Stepping Back to Step Forward: Lessons From the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

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Clinical Status at Baseline: The Burden of Bipolar Depression

The purpose of the current article is to provide a broad overview of the main findings of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), sponsored by the National Institute of Mental Health (NIMH). STEP-BD was a multisite, nationwide clinical research program designed to study treatment effectiveness and phenomenology, course, and outcome in adults with bipolar disorder. The nature, scope, and overall design of the research program have previously been described.[1] Entry criteria included meeting lifetime *DSM-IV* criteria for bipolar I disorder, bipolar II disorder, bipolar disorder not otherwise specified, cyclothymia, or schizoaffective disorder bipolar type. Participants could enter the study in any mood state. The majority of the sample met *DSM-IV* criteria for bipolar I disorder (71%). Mean age of patients was 40.6 (SD = 12.7) years, and mean duration of bipolar illness was 23.1 (SD = 12.9) years. Among the first 1,000 subjects enrolled, 58.6% were female and 92.6% were white.[2] Aside from the subjects who were already recovered at study entry, more subjects entered STEP-BD in a depressive episode than in any other mood state. Of the first 2,000 participants to enter STEP-BD, only 530 participants (26.5%) were recovered at study entry, while 1,469 participants (73.5%) were not recovered. Among the 1,469 who were not recovered, 522 (35.5%) met criteria for a current major depressive episode, 58 (3.9%) met criteria for a current manic episode, 72 (4.9%) met criteria for a current hypomanic episode, and 172 (11.7%) were in a mixed state. An additional 257 (17.5%) were experiencing subsyndromal mood symptoms, and 388 (26.4%) were recovering (ie, had achieved a euthymic state but for fewer than 8 weeks).[3]

On the Effectiveness of Antidepressants for Bipolar Depression

Despite the burden of depression in bipolar disorder, most drug development has addressed treatment for acute mania. Practitioners have assumed that an antidepressant should work for bipolar depression as well as it does for unipolar depression. Evidence is, however, insufficient to prove or disprove the efficacy or effectiveness of antidepressants for bipolar depression,[4–6] and concerns about their propensity to accelerate cycling have not been allayed by the clinical trial literature.[7–10]

To address these gaps in the literature, embedded within STEP-BD was a 26-week, randomized, placebo-controlled adjunctive trial of paroxetine or bupropion combined with a mood stabilizer to assess antidepressant efficacy and their risk to induce mania.[7] Recovery was defined as < 2 mood symptoms for at least 8 weeks. To enhance generalizability, the trial used equipoise randomization, which allowed the entry of subjects who preferred to be randomly assigned to one of the 2 antidepressants or placebo on the basis of a history of intolerance or nonresponse. Thus, participants were randomly assigned only to treatments that made clinical sense and closely mirrored clinical practice.

Three hundred sixty-six patients with no history of intolerance or nonresponse to bupropion or paroxetine were randomly assigned to up to 16 weeks of treatment.[7] Overall, about 25% achieved durable recovery from an acute bipolar depressive episode, with 23.5% of the antidepressant group and 27.3% of the placebo group reaching this primary outcome (not statistically significant). Additionally, about 10% of each group had a treatment-emergent affective switch, with no statistically significant difference, suggesting that the short-term addition of bupropion or paroxetine to mood stabilizer therapy does not increase the risk of treatment-emergent mania. In sum, this large, randomized, placebo-controlled effectiveness study found no evidence that treatment with a mood stabilizer and an antidepressant confers a benefit over treatment with a mood stabilizer alone, nor any evidence that antidepressants increase the risk of manic relapse.[7]

Nonrandomized observational outcomes from the first 2,000 STEP-BD depressed patients demonstrated no statistical difference between those recovered after 90 days who were treated with an antidepressant (21.5%) and those recovered who were not treated with an antidepressant (27.2%) (G. S. Sachs, MD; unpublished data, 2002). These data are consistent with the findings from the embedded clinical trial—antidepressants neither improved nor worsened clinical status. Furthermore, about 50% of recovered patients had less than 6 months of remission after recovery (G. S. Sachs, MD; unpublished data, 2002). Although patients received guideline-concordant treatment in specialty clinics, these results emphasize the limitations of available treatments and highlight the need for better acute and maintenance treatment of bipolar depression.

The results of an additional analysis[11] of outcomes of nonrandomized adjunctive antidepressant use for those who were depressed and had concomitant manic symptoms are also consistent with those from the STEP-BD randomized trial for bipolar depression; adjunctive antidepressants did not yield higher recovery rates than mood stabilizer monotherapy. Subjects (N = 335) were chosen on the basis of (1) the presence of a full *DSM-IV* depressive episode, accompanied by ≥ 2

manic symptoms, and (2) prescription of a mood stabilizing agent (lithium [n = 137], divalproex [n = 149], carbamazepine [n = 22], lamotrigine [n = 100]) or an atypical antipsychotic (n = 139) at the first clinical assessment. Subjects were then subdivided into those who were prescribed an antidepressant at study entry (n = 145) and those who were not prescribed an antidepressant (n = 190). The times to achievement of a status of "recovering" (≤ 2 mood symptoms for at least 4 weeks) or "recovered" were comparable for subjects who did and who did not receive an antidepressant (log-rank statistic: $P = .651$). Results also indicated a significant interaction between the number of manic symptoms at baseline and the use of antidepressants in predicting symptoms of mania at 3 months (as assessed by the Young Mania Rating Scale; $F_{3,211} = 4.22$, $P = .006$). For depressed patients with concomitant manic symptoms at intake, adjunctive antidepressant use was associated with higher mania symptom severity levels at follow-up. Although time until symptomatic recovery was no faster with antidepressants added to mood stabilizers versus without antidepressants, even for bipolar depression in the presence of subsyndromal mania (consistent with the STEP-BD randomized trial of pure depression), adjunctive antidepressant use for patients with mixed symptoms may incur liability for exacerbating manic symptoms at follow-up.

In a smaller study[12] of treatment-resistant bipolar depression, 66 patients were randomly assigned to lamotrigine, inositol, or risperidone added to ongoing mood stabilizer treatment. Patients were eligible if they had not responded to treatment in the first 12 weeks of standard or randomized care pathways for bipolar depression or if they had failed to respond to at least 2 trials of antidepressants or an antidepressant and mood stabilizer regimen in the current depressive episode. Patients were required to enter the trial taking a mood stabilizer or agree to begin treatment with a mood stabilizer. Equipoise randomization allowed patients to be randomly assigned to 1 of all 3 options (if all were acceptable) or to only 1 of 2 options depending on patient preference and treatment history. The overall recovery rates were 23.8% (95% CI, 5.8–41.8) for lamotrigine, 17.4% (95% CI, 2.4–32.4) for inositol, and 4.6% (95% CI, 0–14.6) for risperidone. Although no statistically significant difference was found between the 3 treatments, the results are noteworthy for the remarkably limited effect of risperidone. Additionally, several secondary outcome measures (improvements in depressive symptoms, overall illness severity, functioning at exit, amount of time spent on medication) suggest that lamotrigine may be more effective than either inositol or risperidone. Recent research of lamotrigine added to lithium has demonstrated both short-term and long-term benefit compared to the addition of placebo in depressed patients.[13–16]

Adjunctive Psychotherapy

In the randomized psychosocial trial of intensive psychotherapy (cognitive-behavioral therapy, interpersonal therapy, or family focused therapy) compared to less intensive collaborative care (a brief psychoeducational intervention), 58% of participants recovered from their depressive episode by the end of the study year.[17] Intensive psychotherapy, compared to collaborative care, resulted in a greater proportion of those who recovered (1-year recovery rate: intensive psychotherapy group, 105/163 [64.4%]; collaborative care group, 67/130 [51.5%]; log-rank $\chi^2_1 = 6.20$; HR = 1.47; 95% CI, 1.08–2.00; $P = .01$), and those who did so reached recovery 110 days sooner. Furthermore, the intensive psychotherapy group had better overall psychosocial functioning relative to the collaborative care group.[18] In particular, they exhibited better functioning in social relationships and higher overall life satisfaction, beyond the level of improvements expected from changes in depressed mood. The psychosocial interventions were not associated with improvements in vocational functioning or participation and enjoyment of recreational activities.

Conclusions

Five main lessons from STEP-BD inform clinical practice.

1. The STEP-BD study found that antidepressants added to mood stabilizers are no more effective than placebo for treatment of bipolar depression. It is possible even with these results that some bipolar patients may benefit from antidepressants, but no moderating variable is currently available to identify who will and who will not respond to an antidepressant better than placebo as adjunct treatment.
2. Antidepressants did not induce mania more frequently than placebo in bipolar depressed patients receiving a mood stabilizer who had no history of antidepressant-induced mania.
3. The seminaturalistic analysis indicated that patients in an acute depressive episode with subsyndromal manic symptoms who had antidepressants added to mood stabilizers recovered at similar rates as those who did not receive an antidepressant. If anything, adjunctive antidepressant use increased the risk of relapse and exacerbated preexisting manic symptoms. These data support the need for greater vigilance in assessment of subsyndromal manic symptoms, even when depression dominates the clinical profile.
4. The outcomes for lamotrigine from the embedded randomized trial of treatment-resistant bipolar depression showed enough promise to warrant further investigation. Risperidone appears not to have antidepressant efficacy for bipolar depression, but the results from this small study should be interpreted as preliminary.
5. Any of the 3 intensive psychosocial treatments resulted in greater rates of recovery compared to collaborative care. Intensive psychosocial treatment also resulted in more rapid recovery and improved social functioning and life satisfaction.

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Randomized and seminaturalistic results of STEP-BD converge on the conclusion that adjunctive antidepressants provide no advantage over mood stabilizers without antidepressants for bipolar depressive episodes. Future trials are needed to evaluate the effectiveness of US Food and Drug Administration–approved treatments, such as quetiapine, for treating bipolar depression. Such a study is in progress, the Comparative Effectiveness Study for Bipolar Disorder, funded by the Agency for Healthcare Research and Quality and conducted on the Bipolar Trials Network.

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