

March 9, 1967

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Dear Allen,

I was very grateful for the opportunity to read the first report of the collaborative depression study program, and would like to congratulate you on your clear and most interesting presentation. It was especially rewarding to find that the clinical efficacy of chlorpromazine in depressive disorders was confirmed, for I can clearly recall the difficulties and anxieties with the first Hillside study which appeared to be contrary to the prevailing opinions - not only regarding the treatment of depression but in response to a myth that chlorpromazine could induce depressions (1958-59).

Your study indicates that the combination of chlorpromazine and procyclidine was no more effective in the treatment of depression than chlorpromazine alone and the detailed measures show that procyclidine was exerting some pharmacological effects. Perhaps we were still under the influence of the state of the art for we tried chlorpromazine alone in only a few patients, fearing that the side effects would be too great; and then, when we found the patients tolerated the combination, we were so pleased that we undertook the comparative study of the combination against imipramine.

Our focus on the merits of the combination were, in part, a response to the often asked question as to whether the efficacy of the combination in depression may have been due to the procyclidine alone and, in part, to the favorable reports we found in the literature which appeared to be consistent with our observations. We did treat five patients with procyclidine alone, and discontinued the study for reasons that are unclear to me today.

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As I read your report I made a few notes and I share these with you as comments, not criticism.

The comment on page 9 regarding the low incidence of extra-pyramidal reactions with chlorpromazine alone is puzzling. Is it possible that the patients did not get their medication as prescribed, or that antiparkinson medication was made available outside the regular record keeping procedures? On occasions, both at Hillside and in Missouri, such puzzling observations were found to be related to extra-medical procedures and the clinical facts were not so discrepant with our clinical experience as this observation would imply.

Table 3 has most interesting data. The combination appears to enhance or sustain excitement - an observation consistent with the defined EEG effects of procyclidine; and to enhance dryness of the mouth and blurring of vision - possible related to the anticholinergic properties of procyclidine. Most interesting, however, is the clear demonstration that adaptation to the secondary effects of drowsiness, nasal congestion, blurred vision and loss of appetite does occur - thus confirming our clinical experience. It is here that the similarities of the combination to the chlorpromazine alone are so convincing.

In the discussion (page 16) the opening paragraph enlarges on the attrition rate of 15% for the active treatments, and focusses on the incidence of secondary effects. The incidence reported is not too high in comparison to clinical experience, and perhaps the contrast should be made not with no treatment or with placebo treatment but with other accepted treatments for depressive disorder as ECT and imipramine. Are these side effects and the attrition rate discordant with that which was observed in the imipramine study? This emphasis may perhaps be modified by your subsequent experience.

The finding that our dosage range may have been too high is not unexpected, for we had been working with a population of therapy failures and had adjusted our dosage to be above that needed by 80% of the test group. Since then, I have found that chlorpromazine dosages of 500 - 800 mg are generally adequate.

Again, let me thank you for the opportunity to read this report, and for the honor that you have done our 1959 study at Hillside in refining our observations. I look forward with keen anticipation to the next reports of the depression study.

Many thanks and my best regards.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

MF:kp

cc: Dr. Jonathan O. Cole