments than their nondepressed counterparts" [44]. More importantly, regardless of theory, most individuals screened for (and all who are enrolled in) ECT research understand the risks and benefits and the needed study details in order to make proper judgment [46].

In addition, there seems to be a difference in the standard of ECT research compared to ECT practice and other clinical research in the utilization of needed proxy's consent in occasional cases. In clinical practice, most patients consent to ECT, however, occasionally if the patient lacks decisional capacity the clinical informed consent can be obtained from another proxy decision maker (with some variations between jurisdictions). While proxy consent may occasionally happen in the pursuit of the usual clinical practice of ECT [47], proxy consent is rarely, if ever, sought to enroll patients in clinical ECT research. Thus, there is scant evidence-based information on the topic of ECT in vulnerable and incapacitated patients, such as those with catatonia.

It is also important to note that ECT research in patients with acute schizophrenia exacerbation is limited in the US (and to a great extent worldwide) [48]. Although, most patients with schizophrenia have capacity to consent, some may not especially in acute exacerbation. Perhaps the rare use of proxy consent may have, at least in part, limited research in this population. This is unfortunate given that the majority of the ECT treated patients worldwide are suffering from schizophrenia; and conducting ethical research in this group could better improve the outcomes, advise the selection of subgroup or a subtypes that are most responsive to ECT. It could also help further the development of predictors of treatment response. This is also reflected by underutilization of ECT in treatment-resistant schizophrenia [49] despite the fact that the limited available evidence support the better outcome of ECT compared to antipsychotic polypharmacy [48,50,51], and arguably overall lower side effect burden for ECT.

Another area that ECT can be potentially of significant benefit, and perhaps safer than medication (given the limited evidence), is the use of ECT in pregnancy [52-55] and postpartum period [56,57]. This area is also under-researched [52,58], perhaps in part due to the misconceived stigma associated with ECT [53].

Conclusion

ECT research must be based on sound hypotheses in the presence of a clinical equipoise in well-designed studies. ECT studies must select a fair and non-biased sample of participants and it is important that participants represent the broad population of the people that would be receiving ECT for that specific indication. Independent reviewers of ECT research help amend, advise, revise or terminate studies as necessary. This helps protect the participants and ensures the validity of research [22]. These guidelines are not all-inclusive and are simply a framework to guide researchers in designing studies and IRB members in evaluating clinical research in ECT.

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***Corresponding author:** Nagy A. Youssef, Department of Psychiatry and Human Behavior, Medical College of Georgia, Augusta University, 997 St. Sebastian Way, Augusta, GA 30912, USA, Tel: 1706-7216-597; E-mail: nyoussef@gru.edu

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