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COMMENTARY

Need for a New Paradigm for the Clinical Trials of Antidepressants

Martin M. Katz, Ph.D.

The current clinical trials model for antidepressants (AD) was developed in the 1960s. It views major depression as a unitary disorder, and "antidepressants" as having illness-specific therapeutic actions. The established efficacy measures are the Hamilton symptom rating scale and the CGI, which provide summary measures of improvement. In contrast, the DSM IV defines depression as heterogeneous, with such broad classes as unipolar and bipolar showing different response to treatments. Research further indicates depression to be comprised of major affective and behavioral components which vary in intensity across patients, and the tricyclic ADs to have multiple actions that affect various components sequentially. "New" ADs, products of rapid advancements in the neurosciences, are more precise in their actions on brain monoamine systems, targeted to affect behaviors with greater specificity. A new trials model sensitive to the varied behavioral effects needs to be developed to adapt to these quicker acting, targeted antidepressants. A componential model is recommended that employs an array of behavioral methods, and subtype classification and statistical approaches to estimate onset and sequence of multiple drug actions. The NIMH can intervene to accelerate improvements by initiating funding programs to implement more effective clinical methods and models.
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KEY WORDS: *Clinical trials; Antidepressants; Componential model; Behavioral assessment; Diagnostic subtypes*

Much discontent has been expressed recently in the field with the procedures for clinical trials of new antidepressants (AD) and anti-anxiety drugs. Clinical investigators expressed this dissatisfaction more directly at a 1997 ACNP satellite symposium, "Multi-site Clinical Trials: Can They Be Improved?"[1] There is, of course, no question that they can be improved. Drug development for antidepressants has reached a highly sophisticated stage based on new knowledge of the functioning of brain monoamine systems, specifically the serotonergic system and the discovery of its many receptor subtypes (Frazer 1997). Laboratory research is at a stage in which central nervous system functions associated with the different receptor subtypes are being identified, leading to the development of drugs with very specific behavioral targets. Psychotropic drugs targeted to influence anxiety level, aggression, psychomotor function, sleep, appetite, separately or in combination, have already been developed and new ones are in the process of development. Several types of "selective serotonergic reuptake inhibitor" (SSRI) drugs are already in clinical use. This new array of agents has been subjected to intense investigation at the clinical level for several years now. To take full advantage of these remarkable advances in drug development, clinical and behavioral evaluation must take account of the refinement of actions these drugs produce. But how are the new drugs likely to be evaluated?

If current guidelines are followed as outlined in the most recent text on the subject, *Clinical Evaluation of Psy-*

[1]Industry-Sponsored Multisite Clinical Trials: Can They Be Improved? Co-chairs: Potter WZ, Demitrack MA, American College of Neuropsychopharmacology 36th Annual Meeting, Hawaii, 1997.

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chiatric Drugs (Prien and Robinson 1994), and as recommended by the Food and Drug Administration (FDA), antidepressants are likely to be evaluated in accord with a model designed in the 1960s. Despite availability of a range of assessment methods and extensive discussions of technical design problems over the past three decades [see, e.g., chapter by Klerman et al. (1994) in Prien and Robinson (1994)], the typical trial is designed simply to determine whether a drug in comparison with a placebo control or standard antidepressant, can significantly reduce the severity of or completely resolve a depressive disorder. Accordingly, global measures such as the Hamilton Depression Rating Scale (Hamilton 1960) or the Clinical Global Impression of Improvement (CGI) (Guy 1976), are used as the main or sole indices of efficacy. In drug development, we have years of intensive research in neuropharmacology and molecular biology, using the most advanced biochemical and brain imaging technology. Yet new highly refined drugs are still being clinically evaluated by a procedure in which a doctor after a brief interview with the patient, provides only a summary score of the severity of the disorder. It is no wonder that most clinical scientists in our field are unhappy about current procedures for clinical trials. More important, years of drug development representing investments of millions of dollars can stand or fall on global clinical tests that are as limited in range and objectivity of measurement, as current procedures.

CONCEPTUAL PROBLEMS UNDERLYING CURRENT CLINICAL TRIALS

The new drugs are designed to be more precise in their actions on behavior. They are expected to have fewer or less intense side effects than the earlier antidepressants and to act faster in reducing the target symptomatology, and subsequently, in resolving the disorder. Since speed of action has for many reasons been a major concern in the development of new antidepressants, we (Katz et al. 1997) recently reviewed the clinical literature on how onset of drug action is measured. It has been only during the last decade that serious research effort was made to determine time of onset, clarify how the sequence of drug-induced actions on behavior is measured, and develop behavioral and statistical procedures to resolve the still complex problem of determining time of onset. This literature review made clear that clinical trials' research has in its emphasis on measuring severity of depression as a "whole" disorder, appeared to ignore advancements in the conceptualization of depression. The depressive disorder is, for example, not unitary, but multifaceted in nature. It is heterogenous, including such subtypes as unipolar and bipolar. The state itself is comprised of major mood, behavior, cognitive, and somatic components which vary in intensity and pattern across patients (see Katz and Maas 1994).[2] Typical clinical trials also downplayed findings that earlier antidepressants, the tricyclics, have multiple actions on behavior; the drugs have been shown to have both tranquilizing and stimulating effects at different times in the sequence of their behavioral actions (Kielholz and Poldinger 1968; Carlsson 1976; Katz et al. 1987, 1991). The ways in which the behavioral facets change are of importance in determining the nature of the recovery process and how the "whole" disorder is affected. Thus, determining time of onset requires examining the effects of drugs on the major components of the disorder (e.g., on anxiety level, aggression, and psychomotor function).

That drug actions must be studied on each of these components appears to be an obvious point but apparently one that has not been acted on very often in clinical investigations. Further evidence for the necessity to apply diverse behavioral methodology was the finding early in the study of imipramine that one of its first actions in depressed patients was to reduce anxiety (Kielholz and Poldinger 1968; Klein et al. 1978). Later that action was identified as a "calming" or tranquilizing effect which appears to initiate the recovery process. These findings then served as the basis for a carefully designed study of diagnosed "anxiety disorders" in which it was demonstrated that the tricyclic antidepressant, imipramine, was a more effective anti-anxiety drug than was chlordiazepoxide, an established anti-anxiety drug (Kahn et al. 1979). A similar story could be developed for the action of tricycylics in reducing hostility in depression. For many years it has been clear that the tricyclic antidepressant agents act on several major components of the depressive disorder. In fact, evidence of early, significant actions on components such as anxiety led to trials and eventual approval of certain of the newer SSRIs for treatment of anxiety and obsessive-compulsive disorders. Why then, in studies of new antidepressants, have we not applied an array of behavioral measures as methods of evaluation?

ON DIAGNOSIS AND THE COMPONENTIAL MODEL

One of the major accomplishments of psychiatric research over the past two decades has been the devel-

[2]In this view, behavioral components are distinguished from "symptoms"; the former are seen as structural parts of the disorder rather than as subjective or outward signs of the underlying illness. Anxiety for example, is not viewed as a symptom of the depressive disorder but as a functional component, equal in importance to the structure of the disorder as depressed mood or a specific psychomotor disturbance. This position is presented in more detail in Katz and Maas (1994).

opment of an empirically based classification system with operational criteria for diagnosis of mental disorders (American Psychiatric Association 1987). This system which is associated with standardized methods for data collection and clear decision rules has simplified greatly the conduct of clinical trials and clinical research, generally. The DSM III system provided a new base for clinical investigations. Even today the associated methods, the Research Diagnostic Criteria (RDC) (Spitzer et al. 1978), the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer 1978), and the Structured Clinical Interview for the DSM-III-R (SCID) (Spitzer and Williams 1983) are part of every serious research effort to investigate etiology, course, and new treatments for the mental disorders. Most clinical trials of antidepressants utilize standards from the DSM-III-R system which acknowledges the heterogeneity of the depressive disorder. However, the clinical trial model itself appears to be based on the premises that the disorder is unitary and that the drugs have a specific "antidepressant" action.

This model evaluates the effects of the drug on the disorder as a whole, and has for the past three decades, been the main instrument for selecting effective ADs. It has its place in the investigation of new therapeutic agents. Clinical trials in this field should not however, be limited by treating it as the only model for clinical drug investigation. Future trials utilizing the DSM criteria for depression should be designed to indicate when and how the drugs affect the disorder's major mood, behavioral, and cognitive components. That also means a clinical trial will require the most advanced measuring techniques for each of the major components. Global instruments which measure the severity of the "whole" disorder will play a part. But the intent of the trial should be to determine the sequence and the parameters of drug action. Instruments which measure the major components of the disorder should therefore play the primary role in the evaluation.

METHODS FOR MEASURING THE COMPONENTS

Current methods to evaluate drug effects on the behavioral components do not have the refinement or precision of methods employed in the physical sciences. However, reliable, valid instruments to assess the components which meet current psychometric standards have been available for several years. During the past few decades, much relevant research (Grinker et al. 1961; Wittenborn 1966; Raskin et al. 1967) to identify underlying constructs has been conducted using in most cases already established or validated instruments such as the Symptom Checklist-90 (SCL-90) (Derogatis et al. 1974) and the NIMH Mood Scale (Raskin et al. 1967). Recent years have seen greater attention to refining the measurement of mood. The relative neglect in earlier studies of the "negative" affects of anxiety and hostility, major components of the depressive disorder, and their counterparts, the "positive" affects, has been partly rectified. The Profile of Mood Scales (POMS) (McNair et al. 1971) and the NIMH Mood Scale which contain separate factorial measures of anger and anxiety along with scales for increased "vigor" and cognitive "clarity" are now more widely used in trials. Such methods extend the analysis of treatment-induced changes. In addition to the decrease or disappearance of symptoms, they register the return of positive behavioral characteristics in the patient. Further refinements in the measurement of the central mood of depression itself have been introduced by Beck and associates (Beck et al. 1974) so that a scale (e.g., that distinguished "hopelessness") can be partially separated in the measurement framework from mood itself. One of the thorniest issues, critical to differentiating the effects of AD drugs on the various subtypes of depression, is the capacity to disentangle the affects of anxiety and depressed mood within the depressive disorder itself. The literature on this issue has been reviewed over the years from several perspectives (Beck et al. 1987; Wetzler and Katz 1989; Clark and Watson 1991; Gorman 1997). Watson et al. (1995) based on a "tripartite" theory of the relationship between "positive" and "negative" affects in normals and patients developed a factorial self-report method of measurement, the Mood and Anxiety Symptom Questionnaire (MASQ). This method separates the mixed dimension of "subjective distress" that contains elements common to both anxiety and depression, from the relatively specific factors of "anxious arousal" and "anhedonic depression." Data is not yet available from treatment research with depressed and anxious patients. But the method appears promising for use in outcome studies. The difficulty in disentangling the mood concepts, the importance of measuring the major behavioral components of the disorder, and the need to combine observer and patient vantages on the clinical phenomena, prompted our group to develop a set of constructs and componential measures to assess the major facets of the depressive disorder (Katz et al. 1984, 1989). The set of state and outcome constructs based on the integration of established and new clinical methods includes the Video Interview Behavior Evaluation Scales (VIBES) (Katz et al. 1989). The derived component measures made it possible to detect specific behavioral effects in treatment responders early and to describe the sequence of tricyclic drug actions (Katz et al. 1991).

SUBTYPES AND ONSET OF ANTIDEPRESSANT ACTION

Of further relevance to the trials issue is the limited and somewhat controversial work which showed that certain subtypes of the disorder were specifically responsive to one of the antidepressant drugs then available, but not to another, such as a monoamine oxidase inhibitor for "atypical depressives" (Quitkin et al. 1990), and imipramine for the "retarded" depressive subtype (Hollister and Overall 1965). Further studies of the validity of the "atypical depression" subtype have clarified its distinctive clinical characteristics and treatment response characteristics. They led to its inclusion in the DSM IV as a "specifier." Recent research also uncovered a possible neurochemical basis for the atypicals' preferential treatment response to monoamine oxidase inhibitors versus tricyclic antidepressants (Asnis et al. 1995; McGinn et al. 1996). The relationships among the behavioral and biochemical components within the subtype are likely to be different than in the broader "major depressive disorder" (MDD). Thus, it is important to take the classification into account when designing trials for new drugs. Other subtypes which show evidence of preferential response to the various ADs are the classical unipolar and bipolar subtypes and the melancholic and dysthymic subtypes. Han et al. (1995) analyzed the DSM IV criteria and the present status of dysthymia as a distinctive disorder. They conclude that despite the progress in sharpening the criteria, there is still significant overlap with the criteria for MDD. The generally accepted notion however, that although dysthymia is more chronic, it is a milder disorder than MDD, accounts in part for the few reported differences in treatment results. Mitchell et al. (1996) studied hypothalamic-pituitary-adrenal (HPA) activity in melancholics and non-melancholics. They concluded that classifying patients in accord with the diagnosis, is less effective in exploring relationships with biological factors, than applying a dimensional approach (i.e., quantifying the extent of melancholia in individual patients through an assessment scale of psychomotor disturbance). This last example acknowledges the importance of the diagnostic concept of melancholia in structuring the study of relationships between biological and behavioral factors. But it demonstrates the limited sensitivity of the diagnostic model in uncovering the existence of the more subtle relationships. One can conclude from these examples of the current literature that the design of clinical trials, in addition to acknowledging the classical unipolar-bipolar distinction, must take account of recent research which identified valid subtypes. These include the atypical, which has been shown to respond differently than the major depressive disorders to the various classes of antidepressant treatments.

In contrast to the general notion that antidepressant clinical actions do not occur before 2 to 3 weeks of treatment, a number of studies of the tricyclic drugs (Small et al. 1981; DiMascio et al. 1968) and of the newer antidepressants including the SSRIs (Tollefson and Holman 1994; Dunbar et al. 1991; Rickels et al. 1995; Montgomery 1995; Smith et al. 1990) have shown in placebo-controlled studies, onset of drug action to occur within the first 7 to 10 days. Working with a componential approach Katz et al. (1987, 1991) evaluated response in severely disturbed, hospitalized unipolar and bipolar depressed patients. In those patients who clearly responded to 4 weeks of intensive treatment with imipramine or amitriptyline (250 mg/day during the last 3 weeks), anxiety, hostility, and certain aspects of disturbed motor function were reduced within the first 2 weeks of treatment. As indicated in our recent review of the research on onset of antidepressant activity (Katz et al. 1997) definitive results on these issues, however, await completion of studies which conform to a broad set of methodologic requirements (e.g., measurement of multiple drug actions, inclusion of a placebo control group).

CONCLUSIONS

The "model" clinical trial for antidepressants should be redesigned based on the limitations in the range of investigations reported in the field over the past two decades. The new model should deal more appropriately with current conceptions of the depressive disorders, with the greater likelihood that drugs that are targeted will act on one or more of the major components of the disorder, and that the new drugs will act on behavior within the first 2 weeks of treatment. The diagnostic framework that takes account of the expected variations of treatment response of certain subtypes can be utilized to select appropriate patients for study. However, the new trial's design should be modified to include predefined criteria for the measurement of "significant" change or improvement on each of the major components, and a different set of criteria to identify "full clinical response" or resolution of the disorder.

The "new clinical trial" must therefore, adapt to the testing of classes of drugs which have been developed to be more precise and targeted in their actions. The trial must integrate a more refined timetable for measurement, include a broader range of behavioral methods designed to test hypotheses about expected actions, and allow for the uncovering of unexpected actions of new drugs.

The ACNP symposium on clinical trials focussed positive attention on a number of technical problems (i.e., better methods for evaluating antidepressants, interrater reliability across sites, improvements in re-

search design, new approaches to data analysis). But the discussion did not consider such important issues as the changing conception of depression, the antidepressant-induced multiple actions on behavior, and the modes of action of the new drugs. It has not been acknowledged therefore, that the structure of the clinical trial as we knew it in the '60s and '70s is now becoming obsolete. That model cannot deal with the problems of evaluation that these new more refined drugs are presenting. It is therefore unproductive to continue to view this format as the model for future clinical trials. The conventional trial represented an earlier stage in the development of neuropsychopharmacology. The drug development laboratory is moving rapidly ahead and the field of clinical investigation should adapt to move with it. That can be accomplished by designing clinical studies to fit a new "componential" model. That model will acknowledge that:

1. Depression is heterogenous, comprised of several subtypes; the various disorders are comprised of equally important psychologic and somatic components which vary across patients.
2. New antidepressant drugs will be targeted to act on one or more mood, behavior and cognitive components, not necessarily on the "whole" disorder.
3. The drugs are likely to initiate actions on one or more of these components within the first 2 weeks.
4. To determine onset of action, it is necessary to distinguish early "clinical improvement" involving one or more of these components, from "full clinical response" or "recovery."
5. Behavioral methods which measure the various components separately, must accompany the use of global measures of severity as evaluative instruments.
6. New designs, and in some cases new statistical models, must be applied to address the issues of measuring interim changes (i.e., determining the onset of antidepressant action, and the sequence of drug actions which occur prior to recovery).

It is unlikely that clinical trials which meet all these additional requirements can become part of the Food and Drug Administration (FDA) process of approval. Nor is it likely that if the FDA process does not change, that the pharmaceutical companies will move to change their procedures. The NIMH already supports an elaborate New Clinical Drug Evaluation (NCDEU) program. In the spirit of moving this area of clinical investigation ahead, it would be useful it the NIMH would initiate a plan suggested by ACNP symposium participants. The program would be comparable to those operating in other Institutes which provide funding support for research targeted to improve the methodology of clinical trials and to develop new models.

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