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Unique design issues in clinical trials of patients with bipolar affective disorder

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Abstract

Two National Institute of Mental Health-sponsored meetings of experts on bipolar illness (in 1989 and 1994) noted a paucity of clinical psychopharmacological trials in this illness which has now extended over the past two decades. One of the reasons elucidated for this neglect was a lack of agreement in the field as to what constituted an optimal clinical trial design, consequently resulting in low-priority scores for funding of studies in bipolar illness. In this paper, we note some of the characteristics of bipolar illness that make it particularly difficult to study and find such agreed upon trial designs. Some of the assets and liabilities of the well-accepted traditional parallel group, placebo-controlled, randomized clinical trial (RCT) are reviewed, and a series of other potential design options, such as crossover, enrichment, off-on-off-on (B-A-B-A), and N-of-1 trials, are discussed that may help to better address some of the unique clinical characteristics of bipolar illness. Finally, a variety of statistical approaches to analyzing data in off-on-off-on trial designs, and in helping to predetermine necessary durations of clinical trials in individual patients with bipolar disorders, are suggested. Acceptance of a wider variety of clinical trial designs may help facilitate the funding and accelerate the acquisition of new data on treatment of bipolar illness.
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1. Introduction

In 1989 and 1994 the National Institute of Mental Health (NIMH) sponsored meetings of experts in bipolar disorders in order to elucidate and correct some of the reasons for the relative neglect of clinical trials in the field over the past few decades (Prien and Potter, 1990; Prien and Rush, 1996). The McArthur Foundation in 1992 sponsored a conference with similar goals. Prominent among the many reasons enumerated for this paucity of clinical trials was a lack of agreement as to the optimal clinical trial designs. Thus, the proposals submitted on bipolar illness for funding consideration by extramural advisory groups were not given adequately high priority scores. Controversies also included what were the best rating measures in acute studies, lack of consensus on longitudinal instruments, and the extent of the breadth or narrowness of inclusion criteria for trials in bipolar illness.

The methodological impediments to funding studies in bipolar illness were noted to be of particular importance, given the growing literature that the principle treatment of the illness—lithium—was often ineffective or insufficient for a large proportion of patients, even with the use of diverse augmentation strategies (Gitlin et al., 1995; Goldberg et al., 1996; Denicoff et al., 1997a; Maj et al., 1998; Vestergaard, 1992; Schaff et al., 1993; Post et al., 1998a).

Although the Stanley Foundation Bipolar Network (SFBN; Leverich et al., 2001) and the extramural NIMH-initiated Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD; Sachs, 2001) have addressed some of these issues and expanded collaborative bipolar patient study populations, the design controversies have persisted, and many critically important studies that would help inform clinical therapeutics remain to be initiated or funded. This paucity of studies was clearly evident in the last round of NIMH extramural grant reviews, in which there were no submissions for

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clinical trials related to pharmacotherapeutic approaches to bipolar illness. It is only recently that the pharmaceutical industry has begun to fill the gap in bipolar illness research with the study of potential mood stabilizing anticonvulsants, such as divalproex sodium (Bowden et al., 1994; Bowden, 2000) and lamotrigine (Calabrese et al., 1999, 2000; Bowden et al., 1999), or the atypical antipsychotics such as olanzapine (Tohen et al., 1999, 2002).

In this paper, we outline some of the characteristics of bipolar illness that make it particularly difficult to study and to find agreed upon research designs. We then review some of the assets and liabilities of the traditional parallel group, placebo-controlled, randomized clinical trial (RCT) as well as those of one of the design options (the off-on-off-on trial) that may help address some of the unique clinical characteristics of bipolar disorder. Several statistical approaches to analyzing data in these unusual trial designs and to helping to predetermine optimal clinical trial lengths for individual patients are suggested. We discuss the relative assets and liabilities of several alternative designs potentially applicable in bipolar illness.

Heterogeneous and variable illness characteristics both within and between subjects are paradigmatic in bipolar illness. This heterogeneity is even more problematic when one considers both acute intervention in very different phases of the illness—mania, depression, and mixed states—and long-term prevention strategies. Because homogeneous patient characteristics and study populations are essential ingredients to the success of most RCTs (Leber, 2002), bipolar illness inherently poses great study difficulties.

The illness also has a variety of subtypes, such as bipolar I with full-blown episodes of mania, bipolar II with only hypomanic episodes, and bipolar Not Otherwise Specified (NOS) with very brief or substance-induced hypomanias. Each of these manic presentations can have very different clinical characteristics, i.e. euphoric to dysphoric mania, as well as different cycle frequencies and rhythmic to arrhythmic forms. Patients can have none to a few episodes per year (non-rapid cycling) or four or more episodes per year (rapid cycling), and much faster patterns are now readily identifiable (Kramlinger and Post, 1996; Leverich and Post, 1998; Suppes et al., 2001).

Within any of these phases, subtypes, variations, and patterns of rhythmicity, further variability is almost definitional because bipolar illness has the greatest number of psychiatric comorbidities of any of the other major psychiatric illnesses. Bipolar patients are ten times more likely to have three or more comorbid psychiatric diagnoses than any other illness (Kessler et al., 1994, 1997). Forty percent of the SFBN outpatients have a history of comorbid anxiety disorder and more than 40% have a history of a comorbid substance abuse disorder (either alcohol or drug abuse; Suppes et al., 2001; McElroy et al., 2001).

To some extent, this difficult problem has been dealt with by avoiding patients with one or more comorbidities and excluding them from RCTs (Klein et al., 2002), yielding several obvious disadvantages: (1) the ability to generalize about clinical efficacy to the larger group of patients in the community is limited; (2) the potential research population is approximately halved; and, (3) appropriate medication and psychotherapeutic interventions are not adequately explored for this more-difficult-to-treat subgroup, i.e., the one with the greatest need for new medications (Laska et al., 1994; Licht et al., 1997; Rush et al., 2000, Klein et al., 2002).

Other elements of bipolar mania and depression further complicate study recruitment and retention. Depressed patients' cognitive distortions and presumptions that they are hopeless and untreatable prevent many patients from considering any treatment at all, much less entering a clinical research study. Current estimates from epidemiological studies suggest that some 40% of patients with a bipolar I diagnosis are not in treatment (Kessler et al., 1997), and only one third of those in treatment in community clinics comply with recommendations for lithium therapy.

The characteristics of manic phases, such as impulsivity, poor judgment, and denial of illness, also make it difficult for many patients to adhere to clinical trial requirements. Some patients welcome aspects of their hypomania (e.g. increased energy, motivation, sociability, and decreased need for sleep), and may not even recognize they are in need of treatment. Until recently, bipolar depressed patients have been systematically excluded from most antidepressant trials for fear of the possible induction of a manic episode during the study of an antidepressant (Prien and Potter, 1990; Altshuler et al., 1995; Post et al., 1997, 2001).

1.1. The traditional parallel group, placebo-controlled RCT

1.1.1. Assets and liabilities

Given the difficulties and great expense of the traditional large-scale, multi-center, pharmaceutical industry-sponsored RCT, other design options need to be considered, particularly in the initial phases of drug investigation when dose and potential degree of response in different subgroups are not well defined. Statisticians and research methodologists have commented that a large formal parallel group RCT is often not indicated in the initial stages of drug evaluation (Kraemer and Pruyn, 1990; Brouwers and Mohr, 1991; Laska et al., 1994; Lasagna, 1994; Klein et al., 2002), yet many review committees consider the RCT the exclusive academically-sound design. Table 1 summarizes some of the assets and limitations of traditional RCTs.