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LETTER TO THE EDITORS

Can the Effects of Antidepressants Be Observed in the First Two Weeks of Treatment?

Quitkin et al. (1996) have used data from a series of antidepressant (AD) drug trials carried out in the 1980s (1984, 1987) to conduct an effect-size analysis of early treatment effects, similar to that reported by our group (Katz et al. 1987, 1991). We had originally applied this statistical approach to determine whether behavioral changes following one week of treatment with tricyclic drugs, which were significantly greater in "responders" (patients who would ultimately respond to treatment) than in "non-responders", were of sufficient size to be "visible" to clinical observers. If so, the results would enable clinicians to predict early in the course of treatment whether a patient is likely to respond to this treatment, and to adjust his/her therapeutic approach accordingly. In addition to this practical clinical consideration, the analysis would lend support to the position that AD drugs begin to effect changes in the depressive state early, i.e., within the first two weeks of treatment, and that the generally accepted notion that there is a "lag" of two to three weeks in the onset of action, in not correct. Our results showed that the effect size of several one-week changes were quite large and therefore likely to be "visible", and in accord with the findings of others, these early behavioral changes in responders were clearly associated with a positive therapeutic outcome. A parallel placebo treatment group had not been included in that study. We therefore, later determined which if any, of the one and two week behavioral changes were correlated with concentration of drug in the plasma. Certain of the changes in the responders, e.g., decrease in hostility ($r = 0.61$, $p < .001$), were correlated early with plasma concentration of the drug. These findings (Katz et al. 1991) provided further evidence that these early changes although not specific were associated in a significant way with drug treatment.

Quitkin et al. (1996) confirmed our results (and those of others) that early response is associated with a positive outcome. However, using this approach, they further found a significant effect-size difference between responders and non-responders in the placebo-treated group. They therefore, concluded that the early treatment response shown in their patients was not drug-specific.

Regarding this latter conclusion it is important to note, that there are a number of differences between the Quitkin et al. studies and the Collaborative Study (Maas et al. 1980) from which our results were drawn. In the Quitkin et al. (1996) analysis the effect sizes for the contrasts between responders and non-responders within the drug and the placebo groups were quite small (using Cohen's (1969) criteria), i.e., 0.24 and 0.31, respectively. The effect size of the difference between groups in the Collaborative results, for the clinician's judgment measure of the "severity of the depressed state" was 0.90. Comparable figures were shown for clinician judgments of differences the first week between "responder" and "all other patients" groups, for the specific measures of anxiety (0.76) and depressed mood (0.85). These figures contrast sharply with the figure for the drug group in the Quitkin study. There are several reasons for this apparently large difference in the impact of treatment in the two studies.

The Quitkin et al. studies used outpatients only, described as "mild to moderately depressed" in which 24% of patients showed a significant clinical response to placebo, i.e., a CGI score of 2 or 1 signifying a reduction of 75% in the intensity of depressed mood, during the first two weeks of placebo treatment. Among the various drugs used, the study dosages for imipramine and amitriptyline were 200 mg/day and 150 mg/day, re-

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spectively. These dosages were, however, not achieved until after 15 days of treatment for the large majority of their patients. It is likely, therefore, that the treatment dosages during the first week were rather light. The Collaborative study sample was of inpatients, hospitalized for severe depression. During a pre-treatment phase in which all patients received placebo for a period of two weeks, only 4% had to be dropped from the treatment study because of a positive clinical response. The study dosage was 250 mg/day of amitriptyline or imipramine considered "high" in clinical terms, and was administered rapidly so that the study dose was achieved for 87% of the patients by the end of the first week.

These factors, i.e., the nature of the study population, the amount and rate of drug administration during the first two weeks of treatment, the method for measuring early treatment effects, are obviously critical for determining the time of onset of action of AD drugs. The Quitkin et al. studies fell short of providing the necessary conditions for measuring onset. These limitations are reflected in the "weak" effect size (0.24) of the medication during the first week of treatment.

Quitkin et al. were aware of these limitations; they acknowledged them in their 1984 paper. The fact is that over the past two decades there have been a number of studies which have advanced thinking on how to approach the onset issue methodologically, and which have clarified the sequence of actions initiated by the various classes of AD drugs. It is quite clear, that under the proper study conditions, the AD drugs act within the first two weeks. There are e.g., some 5 or 6 controlled clinical trials of a range of AD drugs including the tricyclics (Small et al. 1981; Dunbar et al. 1991; DiMascio et al. 1968), the newer SSRIs (Tollefson et al. 1994; Dunbar et al. 1991), venlafaxine (Rickels et al. 1995; Montgomery, 1995), mirtazapine (Smith et al. 1990) which demonstrate significant clinical actions when compared with placebo, within the first two weeks of drug treatment. These studies include both inpatients and outpatients and, in certain cases, utilize new approaches to measuring "early response" (as distinct from ultimate outcome) (Montgomery 1995), and survival analysis to control for the large number of placebo dropouts (Stassen et al. 1993). All of these studies have, as we point out in a recent review of the subject (Katz, et al. 1997), some limitations which prevent definitive estimates of the onset of action of the various drugs. Nevertheless, as we also make clear in that review, the evidence is quite strong that when these new methodologic approaches are applied, when there is acknowledgement of the multifaceted nature of depression, and the critical role of the rate of administration of dosage, the ADs act within the first two weeks, in some cases within the first week, and that this information can be used to predict outcome of treatment.

We wish to recognize the contribution of Quitkin et al. (1984) in highlighting the onset issue and in identifying certain of the methodologic pitfalls in extrapolating data from clinical trials toward its solution. However, in our view, their data, although important in their own right, are of limited usefulness for resolving the general issue. It resulted in unnecessarily prolonging the life of the notion that the initial clinical actions of the antidepressants are as a rule, delayed for three weeks or longer. It was true for the Quitkin et al. data. However, as the results of numerous other studies have now shown, the notion of a "lag" cannot be generalized; in fact, given the proper research conditions, and the appropriate methodology for measuring onset, it can be shown that for most efficacious AD drugs, it is wrong.

Most of the information we presently have on the onset issue was derived from clinical trial studies which were designed to solve other problems, i.e., the efficacy of specific drugs in the treatment of depression. This despite the fact that presumptions about the onset of action of ADs have had a major impact on the direction of both basic research on underlying mechanisms, e.g., the recent emphasis on slowly developing or chronic effects of ADs on central monoamine systems (Frazer 1994), and at another level, on clinical treatment practice. Direct attacks on the issue are what are now required to resolve it. Fortunately the past few years have seen work of that nature begin. We believe that our results (Katz et al. 1987, 1991; Casper et al. 1994) contributed to uncovering the methodological limitations in the research underlying the "lag" notion, and along with other methodological studies in this area, have set in motion new, more definitive approaches to the problem.

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