

The Need and Rationale for Shortening the Clinical Trial for Antidepressants Martin M. Katz

The major characteristics of the current model for the clinical trials of new, putative antidepressants (ADs) have not been modified in any substantive manner since its establishment some 5 decades earlier. This is despite the fact that the conception of depressive disorders has been subject to change over the years, a great deal has been learned about the timing and mechanisms of action underlying the efficacy of the ADs, and the most prevalent forms of the disorder presented for treatment today in the outpatient clinic, are probably not as severe as those on whom the original model was targeted. The current model, due in great part to its reduced sensitivity to clinical change when applied to less severely ill patients, resulted in many failures to identify potentially useful drugs. In addition, the sampling and methodological procedures for a trial are known to be excessively expensive for the pharmaceutical companies, resulting in a declining interest in this sphere of activity and complete abandonment of CNS drug development by several major companies. In many ways, it can be shown that applying the established trial as a routine procedure is, in fact, a very wasteful use of resources. There is, in other words, ample evidence of both a scientific and a practical nature to reexamine the established model and to strongly consider major modifications in the trial procedures.

I have, in previous papers (Katz 1998, 2008; Katz et al 2006), acknowledged with others, the existence of certain statistical issues and the limitations of the Hamilton Depression Scale (1960), the sole method of evaluation in the established model. There have over time, however, been significant improvements in procedures. For example,

Bech (2011) and Rush et al (1986) have contributed to increasing the sensitivity of the Hamilton method and Montgomery and Asberg (1979) have sharpened the focus on measuring change, all by introducing new methods of evaluation. They identified the major source of the problem in the methodology of evaluation. In my own work, I further extended the methodological approach by first setting aside the traditional diagnosis and adopting the more precisely descriptive dimensional concept of the depressive disorders. I then developed a set of evaluative methods that measure its major components and dimensions. This revision of methodology thus, provides a way of refining the characterization of the illness and makes possible the profiling of the diverse and multiple behavioral effects of the drugs.

My approach is designed to capture both the changes in overall severity of the disorder, the primary aim of the clinical trial and in the diverse critical behavioral components we have uncovered over the years. It is these components we have learned, that are more specifically targeted by the drugs, rather than the “disease” itself.

This focus on the profile of clinical drug actions contributes to greater sensitivity. Along with this more refined examination of drug actions, it then makes it possible to detect very early changes in the clinical state, not detected by the established model. It was through this approach that it was first confirmed that clinical action of effective drugs begin within the first two weeks, contrary to the then textbook notion that clinical effects do not appear until several weeks of treatment (Katz et al 1987). Since then, there have been several large sample, multisite studies conducted that have established this early onset as fact (Stassen et al 1993, 1997, Szegedi et al 2009), and led to further studies, several of which have shown that 60 to 70% of the efficacious drug’s total clinical effects will occur during those first two to three weeks.

When the clinical implications of these more recent findings are examined, we become aware that it may well be possible, that simply on the basis of the drug’s clinical actions during those first two weeks, to predict whether the drug will be efficacious for the targeted disorder. If so, we could shorten the clinical trial, a modification that would result in major reductions in the excessive cost of the trial, and even more important, make it unnecessary to burden already distressed patients in controlled studies with several weeks of ineffective drug or placebo treatment.

On this particular issue of prediction, here is the evidence so far:

- (1) There are a number of early studies that reported early clinical changes with the ADs and showed them to be predictive of later response to the drugs. They include studies of Coryell et al 1982, Katz et al 1987, 2004, Khan et al 1989, Nagayama et al 1991, Stassen et al 1993, Boyer & Feighner 1994, and Szegedi et al 2003.
- (2) More targeted research over the years has been conducted and reviewed by a number of groups. They have established that “among responders the onset of improvement with ADs occurs in more than 70% of cases within the first three weeks”, later reinforced by Posternak & Zimmerman (2005) who reported that “60% of the improvement that occurred on active medication and placebo, took place during the 1st two weeks of treatment”, and evidence summarized by Taylor et al (2006) in their review, who concluded that “one-third of the total effect of SSRIs after six weeks of treatment is seen in the first week”. Of even more significance, it was quite clear from the Stassen et al (1997) and Szegedi et al (2009) multisite studies of upwards to thousands of patients that absence of clinical changes during the first two to three weeks of treatment with diverse ADs, is associated with less than 10% of patients responding at outcome, i.e., almost certain non-response to the experimental treatment. For a more thorough review of background research on the issue see Katz (2013). There is, in other words, much evidence that the nature of the patient’s response as early as two weeks, i.e., evidencing “improvement” or “no change”, is highly predictive of a putative AD’s efficacy, as measured at outcome of a 4 to 12 week treatment course
- (3) Katz, Berman, Bowden, Frazer (2011, 2015) more recently attempted to evaluate the two week prediction hypothesis in a relatively small size patient sample from the Katz et al (2004) onset study. Viewing the attempt as a “proof-of-concept” effort, they were able to confirm that the two week results were highly predictive of outcome and strongly support the conclusion that two weeks is sufficient time to judge whether it is necessary to proceed further with the clinical trial. That study’s major limitation, as noted, was the

relatively modest sized patient sample. That led to the recommendation that a prospective study, including a large multisite diverse sample of patients diagnosed as major depressive disorder, be conducted that would extend the test study findings. The results could lead to the acceptance of much improved, markedly less expensive models for clinical trials, such as those proposed in the test study.

The conduct of such a prospective trial would, of course, take several years. Based on the evidence, much of which is discussed above, it is my judgment, given the clinical benefits to patients and the need to reduce costs, viewed against a background of declining drug development in this field, that evidence is sufficient to support proceeding, if on an experimental basis, with the “shortened trial” as soon as possible.

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