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Ref: EXNER
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Dear Jack,

While the proposal, "Treatment of Schizophrenia by Regressive ECT" has important and interesting goals, the methods are inadequate to the task. Should the Committee wish to encourage such a program, it would be advisable for the investigators to discuss two issues with others: the interrelations of modifications of the ECT process to therapeutic outcome, and the issues in quantification of the EEG. In addition, since the main issues in regressive ECT from a public health point of view are the long term effects of multiple seizures, seen as an assault on the central nervous system, particularly on measures of brain function and on such capacities as concentration, memory, and thought processes, the evaluation of neurological deficits and psychological tests focussed on what is usually called 'organicity' must be considered.

The investigators have done an interesting clinical study of regressive ECT in schizophrenic patients. There is a need for such a re-evaluation of regressive ECT, for this modification has a chequered history. Older studies found it rarely useful. Recent studies of multiple ECT, under oxygenation control, have indicated that multiple ECT are safe, producing no more memory loss, neurological deficits, or EEG changes than single ECT. Unfortunately, multiple ECT only occasionally produces better results than single ECT in depressed patients. The data for schizophrenic patients is unclear, however; and there now are some reports of better results with multiple ECT. These data require verification, and in this framework, the proposal by Exner warrants some assistance. In its present form, it is inadequate to the tasks outlined by the investigators, and suggested by my view of the public health issues.

The favorable features of the proposal:

- 1) the population is adequate, and the setting is probably a good one for such studies. (In our investigations of ECT at Gracie Square and Hillside, it was in these small hospitals that the staff were favorably disposed to ECT, allowing the investigations to proceed.)
- 2) The investigators have an interest and some experience in regressive ECT.

3) The PI exhibits statistical and design sophistication, and his record as psychometrist is good.

The negative features of the proposal:

1) The design is ECT vs. drug treatment. This is not the most important issue, but were it the design to be followed, there are specific problems.

2) While the evaluation methods may be adequate indices of change in personality and behavior, the issue in regressive ECT is the impact on interpersonal behavior, neurological deficits, thought processes, memory, and concentration. In their first study, they emphasize a persistence of some of the thought disorder-- but is it different and how is it changed? The clinical aspects seem inadequately covered, and the emphasis on a psychiatric interview no less than 30 minutes and no more than 45 minutes is mechanistic and less than helpful.

The EEG evaluation is at the wrong time for any important issue. Perhaps the EEG should be evaluated serially (weekly) to assess the rate and degree of change in brain function. But most critical is the likelihood that the patients will all receive drugs after the treatment course. The drug controls of necessity; the ECT patients most probably. Since no statement is made about the specific drugs, dosages, and relation of EEG measures to drug intake, I have to assume the investigators are not acutely aware of the impact of drugs on the EEG. To unravel EEG effects of ECT from drugs without attention to the controls necessary, is exceedingly difficult.

The same problem in the evaluation and follow-up will occur for other indices-- what is the impact of drugs given after regressive ECT on the ECT process, and on the comparison of ECT and drugs? (For this reason, I would favor regressive ECT vs single ECT).

3) Patient selection is an issue. The statement of process schizophrenia is inadequate. The tests described are too non-specific to help others define the population. It were better for the investigators to specify which criteria of process schizophrenia they use (e.g. Fish, Taylor, others?). Psychological tests are supplementary-- they cannot be used as the diagnostic criteria.

While I am not ordinarily prone to question selection criteria on ethical grounds, in this instance, the authors should be asked to make clear some of their minimum criteria of prior treatments and failure, recent treatment and failure, etc. before regressive ECT. Should not all patients have had a course of 'regular' ECT and failed?

4) Psychological tests are given heavy emphasis, but the theoretic base from which these tests were selected is not indicated. Why the MMPI and the SFSC? Neither is sufficiently specific in its interpretation to be very helpful.

4) There are many problems with the EEG measures, but since the study could be done without EEG measures, I will not go into full detail of the inadequacies. It is not clear why the investigators are measuring EEG effects, for the only specific suggestion comes from the description of lack of abnormality before and after treatment, as evaluated by the neurologists on visual inspection. The issues that could be investigated are the differences in EEG effects of regressive ECT vs other ECT; the rate at which the induced changes disappear; the relation of change to improvement, to memory effects, or to other neurological indices.

They suggest quantification of the EEG, suggesting 8 channel recording and analysis for short epochs. The equipment they request, representing a large part of the budget, is adequate only for the analog to digital conversion, and some simple steps of data reduction. But EEG data is voluminous, even when reduced, and the interrelations among many channels a horrendous task. (Indeed, very few investigators have challenged more than one or 2 channel data, and if more, only for 1 or 2 minute epochs).

Their interest in sleep EEG is unjustified in the protocol. To even suggest sleep EEG recording (8 hours), for 8 channels (!), is so voluminous a task, that I suspect they do not mean this. Their suggestion about doing visual analysis of the sleep records is interesting, but this too is a big task, and will not in their few cases, answer any of the questions. The same problem of drug control must be considered here.

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In re-reading this proposal, I believe the investigator brings to the questions, posed by his clinical colleagues, and experience as a clinical psychologist and psychometrician. These aspects seem well handled. For 'scientific' reasons and interests, they are suggesting EEG analyses, sleep recording, and some follow-up studies. In these aspects, they seem to lack experience, but also sufficient judgment to visualize the tasks and to obtain advice. Perhaps, were they encouraged to visit and work with one of the university based centers studying ECT and one focussed on quantification of the EEG, these issues might become clearer to them. Were they then still interested in the studies suggested here, a better proposal might (?) be forthcoming.

Alternatively, the design could be reduced to a clinical replication of their pilot study, with some better statement of the population, assessment of neurological effects, control of ECT parameters and drugs, etc.-- and a contribution made to the ECT literature. In the latter case, the budget could be subjected to reworking, deleting sleep and statistical consultants (\$3300), equipment (\$20,300), and EEG chart paper (\$600); with additions for neurological evaluation.

I trust these comments are helpful. You already know the principal laboratories interested in these issues, and I am confident that any would be interested in this study.

Sincerely yours,

Max Fink, M.D.