

Dextroamphetamine weight loss per week—0.86 lbs. According to my calculations the average weight loss per week was—1.06 for Placebo—1.41 for Fenfluramine 20 mg.—1.06 for Fenfluramine 40 mg. and—0.89 for Dextroamphetamine. My calculations and their calculations agree on the number of dropouts.

Without protocols I was not able to do very much in assessing the correctness of these statements. Entries on the case records for some studies lead me to believe that the blinds were jeopardized or broken. For example, in Study #2050, there were dosage entries written at the top of the individual case records such as: 40 mg., 20 mg., etc. In another study (2002) the drugs were identified as p+p, p+f, p+m, etc.

As shown on the first page of my report these are very old studies, nearly all were completed in early 1967. Some are still stated to be incomplete. In one study (2009) there was a considerable dropout rate of about 50% in all drug groups. Only 30 subjects finished 5 weeks of study. The placebo had the smallest dropout rate, 33 percent.

I attempted to verify the summary data in #2020. In this study patients were given Fenfluramine for 8 weeks, and Placebo for 8 weeks. The firm reports an average weekly weight loss of: Fenfluramine—1.70 lbs.; placebo—1.46 lbs.

There were no placebo body weights listed on the data sheets; therefore, I could not verify this average. I computed an average for Fenfluramine patients that completed 60 days in this study. It is 0.42 lbs/week loss based on 28 patients.

On four of the case records medication is entered as "Caps" 40 mgm.

For Study #2016 none of the patients followed protocol which required crossover on 3 drugs. Some had crossover in two drugs with the identity of the second Rx in doubt. Of the 34 only 21 had some treatment with two drugs.

The protocol further states that observations were made every two weeks following the start of medication.

Very few subjects satisfied this requirement on both drugs. The treatment and visit regimen is very inconsistent and variable.

Only two subjects were observed every two weeks for as long as 4 weeks.

Only two subjects were observed every two weeks for as long as 6 weeks.

Some patients were observed often irregularly for as long as 12 weeks on one drug. Their comparable duration on the control ranged from 2 to 7 weeks.

Some subjects had only 6 weeks on one Rx and only two or less on the crossover.

The durations of treatment both on a single drug and on its counterpart are so variable and spotty that the data cannot be summarized meaningfully. Further compounding difficulties in working with these data is duplication of case numbers for different subjects and different case numbers for the same subject.

Study #2020 was a double-blind, crossover, randomized. Total length of study was 9 weeks, included 3-3-week periods. Drugs administered were 30 mg. Fenfluramine capsules and Placebo capsules. On the reference to raw data sheet the total average weight loss for those subjects receiving Fenfluramine was 1.4 pounds per week as compared to 0.34 pounds per week on Placebo. My calculations averaged—1.33 pounds per week weight loss on Fenfluramine which included all subjects. Of those that completed the study (n-17), the average weight loss on the drug was 0.96 and for the Placebo average weight loss per week was 0.56.

MEMORANDUM

April 25, 1969.

To: Robert O. Knox, M.D., MD-120.

From: Peter G. James, MD-460.

Subject: Ponderex—Review of older studies.

Attached is a report by Mrs. Jacqueline Tillman based on her review of "controlled" studies included in the last submission to this NDA and which are the subject of your request of March 3, 1969.

Please note that nearly all of these studies were planned and initiated, in some instances, long before the efficacy provisions of the K-H Amendment was promulgated. It is not surprising then to find an inadequate protocol and little in the way of basic information and adequate design to satisfy our current requirements.