

Methodology to Measure Onset of Action

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Onset of action has become one of the most topical issues in antidepressant therapy. In general, the speed of onset of action of antidepressants is regarded as too slow. Most patients who benefit from treatment require 2 or more weeks of therapy to show signs of response. Since the onset of therapeutic efficacy is of current interest to physicians and health authorities, the question arises of how to measure the onset of therapeutic efficacy. There are many different proposals for the statistical analysis of data to determine early onset of action. One of the most important considerations in analyzing early onset of action is the definition of criteria. Conventional approaches, such as the De Paula and Omer approach and the Huitfeldt and Montgomery approach, can provide useful information, although they do not take into account whether the early response is sustained. The use of pattern analyses does overcome the problem, but the generalizability of their findings is somewhat limited by their use of stringent exclusion criteria. Survival analyses can provide a more sensitive measure of early changes. Moreover, this method can easily be adapted to take into account sustained response and be used to restrict attention only to those subjects who achieve onset. In this article, the above-mentioned approaches will be explained with the help of some clinical examples to achieve a further understanding of the methodology of measuring onset of action.

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The rapidity of onset of the therapeutic action of antidepressants is much slower than desired. Drugs with a more rapid onset of action would not only benefit the individual patient, but would be advantageous from a societal perspective in terms of more rapid reductions in disability and improvements in family functioning. For the severely ill inpatient, faster onset could mean a hospital stay reduced by 4 to 7 days. Moreover, a more rapid onset of action can, on occasion, be lifesaving by prevention of suicide. Thus, being able to determine if one treatment acts more quickly than another is an important aspect of

clinical trial design. Nevertheless, there has been relatively little progress in this area, partly because of imprecise or imperfect methods to evaluate differences in onset of action. This article will review the methodology for evaluating the onset of action of antidepressants.

METHODOLOGICAL CONSIDERATIONS

There are a number of key issues that need careful consideration in any discussion of onset of action. First, there needs to be a valid and widely accepted definition of a clinically meaningful change. Second, the temporal resolution of studies is critical; clinical trials that apply rating instruments at weekly or every-other-week intervals are inadequate for measuring onset of action, yet many depression rating scales are designed to be administered weekly. In measuring onset of action, frequent evaluations may be necessary. A third issue pertains to the question, "Compared with what?" The hypothesis that drug A is more rapidly effective than drug B does not necessarily require the inclusion of a third placebo arm. However, what if drug A appears faster than drug B because the latter group has a poor overall response? In addition, the ethics of clinical research require that the use of placebo be minimized as much as possible and that placebo be used only in studies in which the objectives require it. Some drug regulatory jurisdictions, however, require that placebo arms be included in the protocol, even where active comparator agents are used. A final essential methodological consideration is that effective and equivalent doses of

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antidepressants are compared in clinical trials. Because modern antidepressants are better tolerated than older antidepressants, it is easier to achieve optimal therapeutic doses with them more rapidly than with, for example, tricyclic antidepressants. Thus, modern antidepressants may have an inherent onset-of-action advantage.

STATE OF THE ART OF ONSET OF ACTION

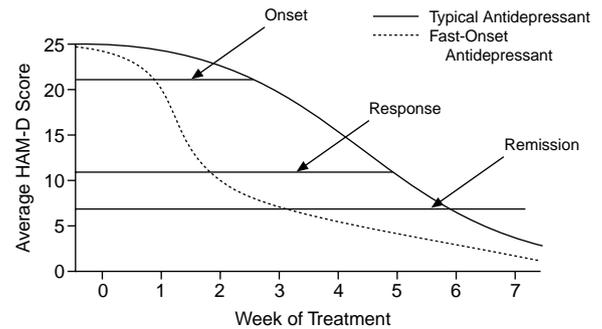
To date, there are no published prospective onset-of-action studies utilizing an appropriately sensitive design and adequate sample size. Onset-of-action studies are, however, currently planned, underway, or complete (but not yet published) in Europe and the United States. Moreover, there is circumstantial evidence from post hoc analyses of retrospective clinical trial databases of new drugs that indicates which agents might be candidates for further investigation into their onset of action. The results of these and other studies will be available over the next several years and will provide more definitive results on the relative onset of action of various antidepressants.

It is hoped that these studies, as well as examining the effect of drugs on the rate of improvement of global depression scores, will also evaluate whether the onset of action advantage is expressed across the full range of depressive symptoms or whether it is only specific symptom clusters that are improved more rapidly. This is an important point, because depression is a heterogeneous illness and antidepressants with a specific effect on sleep, for example, might be of more rapid benefit for patients with marked sleep disturbance, yet would act no more (or even less) rapidly in patients with hypersomnia. Similar arguments can be made for antidepressants that have stronger effects on anxiety or psychomotor retardation, for example. Identification of such differences could provide better options for therapy to be tailored to individual patients and may suggest future avenues of research for novel treatments.

MEASURING EARLY ONSET OF ACTION

Several events need to be defined to determine if an antidepressant has an early onset of action. Figure 1 illustrates these events for hypothetical "typical" and "fast-onset" antidepressants of equivalent efficacy. Onset can be defined as the timepoint at which a statistically significant difference can be perceived between 2 active treatments or between an active medication and placebo in a clinical trial. Alternatively, the time to response, as defined in terms of a degree of improvement on a depression rating scale (typically a 40%–50% reduction in score), or remission (typically a 17-item Hamilton Rating Scale for Depression [HAM-D] score of 7 or less or a Montgomery-Asberg Depression Rating Scale [MADRS] score of 12 or less) can be used as a more rigorous categorical outcome. As depicted in Figure 1, the hypothetical antidepressants differ

Figure 1. Key Events in Defining Onset of Action^a



^aAbbreviation: HAM-D = Hamilton Rating Scale for Depression.

in speed of onset, time to remission, and time to response, even though the drugs are ultimately equally effective.

Traditional Analyses of Depression Scale Scores

During the past 20 years, there have been several suggestions as to how these differences in onset of action could be evaluated in the context of clinical trials. De Paula and Omer¹ proposed that the time to the first statistically significant difference between active and placebo treatment groups could be considered the time of onset. However, statistical significance is quite dependent on study size, and larger studies will more easily show onset at earlier timepoints than smaller studies. Moreover, this method ignores the clinical significance of the difference.

Huitfeldt and Montgomery² added an extra hurdle of clinical significance in proposing that onset is the point at which a statistically and clinically significant difference is apparent between active drug and placebo. They proposed that a 4-point difference in the HAM-D score could be used as the definition of clinical significance. However, since modern clinical studies often do not observe 4-point differences in HAM-D scores between placebo and active treatments, it is unlikely that such differences would frequently be apparent in clinical comparisons of active treatments. Elsewhere, I have suggested that a 2-point difference would be sufficient to indicate a clinically meaningful difference between active treatments.³

For example, statistically significant differences between MADRS scores for the dual-action antidepressant venlafaxine and placebo were shown at early timepoints (during week 1) in double-blind studies using aggressive dose-titration schedules.^{4,5} In these post hoc analyses, the Huitfeldt and Montgomery criteria for clinical significance were also fulfilled during the first week of treatment in inpatients and by week 3 for outpatients.

Pattern Analysis

Quitkin and colleagues^{6,7} evaluated the temporal pattern of antidepressant response in order to differentiate

responses to active antidepressants from responses to placebo. Active antidepressants were associated with a greater proportion of delayed, but persistent, responses, whereas placebo responses were equally likely to appear within the first 2 weeks of therapy, but were more likely to be nonpersistent or fluctuating. An active antidepressant with a more rapid onset of action would shift the proportion of "true" drug responders into the early persistent category. The pattern analysis technique has been applied to 2 double-blind studies of venlafaxine (75 and 92 patients) versus placebo (92 and 95 patients).⁸ Improvement during the first 2 weeks of the study, defined as early and early-persistent responses, was statistically significantly more common with venlafaxine than with placebo in both studies (27% vs. 9% in the first study and 20% vs. 2% in the second study).

Survival Analysis

The most statistically sophisticated approach has been derived from other areas of medicine and engineering in which the time to a particular event is examined. The survival analysis technique, originally developed by Kaplan and Meier,⁹ was first used to analyze the survival of patients after, for example, cancer chemotherapy. In the context of clinical studies of acute-phase treatment of depression, the method is used in a reciprocal sense to evaluate the time to response or remission of depression. This method has the advantage that the parameter of interest (in this case the time to response or remission) is calculated individually for each patient rather than from group means and can therefore be more accurately determined. In addition, data from all patients, even patients in whom the event does not occur (i.e., who do not respond), are included in the analysis. In its original form, the method could be criticized because it does not differentiate between placebo-type responses (unsustained) and more sustained drug responses. However, Stassen and colleagues¹⁰⁻¹² have developed a modification of classical survival analysis in which only sustained remissions or responses are included. Data from a double-blind comparison of imipramine (daily dose escalated to 200 mg during 5 days) versus venlafaxine (daily dose escalated to 375 mg during 5 days and subsequently reduced to 150 mg) have been analyzed using the survival analysis technique.¹³ In this study, the modification of Stassen and colleagues was used (only persistent responses were analyzed). Survival analysis showed a statistically significantly shorter time to sustained response for venlafaxine among HAM-D, but not MADRS, responders.

EFFECTS ON CORE VERSUS ASSOCIATED SYMPTOMS OF DEPRESSION

In determining if a novel antidepressant drug has an onset-of-action advantage over standard medications, it is important to show that the advantages demonstrated repre-

sent real effects on the overall depressive syndrome, rather than on, say, sleep or anxiety. Although advantages in improving selected symptom constellations more rapidly might be of benefit for some patients, the objective is to identify drugs with a more rapid action on the core symptoms of depression. Cluster and factor analysis can be applied to analyze the relationship between different components or subscales of symptom rating scales and provide information about the structure of the response to a particular drug. Conversely, the Bech Melancholia factor, which has been derived from the HAM-D, represents a more unitary measure of symptom severity.

CONCLUSIONS

The lack of data from properly designed, well-controlled studies on the onset of action of antidepressant therapy marks a notable and lamentable gap in our knowledge. This is an important issue for patients, their families, and the wider society. Overlapping methodologies exist for evaluating onset of action, but skepticism is warranted when a drug shows an onset of action advantage on only 1 type of analysis. Conversely, a consistent advantage found across multiple methodologies is likely to be a meaningful indicator of a genuine effect.

The lack of published evidence on the comparative onset of action of antidepressant medications may well be remedied in the coming years as the results of several ongoing onset-of-action studies are reported. For the moment, circumstantial evidence exists suggesting that venlafaxine may have faster onset of action than selective serotonin reuptake inhibitors (SSRIs). Studies reviewing the onset of action of mirtazapine (versus SSRIs) are reviewed elsewhere in this supplement.

Drug name: venlafaxine (Effexor).

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