REVIEW

Aims and Results of the NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

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SUMMARY

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) was funded as part of a National Institute of Mental Health initiative to develop effectiveness information about treatments, illness course, and assessment strategies for severe mental disorders. STEP-BD studies were planned to be generalizable both to the research knowledge base for bipolar disorder and to clinical care of bipolar patients. Several novel methodologies were developed to aid in illness characterization, and were combined with existing scales on function, quality of life, illness burden, adherence, adverse effects, and temperament to yield a comprehensive data set. The methods integrated naturalistic treatment and randomized clinical trials, which a portion of STEP-BD participants participated. All investigators and other researchers in this multisite program were trained in a collaborative care model with the objective of retaining a high percentage of enrollees for several years. Articles from STEP-BD have yielded evidence on risk factors impacting outcomes, suicidality, functional status, recovery, relapse, and caretaker burden. The findings from these studies brought into question the widely practiced use of antidepressants in bipolar depression as well as substantiated the poorly responsive course of bipolar depression despite use of combination strategies. In particular, large studies on the characteristics and course of bipolar depression (the more pervasive pole of the illness), and the outcomes of treatments concluded that adjunctive psychosocial treatments but not adjunctive antidepressants yielded outcomes superior to those achieved with mood stabilizers alone. The majority of patients with bipolar depression concurrently had clinically significant manic symptoms. Anxiety, smoking, and early age of bipolar onset were each associated with increased illness burden. STEP-BD has established procedures that are relevant to future collaborative research programs aimed at the systematic study of the complex, intrinsically important elements of bipolar disorders.

Introduction

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), was to date the largest federally funded treatment study ever conducted for bipolar disorder (BD) and enrolled 4361 participants from 1999 to 2005 [1]. The broad objectives were to determine which treatments, or regimen of treatments, were most effective for treating the fundamental clinical states in BD, including acute and sustained response and preventing recurrence of episodes. STEP-BD uniquely incorporated both randomized controlled clinical studies and uncontrolled, evidence-based clinical care in designs intended to be generalizable to routine

clinical care settings. The unprecedented size, broad inclusion criteria, and ethnic and socio-economic spectrum of subjects were intended to make its findings applicable to most patients seeking care for BD. The sample was limited mainly by the participant's willingness to be seen by a STEP-BD physician, agree to complete self-ratings and have independent study assessments at baseline, quarterly for the first year and semiannually thereafter, the exclusion of patients needing acute substance use disorder detoxification, and for academic centers (which recruited the majority of the patients), the need for medical insurance to cover the cost of appointments with physicians. All subtypes (BD I, BD II, BD NOS, or cyclothymia) in any phase of illness once enrolled were

encouraged to continue treatment until conclusion of the STEP-BD program and were monitored systematically, even when euthymic, as in any routine clinical setting. STEP-BD promulgated a Collaborative Care approach to enhance the therapeutic alliance between patients, their clinicians, and their family members, allowing patients and their families to be more committed to treatment goals via systematic instruction on managing stress, improving communication, targeting sleep disturbances, and addressing dysfunctional cognitions [1]. STEP-BD sites were not funded to offer free clinical care, with the exception of a subcontract for inclusion of a public sector, medically indigent, principally ethnic minority subsample of 200 patients. STEP-BD otherwise required that the study group be representative of those presenting for treatment in the United States, with subjects continuing to pay for care at each visit as they would if seeking routine clinical care in the absence of the study, principally through health insurance plans.

Administration and Infrastructure

Screening of sites for inclusion in STEP-BD was limited to BD specialty programs caring for at least 100 active patients, selected to assure geographic balance and demographic diversity. Of the 22 centers engaged for the STEP-BD, 13 enrolled 90% of the total and six contributed two thirds of patients [2–4]. A characteristic of the six highest enrolling sites was their history of maintaining systems of indefinite clinical care, rather than clinical research efforts detached from such care provision. The treatment guidelines in STEP-BD focused on nine clinical state “pathways,” for example, refractory depression, relapse prevention [1]. STEP-BD utilized a Clinical Monitoring Form (CMF) as the source document for key outcome measures and also provide the progress note in the patient’s medical record [2]. To be certified in use of the CMF and other key clinician ratings, all treating psychiatrists completed standardized training and met requirements for interrater agreement with “gold standard” ratings. Both current and lifetime psychiatric comorbidities were ascertained. The most common current psychiatric disorder comorbidities in descending order were: any anxiety disorder (30.5%), alcohol use disorder (11.8%), drug use disorder (7.3%), ADHD (5.9%), and eating disorder (2.0%) [6,7]. General medical comorbidities were not determined, with the exception of current thyroid disease at 18% (see Table 1).

For the full STEP-BD sample, the mean age was 40, 56% were female and 85% were non-Hispanic white. Fifty three percent had a high school education; 40% had obtained a bachelors degree or above; and 58% had private insurance.

Table 1 Psychiatric comorbidities among STEP-BD patients

	Lifetime	Current	Sample size
Anxiety disorder [5]	51.2	30.5	500
Alcohol use disorder [6]	32.2	11.8	4000
Drug use disorder [6]	21.7	7.3	4000
ADHD [7]	9.5	5.9	1000
Eating disorder [8,9]	7.9	2.0	1000

Longitudinal Study of Recovered Individuals

One major thrust of STEP-BD was to document the longitudinal course of people with BD who were receiving guideline-based care. The most relevant report from the follow-up concerned 858 patients who entered STEP-BD in a symptomatic state and achieved remission within 2 years of prospective follow-up [10]. The study group was, on average, about 40 years old, and 71% had bipolar I disorder. At study entry, 30% were in a major depressive episode; 10% were in a manic or hypomanic episode; 8% were in a mixed episode; the remainder had subsyndromal symptoms.

About three-fourth of the patients ($N = 644$) recovered, of which 22.4% subsequently suffered a new major depressive episode and 6.4% suffered a new manic, hypomanic, or mixed episode. Risk of manic/hypomanic/mixed recurrence was significantly increased by (in order of the strength of the risk factor): rapid cycling within the past year, bipolar I subtype, current substance abuse, number of lifetime manic episodes, presence of residual manic symptoms, and number of depressive episodes within the past year (i.e., a proxy of rapid cycling). Risk of depressive recurrence was increased by: history of an eating disorder, rapid cycling within the past year, current comorbid anxiety disorder, number of lifetime depressive episodes, presence of residual manic symptoms, and presence of residual depressive symptoms. The presence of residual symptoms of mood elevation was the largest independent predictor of risk of recurrence for both depressive and manic/hypomanic/mixed episodes. The rates of development of new depressive episodes was just over twice the rate for development of manic, hypomanic, or mixed episodes [5]. Although this generally consistent with other reports, it suggests that the predominance of depressive relapse compared with manic relapse is substantially lower than was reported from 6 to 12 month interval phone interviews [11]. Direct clinical observation in the course of care, as occurred in the STEP-BD, would be less likely to miss brief hypomanic/manic periods than would infrequent phone based inquiries.

Predictors of Outcome

As a cohort study, STEP-BD was intended to allow for characterization of outcomes with evidence-based, optimized treatments, both pharmacologic and psychosocial. Among the 1469 patients who were symptomatic at study entry, 858 (58%) subsequently achieved remission during follow-up [10]. Nearly 50% of these patients experienced recurrence during up to 2 years of follow-up. Secondary analyses suggested increased risk of recurrence among benzodiazepine-treated patients [12]. Another analysis examined predictors of transition directly from manic/hypomanic/mixed episodes to mania [13]. Earlier work in a subset of STEP-BD patients suggested subthreshold manic symptoms might be associated with risk for subsequent manic symptoms with antidepressant treatment [14], consistent with other cohorts [15]. Notably, while baseline subthreshold manic symptomatology and other risk factors were identified, nearly all were not specific to antidepressant-treated patients. That is, the risk factors for transition to mania did not appear to differ

substantially between individuals with, and without, antidepressant treatment.

A third line of investigation examined the consistency of mood symptoms across episodes—to what extent were mood symptoms stable across episodes [16]. In general, STEP-BD results suggested that symptoms differ greatly in their stability, but some (most notably suicidality) did appear to recur with some consistency and thus might allow planning interventions for future episodes.

Predictors of Adherence and Function

STEP-BD studies addressed baseline correlates and longitudinal predictors of medication nonadherence and functional outcomes. In a 3640-patient, 1-year longitudinal study, 24% reported poorer adherence, with more severe baseline illness predicting poorer adherence, which in turn predicted less functional improvement at 1 year [17]. Thus, studies are needed to assess whether special attention to adherence in patients with more severe baseline illness yields better functional outcomes.

Sleep disturbance was common and was associated with poorer function and quality of life. In a 2024-patient, baseline cross-sectional study, 32% had short and 23% had long sleep duration, both of which were associated with poorer function and quality of life [18]. Hence, studies are needed to assess how specific attention to remediation of sleep disturbance impacts function and quality of life.

Not surprisingly, bipolar depression was associated with poorer quality of life. In a 2000-patient, baseline cross-sectional study, depressive symptoms were associated with poorer mental and overall quality of life [19]. Thus, studies of interventions for bipolar depression need to include assessments of impact upon quality of life.

Serious adverse events (SAEs) were common, and associated with more severe baseline illness. In a 1000-patient, 1-year longitudinal study, 12% had SAEs, with hospitalization for suicidal ideation being the most frequent SAE [20]. More severe baseline illness predicted SAEs. Hence, patients with more severe baseline illness merit special attention with respect to the risks of SAEs in general and hospitalization for suicidality in particular.

Impact of Substance Use Disorders on Course and Treatment

Several important findings regarding substance use disorders and their impact on illness course arose from STEP-BD. The high comorbidity of substance use in BD was confirmed, even in this ambulatory, research setting, with nearly 50% of subjects having a lifetime history of such comorbidity. The proportion of subjects in STEP-BD with current substance use disorders was 12%. It is unclear whether or not this rate is lower than expected for patients seeking treatment in ambulatory psychiatric setting, but it is lower than that found in the Epidemiological Catchment Area Study for patients seeking treatment in all alcohol, drug, and psychiatric treatment settings [21]. Having a substance use disorder was not an exclusion for participations in STEP-BD, with only those pa-

tients requiring acute detoxification excluded at entry, but the requirements of participating in an ambulatory study may have decreased the overall illness severity of participants.

It has been accepted clinical wisdom that bipolar patients with substance abuse have worse mood outcomes, but data from STEP-BD suggest that this is not necessarily the case. In a prospective analysis of 3950 subjects with bipolar I and II disorder, time to recovery from an index episode of major depression was not longer for subjects who had an alcohol use disorder or a drug use disorder, either past or present, compared to those with no such history [7]. Other investigators have found similar outcomes for these patients [22]. Nevertheless, this finding, in conjunction with the finding that adherence is worse in subjects with alcohol use disorders, suggested that withholding of medication treatment for patients with comorbid substance use disorders may be misguided—and it may be especially important to target these patients for interventions to improve adherence [17]. Subjects with any history of substance use disorder in STEP-BD lagged in functioning compared to those with no such history; in spite of a lack of difference in prospectively observed mood episodes, the deleterious effects of comorbid substance use disorders were clear [23].

What also was apparent is that earlier age of first onset of bipolar illness, collected retrospectively, was associated with higher likelihood of developing a substance use disorder, and that early onset (first mood episode by age 18) and very early onset (first mood episode by age 13) subjects were less likely to have prolonged periods of recovery than are those whose onset was in adulthood [24]. Because of the functional consequences of substance use disorder, the STEP-BD data underscored the importance of early recognition and early intervention in adolescents in an effort to reduce this comorbidity.

Cigarette smoking was also greatly elevated in subjects in the STEP-BD cohort, and appeared associated with increased risk of suicide attempts, suicide measures, and impulsiveness. Prospective findings from a STEP-BD ancillary study found that observed suicide attempts were more frequent in a group of smokers compared to a group that did not smoke [25]. The significant adverse medical consequences of smoking are already well known, but STEP-BD data indicated that its association with poor outcome in BD also needs to be appreciated.

Patients with BD and comorbid substance use disorder clearly required vigilant monitoring and proactive interventions. However, an early analysis in STEP-BD found that only a negligible number of subjects with comorbid drug or alcohol use disorders were being prescribed approved pharmacological treatments for substance use disorders [5]. Substance use disorders were common in the STEP-BD cohort, associated with earlier onset of illness, suicide attempts, and worse functioning, but did not appear to be directly associated with poorer mood outcomes, again perhaps related to excluding patients with a need for acute detoxification at enrollment.

Combination Therapy, Comorbidity, and Treatment Outcome

The STEP-BD findings supported the impression that BD is accompanied by high rates of cooccurring psychiatric comorbidity

and that complex regimens of pharmacotherapy are necessary to achieve mood stabilization. However, only 59% of patients presenting with comorbidities had previously received adequate trials of mood stabilizers. An examination of the naturalistic pharmacotherapy to study whether the presence of comorbidity was associated with adequate pharmacotherapy found that only 20% reported the use of benzodiazepines for anxiety despite its evidence base [5]. Whereas benzodiazepines were underutilized in subjects with cooccurring anxiety, this class of medication appeared to be over-utilized in subjects with cooccurring substance use. Another analysis of benzodiazepines was undertaken to determine if the concurrent use of benzodiazepines in BD was associated with relapse/recurrence [24]. Of 349 subjects prescribed a benzodiazepine at the time of remission, there did appear to be a greater risk for recurrence of mood episodes; however, this prompted the conclusion that the use of this class of medication appeared to be a marker for more severe course of illness rather than causing relapse/recurrence. Benzodiazepines used for treatment of sleep disturbance, for anxiety, or for anxiety as a component of mixed states, since anxiety is prominently associated with mixed states, could, individually or in combination, have contributed to the 21% greater hazard ratio for relapse amongst the 1365 patients who had achieved remission. The baseline sample was also used to ascertain if the use of antidepressants in bipolar depression was associated with increased risk of suicidal ideation as reported elsewhere for children and adults with depressive and anxiety disorders. Of the 425 who experienced a prospectively observed, new-onset major depressive episode without initial suicidal ideation, 24 participants developed new onset suicidality, with no association with antidepressant use [26,27].

Antidepressant Use and Outcome

Antidepressants continue to be widely used, acutely and long term, to treat bipolar depression despite the paucity of evidence to support this strategy. Additionally, there is a lack of data on the role of antidepressant in affective switches as well as treatment options in nonresponsive patients with bipolar depression. A randomized double-blind, placebo-controlled study comparing the efficacy of an antidepressant (sertraline or bupropion) plus mood stabilizer (MS; $n = 179$) to MS alone ($n = 187$) in bipolar depression did not differentiate between the two groups in the rates of recovery (23.5% vs. 27.3%; $P = 0.40$) [4]. Patients in the MS alone group also demonstrated nonsignificant superiority on secondary outcome measures. There was no difference between the two groups in the rate of treatment-emergent affective switch. The study used a broad definition for mood stabilizers, allowing lithium, valproate, antipsychotic drugs, or lamotrigine to so qualify. At least some acute antidepressant activity has been described for lithium, valproate, quetiapine, in randomized trials; however not for other antipsychotic drugs or, at least acutely for lamotrigine. Therefore one interpretation of the results is that the two antidepressants did not further augment a bona fide benefit of some of the mood stabilizers.

In an open, randomized study patients who attained recovery with antidepressants plus MS were assigned to continue on antidepressants plus MS or MS alone. Long term, there were no signifi-

cant differences between the two groups in prevalence or severity of new depressive or manic episodes, or overall time in remission. However, antidepressant continuation was associated with greater likelihood of depressive relapse in those with, versus those without rapid cycling course [19]. A naturalistic study of 335 STEP-BD participants who did or did not receive antidepressants along with mood stabilizers for a depressive episode found that adjunctive antidepressant use was associated with significantly higher mania symptom severity at the 3-month follow-up. Additionally, antidepressant use did not hasten time to recovery relative to treatment with mood stabilizers alone [14].

A randomized study ($N = 66$) assessed the effectiveness of adjunctive open label lamotrigine, inositol or risperidone, in patients with bipolar depression who failed to respond to a combination antidepressant plus MS. No difference in efficacy was observed between the three agents, although limited statistical power may have contributed to this negative finding [3].

Findings from these studies brought into question the widely practiced use of antidepressants in bipolar depression as well as substantiated the poorly responsive course of bipolar depression despite use of combination strategies.

Psychosocial Interventions

STEP-BD found that intensive psychosocial treatments (cognitive-behavior therapy, family-focused therapy, or interpersonal and social rhythm therapy) as adjuncts to pharmacotherapy were more beneficial than a brief psychoeducational treatment (collaborative care) in enhancing stabilization from bipolar depression. Two hundred ninety three depressed outpatients with bipolar I or II disorder were randomly assigned to an intensive psychotherapy ($n = 163$) or collaborative care ($n = 130$). Intensive psychotherapy was given weekly and biweekly for up to 30 sessions in 9 months. Collaborative care consisted of three sessions in 6 weeks. Patients receiving intensive psychotherapy had significantly higher year-end recovery rates and shorter times to recovery than patients in collaborative care. Patients in intensive psychotherapy were 1.58 times more likely to be clinically well during any study month than those in collaborative care. No statistically significant differences were observed in the outcomes of the three intensive psychotherapies [28]. It was noteworthy that regardless of assignment to the intensive psychotherapy or brief psychoeducation intervention, recovery rates were more than 20% higher for patients randomized in the adjunctive psychotherapy trial compared to those randomized in the adjunctive antidepressant trial, indicating that bipolar depression patients who are willing to accept even the possibility of assignment to intensive psychotherapy may have better outcomes.

In a subset ($n = 152$) of the above sample, STEP-BD also examined the impact of intensive psychosocial treatment plus pharmacotherapy on the functional outcomes of patients with BD over the 9 months following a depressive episode. Patients in intensive psychotherapy had better total functioning, relationship functioning, and life satisfaction scores over 9 months than patients in collaborative care, even after accounting for pretreatment functioning and concurrent depression scores [29].

While intensive psychotherapy may be most applicable to severely ill patients with BD, a prospective, naturalistic examination of psychotherapy use among STEP-BD participants found that briefer treatments may be adequate for less severely ill patients [30].

Ethnic and Provider Burden

At study entry, African Americans reported fewer medication prescriptions and Hispanics reported fewer specialty treatment visits than Caucasian control subjects. African Americans had increased rates of psychosis, while Hispanics reported higher current and past alcohol comorbidity [31]. Despite such disparities, African Americans, Hispanics and non-Hispanic whites did not differ on outcomes. Using the final STEP-BD data set ($n = 4100$), we prospectively compared outcomes for African Americans ($n = 155$) and Hispanics ($n = 152$). African Americans and Hispanics were more likely than non-Hispanic whites to discontinue STEP-BD within the first year. African American and Hispanics experienced similar recovery on depression and days spent well as non-Hispanic whites. African Americans had lower GAF scores and a trend toward worse overall clinical status. Psychosis was a predictor of poor depression outcomes for African Americans [32]. These results suggested that while outcomes differences should be considered in treatment planning, when evidence-based treatments are provided outcomes can be similar across ethnic groups, thus remediating baseline illness severity disparities.

In an ancillary study, 500 STEP-BD caregivers were assessed with regard to stigma, mood, burden, and coping alongside patient assessments of clinical status [33]. Greater subjective caregiver burden was associated with episodes of patient depression and fewer patient days well over the previous year. Perceived stigma was common among caregivers not only while patients were actively symptomatic, but also when they were doing well [34]. Greater mental illness stigma was associated with bipolar I disorder, less social support for the caregiver, fewer caregiver social interactions, and being Hispanic. In a patient group selected for overall better clinical status, greater stigma was associated with being an adult offspring of a parent with BD, a college education, fewer social interactions, and female gender.

Genomic Analyses of STEP Sample

STEP-BD collected DNA from more than 2300 participants. This genetics repository, the largest DNA collection formed exclusively from persons with BD, has been included in landmark genomic analyses in BD [35,36]. In addition to facilitating disease association studies, STEP-BD was utilized for the first genome-wide association study of lithium response, and recurrence risk [37]. While no single locus achieved a genome-wide significance threshold, these results provided an important resource for ongoing investigations of lithium, implicating candidates for future study including genes related to glutamatergic neurotransmission.

Summing Up

STEP-BD substantially impacted both clinical practice and research perspectives on future BD studies. The combination of unprecedented sample size and a multifaceted series of clinical studies on key current issues challenging both clinical practice and research designs have in numerous areas of study summarized here provided adequately powered studies and subset analyses not generally achieved in earlier small studies. For example, the key-stone randomized study on adjunctive antidepressants, reviewed here, did not indicate that the adjunctive antidepressants provided greater benefits than mood stabilizers alone. However, others who have systematically reviewed STEP-BD activities reasonably have questioned whether patients not enrolled or accepting of participation in the study might have had different, and plausibly better experiences with adjunctive antidepressant use [9,38]. In a separate randomized study, STEP-BD patients in depressed episode who had initially responded to treatment with antidepressants plus mood stabilizers, and had been euthymic for 2 months, were openly assigned to antidepressant continuation versus discontinuation for 1–3 years. Mood stabilizers were continued in both groups. Continuing antidepressants yielded no significant benefit in prevalence or severity of new depressive or manic episodes, or in overall time in remission [39]. An investigation of patients entering the STEP-BD program showed significantly increased risk for affective polarity switch amongst patients who had previously switched to mania/hypomania while taking tricyclic antidepressants ($OR = 7.80$), serotonin reuptake inhibitors ($OR = 3.73$), or bupropion ($OR = 4.28$) [40]. Finally, STEP-BD established that strictly DSM-IV defined bipolar depressive episodes without some manic symptomatology were infrequent, occurring in only 31% of the 1380 patients who entered in a depressive episode [41]. Thus, the multifaceted individual studies, coupled with the broad research and clinical backgrounds of multiple scientists, combined to provide a comprehensive set of results on this treatment and illness course issue.

STEP-BD also took initiatives to define longitudinal outcomes in BD to incorporate sustained benefits, multifaceted symptomatic recovery, and functional as well as syndromal/symptomatic recoveries. These efforts enhanced the generalizability of results to clinicians caring for bipolar patients and highlighted the need to reconsider the overly simplistic single point in time relapse designs favored in recent registration studies [38].

STEP-BD established the feasibility of a large consortium to aggregate subjects to yield investigations simply not possible, or sorely underpowered in single site or small collaborative studies regarding pathophysiologically important questions, but ones not central to day to day management of BDs. The 60 plus STEP-BD studies published to date included reliable information regarding many such subjects, for example, lithium compared with other mood stabilizer impact on suicidal behavior [42], handedness in BD [43], cigarette use and its impacts [25], comorbidities [5], and caretaker burden and illness stigma [33].

STEP-BD also had several limitations that are relevant to persons accessing the resulting reports, as well as planning collaborative research ventures. The choice of the instruments routinely completed represented a compromise between comprehensiveness and practicability in terms of staff and subject time.

Moreover, certain symptom areas that at present seem particularly important in terms of bipolar pathophysiology, for example, discrete aspects of anxiety, affective, or mood instability and impulsivity, have little or no representation in the data set. Although the study has generally excellent generalizability due to minimal exclusionary criteria; in fact this, or any prospective intervention trial only engages persons sufficiently motivated to collaborate actively with a treatment and evaluation team. This results in some under representation of persons with impaired insight regarding their clinical state and the need for treatment, likely also understudying persons with active substance use disorders. Although the large sample and multiple sites allows for confidence in data based on adequately powered and not site idiosyncratic results, such a study is not the primary place to look for epidemiological data about BDs. Although we were able to conduct important and meaningful randomized studies along with the naturalistic investigation of illness course, for many purposes a free standing randomized efficacy or comparative effectiveness study of a particular intervention, or with a specific subset of bipolar patients, will likely be a more effective design strategy. To base recruitment of such discrete intervention protocols on persons who agreed to participate in the primary study because of a more general interest in their illness management may partially exclude subjects with the specific features important for the instant trial.

Additional results relevant to contemporary treatment can be expected from this unprecedented data set. The STEP-BD data

set is now available through NIMH to qualified investigators for application to hypotheses beyond those planned by the group of investigators who have contributed to the work summarized here.

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Authors' Contributions

Dr. Bowden Dr. Perlis, Dr. Thase, Dr. Ketter, Dr. Ostacher, Dr. Calabrese, Dr. Reilly-Harrington, Dr. Gonzalez, and Dr. Singh participated in the concept, data collection, analysis, drafting and approval of this article.

Dr. Nierenberg participated in data collection, analysis, and approval of this article.

Dr. Sach participated in the concept, data collection, analysis, approval and securing of funding for the study.

Conflict of Interest

The authors have no conflict of interest.

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