

January 21, 1966

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Dear Al:

Thank you very much for making your manuscript "Combined Drug Treatment of Acutely Ill Patients" available to us. We have read it with a great deal of interest, and despite your comments at it length and statistical interjections, we found these interesting and valuable. As with our own study, the principal question which is in the forefront is the influence of dosage on these combinations. In this study, the chlorpromazine-imipramine combination showed, in many scores, differences from the chlorpromazine-placebo combination and also chlorpromazine-chlordiazepoxide. The problem with seeking levels of significance from this data is that the best dosage combination may not have been achieved, and the variability among the patients is sufficiently great so that even in populations of forty subjects, the differences do not achieve the statistical differences required. However, the fact that chlorpromazine-imipramine shows changes in some psychopathological symptoms while the combination of chlorpromazine and chlordiazepoxide is often notably poorer, provides behavioral clues which are consistent with the electrographic effects noted for such combinations.

I found the observation that chlorpromazine-imipramine seemed better in those with high depression scores, high retardation scores, and low agitation of great interest since this parallels the uncontrolled observations which were carried out at Hillside Hospital.

Another observation which seems important to me is the differences between males and females. There have been many suggestions that female patients are more sensitive to phenothiazines and exhibit parkinsonism earlier and at lower dosages. I know a few studies where the clinical effects have been shown different for the sexes when the dosage was controlled according to body weight. Also, in a number of analyses of the Hillside Hospital data, the EEG changes induced by chlorpromazine and by imipramine were different for males and females. Chuck Hall, working with Dean Clyde, undertook the analysis of the Hillside Hospital 1959-1962 data and showed that the amount of beta activity produced in females was higher than that in males on the same drug dosage. With this in mind, the differences might still be related to neuro-physiological factors, even if dosage were controlled.

I also found of interest your observation that chlorpromazine and placebo was successful in the alleviation of retardation. This also is consistent with our own observations and I believe this is another important note in this report.

In your revision of this draft, perhaps the focus could be placed on the clinical observations, simply describing the methods used and omitting the extensive discussion of methodology and methodological problems. These are important to us, but the usual readers are interested in the clinical data alone. I think the clinical data is very important and surely a clinical data presentation should be published in the Archives or the American Journal of Psychiatry.

We have begun the analysis of a group of schizophrenic patients who have been placed serially for eight week periods on placebo, chlordiazepoxide alone (1 mg/kg), thioridazine alone (5 mg/kg) and the combination using half strength of each. Dosages were fixed and the evaluations were done during the second four week period. The patients were long-term schizophrenic subjects and all male. A copy of the present, revised data analysis sheet is enclosed, and this will give the picture that we now have. It is of interest to us that chlordiazepoxide alone was not significantly different than placebo. But the small amount added to a small dose of thioridazine was sufficient to produce significant changes in all the rating systems. This, we believe, argues for an augmentation of the thioridazine effects by chlordiazepoxide. As you can guess, we are now involved in the further analysis of the individual items, and in the EEG relationships.

Again, my many thanks for the opportunity to read your report. I do hope it will be published soon.

My best regards.

Sincerely yours,

Max Fink, M.D.  
Professor of Psychiatry

MF:jmh  
Enclosure