

Chapter 2

Why Now the Need for a New Clinical Trials Model for Antidepressants?

What have we learned during the past 5 decades that makes the established model appear to be out of date, too expensive and based on the wrong principles? If we review the theoretical context upon which the original model was based we recall that it drew its strength from the following assumptions held at that time about how the drugs, in this case the revolutionary antidepressants, actually worked, that is, the neurochemical bases of their efficacy.

These assumptions were as follows: (1) Imipramine due to its capacity to inhibit the reuptake of monoamine neurotransmitters, norepinephrine and serotonin, results in higher levels of these neurotransmitters made available in the synapses of the nervous system. (2) It may not have been shown that these neurotransmitter concentrations are significantly lower in the depressive disorders than in healthy controls. However, it is clear that increasing the availability of these neurotransmitters, as occurs with the administration of the tri-cyclic antidepressants, results in significant improvement *of the disorder*. (3) It therefore, appears that the tri-cyclic antidepressants are specific as treatments for the major depressive disorders. (4) Kuhn in his original report on the efficacy of imipramine (1959) also noted that some patients responded quickly, within the 1st week. The general rule for the majority of patients, however, was to require several weeks to achieve remission of clinical symptoms.

Thus, it was generally accepted that the tri-cyclic antidepressants were in fact, “antidepressants”, meaning treatments specific for the diagnosis of major depressive disorder. Despite the almost immediate effects on monoamine neurotransmitters, however, the usual course for the patient responder was not to achieve full clinical response, until several weeks of treatment.

The established clinical trial for evaluating new putative “antidepressants” was designed in accordance with these assumptions. Thus, the trial would extend over 4–12 weeks. The patient sample would consist of diagnosed major depressive disorders; the major assessment points for measuring change would be at baseline and

outcome (since clinical effects, were not expected for several weeks). The major instrument for evaluating change would be a scale of overall severity of the diagnosed disorder. That model has been applied in the hundreds (possibly thousands) of clinical trials since the discovery of imipramine in 1959. It has been a generally effective model for identifying efficacious treatments, including the more recently developed selective serotonin re-uptake inhibitors (SSRIs) (Wong et al. 1974).

During the course of these 50 years, there have been many attempts to improve components of the model. As noted, statistical analyses were refined, and the efficiency or sensitivity of the Hamilton rating scale was improved. A scale focused on measuring change, for example, the Montgomery-Asberg Depression Rating Scale (MADRS) (1979), was introduced. However, there have been no substantive changes in the model, which viewed the target of treatment as the diagnosed disorder. That approach only noted the important change in severity as not occurring for several weeks, and focused exclusively on change of overall severity of *the disorder* as the measure of the efficacy of treatment.

There was in other words, no attention to the not-so-subtle changes in the understanding of how the drugs work and the nature of the clinical condition as these concepts have evolved based on new research during these past 5 decades. It is useful at this point to revisit questions and to review some of the more recent findings that introduce new information and have had some impact on how we develop and then evaluate new treatment agents for these disorders. For example:

1. Are established agents, the tricyclic antidepressants (TCAs) and SSRIs, specific for the treatment of diagnosed depressions?

Basic investigations of the mechanisms of neurobehavioral actions of TCAs and the SSRIs since then have painted a more refined picture of their actions. It has been determined that drug-induced change in the concentration of the norepinephrine metabolite, MHPG, is associated specifically, for example, with motor activity, changes in the serotonin metabolite, 5-HIAA, with anxiety and impulsive hostility. These changes in concentration are not therefore, associated specifically with a diagnosed disorder, but their actions explained more parsimoniously, as associated with the components of the disorder, that is, with behaviors, mood, and/or cognition. We found in our own research (Katz et al. 1994) such specific associations when treating depression in the studies in psychobiology (Maas et al. 1980).

2. Do clinical actions begin within the 1st 2 weeks, sometimes within the 1st week of treatment?

Research from 1987 on has established this. A series of independent and several multisite, large patient sample studies (Katz et al. 1987; Stassen et al. 1993; Machado et al. 2008; Szegedi et al. 2009) have shown that the major part of the clinical response to the drugs occurs within the 1st 2 weeks. In fact, 70 % of the total response occurs during the 1st 3 weeks (Stassen et al. 1997, 2007); 70 % of patients who show this early improvement go on to achieve a full response; less than 10 % of patients who do not show this early improvement, do not respond at outcome to the drug (Posternak and Zimmerman 2005; Taylor et al. 2006).

It is clear that serious assessment of clinical changes must begin at one week of treatment and be assessed weekly throughout the treatment period.

3. Changes brought about on behavioral components of the disorder are shown to begin as early as 1 week. That supports the judgment that the mechanisms that lead to full clinical response, are initiated by the effects on neurotransmitters. Those neurochemical effects have been found in turn, to be associated differentially with specific behaviors, mood or and cognition, not directly with “whole disorders” (Morilak and Frazer 2004).

These findings do not fully explain the bases for the efficacy of the tri-cyclic antidepressants and the SSRI's in resolving depression, but they do extend understanding of the neurobehavioral mechanisms underlying their efficacy.

It can be shown that the increased availability of serotonin results in reductions in anxiety and anger in the patient, and that increased norepinephrine reduces motor retardation and relieves depressed mood. These, potential changes in the disorder of the patient appeared to evolve into resolving the disorder as a whole (see Delgado (2000) for evidence that confirms the specific therapeutic roles of serotonin and norepinephrine). It is also true that despite all of these advances in understanding, there are still no “biological markers” for the depressive disorders.

Nevertheless we are today in a more advanced stage of understanding how these drugs work, than we were 5 decades ago. These new findings should affect how we develop and how we evaluate new agents for the depressive disorder.

To summarize, the following findings should contribute to modifying how we design a clinical trial: (1) the neurotransmitter systems most impacted by the TCAs and SSRIs are apparently responsible for the changes in the disorder, and (2) the noradrenergic and serotonergic systems are associated with the regulation of different patterns of mood and behavioral components of the disorders. They are not shown to be associated specifically, with the “whole” diagnosed disorder. The focus on assessing changes in the disorder in any new trial should be on the new drugs' impact on these components, as well as on changes in the severity of the overall disorder. That means in practical terms that the methods of evaluation of drug clinical actions should include, but go beyond that measured by the Hamilton or MADRS scales, i.e., methods should be added that are designed to measure the major behavioral, mood and cognitive components.

1. Contrary to earlier notions that nothing of clinical importance changes during the 1st few weeks of treatment, it is very clear that when the drug is effective for treating a targeted disorder, that not only does early improvement appear but that its presence or absence, is predictive of the type of response, positive or negative, to occur at outcome of treatment. Therefore, assessment must begin early, preferably by the end of the first week and then be conducted on a weekly basis throughout the course of treatment. Further, since it has been established that such early changes that may occur may more likely be on components rather than simply on severity of the whole disorder, behavioral methods for the measurement of these behavioral componential changes should be part of the assessment battery.

2. It has also been found that drugs that have specific actions on dimensions of psychopathology, such as anxiety-agitation, dimensions that are critical parts of other mental disorders, like generalized anxiety or obsessive-compulsive disorders, may, although found to be ineffective for the targeted disorder, such as depression, be applicable to the treatment of other allied conditions (for example, as noted the SSRIs are now the preferred treatment for generalized anxiety disorders). Therefore, it is essential to both determine, whether the experimental drug is effective or ineffective for the targeted disorder and the drug's profile of clinical actions on the components of the disorder. The latter assures that this potentially very important information is not lost or neglected, markedly limiting the overall value of this highly expensive clinical trial. It is also necessary to test whether early improvement appears, and be aware that its presence or absence is predictive of the type of clinical response, positive or negative, that will occur at outcome of treatment. Therefore assessment of change must begin early and be conducted sequentially, starting preferably at the end of the 1st week and then conducted regularly on a weekly basis throughout the course of treatment. Further, since it has been established that such early changes that may occur will more likely be on components, rather than simply on overall severity of the disorder, behavioral methods for the measurement of these componential changes should be part of the assessment battery.

These facts accumulated over the past five decades, the results of basic and clinical investigations of the neurobehavioral mechanisms underlying the efficacy of the new drugs, should of course, be put to use in the development of new antidepressants and in redesigning the clinical trial of the future to better evaluate these new agents. It is as if the results of the hundreds of clinical trials conducted during this period, although successful in rare cases of identifying new efficacious drugs, have provided extremely limited information about the actions of these many drugs. We know only whether they were effective or ineffective in resolving the targeted depressive disorders. Despite the great expense and great effort expended, no other reliable information has resulted that would expand knowledge and information on the impact of these chemical agents on the clinical aspects of psychopathology. No network of important information on their profiles of behavioral actions exists. Nor have the correlations of those actions with the effects on neurochemistry been assembled, information of obvious value in the design of new treatment drugs. Such information is critical for the clinician in potentially finding applications of these drugs for the treatment of other mental disorders, or to provide information toward improving their management of treatments. Critics would certainly view the conventional clinical trial as not only outdated from the standpoint of recent research advances, but exceedingly wasteful in its mode of research operations.

In the next chapter, I present an example of the proposed new model which would in fact, take advantage of this new information based on decades of research and make more effective use of the high expense in funds, time and effort that go into creating and conducting a clinical trial.

Clinical Trials of Antidepressants
How Changing the Model Can Uncover New, More
Effective Molecules

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