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Editorial

On Brightening Up: Triggers and Trajectories to Recovery from Depression

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Depression researchers have long shown interest in factors influencing onset and recovery, but have given little attention to patterns of improvement. This editorial considers the importance of studying onset and trajectories of improvement.

A depressed mood is a relatively common response to life's vicissitudes. Even if severe, most individuals with 'non-clinical' depression expect and experience a spontaneous and rapid remission. Depression observed in clinical practice appears to differ as much by its longer duration as by its greater severity. This poses several key questions, including why and how some depressive disorders become 'stuck' and, conversely, how do effective antidepressant therapies then act? As 'depression' encompasses heterogeneous conditions, single answers should not be sought.

A Zurich-based group have produced some provocative data (Stassen *et al*, 1993) which challenge assumptions about improvement patterns, with findings now replicated across several differing antidepressant drug classes (Stassen & Angst, 1994). In the initial study, the authors undertook a multicentre, double blind trial of 429 moderately depressed patients receiving amitriptyline, oxaprotiline (a selective noradrenaline uptake inhibitor) or a placebo. A 50% or greater reduction in Hamilton depression scores at four weeks defined a "responder", while a 20% reduction (whenever) defined "onset of improvement". When grouped data were examined in orthodox analyses, amitriptyline – but not oxaprotiline – was superior to placebo over the five-week trial. However, differences in efficacy appeared significantly inflated by differential drop-out rates (46% for the placebo, 19% for the oxaprotiline and 9% for the amitriptyline group) and by trial withdrawals occurring earliest in the placebo group. When these differences were addressed analytically, the "time course of improvement among responders was independent of the treatment modality, and thus identical in all three groups".

The authors concluded that, once triggered, the time course of improvement was identical for those receiving either an antidepressant or the placebo. They suggested that depressed patients may have a "biological predisposition" to be a responder or non-responder, and that antidepressant therapy converts a percentage of 'non-responders' to 'responders', triggering and maintaining the conditions necessary for improvement.

Additionally, in their conference presentation, Stassen & Angst (1994) challenged the concept of a significant reponse lag for antidepressant medication. For trial 'responders', improvement emerged within the first five days – whether the improvers were taking antidepressant drugs or placebo. We have similarly described an early improvement trajectory in non-melancholic depressed subjects not treated with any antidepressant medication. In a sample of 43 depressed patients referred to a psychiatrist (Parker *et al*, 1985), improvement in Zung depression scale scores at both six and 20 weeks was predicted from improvement by the sixth day ($r=0.52$ and 0.44 respectively), a finding replicated in a sample of significantly depressed community subjects who volunteered to a research interview only (Parker & Blignault, 1985).

While a response lag is commonly described for ECT, Scott & Whalley (1993) observed that preliminary studies neither supported a delayed onset of effect, nor the view that there is little early improvement. Early benefit was supported in their subsequent empirical study, where improvement after the first three treatments of bilateral ECT was six times greater than that occurring over the remainder of the course (Rodger *et al*, 1994).

The widely held wisdom of delayed action of antidepressants is, like many other clinical 'givens', rarely queried. Scott & Whalley (1993) offer a number of reasons for such a self-fulfilling opinion about ECT (e.g. textbooks describing a delay; imprecise outcome terminology). As the concept of slow or delayed onset of action is probably most entrenched in relation to antidepressant drug therapy – despite and as noted by Stassen *et al* (1993) being contrary to both the original report on imipramine (Kuhn, 1957) and subsequent reviews of antidepressant drugs – we should pursue reasons there.

Firstly, standard drug trial procedures may disguise such evidence, when the plot of mean depression scores usually demonstrates distinct, but non-differential, improvement between active drug

and placebo over the first two weeks. Subsequently (i.e. between weeks three and six), the cross-sectional analyses generally demonstrate a significant advantage to those receiving the active drug – implicitly suggesting delayed effectiveness. Secondly, trial observations usually involve weekly assessments of aggregated responders and non-responders, limiting identification of a "rapid improver" sub-group. Further, trials tend not to respect the heterogeneity of depression, with most having the non-specific inclusion criterion of 'major depression'. While it has been estimated (Fairchild *et al*, 1986) that patients with melancholic and non-melancholic depression have placebo response rates of 6% and 54% respectively, and melancholia is generally viewed as more responsive than non-melancholic depression to antidepressant medication (Rush & Weissenburger, 1994), such potential sub-group differences are obscured in the standard trial. Any study which amalgamates separate depressive sub-groups, rapid and slow remitters, as well as partial remitters and non-remitters, will give limited information as the 'group' trajectory subsumes a set of potentially distinctly differing trajectories.

And what of the Zurich team's most provocative claim – that antidepressants "merely... trigger and maintain the conditions necessary for improvement. Once triggered, the recovery follows its natural course identical to that of spontaneous remission, as observed under the placebo treatment" (Stassen *et al*, 1993). Provocative findings should provoke testing of refined hypotheses.

The Zurich analyses challenge much of our current understanding of the course of recovery from depression for those receiving antidepressant drugs. Thus, 'delayed onset' of therapeutic effect may be an erroneous myth. It requires close research attention, with studies involving daily rather than weekly ratings, and identification of any differential improvement in particular symptoms and signs, as well as examination for differential trajectories across depression sub-types. In addition to double-blind studies, naturalistic studies of outcome are required (Lavori *et al*, 1994) to identify the interval that might be allowed before considering changing therapy, to clarify the nature of 'spontaneous remission' and to pursue why some of our depressed patients lack the normal remission phase and become 'stuck'. Finally, we should pursue the extent to which antidepressant therapies act by 'kick starting' a remission as against more conventional explanations of their restitutive actions, and whether such an effect is limited to the non-melancholic type.

If effective antidepressant drugs do not have substantially delayed onset of action, what are the implications for the clinician? Lack of any improvement in the first week would appear to predict a poor outcome, suggesting either that the drug is being prescribed at an inadequate dose or that it is ineffective. That hypothesis, at odds with the 'delayed onset' *Zeitgeist*, requires testing and could readily be commenced by analysis of drug trial responder data already held by the pharmaceutical companies. It also warrants new studies, with the orthodox designs modified to accommodate questions posed by these provocative findings.

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