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Drug Effects and Initial Severity of Symptomatology *

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With 2 Figures in the Text

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While it seems obvious that a "symptom-free" population would not be a reasonable target group for a test of the clinical efficacy of a psychopharmacological drug, it is not so obvious whether or not the magnitude of a drug effect would vary as a function of initial severity of symptomatology. In treating anxiety in neurotic patients, for example, it has often been suggested that with the minor tranquilizers the most marked "drug effects" are seen in those patients who are most distressed initially[1]. In attempting to investigate a possible relationship between initial level and drug effect, it is not sufficient to observe that drug patients with higher initial symptom levels show more improvement than do drug patients who are less ill initially—this does not really answer the question, since the possibility exists that a similar relationship would hold for non-drug patients. The critical point here, of course, is that a clinical response following treatment (*drug response*) is not synonymous with an effect

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[1] If this assertion should indeed be valid, then most of the commonly used statistical techniques (e.g., analysis of covariance, or the use of difference scores based on change from pre-treatment to post-treatment) might no longer be directly applicable for estimates of main drug effects. A basic assumption underlying many of these techniques is concerned with homogeneity of regression: the models generally assume that the regression of post-treatment scores has the same slope as (i.e., is parallel to) the regression of post-control scores on the pre-control scores, thus allowing a common regression to be estimated from the combined treatment and control groups. Furthermore, if the assertion that "the sicker the patient initially, the greater the drug effect" is valid, then one is confronted with problems related to Wilder's Law of Initial Values (for a recent review and discussion, see BENJAMIN 1963).

which can be attributed to the treatment (*drug effect*). The latter can only be accurately estimated with reference to an appropriate control group.

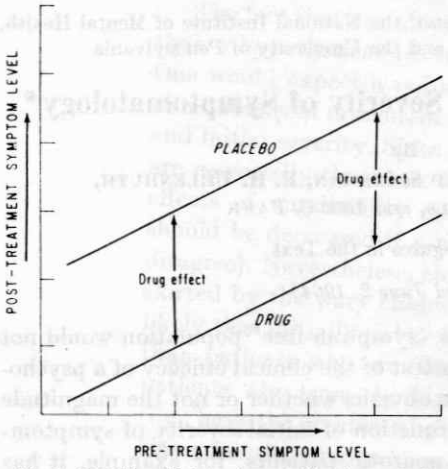

Fig. 1. Model in which treatment effect is constant

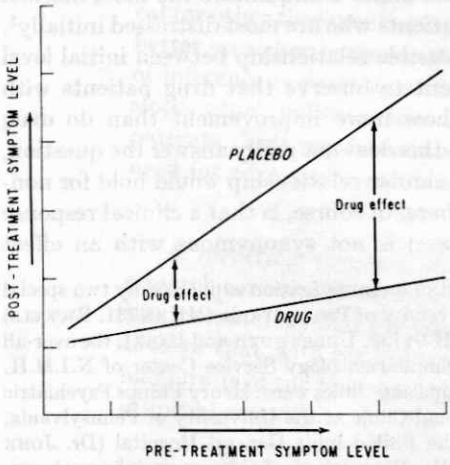

Fig. 2. Model in which treatment effect is a function of initial level

Basically, then, the question at issue here concerns the possible presence of statistical interaction between initial level of symptomatology and the magnitude of a drug effect (defined as a drug-placebo difference). The answer to this question would come from a comparison of the drug and placebo regressions of post- on pre-scores: the regression lines may be parallel as in Fig. 1, offering no evidence for the presence of interaction; or, if the regression lines are not parallel as in Fig. 2, interaction may be suspected. Of parenthetical interest perhaps is the reminder that a truly effective chemotherapeutic agent would indeed be expected to interact with initial level: e.g., the regression equation for an ideal drug would have a slope of zero, inasmuch as regardless of initial level, the post-treatment level will be at "normality" (for the Y intercept); the corresponding slope of a nontreated group should have a value greater than zero, and possibly close to 1. Thus, the presence (and amount) of interaction is probably a monotonic function of the potency (i.e., efficacy) of the treatment.

The present note draws upon data collected in the course of a six-week, double-blind, study of meprobamate (1,600 mg total daily dosage) and placebo in a sample of anxious neurotic outpatients[1]. The three participating clinics followed an identical protocol and contributed a total of 138 patients who completed the full trial with absolute adherence

[1] A more detailed account of the full experiment can be found in FISHER et al. (in press).

to the experimental protocol. Our clinical criterion data were analyzed for over-all drug effects (a second independent "set" variable was included in a factorial design, but its influence is not germane to this report), and the particular measure reported here is one on which a significant meprobamate effect was detected. This measure is called a "Target Symptom" score[1], and is derived from the Johns Hopkins symptom scale used with

Table. *Means, standard deviations and regression equations for meprobamate and placebo groups on a measure of Target Symptoms*
(theoretical range: 1—4, with high scores reflecting greater average intensity of psychopathology)

	Meprobamate ($N = 72$)		Placebo ($N = 66$)	
	Mean	s.d.	Mean	s.d.
Pre-medication	2.72	0.43	2.67	0.42
Post-medication	2.06	0.58	2.21	0.52
Regression Equation	$Y = 0.66X + 0.27$		$Y = 0.60X + 0.61$	

neurotic outpatients (GLIEDMAN 1958): the Target Symptom score reflects the patient's self-rating on a cluster of symptoms which were initially particularly distressing to a patient. Each symptom is rated on an intensity scale ranging from 1—4, and the results are presented in terms of average intensity.

The Table summarizes the pertinent results. An analysis of covariance was used to test the homogeneity and fiducial limits of the two regression coefficients, following which a test was made of the elevation differences between the drug and placebo regressions (SNEDECOR 1957). The drug and placebo slopes, 0.66 and 0.60 respectively, do not differ significantly from each other ($F<1$), but the pooled slope is very significantly different from a hypothetical slope of 1.0 ($p<0.001$); the significant drug effect shows up in testing the difference between the elevations ($F = 4.86$ for 1, 135 df, $p<0.05$).

In short, these results indicate that with a drug which has a demonstrable—albeit mild—clinical effect, there is no evidence of any interaction between initial level and magnitude of effect. In clinical terms, this is equivalent to saying that the drug effect appears approximately constant regardless of how ill a patient may be initially—provided, of course, that there is at least some minimum initial illness (which defines the population qualitatively). Many mathematical models assume that the effect of a treatment is to add a constant to an individual's score,

[1] Our experience with this population indicates that the following complaints, in decreasing order of frequency, represent Target Symptoms in roughly 50% of the patient sample: "nervousness or shakiness inside", "feeling tense or keyed up", "worrying or stewing about things", "feeling easily annoyed or irritated", "headaches", and "feeling fearful".

regardless of its initial magnitude. The results reported here are consistent with such assumptions, but it is doubtful whether their tenability should ever be taken for granted when dealing with biological mechanisms.

The fact that our obtained regression coefficients are significantly less than a hypothetical 1.0 raises an interesting problem of interpretation. One would expect a reduced slope under either one of two conditions: unreliability of measurement or a real relationship between improvement and initial severity. Since the pre- and post-standard deviations (Table) are essentially the same, it is possible that we are primarily seeing the effects of unreliability (some statisticians suggest that post-variation should be decreased if a real relationship exists, but other statisticians disagree). Nevertheless, these findings point up a pitfall which must be skirted by the wary clinical researcher. Over a period of time, it is very likely that initially sicker patients will appear to improve on drugs more than patients who are "less ill" initially: our drug slope suggests that patients who have the highest initial severity tend to "improve" most (i.e., have the greatest absolute change from pre- to post-). Hence, a clinician administering treatment to his patients, noting that the sicker ones seem to do better, may attribute this improvement to the pharmacological (or other therapeutic) intervention and infer that the treatment works better on sicker patients. However, the danger associated with this kind of inference is patently underscored by our essentially identical placebo slope, which indicates that a similar relationship may obtain for control patients. This emphasizes another aspect of a time-worn caution: the need for adequate controls in interpreting treatment effects.

Summary

A recurring question appearing in clinical psychopharmacological research concerns the nature of the relationship between initial severity of symptomatology and the magnitude of a drug effect. Data are presented to show that, with meprobamate and placebo in neurotic outpatients, the magnitude of the pharmacological effect remains constant across all levels of initial severity.

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