

## The Devil in the Details: Symptom Trajectories in Discontinuation Trials

Michael Browning

Dept. of Psychiatry, University of Oxford and Oxford Health NHS Trust.

Michael.browning@psych.ox.ac.uk

Many patients with clinical depression, particularly those with recurrent illness, are treated with 'maintenance' antidepressants after an acute phase response. But how effective is this approach? This is most commonly tested in trials by the use of a discontinuation design<sup>1</sup> in which patients, who have already responded to a treatment, are randomised to either ongoing treatment or placebo. Such studies provide a measure of the benefit of maintenance treatment over discontinuation. However, discontinuation studies suffer from a number of limitations. The first is common to psychiatric treatment studies generally; how and when should we assess whether a patient's symptoms have changed after discontinuation? The second is more specific to discontinuation designs; the selection of patients based on a positive response to that treatment is likely to inflate the apparent beneficial effect of the treatment, as this subgroup of patients has the most to lose from stopping<sup>2</sup>.

The paper by Gueorguieva and colleagues reports a reanalysis of data from four discontinuation studies of fluoxetine and duloxetine and provides a number of interesting findings which speak to these issues. Using patient level data, the authors report the results of growth mixture modelling (GMM) of patients' symptoms, measured using the Hamilton Depression Rating Scale (HDRS) across the six months following patient randomisation to either continue or discontinue treatment. GMM is a data driven technique which "clusters" the trajectories of data as it changes over time. In this study GMM was used to identify whether it was possible to classify patients into separate

subgroups, each with a distinct progression of HDRS score, across the six months of the study.

Having ensured that they were able to identify distinct trajectories reliably, the authors performed a GMM analysis separately on the group of patients who remained on treatment and those who discontinued. They found essentially identical trajectories in the two groups, although a somewhat higher proportion of patients followed “non-relapse” trajectories if they stayed on the medication.

The most interesting aspect of this study is how much more it tells us about the evolution of patients’ symptoms over time than standard approaches to clinical trial data. Clinical trials, particularly those which inform regulatory decisions, will often report the simplest form of binary outcome coding for whether, at a particular point in time, a patient’s symptoms on a standard rating scale have dropped below a threshold level<sup>3</sup>. This type of radically simple outcome is completely blind to variations in response over the course of treatment. In contrast GMMs provide much richer information about symptomatology over time.

An example of the insights this may provide can be seen in Figure 1 of the Gueorguieva paper which shows the mean HDRS score of the three trajectories of symptom score identified in the study; one trajectory shows a clear worsening of symptoms, whereas in the other two, low levels of symptoms are maintained. The difference between the “relapse” and “non-relapse” trajectories is clear from this figure, however it is less clear what differentiates the two “non-relapse” trajectories. The answer to this is provided in figure S9 of the supplementary materials; one group of patients shows a stable pattern of low symptom scores, whereas the other has a much more variable symptom trajectory. That is, the GMM analysis has identified a distinct group of patients, both on and off medication, who have not relapsed, but who are showing a high level of symptom variability. Mood instability is common in depression<sup>4</sup> and is generally associated with poor outcome across diagnoses<sup>5</sup>, so it may be that the prognosis of this variable subgroup of patients is less favourable than the stably remitted group. This would be an interesting question for further study. In addition, the ‘relapse trajectory’ identified by the GMM model included a number of patients whose

symptoms worsened markedly but who were not identified by the binary relapse/non-relapse distinction suggesting that the proportion of patients suffering from persistent illness is higher than shown by the conventional measures. The Gueorguieva paper thus provides a useful illustration of the potential benefits of considering more sophisticated, dynamic measures of treatment effect.

A second interesting insight from this study concerns the potential harmful effects of antidepressant use, sometimes referred to as the oppositional model of tolerance<sup>6</sup>. By this view, antidepressant use itself encourages processes which oppose the initial effect of the drug leading to a loss of efficacy during treatment and a worsening of symptoms on discontinuation of the medication when the oppositional processes become suddenly unchecked. In a sense, the methodological limitation of discontinuation studies, that patients are selected based on their initial response to the antidepressant, also makes these studies a particularly sensitive test of discontinuation effects. In the GMM analysis reported by Gueorguieva and colleagues, a specific effect of antidepressant discontinuation on depressive symptoms should manifest as a distinct class of relapse trajectory in the group of patients who stop medication. That this wasn't seen provides some reassurance that stopping fluoxetine or duloxetine (at least using the down-tapering regimes employed in the primary studies) is unlikely to cause an acute worsening of illness course.

By extracting more nuanced patterns from depression rating scale measures this work illustrates how sophisticated analytical and computational techniques may enhance the degree to which trial data can inform clinical practice.

#### Funding and COI

MB is supported by an MRC Clinician Scientist Fellowship (MR/N008103/1). He is employed part time by P1vtial Ltd. No conflicts of interest to report.

- 1 Perahia DG, Gilaberte I, Wang F, *et al.* Duloxetine in the prevention of relapse of major depressive disorder: double-blind placebo-controlled study. *Br J Psychiatry J Ment Sci* 2006; **188**: 346–53.
- 2 Kopec JA, Abrahamowicz M, Esdaile JM. Randomized discontinuation trials: utility and efficiency. *J Clin Epidemiol* 1993; **46**: 959–71.
- 3 Rush MD A. STAR\*D: What Have We Learned? *Am J Psychiatry* 2007; **164**: 201–4.
- 4 Thompson RJ, Berenbaum H, Bredemeier K. Cross-sectional and longitudinal relations between affective instability and depression. *J Affect Disord* 2011; **130**: 53–9.
- 5 Patel R, Lloyd T, Jackson R, *et al.* Mood instability is a common feature of mental health disorders and is associated with poor clinical outcomes. *BMJ Open* 2015; **5**: e007504.
- 6 Fava GA. Rational use of antidepressant drugs. *Psychother Psychosom* 2014; **83**: 197–204.