Two-week delay in onset of action of antidepressants: new evidence

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Summary Many sources purport that antidepressants have a delayed onset of action, measured in weeks rather than days. Recent data using weekly or daily mood ratings demonstrate that maximum improvement occurs during the first 2 weeks, with some improvement within the first 3 days. Methodological issues may underlie the delayed-onset hypothesis.

Declaration of interest None.

The notion that onset of action of antidepressants takes several weeks is widely quoted in clinical guidelines (Anderson *et al*, 2000; National Institute for Clinical Excellence, 2004) and has formed the basis for considerable biological and pharmacological research (Blier, 2003). It is also a notion that has been thoroughly translated into clinical practice, where clinicians regularly tell patients that the antidepressant is likely to take 2 to 4 weeks to start to work (Garfield *et al*, 2004). Yet this was not always the accepted view, and new data suggest that this statement may be at best misleading and at worst inaccurate.

THE DELAYED-ONSET HYPOTHESIS

Conceptually, any drug that has a delayed onset of action would be expected to show weak or negligible early efficacy but superior efficacy in the medium term. This was examined in three antidepressant trials by a group from Columbia University, New York; Quitkin *et al* (1987) observed that patients who achieved a sustained response tended to do so after several weeks' delay and, furthermore, those who responded early often failed to continue to full remission. Yet in the past 15 years this observation has been challenged, because a delayed response has not been replicated by a number of independent groups (Dew *et al*, 2001; Szegedi *et al*, 2003). Posternak & Zimmerman (2005) recently conducted a meta-analysis of 47 double-blind placebo-controlled antidepressant trials encompassing 5100 patients on active medication and 3400 on placebo. Across all studies when outcome was defined as a reduction in Hamilton Rating Scale for Depression (HRSD) score, the authors showed that 23% of all differences between drug and placebo groups were already apparent by week 1, and that 57% of possible differences had appeared by week 2. Close inspection of responders in both arms for the exact timing of their improvement revealed no differences in the antidepressant *v.* placebo response rates during any week of treatment. Examination of antidepressant improvement trajectories in isolation was also valuable. It was found that 60% of improvement that occurred across all trials with antidepressants took place during the first 2 weeks. To look at this another way, in 80% of all trials the response was greater in weeks 1 and 2 than it was either in weeks 3 and 4 or in weeks 5 and 6. On the basis of these data there seems to be little doubt that the largest improvement per unit time produced by antidepressants occurs within the first 2 weeks of treatment. Yet we still do not know exactly how early within this period antidepressants begin to work – that is, whether there is any *clinical* delay in the onset of action.

MEASURING INITIAL ONSET OF THERAPEUTIC ACTION

If we are to address initial onset of action – that is, how long it takes a drug to *begin* to work – we should not be satisfied with studies that use standard definitions of response or remission, as neither of these accurately gauges first onset. Although some authors have defined onset of action as a 20% or 33% reduction in baseline severity scores, this approach conflates a true continuous variable (degree of suffering from depression) with a pseudo-linear one (Parker *et al*, 1997). In addition, most clinical trials have not considered what proportion of improvement is due to natural (untreated) remission, because few studies leave cohorts completely untreated. Of the handful of studies that have used a waiting-list arm (mostly psychotherapy studies), the typical rate of *spontaneous* remission of major depression (many studies allow waiting-list patients to receive naturalistic treatment) is approximately 10% per month, with a mean episode duration of 6 months (Posternak & Miller, 2001). This indicates that although both drug and placebo arms offer substantial benefit, some early remission would have occurred without intervention, particularly if patients were recruited at peak depression severity.

When trying to measure initial onset of therapeutic action, a major methodological problem is finding an appropriate outcome measure (Leon *et al*, 2001). An ideal measure should have inherent linearity across a broad range of psychopathological domains which translates into sensitivity to early change (Maier *et al*, 1988). This hypothetical tool should also be applied early and frequently to increase temporal resolution. The last point requires clarification. If there is even a possibility that antidepressants begin to work *within* 2 weeks, how could this be detected if the first measurement takes place 2 weeks after starting the drug? The same argument holds for 1 week or even 1 day. So although there are definite disadvantages of measuring mood too often in a long-term study, if a study is concerned with early onset of action, measurement at 1 week (currently an unusually prompt measurement) is certainly too late. This approach is not new. Studies of the response to electroconvulsive therapy (ECT) often measure mood after each application two or even three times weekly (Husain *et al*, 2004). As an aside, it would be interesting to see how much of the variance in rapidity of onset of action of ECT compared with pharmacotherapy or psychotherapy is explained by differences in the frequency of assessment alone. Scales designed for regular daily mood ratings have already appeared in other medical specialties (Peters *et al*, 2000). Although these have often been in the form of simple visual analogue scales or mood diaries, one group has used factor analysis to develop a daily mood scale for depression (Parker & Roy, 2003). Daily or even twice daily manual or electronic mood diaries, although currently unfashionable, appear

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to be easy to use and reliable (Sherliker & Steptoe, 2000). Subjective self-rating methods are an equally important and powerful method of assessing first onset, and provide different information to classical objective scales when compared head to head (Moller *et al*, 1996).

LARGE-SCALE STUDIES

Some clinicians will remain unconvinced by evidence extracted from multiple small trials, albeit in the form of a meta-analysis (Posternak & Zimmerman, 2005). Support for this argument would be strengthened by at least one really large study with measures providing sufficient resolution in time. Three such studies have in fact been published involving 429 (Stassen *et al*, 1996), 1277 (Stassen *et al*, 1997) and 369 patients (Parker *et al*, 2000) respectively. The results mirror those of the meta-analysis mentioned above. The Zurich group used daily depression ratings on the HRSD and Zung Self-Rating Depression Scale. They found that regardless of which antidepressant the patient was taking, there was a measurable early effect on day 1. By day 3, 20% of patients had shown some improvement, and by day 7 50% had improved. Furthermore, 90% of those who showed any response during the first 3 weeks went on to become full responders. Drug–placebo differences (where apparent) could be detected as early as day 5. In the third study, Parker's group examined responders and non-responders treated by 27 Australian and New Zealand psychiatrists (Parker *et al*, 2000). Patients were requested to complete a self-report mood rating every third day. All patients showed a decrease in depression (and anxiety) within the first 3 days, but with little further improvement in non-responders from days 4 to 6. Again, early improvement within 1 week was a strong predictor of responder status.

Given these findings, it is pertinent to ask why the view that antidepressants have a delayed onset of action is so commonly held. There are two possibilities. The first is imprecision concerning the use of the term 'onset of action' when we really mean 'time to substantial remission'. This is understandable if we assume that patients want to know when they will feel much improved rather than when they will begin to feel a little better. The second is a failure to distinguish initial therapeutic benefit, which occurs within days of starting an antidepressant, from the concept of drug *v.* placebo separation, which accrues more slowly. In the Posternak and Zimmerman meta-analysis of antidepressant *v.* placebo responses, the active arm showed modest but definite early efficacy, but this was difficult to separate from a significant placebo response until a week or more of cumulative benefit had occurred. These limitations are amplified by relying on relatively blunt instruments applied infrequently by observers. The implication for research is that sensitive daily measures are required to elucidate whether these early patterns of response are dependent on biological correlates of antidepressant or placebo treatment (Mayberg *et al*, 2002). The implication for clinical practice is that current evidence suggests it would be more accurate to say to patients that in 90% of cases substantial improvement occurs within the first 2 weeks, but that benefit continues to build up over several weeks. (In the meta-analysis by Posternak & Zimmerman (2005), 60 out of 66 study cohorts on active medication showed a reduction in HRSD score of 50% or more within 2 weeks.) In those who have shown no response by 2 weeks there appears to be a law of diminishing returns, which suggests that it may be pertinent to re-examine another commonly quoted recommendation – that an antidepressant trial must be at least 6 to 8 weeks before switching drugs.

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