

Letter from the editor

Is the onset of action of antidepressants truly delayed?

One of the most important current controversies in the field of evidence-based mental health concerns the time of onset of the clinical response to antidepressant drugs in people with depressive disorder.[1] In the 1950s, the prevalent view among researchers was that the response to antidepressant drugs was rapid, becoming evident within two to three days after the start of treatment,[2] but subsequent empirical data suggested that antidepressants take two to four weeks to produce clinically noticeable effects.[3] This 'delayed antidepressant response' theory led to the belief that any abrupt (or non-persistent) clinical improvement within the first two weeks of initiating treatment with antidepressants is a placebo response and, by contrast, only a delayed (and persistent) response can be considered a true drug effect.[3] Recent clinical trials have, however, consistently shown that a significant proportion of people who ultimately respond to an antidepressant show clinically important improvement within the first or the second week of treatment.[4] [5]

The speed of onset of antidepressant effects has great clinical relevance for both the patient and physician. A shorter response time reduces the overall personal and economic burden of major depressive disorder by rapidly improving patient wellbeing, decreasing length of hospitalisation, and reducing the amount of time the patient spends away from work, and the time the impairment affects family and friends.

A clear idea of the expected time of response to antidepressant drugs also influences patient management. One of the most vexing dilemmas faced by clinicians treating people with depressive disorder is how long to wait for an initial response before considering a change in therapy. A predictable time of response to antidepressants would greatly facilitate decisions about changing or optimising treatment.

Although data from standard clinical trials designed to measure the efficacy of antidepressants might be useful for the preliminary evaluation of the time of onset of action of these drugs, studies specifically designed to detect timing of onset are still lacking.

There are many complex methodological issues that must be considered when designing trials that investigate onset of action. Study design is of paramount importance in these trials, and a specific strategy for data analysis should be pre-decided to allow analysis of the time of onset of drug action in addition to clinical outcomes.

A key question to consider is how to measure and thereby define the time of onset of action of an antidepressant. For example, it is important to distinguish between a drug that has an earlier onset of antidepressant effect and a drug that has earlier onset of side effects that are not related to the antidepressant effect, but which may still improve symptoms (for example, sedative effects).[1] On the other hand, there are treatments (such as benzodiazepines) that make people feel better quickly, but that will probably never produce a satisfactory antidepressant response, and these, in turn, should be distinguished from interventions with true antidepressant effects.[6]

What magnitude of clinical improvement should be used to define an early-onset response to antidepressants? Is an early-onset responder a person who improves rapidly and to such an extent that he/she no longer meets the diagnostic criteria for major depression, or someone who shows an early

reduction in the intensity of symptoms? And if an early-onset response is defined as a reduction in symptom intensity, what degree of symptom reduction is required to fulfil this definition — early signs of improvement; a full clinical response (usually reported in trials as a 50% or greater reduction of rating scale score from baseline); or an early remission (a Hamilton Depression Rating Scale [HDRS] score of not more than 7, sustained for 3 weeks or more)? Most of the standard instruments used to define clinical response in studies of antidepressants are not designed to measure change over brief intervals of time. The HDRS, for instance, records symptom severity over the preceding 2 weeks. To detect subtle differences in timing of onset, frequent psychometric assessments — on a weekly or twice-weekly basis — are required, and the use of a prospective daily mood record or a mood diary to facilitate frequent measurements might be worthwhile.[7]

When comparing the time to response of two active treatments, it's also important to predetermine how much faster constitutes a clinically important difference. For example, whereas a difference in response time of one or two days is probably not clinically relevant, a difference of weeks may be relevant to the patient and clinician. This point highlights a key concern about current evidence on early onset of response to antidepressants. Most clinical trials of antidepressant drugs have addressed time of onset of action as a *post hoc* analysis, and therefore such studies are not sufficiently powered to provide a definitive estimate of time of onset of effect. Also, these studies often differ markedly from each other (because of different dosing schedule or differential use of rescue medications), and meta-analyses of these studies are often complicated by heterogeneity.

The statistical tools used to analyse data when studying onset of action of antidepressants should also be carefully selected. The chi-square test (the statistical test of significance used to test the null hypothesis when data do not follow a normal distribution) is used in clinical trials that compare response rates to medication between different intervention groups. But the chi-square test provides only a cross-sectional estimate of the proportion of responders at a particular timepoint and fails to capture the change in symptoms over time. Because of these limitations, it has been suggested that the use of the chi-square test in onset of action trials oversimplifies the research question.[7] Survival analyses — in which the time to the onset of an event (such as an HDRS score indicating response to therapy) is recorded — provides some measure of the dynamic nature of symptom response, but the problem of missing data in clinical trials (which is usually not random) can bias results. To make allowance for loss to follow-up in an onset study, the statistical analysis should consider the number of participants that corresponds to each outcome measure on a weekly basis, and should assess subjects even after they drop out of the study.[8] However, one of the main problems relating to this issue is that most trials of antidepressant drugs are conducted or supported by the pharmaceutical industry. There is evidence to suggest that clinical studies funded by the pharmaceutical industry are more likely to report favourable outcomes.[9] In a competitive market, companies are usually reluctant to share results of clinical trials (either positive or negative), and authors of systematic reviews frequently report the frustrating experience of requesting unpublished data from authors of primary studies without success. This lack of access to primary data prevents the reliable integration of study results to produce meaningful findings.[10]

Several studies have also shown that there are early and late responders to the same medication, and analysis of differences in response time should take this biological variability into account.[11] [12] Not only what medication is being given, but who is taking the medication can have a significant impact on onset of action. Onset of action should also be considered in the context of treating a disease which is recurrent, and therefore requires maintenance medications.

Lastly, investigators and clinicians should bear in mind that the time of onset of action of antidepressants is not simply a scientific or a clinical issue, but a commercial concern as well. There is

evidence indicating that people who respond to antidepressant medication incur lower costs than non-responders primarily because of decreased indirect costs associated with response to treatment (for example, the reduction in absence from work for responding patients).[13] These financial incentives provide pharmaceutical companies with an important marketing strategy. As clinicians, we must ensure that fast onset of action is not valued at the expense of tolerability or long-term effectiveness of antidepressant treatment.

Andrea Cipriani

Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Verona, Italy

andrea.cipriani@univr.it

Corrado Barbui

Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Verona, Italy

John R. Geddes

Department of Psychiatry, Warneford Hospital, University of Oxford, United Kingdom

References

1. Tylee A, Walters P. Onset of action of antidepressants. *BMJ* 2007;334:911–912.
2. Kuhn R. The treatment of depressive states with G 22355 (imipramine hydrochloride). *Am J Psychiatry* 1958;115:459–464.
3. Quitkin FM, Rabkin JG, Ross D, et al. Identification of true drug response to antidepressants. Use of pattern analysis. *Arch Gen Psychiatry* 1984;41:782–786.
4. Taylor MJ, Freemantle N, Geddes JR, et al. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry* 2006;63:1217–1223.
5. Remick RA, Fleming JA, Buchanan RA, et al. A comparison of the safety and efficacy of alprazolam and desipramine in moderately severe depression. *Can J Psychiatry* 1985;30:597–601.
6. Leon AC. Measuring onset of antidepressant action in clinical trials: an overview of definitions and methodology. *J Clin Psychiatry* 2001;62 (Suppl):12–16; discussion 37–40.
7. Lavori PW. Clinical trials in psychiatry: should protocol deviation censor patient data? *Neuropsychopharm* 1992;6:39–48; discussion 49–63.
8. Kelly RE Jr, Cohen LJ, Semple RJ, et al. Relationship between drug company funding and outcomes of clinical psychiatric research. *Psychol Med*. 2006;36:1647–1656.
9. Barbui C, Cipriani A. Evidence-based psychopharmacology: an agenda for the future. *Evid Based Ment Health* 2007;10:4–6.

10. Trivedi MH, Morris DW, Grannemann BD, et al. Symptom clusters as predictors of late response to antidepressant treatment. *J Clin Psychiatry* 2005;66:1064–1070.
11. Mulsant BH, Houck PR, Gildengers AG, et al. What is the optimal duration of a short-term antidepressant trial when treating geriatric depression? *J Clin Psychopharmacol* 2006;26:113–120.
12. von Knorring L, Akerblad AC, Bengtsson F, et al. Cost of depression: effect of adherence and treatment response. *Eur Psychiatry* 2006;21:349–354.