

November 2, 1965

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Dear Ray:

Following our initial discussions in June, we established a preliminary protocol for the Dorsey-EEG study. It was our purpose to measure the EEG changes induced by low dosages of pyrovalerone, and to compare the changes with placebo for a prospective study comparing the changes with those induced by amphetamine. Our initial trials were with 30 mg and 60 mg pyrovalerone. These dosages were selected as those related to the clinical state which interested you and which was similar to the studies published by Dr. Halliday.

In view of the problems of behavioral control in our first study, we decided that the initial trials during the summer would be varied with regard to the measure of behavioral control. For this purpose we selected a reaction time model.

Four subjects were initially introduced to the study program but as we found it necessary to vary the behavioral parameters, two of the subjects were excused and await the definitive study itself. In two subjects we varied the behavioral parameters and form of examination in numerous trials.

Initially, we studied the effects of a continuous performance task with the auditory signal applied on a random basis throughout the four hour session. In later trials we used the stimulus on a block basis and by the end of our experimental studies decided that the best control was provided by ten stimuli presented every 12 minutes. The stimulus is a 1000 cps signal.

We undertook twenty studies during the two and one-half month summer period and of these, thirteen are satisfactory for our present initial analyses. These are equally divided between pyrovalerone 30 mg, pyrovalerone 60 mg, inactive placebo and an active placebo (papaverine-like central vasodilator). Two lead combinations for EEG were recorded. The EEG analyses were undertaken principally for the occipital-frontal lead combination, but in four records, the bi-frontal leads were also studied.

The effects of the active placebo and inactive placebo were indistinguishable in the later behavioral controlled experiments. In the experiments earlier, when the stimulation was continuous, subjects failed to respond and developed drowsiness and in one instance fell asleep despite the stimulation. In the later experiments, the periodic stimulation provided better behavioral control and the EEG variables did not show changes beyond one standard deviation from the pre-treatment record.

Both the 30 mg and 60 mg pyrovalerone dosages demonstrated changes in average frequency which was prominent during the first hour and again during the third and fourth hours of the experiment. In each instance the average frequency appeared to increase so that the records showed periods with more than 1 1/2 standard deviations shift from the pre-treatment baseline. The observations were clearer for 60 mg than for 30 mg doses.

The changes induced by pyrovalerone were smaller than those induced by barbiturates on visual analysis, and the variability appeared to be greater in these two subjects. As a consequence, we feel the changes in frequencies and in average frequency which may distinguish pyrovalerone from placebo will be observed only for the group data using the statistical techniques which were successful in the barbiturate study. For this reason, we are prepared to undertake a full trial of pyrovalerone against placebo in volunteers, estimating that 12 subjects would be the initial population for analyses. The behavioral control in such a study should follow the experiences which we had in the latest experiments.

The results of this review were summarized in a protocol dated 10-21-65, and its modification-Number 1. This protocol encompasses your recommendations, especially with regard to dietary control. A copy is enclosed.

While the 60 mg pyrovalerone would probably give a better discrimination than placebo, we are preparing trials with the 30 mg dosage form to provide data which is comparable to that of Dr. Halliday. If this protocol (10-21-65) is satisfactory, we would be pleased to undertake the definitive study.

Thank you very much for visiting our laboratories.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

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