An Ideal Trial to Test Differential Onset of Antidepressant Effect

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Although various published clinical studies have suggested that some antidepressants may have a more rapid onset of therapeutic effect than others, none of these trials was adequately designed to measure differential time to onset of effect. Thus, existing data do not support claims that one drug reduces the symptoms of depression faster than another. In this article, we propose a study that would be ideal for measuring comparative onset of antidepressant effect. The key features of this ideal trial include (1) a prospective definition of early onset of action, (2) increased frequency of assessment, (3) a data-analytic approach capable of capturing the dynamic nature of symptomatic change, and (4) various strategies to minimize bias and heterogeneity of response.

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An antidepressant with an earlier onset of therapeutic effect than other antidepressants could have wide-ranging clinical and economic benefits, from reducing the risk of suicide to shortening hospital stays to returning patients to normal activity sooner. Although data from several published clinical studies have hinted at time-effect differences among antidepressants,[1–4] none of the trials was adequately conceived or conducted to measure such differences. The aim of the following exercise was to design a study that would be ideal for assessing comparative onset of antidepressant effect.

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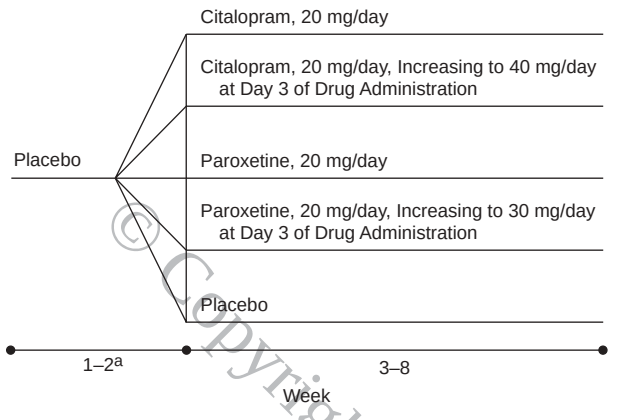
In devising the ideal trial, we have attempted to address most of the issues and concerns raised in the foregoing articles and discussion. First, we have prospectively defined early onset of action. Second, we have increased the frequency of assessment to detect more subtle changes in symptom severity. Third, we have selected a data-analytic approach capable of capturing the dynamic nature of symptomatic change. Finally, we have adopted various strategies to minimize bias and heterogeneity of response. While it would be impractical, if not impossible, to conduct a study based on our design, we hope that the exercise will foster fresh thinking and debate on how better to define and measure onset of antidepressant action.

A PROSPECTIVE DEFINITION OF EARLY ONSET OF ANTIDEPRESSANT ACTION

Our prospective definition of early onset of action comprises the following elements: (1) it must appear by week 4, (2) the action we are assaying is a significant reduction in depressive symptoms, (3) it must be linked to a clinically significant treatment outcome (i.e., early improvements should be sustained for the duration of the study), and (4) a differential time to onset of action of a week or more is clinically relevant.

Although these criteria are subject to debate, we feel that they accommodate both theoretical and practical concerns. For example, few clinicians expect that their patients will respond to an antidepressant after a week or less of treatment, but most expect that the drug will begin to

Figure 1. Schematic Overview of an Ideal Trial Design to Test Differential Onset of Antidepressant Action



[a]For both drugs, start time is variable.

have some salient effects within a month. Similarly, a time-to-onset difference of a few days would probably be of little value, whereas a difference of a week or more might have a significant clinical impact. Finally, differences in time to onset of effect would be irrelevant if early benefits did not lead to long-term improvement.

TRIAL DESIGN

We have conceived the ideal test of differential onset of antidepressant action as a prospective, double-blind, randomized, placebo-controlled comparison of 2 dosing regimens of 2 active drugs in a trial lasting 8 weeks. The primary rating instruments of the study would be the Clinical Global Impressions-Improvement scale (CGI-I), which would provide ordered categorical data, and the 24-item Hamilton Rating Scale for Depression (HAM-D), which would provide dimensional information. *Early onset* would be defined as a CGI-I score of 1 or 2, appearing by week 4 and enduring through week 8 of the trial. A clinically meaningful improvement would be defined as a 30% reduction from the baseline HAM-D score or a 2-point drug-placebo difference, and remission would be defined as HAM-D score < 8 at week 8. As mentioned above, a 1-week difference in onset of action would be considered clinically relevant.

Assessments would take place twice a week, and the assessors would be blinded to the study week. To control for bias in rater assessments, there would be a 1- to 2-week double-blind period during which treatment would begin at variable times, such that neither the patient nor the rater would know when active treatment began.

Patients included in the trial would (1) have a diagnosis of DSM-IV major depressive disorder (MDD), with a HAM-D score ≥ 20, (2) be naive to treatment with study drugs (to exclude past nonresponders), (3) be in their first episode of MDD with a duration ≥ 3 months and < 2 years, and (4) be men and women aged 25 to 50 years (to avoid significant age-related differences in time to response). The use of concomitant benzodiazepines or other confounding medications would not be allowed in the study.

Study drugs would be comparably and aggressively dosed. Figure 1 shows a schematic overview of the trial, including the time frame and the dosing schedule of the 2 active drugs, citalopram and paroxetine, which were chosen for comparison. To have adequate statistical power (≥ 0.80) and to detect the changes we have prospectively defined as being indicative of a clinically relevant difference in onset of action, each of the 5 treatment groups would require approximately 350 patients.

STATISTICAL ANALYSIS

Mixed-effect regression models[5,6] would be used to capture the dynamic process of onset of action. This data-analytic strategy has been chosen for several reasons. First, mixed-effect regression models are sensitive to change over time. They are not restricted to analyses of endpoint or completer data but instead analyze data from all assessment points. Second, mixed-effect regression models are flexible enough to include subjects who have missing data at some point in the trial. As a consequence, the mixed models can incorporate a varying number of assessments per subject. Third, mixed-effect regression models can accommodate various forms of dependent variables, including dichotomous (e.g., responder or onset status), dimensional (HAM-D), or ordered categorical (ordinal levels of symptomatic severity [CGI-I]).

DISCUSSION

A clinical trial capable of detecting time-effect differences among antidepressants would have to be far more rigorous than any completed to date. In this article, we have attempted to design the ideal study to measure comparative onset of antidepressant effect.

The model trial we have proposed is, by its very nature, impractical. The time required to recruit 1750 patients who meet our rigorous inclusion criteria would be excessive, the number of centers required to secure such a population would be almost unmanageable, and the cost of mounting such a complex, sprawling, and labor-intensive investigation would be prohibitive, especially for drugs that are already approved and successful. Perhaps above all, this exercise illustrates how difficult it would be to detect an unequivocal difference in onset of therapeutic effect between 2 antidepressants.

We do not mean to suggest that more realistic studies—smaller in size, less ambitious in scope, comprising a more

heterogeneous patient population—could not provide valuable information on differential onset of effect. Rather, we insist that the results of such trials be interpreted with full consideration of the limitations of the design and/or execution of the trials.

Nor do we wish to discourage further investigation by setting an impossible standard. Apart from the size and quality of the patient population, most of the features of our model trial are feasible, if not essential. For example, the prospective, randomized, placebo-controlled design and the use of appropriate data-analytic methods are indispensable for a valid assessment of differential onset of effect. Other elements of our model—such as restrictions on confounding concomitant medications and blinding of the rater as to the week of the study—would likely benefit any clinical trial of an antidepressant.

Drug names: citalopram (Celexa), paroxetine (Paxil).

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