

December 19, 1966

Dr. Turan M. Itil
Missouri Institute of Psychiatry
5400 Arsenal Street
St. Louis, Missouri 63139

Dear Turan,

I have read the protocol of the proposed thioridazine and diphenylhydantoin study with great interest. This is an important study and I think the combination of controls, EEG criteria and random assignment of patients provides the basis for a definitive study. I have four questions which may be useful in clarifying the protocol. These are chiefly in the direction of clarification but do not modify the study at all.

The criteria for age and EEG abnormalities are not clear. Since the EEG is undergoing changes with age during the adolescent period, perhaps the limits should be defined on the populations equated for age as the single most important variable, especially for the EEG component. With regard to the abnormal EEG criterion, does it mean that patients who do not have an abnormal EEG will be excluded from the study? If so, perhaps at least two lengthy recordings should be done so that this criterion in the sample can be adequately defined.

Is the duration of the study a definite one or to be clinically determined by the youth center director? Is it possible to define a minimum treatment period of either four, six or nine months? Just as the criterion that a patient who must be given other drugs for more than five days are automatically excluded is a definite one, perhaps any patient who received medication for less than four months continuously should also be excluded from the study.

The single most important omission is a definition of the criteria for improvement. Since you have a specific rating scale for psychopathological aspects, would it not be helpful to define in the protocol the criteria to be used for the degree of change? These possibly should include alterations in disturbances in psychomotor activity, thought, episodic outbursts and emotionality.

Finally, the dose of diphenylhydantoin is specified as 200 mg and this may be too low. Surely these adolescent subjects are able to tolerate 300 mg and this may be a more effective dose. Also, the thioridazine dosage is given as a range of 75 to 200 mg and this should be made clearer. Is the dosage a minimum according to body weight? Is there a maximum to be given?

The additional thought, which I am sure you considered, is that of sleep EEG's taken prior to treatment and perhaps at the end of three or six months. This may provide special information regarding fourteen and six positive spikes.

I am enclosing an additional carbon for Dr. Turner, in the event that you believe these comments may be helpful.

My best regards.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

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