

Advancing Bipolar Disorder: Key Lessons From the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

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Objective: To review the overall clinical research findings from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), the world's largest study of BD.

Methods: STEP-BD was conducted from 1998 to 2005, enrolling participants ($n = 4361$) across 22 clinical sites in the United States. Each individual was followed for up to 2 years in naturalistic practice with blinded research assessments, while subgroups participated in randomized controlled trials (RCTs) for bipolar depression. The naturalistic database was used to examine the course of BD, comorbidity with other psychiatric disorders, and suicidality. Relevant studies in English, published from January 1, 1994, to May 31, 2009, were identified using computerized searches of electronic databases (PubMed, PsycINFO, and Cochrane Register of Clinical Trials), inspection of bibliographies, and review of other major reports.

Results: One large RCT involving the addition of either paroxetine or bupropion to mood stabilizers in acute depression found neither more effective than placebo in achieving sustained recovery (8 weeks of euthymia). A second large RCT found intensive psychosocial interventions superior to a brief psychosocial intervention as an adjunct to medication in acute depression. A third small RCT found minimal effects of lamotrigine, risperidone, or inositol in refractory depression. Recovery was difficult to achieve, with subsyndromal symptoms or full relapse very common. Anxiety disorders and smoking in particular were treatable conditions that adversely affected the course of BD.

Conclusions: STEP-BD yielded numerous clinical and systems observations that provide fresh direction for research and treatment of BD, including setting new benchmarks for outcome and demonstrating the viability of large BD networks.

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Highlights

- STEP-BD was the largest BD research program ever conducted, and included data from 3 major RCTs and findings from many observational studies.
- Few treatments were successful in bipolar depression, with psychosocial interventions combined with mood stabilizers the most positive.
- Comorbidity of BD with substance abuse and smoking were common and adversely affected clinical outcome, while comorbidity with adult attention-deficit hyperactivity disorder was modest.

Key Words: bipolar disorder, bipolar depression, antidepressants, mood stabilizers, mania, suicidality, Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), clinical trial, psychosocial treatment

Evidence-based medicine postulates that RCTs are the ideal source of information regarding treatment. However, from a public health perspective, there are limitations to reliance on typical efficacy trials, where often small samples of so-called uncomplicated patients receive tightly circumscribed interventions. In response, the US NIMH in the 1990s commissioned a series of effectiveness study programs in so-called real-world settings; for BD, this was known as the STEP-BD.¹ Conducted from 1998 to 2005, this program enrolled participants ($n = 4361$) across 22 clinical sites in the United States, funded by an NIMH grant of US\$26.8 million (with no pharmaceutical funding except for donated ADs for one study). To ensure generalizability, there were essentially no contraindications to enrolment in the overall program. All sites had special expertise in caring for BD, with at least 100 active patients, and, further, all treating psychiatrists had to undergo at least 20 credit hours of training in BD management, based primarily on major treatment guidelines. With this background of experienced sites and specially trained psychiatrists, a series of objectives was pursued with 2 broad treatment pathways: a standard care pathway where all patients started, with naturalistic treatment for 2 years; and, randomized care pathways, where a smaller number of patients participated for short periods of time in specific trials, followed by return to the standard care pathway. All patients received standardized assessment every 3 months (for 2 years) via a battery of measures by a blinded assessor; those participating in any RCTs received additional assessments as per the specific study protocol. This blend of pathways thus allowed for generation of knowledge of patients in a so-called usual practice setting, as well as the collection of data for specific trials, with the additional benefit that those who finished an RCT continued to be monitored via the usual care pathway. This allowed both greater continuity of care and continuity of data.

The official aims of STEP-BD were to: generate general clinical data on a wide cross-section of patients with BD; and conduct 4 major RCTs, including a study of ADs in acute bipolar depression, a study of psychotherapies in acute bipolar

depression, another study of adjunctive pharmacotherapy for refractory bipolar depression, and a final study on relapse prevention after mania. The latter study involved taking patients who became manic while still on lithium or valproate, and randomly assigning them to either increased doses of a single mood stabilizer or the combination of both. Owing to poor recruitment, the study of relapse prevention, post mania, was abandoned; therefore, the remaining RCT findings all relate to bipolar depression.

By May 2009, more than 30 publications had emerged from this rich database. As it is impossible to summarize all the findings here, the major findings will be reported, starting with the 3 RCTs for bipolar depression. Subsequent sections of this paper will highlight key clinical findings, including observations on clinical characteristics of patients, the extent and impact of comorbidities, the extent and course of suicidality, and various aspects of the clinical course of BD.

Lessons in Treating Bipolar Depression

It has long been recognized that bipolar depression is more difficult to treat than mania, yet less research exists to inform treatment choice.² For this reason, most of the RCTs in STEP-BD involved this entity. As these RCTs were effectiveness studies, not efficacy trials of new interventions, only existing compounds and psychotherapies were used as interventions. Below, each trial is reviewed in design, results, and implications.

The Role of ADs in Acute Bipolar Depression

In the mid-1990s, clinical treatment guidelines recommended caution in the use of ADs in BD owing to concerns about switches into mania and the possible induction of rapid cycling.³ When ADs were considered, guidelines recommended either bupropion or an SSRI, while acknowledging that evidence was very limited. Among the major trials of that era were ones involving the SSRI paroxetine^{4,5} and bupropion,⁶ which solidified the role for paroxetine and bupropion while discouraging the use of tricyclic ADs. Thus, for STEP-BD, an acute AD study⁷ was created using bupropion and paroxetine, always as an add-on to ongoing mood stabilizer treatment (lithium, carbamazepine, or valproate).

Consistent with the requirements of high-quality studies, the design involved an RCT with placebo controls. Patients entered the trial if they were in an acute bipolar depression and on a mood stabilizer (whose definition was expanded to allow atypical antipsychotics indicated for BD midway through the study). They were then randomly assigned to either bupropion or paroxetine, with the recommendation that mood stabilizer treatment be continued in adequate doses. As this was an effectiveness study, not a strictly regulated efficacy study, actual doses administered both of ADs and of mood stabilizers were recorded but noncompliance was not used to expel subjects from the study. What was most unusual was the selection of outcome measures: unlike

Abbreviations used in this article

AD	antidepressant
ADHD	attention-deficit hyperactivity disorder
BD	bipolar disorder
CC	collaborative care
DSM	Diagnostic and Statistical Manual of Mental Disorders
IPS	Intensive Psychosocial Study
NIMH	National Institute of Mental Health
RCT	randomized controlled trial
SSRI	specific serotonin reuptake inhibitor
STEP-BD	Systematic Treatment Enhancement Program for BD
SUD	substance use disorder

virtually all previous acute phase bipolar studies, subjects' symptoms at a specified timepoint (for example, 6 weeks) were not the primary outcome. Instead, the investigators sought to adhere to the DSM-IV definition of recovery, where 2 months of normal mood is specified. Thus the subjects in the study were followed for 26 weeks, during which time subjects had to be in remission (from both depression and mania) for 8 consecutive weeks. In addition, subjects were carefully monitored for induction of mood switches and other safety issues.

For recruitment, 366 patients consented to this study and had the typical demographics of most studies of people with BD: average age 40 years, 90% Caucasian, 57% female, and 68% with BD I. One-quarter of the sample was on lithium alone, with another one-quarter on valproate alone; of the rest, a plurality were on combinations of mood stabilizers, while less than 10% were on atypical antipsychotics. Among the 366 subjects, 179 were randomized to active treatment (86 to bupropion and 93 to paroxetine), while 187 were randomized to placebo. Interestingly, during the study, about one-quarter of all patients did not stay on adequate doses of a mood stabilizer. Patients receiving bupropion achieved a median dose of 300 mg/day, while subjects on paroxetine had a median dose of 30 mg/day (both doses were considered adequate).

For primary outcomes, there were no significant differences in recovery between patients receiving mood stabilizer plus AD, compared with mood stabilizer plus placebo. There were also no differences in safety outcomes, with both groups showing less than 11% rates of mood switch. Almost 34% of each group dropped out prematurely. Overall, 8 consecutive weeks of euthymia (recovery) was achieved in just 24% of patients taking AD, and 27% of patients on placebo. Even when the more traditional outcome measure—comparison of groups at a fixed end point—was used as a secondary outcome, at no point did the AD group have higher rates of euthymia than the placebo group. The study authors concluded that ADs were not routinely indicated for bipolar depression; in fact, one author went on to recommend that mood stabilizer alone should be considered first-line treatment for acute bipolar depression.⁸ While many potential limitations have been raised, perhaps the most important involve the generalizability based on who may have been enrolled. First, while the study was large, compared with most RCTs in BD, it included less than 10% of patients enrolled in STEP-BD, and once these patients were randomized, more than one-third dropped out. Further, it is quite plausible that people with histories of good response to AD would not have been interested in participating, nor would they have been referred by their psychiatrists. Similarly, people with histories of AD-induced manic switches may not have been enrolled—as evidenced by the equivalent AD and placebo switch rates during the prospective study—which would also have depleted the study of subjects who potentially could have responded well to AD. On balance, the study suggests that AD response is likely limited in bipolar depression, but

does not provide a definitive answer. Only about one-quarter of all subjects achieved sustained recovery, underscoring the difficulty in managing BD and emphasizing the need for alternative treatments including psychotherapy.

The Role of Intensive Psychotherapy in Acute Bipolar Depression

Psychosocial interventions in BD have been relatively poorly studied in BD, and the data available when STEP-BD was designed in the late 1990s was particularly scant.⁹ Given the severity and length of bipolar depressive episodes, and the clinical sense that more intensive therapy may be more beneficial, a study,¹⁰ we will call the IPS, was designed as an RCT of 1-year's duration, with 4 arms (3 intensive psychotherapies and 1 brief control condition [known as CC]). One unusual feature of the IPS was that it was conducted simultaneously with the RCT of AD; thus people could be simultaneously randomized to medications and to psychotherapy (both the AD study and this psychotherapy study did subsequent secondary analyses to control for dual randomization). The total enrolment of subjects in IPS ($n = 293$) included people from the AD study ($n = 236$) and people receiving usual medication ($n = 57$). All subjects were requested to be on a minimum of one mood stabilizing medication or to start one—at the outset of the study, 93% were on mood stabilizers. Study participants' demographics included: a mean age of 40 years, 59% women, 83% Caucasian, and 67% BD I. Although the interventions included 3 intensive therapies and CC, for practical reasons, each site offered only 2 intensive interventions and CC. Each of the 3 intensive interventions—cognitive-behavioural therapy, interpersonal and social rhythm therapy, and family-focused therapy—had been previously been shown in at least 1 major RCT to be effective in the maintenance phase of BD in prevention of relapses, and allowed for some flexibility in adapting to acute depressive symptoms.¹¹ Each of the intensive interventions allowed for up to 30 sessions of 50 minutes each, to be completed in the first 9 months of the study. The CC intervention consisted of only three 50-minute sessions, done in the first 6 weeks of the study, using a psychoeducational videotape and workbook that touched on key elements of psychoeducation, medication adherence, schedule management, mood-induced thought distortions, improving relationships, and relapse prevention. Regarding study completion, two-thirds finished a full year; attrition was comparable across all 4 interventions. People receiving CC completed a mean of 2.2 sessions, while the intensive intervention subjects completed a mean of 14 sessions (similar across all intensive psychotherapies). In addition, subjects in all 4 psychosocial interventions received a mean of 23 medication visits to their psychiatrists during the study year.

Primary outcomes were time to recovery (8 consecutive weeks of euthymia) and likelihood of remaining well during the 12-month study; secondary outcomes examined whether the 3 intensive treatments had differing impact on depressive

symptoms. By study end point, 64% of subjects receiving intensive interventions had recovered, compared with 52% of the control group. In addition, 50% median time to recovery was 169 days, compared with 279 days for the CC group. Both of these outcomes were statistically significant. Intensive intervention subjects were significantly more likely to be well in any study month, compared with the CC group. None of the intensive interventions showed advantage over the others, although the power to detect such differences was very limited. Thus the study authors concluded that intensive psychosocial interventions were helpful in recovery from acute bipolar depression; this was a meaningful finding given the lack of efficacy from AD in the medication study. Limitations included problems familiar from the AD study: less than 10% of STEP-BD subjects participated in this study, and one-third dropped out. Medication treatment during the study was uneven; about 20% of the subjects did not receive treatment concordant with national guidelines. More importantly, the mean number of sessions of intensive interventions was less than one-half the originally planned amount (14, compared with 30). This relatively low so-called dose of each of the individual psychotherapies raises questions about the specific model underlying each psychotherapy and hints at a common mechanism of action as the therapies performed equivalently. It also raises another question: If most patients will not complete a full course of psychotherapy in the real world, do we need to have briefer psychotherapy models to which they will adhere? As most of the subjects had also consented to the AD study,⁷ the referral biases for that study may also have influenced referrals to the IPS study,¹⁰ thus limiting generalizability. On balance, though, the IPS does match intuitive predictions that people with bipolar depression benefit from more intensive and personalized attention, over and above frequent medication visits.

The Role of Medications for Refractory Bipolar Depression

The final RCT exploring treatments for acute depression involved using what were relatively new medications in 1999 for the treatment of refractory illness.¹² This RCT was designed with 3 arms, to be conducted over 16 weeks, as an adjunctive study: all patients continued to receive open-label mood stabilizers and could be receiving an AD. Research in the 1990s had identified 3 promising medications for study: lamotrigine,¹³ inositol,¹⁴ (a sugar derivative implicated in intracellular signaling), and risperidone.¹⁵ Among the subjects who participated ($n = 66$), over 80% were Caucasian, equal numbers were female and male, and equal numbers had BD I and II. Subjects had some choice about randomization options, in that they could choose to opt out of potential randomization to any 1 of the 3 choices; in fact, only 3 subjects agreed to be randomized to any of the 3 medications. Most patients chose to be randomized to only 1 of 2 drugs: 31 chose lamotrigine or inositol, 17 chose to be randomized to lamotrigine, compared with risperidone, and 21 agreed to be

randomized to risperidone, compared with inositol. Thus this 3-arm study resembles 3 smaller 2-arm studies.

Outcomes were defined in terms of recovery, defined as having no more than 2 symptoms meeting DSM-IV threshold criteria for a mood episode and no significant symptoms present for 8 weeks. With these stringent criteria, less than 25% of the entire sample recovered, with numerical but not statistical significance in favour of lamotrigine. Overall, the study reinforces the difficulty of treating bipolar depression and hints at the superiority of lamotrigine in improving treatment-resistant bipolar depression, although findings were not statistically significant.

Observations on Bipolar Depression From the Standard Care Pathway

In addition to the 3 RCTs in bipolar depression, important data flowed from the Standard Care pathway, where subjects were followed for up to 2 years with naturalistic treatment enhanced by attention to treatment guidelines and other tools. At study entry, participants ($n = 1380$) from an enrolment in STEP-BD ($n = 4107$) were in an episode of bipolar depression (mostly BD II subjects, $n = 979$).¹⁶ Among these depressed subjects, only one-third had no symptoms of mania; 54% had at least one symptom, commonly distractibility or flight of ideas or racing thoughts. A smaller group—14.8 % of the depressed participants ($n = 1380$)—met full criteria for a mixed episode. Further, subsyndromal manic symptoms are associated with earlier relapse.¹⁷ These observations highlight the need for careful symptom appraisal both for mania and for depression, even if one pole appears predominant. A second major observation from the open pathway was the course of the first 2000 subjects enrolled, of whom only 26.5% ($n = 530$) were recovered (asymptomatic for 8 consecutive weeks) at time of entry.¹⁸ Among the subjects not fully recovered at entry ($n = 1469$), 58.5% ($n = 858$) eventually achieved recovery at some point during the next 2 years. However, only 48.5% of the 858 subjects stayed well for 2 years, with most relapses consisting of depressive episodes. Finally, in another analysis,¹⁹ a sample of currently or recently depressed subjects was assessed during a 2-year period to examine the impact of residual subsyndromal symptoms. This subsyndromal group mostly resembled the full depressive group for many symptoms and disability, demonstrating that impairment is not contingent on achieving DSM-IV thresholds. Thus the STEP-BD study highlights the preeminent role of bipolar depression in the course of the illness, and the limited efficacy of depression treatments.

Key Clinical Observations on the Course of BD

STEP-BD provides many rich observations about the clinical course of BD. Two findings are particularly relevant. First, given the increasing recognition of BD in youth, the relation between age of onset (as ascertained retrospectively by clinicians at study entry) and course of illness was studied.²⁰

Among adult outpatients with BD I and II ($n = 3658$), those with onset before age 13 years ($n = 1068$) experienced earlier recurrence of mood episodes after initial remission, fewer days of euthymia, and greater impairment in functioning and quality of life during the 2-year follow-up, compared with patients with onset of mood symptoms aged 18 years or older ($n = 1187$). Outcomes for patients with onset between the ages of 13 and 18 years ($n = 1403$) were generally intermediate between these 2 groups. The large number of people having BD before age 13 years is in sharp contrast to major other studies, but may be a true finding in view of recent advances in the diagnosis of pediatric BD.^{21,22} Confirming earlier observations, early age of onset is predictive of worse outcome.²³

Another vital clinical observation examines the prospective course of rapid-cycling in BD.²⁴ Using a convenience sample of enrollees ($n = 1742$), mood episodes were prospectively observed. Among the 1742, 32% had experienced rapid cycling in the year preceding the STEP-BD study, and 32% dropped out before 1 year of treatment was completed. Among the remaining patients ($n = 1191$), those with prior rapid cycling ($n = 356$) were more likely to have further recurrences but only 5% ($n = 58$) of the patients could be classified as rapid cyclers. This dramatic reduction in rapid cycling is likely due to a composite of overestimation of previous rapid cycling, successful treatment, and a reflection of the natural course of BD with a so-called regression to the mean for episode frequency. Patients who entered the study with earlier illness onset and greater severity and those exposed to ADs were more likely to relapse. These findings are in line with previous observations that rapid-cycling may be a phase of illness that does not persist, and that caution is needed in employing ADs.²⁵

Comorbidity With Other Psychiatric Disorders

BD has long been recognized as highly comorbid with many other disorders, particularly anxiety disorders, substance abuse, ADHD, and smoking. Each of these important comorbidities was examined in STEP-BD, with striking findings on the impact of anxiety disorders. From the first 1000 enrollees, current comorbid anxiety disorder (present in 31.9% of participants) was associated with fewer days well, a lower likelihood of timely recovery from depression, risk of earlier relapse, lower quality of life, and diminished role function during 1 year of prospective study. People with anxiety disorders fared poorer in bipolar outcome, even if euthymic at study entry. The need for treatment of the comorbid anxiety disorders was stressed, both to improve the anxiety and to prevent worsening of the BD.²⁶

Controversies abound on the links between ADHD and BD, where some child psychiatrists claim very high rates of comorbidity²⁷ and adult bipolar specialists observe much lower rates.²⁸ The first consecutive 1000 adults in STEP-BD were assessed for lifetime ADHD in conjunction with the retrospective course of BD, current mood state, and prevalence

of other comorbid psychiatric diagnoses. The overall lifetime prevalence of comorbid ADHD was 9.5% (14.7% of male patients and 5.8% of female patients). Patients with BD and ADHD had an earlier age of onset for BD, as well as shorter periods of wellness, and were more frequently depressed. Further, these ADHD and BD subjects also had higher rates of several anxiety disorders and alcohol and substance abuse and dependence.²⁹

STEP-BD findings on the comorbidity with alcohol disorders were modest. Examining the first 1000 STEP-BD participants, recovery in BD was less common in those with either current or previous SUDs.³⁰ Interestingly, the distinction between primary and secondary SUD was examined as well. In the case of BD, a primary SUD indicates that the onset of a SUD preceded the onset of BD. A secondary SUD indicates that the onset of the SUD began after the onset of BD.³¹ Patients with primary SUD ($n = 116$) were compared with those with secondary SUD ($n = 275$) on clinical course variables. While patients with secondary SUD had fewer days of euthymia, more episodes of mania and depression, and a greater history of suicide attempts, these findings were fully explained by variations in age of onset of BD. The researchers concluded that the primary and secondary distinction for SUD is not valid when variations in the age of onset of the non-SUD are linked to course characteristics.

Tobacco use has increasingly been recognized as a major problem in people who are seriously mentally ill, contributing to poorer outcomes both in physical health and in mental health.³² The first 2000 enrollees in STEP-BD were examined for prevalence and consequences of comorbidity with smoking, with an initial prevalence of 31.2%.³³ Current smoking was linked both to demographic factors (male, less educated, and lower income) and to retrospective clinical factors (rapid cycling, comorbid psychiatric disorders, substance abuse, and current mood episode). More lifetime depressive and manic episodes as well as greater severity of depressive and manic symptoms were also associated with smoking.

Suicidality in BD

BD is the most lethal of major psychiatric disorders, with an estimated 15% mortality owing to suicide alone.³⁴ Understanding the phenomenology and correlates of suicidality was a significant focus with STEP-BD, with particular interest in links to pharmacotherapy. Three studies highlighted broader aspects, starting with an analysis of vulnerability factors to suicidal ideation.³⁵ Starting with a sample of subjects ($n = 477$), comprehensive data were available for 243 people. These people were divided into 2 groups, those with and those without prior suicide attempts. Depressive symptoms correlated with suicidal ideation most highly for both groups, but the groups differed as to which personality factors correlated to suicidal ideation. Among attempters, poor psychosocial adaptation and the personality factor of openness were stronger contributors to suicidal ideation, while anxiety

and extraversion appeared protective against ideation. Among nonattempters, depression, anxiety, and neuroticism were the predominant influences on suicidal ideation. The findings emphasized the need for tailoring interventions based on history of attempts. Looking prospectively, another study³⁶ evaluated the first 1000 study subjects on their care satisfaction and links to functioning and hopelessness. Subjects were evaluated over the course of 1 year; those with greater care satisfaction also reported better functioning and decreased hopelessness. Given the importance of hopelessness as a predictor of suicide, this study suggests that improving care satisfaction may improve outcomes and decrease suicidality. A third study³⁷ carefully looked at the association between baseline clinical and demographic variables and subsequent suicide attempts and completions through 2 years of follow-up, using a statistical method that allowed for control of redundant prediction from other baseline characteristics. The first observation of note was the prevalence of suicidal events in this sample of patients with BD who were closely followed by very experienced clinicians. Among the sample with complete data ($n = 1556$), 57 patients (3.66%) experienced an attempt or suicide; of these, 7 patients completed suicide. After careful control of other variables, only history of previous suicide attempts and percent of days depressed in the past year were significant predictors.

Medications remain a significant factor that can potentially modify suicidality in people with BD, with a special antisuicidal role noted for lithium.³⁴ Two STEP-BD studies examined this issue. In the first study,³⁸ the question of ADs inducing suicidality was examined, with 2000 participants monitored for 18 months, finding 425 people experiencing a new onset of depression without suicidality. Among this group, only 24 (5.6%) subsequently developed new onset of suicidality. Subjects receiving AD were compared with those who did not receive ADs; there was no association between new use of ADs and new onset of suicidality. A broader look at all psychotropic agents was done in another study³⁹ enrolling the first 1000 subjects from STEP-BD. Patients could be in any clinical state, and comprehensive records of medication use were examined. There was no statistical difference in suicidality between patients taking and those not taking lithium (22.2% and 25.8%, respectively); similarly, no difference was found for those taking and those not taking divalproex (20.3% and 21.5%, respectively). This contrasts with a large naturalistic study⁴⁰ from California that showed lithium had more antisuicidal effects than valproate or carbamazepine. However, taking and not taking antipsychotics (26% and 17%, respectively) and taking and not taking ADs (25% and 14%, respectively), were associated with higher rates of suicidality. Lithium prescriptions also were significantly higher among patients who experienced suicidal ideation. On further analysis, ADs and antipsychotics were prescribed more frequently to patients with suicidal ideation, while lithium was prescribed for those with more severe illness.

Conclusion

BD is a uniquely challenging disorder to treat, with the most lethality, the most recurrences, and the most varied clinical presentations of any major psychiatric disorder.⁴¹ Given the panoply of symptoms and circumstances, together with individual variations in psychology and biology, it is understandable that finding successful treatments is also uniquely challenging. STEP-BD offers us 2 types of contributions—those that are directly clinical, and those that are somewhat distal yet still vital. In the direct clinical realm, STEP-BD demonstrates 7 contributions:

1. ADs remain poorly effective in BD.
2. Bipolar depression is particularly disabling, and frequently does not respond to various medications.
3. Bipolar depression does respond modestly to intensive psychosocial interventions.
4. Psychiatric comorbidities are common and destabilizing, with anxiety disorders and smoking as 2 entities that are particularly open to amelioration.
5. Early age of onset heralds a more severe illness course, but rapid-cycling usually abates.
6. Subsyndromal symptoms are common and herald relapse and ongoing disability, suggesting a greater emphasis on achieving symptomatic remission.
7. Suicidality persists even in good treatment circumstances, with prior attempts the most significant predictor and the possibility of improving hopelessness to reduce suicidal risk.

STEP-BD also offers lessons from a systems perspectives.⁴² From its design and emphasis on integration of measurement and management, it champions the role of CC and the use of validated instruments in routine clinical practice.⁴³ By choosing recovery—sustained wellness for 8 weeks—as a primary outcome, STEP-BD invites psychiatry to aim higher and use more meaningful outcomes for all BD treatment studies. Through its execution involving multiple sites and thousands of patients, it demonstrates that psychiatric research and collaboration can occur on a scale that is appropriate to the magnitude of the problem. STEP-BD has fostered the creation of clinical and professional partnerships that will further advance the field of BD. Enriched with clinical data and emboldened by systems advances, the future of BD research induces hope rather than despair and augurs well for a better life for people struggling with the illness.

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Résumé : Faire progresser le traitement du trouble bipolaire : leçons clés du programme d'amélioration du traitement systématique du trouble bipolaire (STEP-BD)

Objectif : Examiner les résultats d'ensemble de l'étude clinique programme d'amélioration du traitement systématique du trouble bipolaire (STEP-BD), l'étude du trouble bipolaire (TB) la plus vaste jamais entreprise.

Méthodes : Le STEP-BD a été mené de 1998 à 2005, auprès des participants ($n = 4361$) de 22 sites cliniques aux États-Unis. Chaque personne a été suivie jusqu'à 2 ans en pratique naturaliste avec des évaluations de recherche à l'insu, tandis que des sous-groupes ont participé à des essais randomisés contrôlés (ERC) pour la dépression bipolaire. La base de données naturaliste a servi à examiner le cours du TB, la comorbidité avec d'autres troubles psychiatriques, et la suicidabilité. Les études pertinentes publiées en anglais du 1^{er} janvier 1994 au 31 mai 2009 ont été relevées au moyen de recherches informatiques des bases de données électroniques (PubMed, PsycINFO, et Cochrane Register of Clinical Trials), d'inspection des bibliographies, et de revue d'autres articles majeurs.

Résultats : Un vaste ERC, comportant l'ajout de paroxétine ou de bupropion aux psychorégulateurs dans la dépression aiguë, a révélé qu'aucun n'était plus efficace qu'un placebo pour atteindre un rétablissement soutenu (8 semaines d'euthymie). Un deuxième vaste ERC a révélé que les interventions psychosociales intensives étaient supérieures à une brève intervention psychosociale comme auxiliaire à la médication dans la dépression aiguë. Un troisième ERC plus modeste a constaté les effets minimaux de la lamotrigine, la rispéridone, ou l'inositol dans la dépression réfractaire. Le rétablissement était difficile à atteindre, les symptômes subsyndromaux ou la rechute complète étant très communs. Les troubles anxieux et le tabagisme en particulier étaient des affections traitables qui avaient une incidence défavorable sur le cours du TB.

Conclusions : Le STEP-BD a livré de nombreuses observations cliniques et sur les systèmes de services qui offrent de nouvelles directions à la recherche et au traitement du TB, notamment, de nouveaux repères pour les résultats et la démonstration de la viabilité des vastes réseaux de recherche du TB.

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