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While there has been much research on psychological factors and drug response, the intensity of the search appears to vary inversely with the potency of the drug studied. There seems to be little replication in the studies. The four studies summarized here involved the same psychological variable measured by an abbreviated version of the Bass Social Acquiescence Scale. Studies one and two involved a double-blind comparison of diazepam (valium) and a placebo, and involved 20 psychiatrists and 60 anxious outpatients. In a third study, four pairs of women outpatients selected on the basis of extreme acquiescence scores were treated in a double-blind study of chlordiazepoxide (librium) and a placebo. In the fourth study, 28 medical students were selected on the basis of extreme acquiescence scores and randomly assigned to secobarbital and placebo groups. These experiments indicate a link between over-generalizing and reactions to mild tranquilizers. The findings also raise questions about effective treatment for high acquiescers and about the relationship between acquiescence and both beneficial and adverse drug effects. (KP)

The Influence of a Psychological Factor on Drug Response[1]

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Since this paper concerns overgeneralizers and drug response, I would like to begin with a couple of glib generalizations. There has been no dearth of research in the area of psychological factors and drug response. At least three volumes and, probably more than a hundred papers have contributed suggestions or cited evidence, or both, about presumably potent psychological variables. Sometimes it seems as if every psychological characteristic ever captured between journal covers has been related to drug response. Everything about the patient's and the doctor's psychology--from the square root of the patient's mother's age at conception to the log number of cigarettes smoked by the doctor in the drug-dispensing interview--has been studied or postulated. And the search goes on.

Another point is that the intensity of the search for psychological factors appears to vary inversely with the potency of the drug studied. Thus, more psychological hunting is done in the territory of anti-anxiety agents than in some other areas. This is perhaps natural since a highly potent drug could presumably abolish or obscure the influence of weaker variables. However, some of the current work with hallucinogens, which certainly have powerful effects on society if not on the subject, suggests that psychological factors may be important determinants of response to such drugs.

When you sift the evidence you find a long list of psychological variables which have passed conventional significance hurdles in one study or another. When you get through sifting there is at least one problem. There has been damn little replication. If you ask the past evidence what psychological variables should be controlled to improve the methodology of a new study, the answer seems to be "control everything" or "you pays your money and you picks your choice."

One thing these symposium members have in common, besides a desire to improve drug study methodologies and an interest in psychological factors, is a strong concern for replication. What I would like to do with my time is to summarize four studies by our Laboratory. All four involved the same psychological variable. In all four the same drug-personality interaction appeared consistently.

The Psychological Measure

The psychological variable was measured by a simple paper-and-pencil test, the Bass Social Acquiescence Scale (1). We used an abbreviated version consisting of 35 rather trite and glib generalizations. Sample items are shown in the first table. The subject simply indicates whether he agrees, disagrees or is uncertain about each item.

Insert Table 1 about here

The scale purportedly measures social acquiescence, conformity or "Babbittism". Our evidence and that of others suggests that it does not. In fact, high scorers on this scale give us more problems than low scorers in adhering to research protocol, in volunteering for studies, appearing for scheduled interviews, etc. Our studies also suggest the scale is only mildly-to-moderately related to the acquiescent response set measured by the MMPI and similar tests. Therefore, even though we label our experimental groups as High and Low Acquiescers from their test scores, we prefer at this time not to attach any meanings to these labels beyond a tendency to indulge in glib generalizations.

We became interested in the Acquiescence Scale after Fisher and Fisher (2) (neither is our chairman), in a rather poorly controlled study, found that the response of college students to a placebo was positively related to scores on the Bass Scale. The measure, thus, showed promise as a means of identifying that slippery

character, the placebo reactor, and that was our original interest in the measure.

Study One

The first study was a 2-week double-blind comparison of diazepam (Valium) and placebo (3,4). The study methodology was fairly st. ard an' involved 20 psychiatrists and 60 anxious outpatients. Acquiescence was not an experimental variable, but the test was administered prior to treatment to permit a post hoc classification of patients into groups of High and Low Acquiescers.

Insert Figure 1 about here

Figure 1 shows for a typical criterion the results of two weeks of treatment. The four points represent the 2-week adjusted means for four groups of 1[illegible] patients each. It can be seen that the Low Acquie..ers responded to the drug but not to the placebo. The High Acquiescers responded rather extremely to the placebo but not to the active drug. In fact, compared with their pre-treatment status, High Acquiescers became a little worse on the drug. If Acquiescence had been ignored, the drug-placebo differences would have been nil.

Study Two

The second study followed-up the first and concerned the persistence of the interaction pattern (5). Follow-up took place four months after each patient completed the controlled phase. Most patients discontinued drug treatment after the study but did receive other treatment.

Insert Figure 2 about here

Figure 2 illustrates the relative symptom status of the four treatment groups at pretreatment, after the 2-week study and at follow-up. Prior to therapy, High

Acquiescers reported slightly less distress from Depressive Symptoms, but there was no warning of the interaction pattern shown both at two weeks and at four months. The Low Acquiescent drug group clearly showed progressively more improvement over time. Just as clearly, the High Acquiescent placebo group improved more over time than the High Acquiescent drug group. While the total group improved somewhat after the drug study, it is clear that the interaction pattern persisted at least four months later with only slight attenuation.

Study Three

In a third study we selected four pairs of women outpatients on the basis of extreme Acquiescence scores, four Highs and four Lows. All were t eated by the same doctor in a double-blind study of chlordiazepoxide (Librium) and placebo (6). Each patient was treated 10 weeks and we obtained daily patient ratings of Tension-Anxiety and Sedation-Fatigue. The study involved multiple crossovers from drug to placebo at weekly intervals. Thus each patient had five weeks on drug and five weeks on placebo with appropriate counterbalancing for order. The study also incorporated a preliminary phase in which patients selected their own optimal daily drug dose. High Acquiescers systematically selected and were treated with lower daily dosages. They would not tolerate as much drug as Low Acquiescers.

Insert Figure 3 about here

Figure 3 divides each 7-day drug and placebo period into three periods: Day 1, Days 2-4, Days 5-7. It shows on the subjective measure of Tension-Anxiety the response of High and Low Acquiescers to each medication by phase in the cycles. Each point in this figure represents between 18 and 60 daily self-ratings. In all, the figure summarizes about 500 daily ratings.

On Day 1 of the cycles, there was no drug-placebo difference for either

High or Low Acquiescers. During Days 2-4, Low Acquiescers reported the drug to be more effective in reducing Tension-Anxiety, while High Acquiescers reported no difference. Days 5-7 replicated the interaction pattern seen in the first two studies. You can see the trend for Low Acquiescers to become progressively less anxious with time on the drug, while High Acquiescers became progressively more anxious. In contrast Low Acquiescers became more anxious the longer they stayed on placebo, while High Acquiescers remained at about the same anxiety level throughout the placebo cycle.

Insert Figure 4 about here

Figure 4 shows similar data for Sedation-Fatigue. Both groups had some mild sedative effect on Day 1. This sedation dissipated after Day 1 for Low Acquiescers, but it lasted through Day 4 for HA patients, in spite of their lower dosage schedules. We once erroneously anticipated that High Acquiescers might simply fail to detect drug-placebo differences because of overreaction to a placebo. These findings refute this view and indicate that at least subjectively they feel some adverse drug effects.

Study Four

The fourth study involved 28 medical students participating in a more complex unpublished study. They also were selected on the basis of extreme Acquiescence scores and randomly assigned to secobarbital and placebo groups. About 90 minutes post-medication, they took part in a simulated public speaking procedure. The procedure involved standing and speaking extemporaneously for three minutes to an audience of two. The measure of anxiety was finger sweating measured by taping treated filter paper to the index fingers.

Insert Figure 5 about here

Figure 5 shows the relative increase in finger sweating from a non-stress baseline to the stress of simulated public speaking. Here, with a group of normal subjects, a different drug, a single dose, and a psychophysiological measure, the same personality-drug interaction pattern appeared that we had found in patient subjective ratings. The stress response was less extreme for Low Acquiescers on drug than for those on placebo. For High Acquiescers, the placebo appeared more effective than the drug. The probability that the interaction here is chance is less than one in a thousand; however there were some complications with the baseline levels that made this finding less solid than we would wish.

Conclusions

Taken as a whole, these experiments indicate a substantial link between a tendency to overgeneralize and reactions to mild tranquilizers. They do need extended replication in other laboratories. From one point of view the Acquiescence Scale appears to provide an easy means for pre-treatment identification of patients who will foul-up controlled drug studies and will prevent the identification of drugs that have anti-anxiety effects for many patients. As a corollary, the Acquiescence scale does seem to identify placebo reactors reliably. Some investigators have concluded no such beast exists. Dr. Fisher has discussed this issue recently (7).

From another angle, the findings raise questions about what treatment is effective for High Acquiescers. Preliminary results of two other studies by research fellows in our Laboratory indicate High Acquiescers do not respond very well to time-limited psychotherapy either. So far, placebo is the only treatment in which we have found High Acquiescers to report much improvement.

Finally these results raise a host of questions concerning the detailed understanding of the relationship between Acquiescence and both beneficial and

adverse drug effects. Some studies of these issues have been done or are in progress in our Laboratory, but we have little to report as yet. It is going to require more work before we know whether, with Acquiescence, we have a bull's-eye or a boomerang.

Table 1

Patient Acquiescence and Drug Effects

Sample Items from Bass Social Acquiescence Scale

(3) They never fail who die in a great cause.

(5) Love of the opposite sex makes the world go round.

(17) Stay away from the proud man who is ashamed to weep.

(25) Wild colts make good horses.

(26) You can't teach an old dog new tricks.

(33) Still water runs deep.

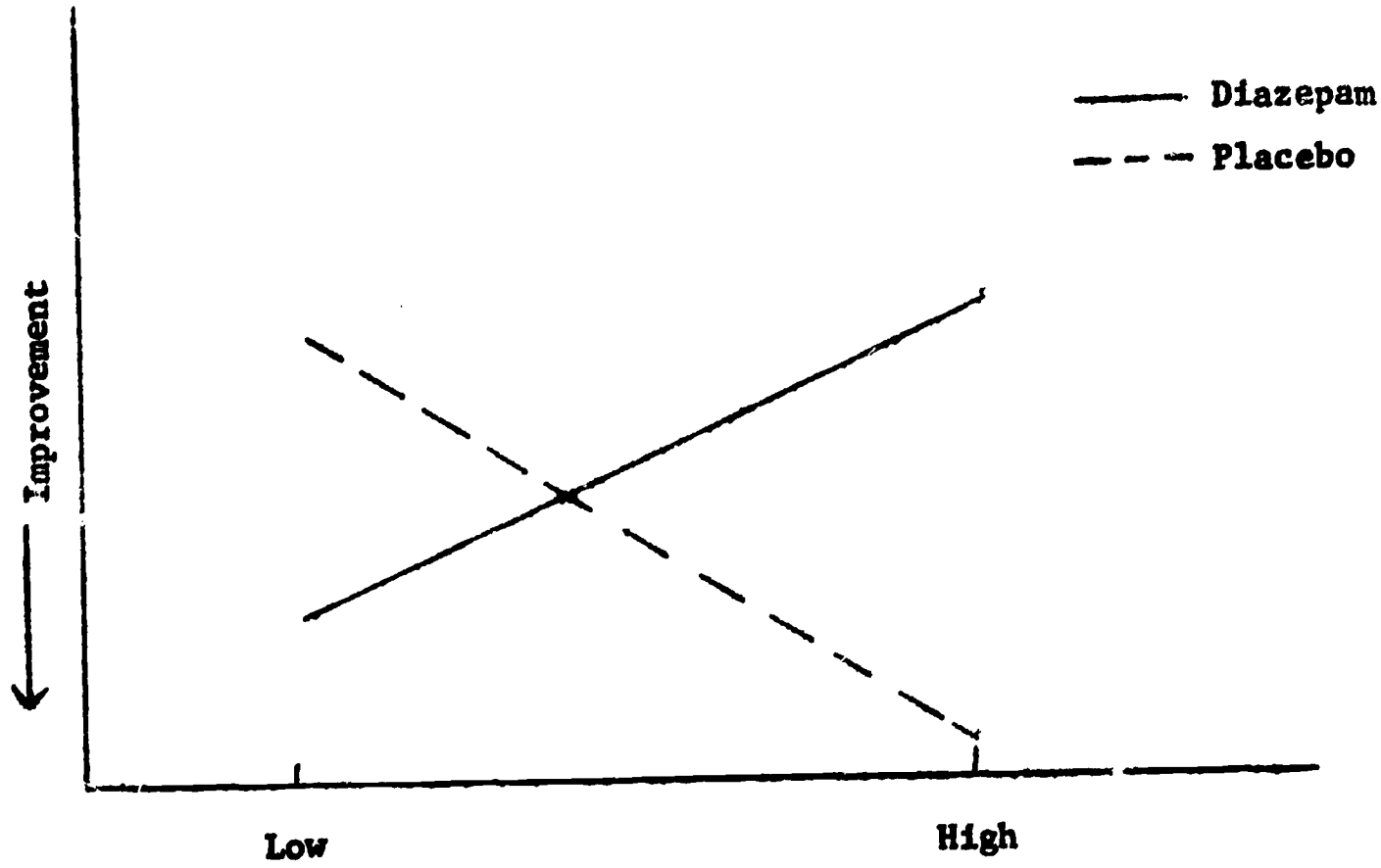

Fig. 1. Valium study--acquiescence by medication interaction on a typical criterion.

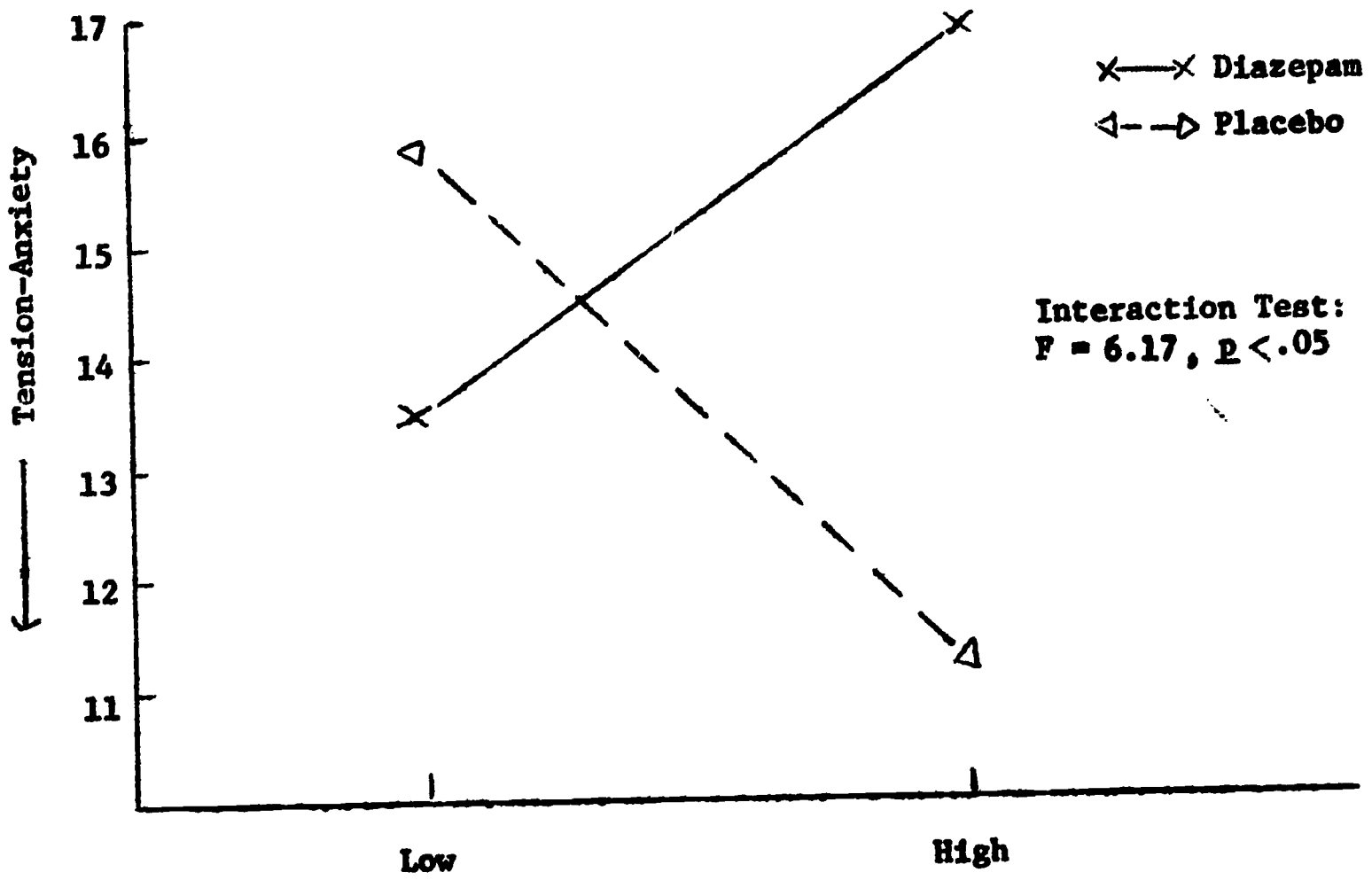

Fig. 2. Follow-up study--acquiescence by medication interaction on Tension-Anxiety Mood score.

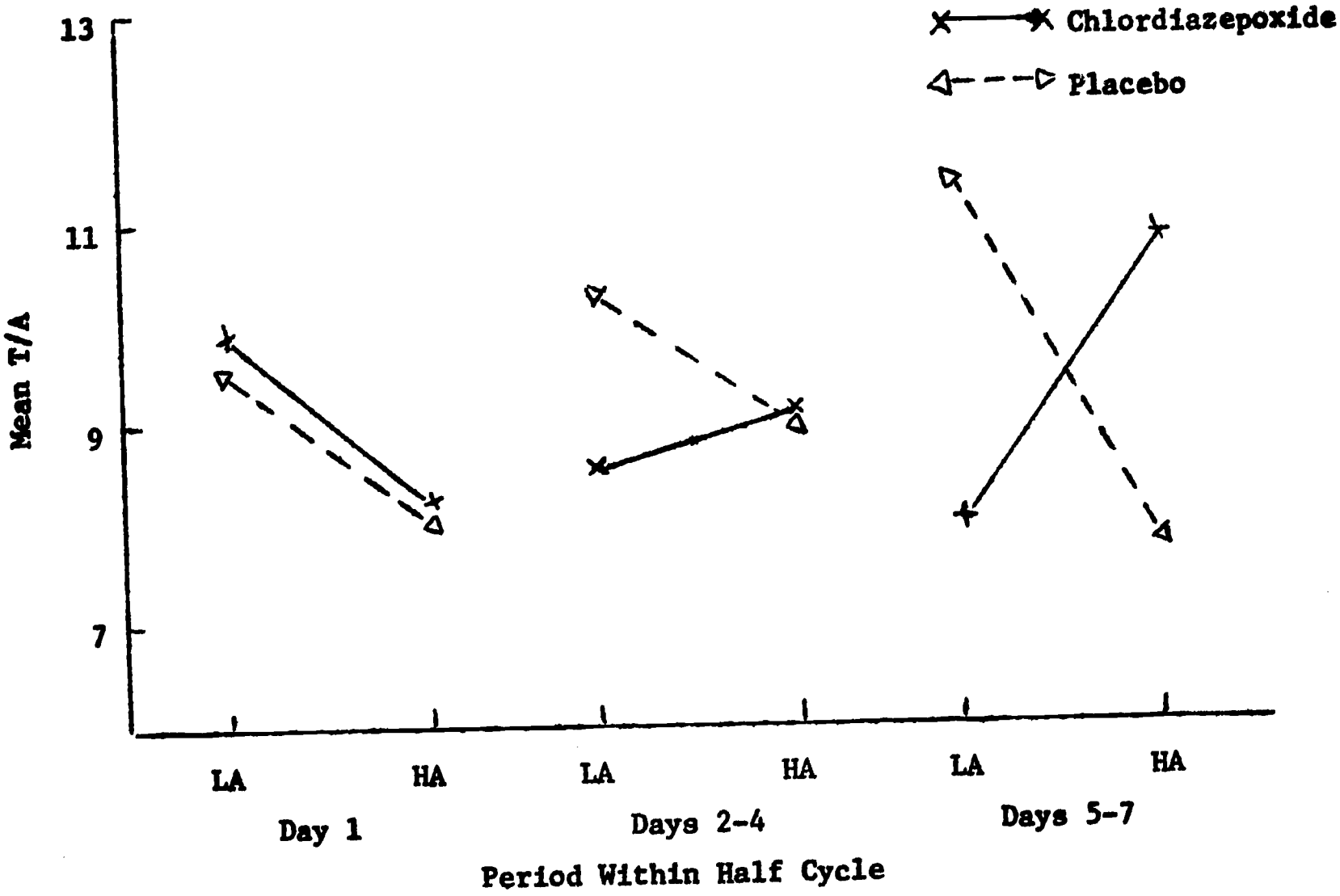

Fig. 3. Intensive treatment study--mean Tension-Anxiety scores by period within cycles.

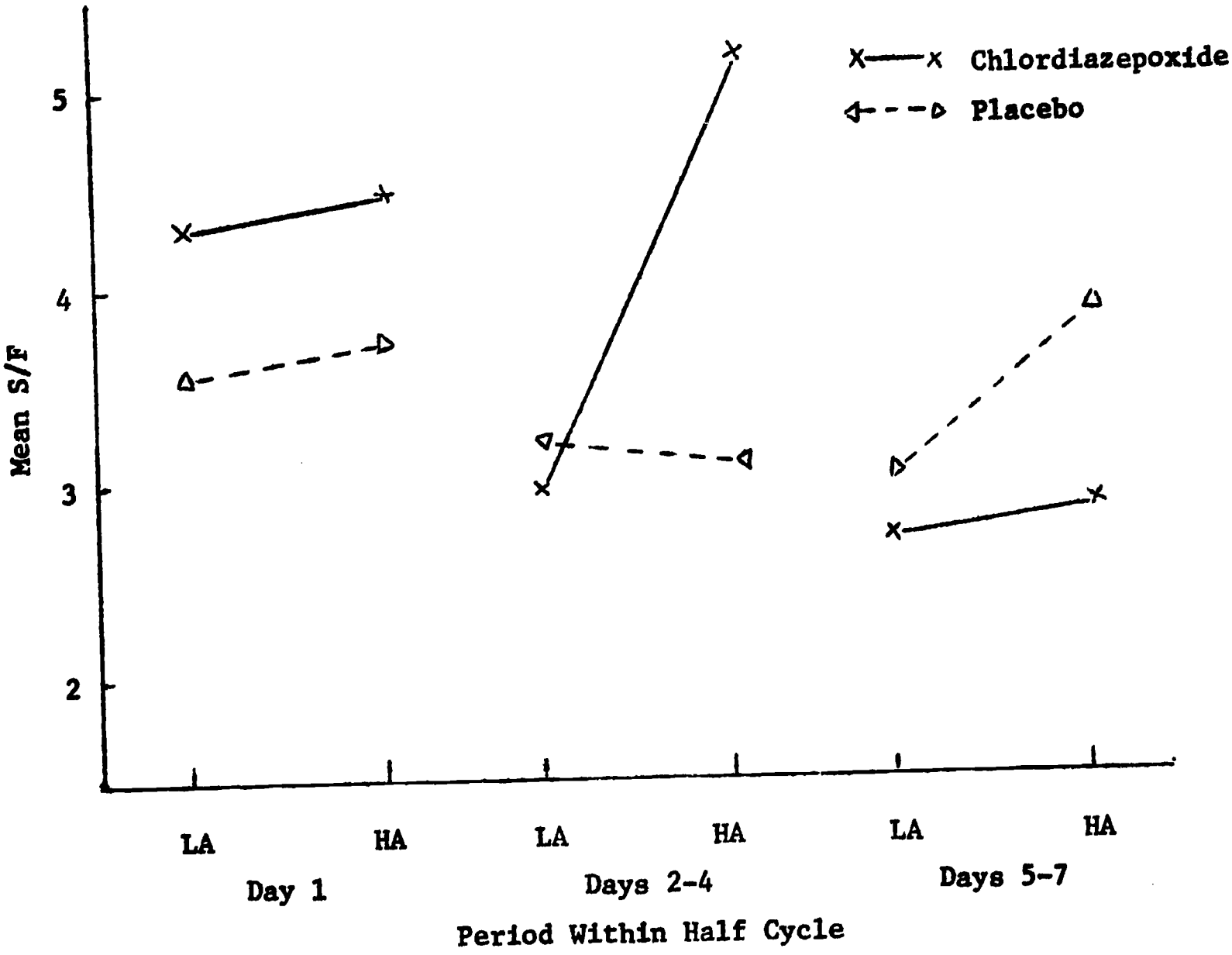

Fig. 4. Intensive treatment study--mean Sedation-Fatigue scores by period within cycles.

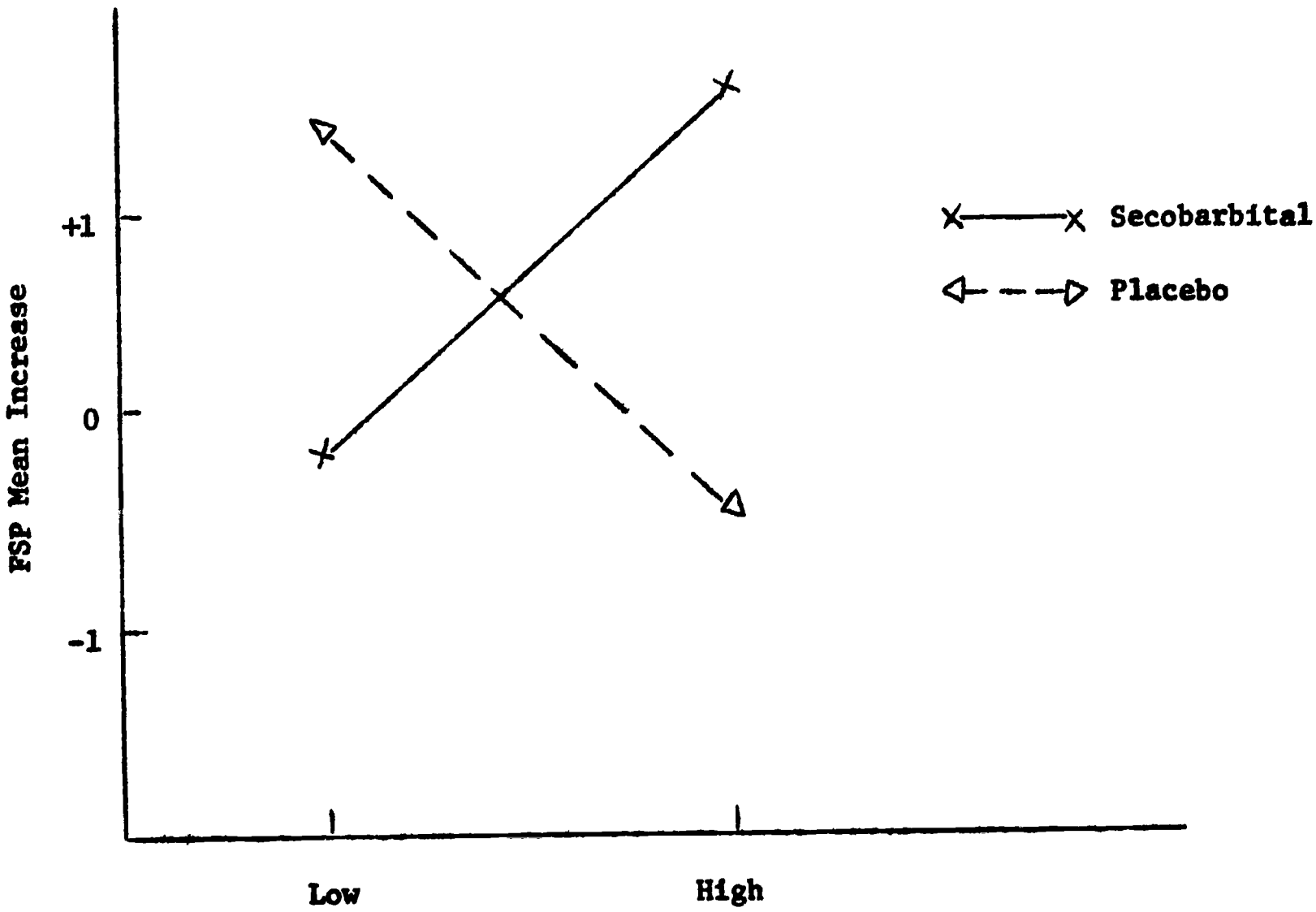

Fig. 5. Medical student study--mean FSP change from baseline to stress minus control score.

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Footnotes

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