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Effectiveness and Safety of Adjunctive Antidepressants in the Treatment of Bipolar Depression: A Review

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Abstract: The treatment of the depressed phase of Bipolar Disorder (BPD) is understudied and poses a widespread clinical dilemma. While the use of mood stabilizers in BPD is a common practice, the role of antidepressants in the depressive phase of the illness remains controversial. This paper reviews the available literature on the subject and highlights the factors essential for making clinical decisions for treating BPD. Most of the standard randomized controlled trials report the efficacy of antidepressants in the acute phase of BPD, but the data also indicate higher switch rates to mania and acceleration of mood cycle with their use. Nevertheless, a recent large effectiveness study (STEP-BD) found no superiority or risk of adjunct antidepressants to a mood stabilizer in the treatment of BPD. In light of the available data, future large clinical studies are essential for elucidating the role of antidepressants in the treatment of the depressed phase of BPD. Until then, factors such as history of severe manias, past depression severity and length and rapid cycling will continue to play a role in the decision of clinicians in prescribing antidepressants for BPD in different phases of the disorder.

Introduction

Bipolar disorder (BPD) is a chronic and recurrent psychiatric illness with a lifetime prevalence of 2.1% (1% for BP I, 1.1% for BP II) according to National Comorbidity Survey replication, 2007 (1). Although abnormal mood elevation is the cardinal diagnostic feature that distinguishes BPD from recurrent major depressive disorder, depression, more than mania, is the leading cause of impairment and death among patients with BPD. Judd et al. (2) reported that patients with BPD experience depressive symptoms more than three-fold longer than they experience manic symptoms. Treatment of BPD with standard antidepressant medication is controversial for two main reasons. First, the data providing support for their use in treating BPD are limited and insufficient to provide guidelines in clinical practice. Second, the widely held belief that antidepressants can induce new episodes of abnormal mood elevation (manic/hypomanic switch) or accelerate the rate of cycling has been neither confirmed nor refuted by placebo-controlled studies. The Food and Drug Administration (FDA) has not approved any standard antidepressant drug for the treatment of bipolar depression. Nevertheless, standard antidepressants are commonly used as adjuncts to mood-stabilizing medication for the treatment of bipolar depression, despite the limited evidence of the short- and long-term benefits and risks (treatment-emergent mania, hypomania, cycle acceleration). There is more than one traditional clinical approach to the treatment of BPD: the academic authorities in Europe favor the use of antidepressants and the U.S. authorities favor the so-called mood stabilizers. An example of this difference in approach is reflected in the treatment guidelines for the condition. The American Psychiatric Association Treatment Guidelines (3) for the treatment of non-psychotic BPD recommends lithium as a first-line drug (recommended with substantial clinical confidence) or lamotrigine (recommended with moderate clinical confidence) without a concurrent antidepressant even in severe depression. In addition, The Expert Consensus Guidelines for treating depression in BPD (4, 5), recommend the combination of a mood stabilizer and an antidepressant as first-line treatment for severe non-psychotic BPD. These guidelines also suggest that monotherapy with a single mood stabilizer should be used for milder episodes of bipolar depres-

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sion. In contrast, the British Association for Psychopharmacology's evidence-based guidelines for treating BPD (6) recommend a combination of an antidepressant (selective serotonin reuptake inhibitors, SSRIs) and an anti-manic agent (lithium, valproate, or an antipsychotic) for the treatment of bipolar depression, regardless of severity.

In general, all these guidelines have eventually accepted the limited use of antidepressants in combination with a mood stabilizer (7). The questions regarding the efficacy and safety of antidepressants for treating bipolar depression still remain unanswered, mainly due to the limited number of placebo-controlled trials and to the enrollment of selected populations in such studies. This paper will review the existing data which can contribute to the resolution of these questions.

Are Antidepressants Effective in the Treatment of Bipolar Depression?

The first question that needs to be addressed when evaluating the role of antidepressants in the treatment of bipolar depression is the efficacy of antidepressants in the setting of that specific disorder. The only quantitative review on this topic is that of Gijsman et al. (8) who reported that the number of bipolar depressed patients who were entered into clinical trials is around 1% of the patients who were entered into studies on unipolar depression. These numbers emphasize the lack of randomized controlled data that exists for evaluation of this topic. The main findings of their review are that antidepressants are effective in the short-term treatment of bipolar depression. This review included 12 randomized trials, with a total of 1,088 randomly assigned bipolar depressed patients. Five trials compared one or more antidepressants with placebo in the treatment of the acute phase of bipolar depression, and 75% of these patients were receiving a concurrent mood stabilizer or an atypical antipsychotic. Clinical response could be evaluated in only four trials with a total of 662 randomly assigned patients. Specifically, Tohen et al. (9) studied fluoxetine vs. placebo in 456 patients (all taking olanzapine), Cohn et al. (10) studied fluoxetine vs. imipramine vs. placebo in 89 patients (22 taking lithium), Himmelhoch et al. (11) studied tranylcypromine vs. placebo in 59 patients (29 with BPD), and Mendlewicz and Youdim (12) studied deprenyl vs. placebo in 58 patients (34 with BPD). A fifth published trial by Nemeroff et al. (13) was excluded because therapeutic response was not an outcome measure. In the four above-cited clinical trials, clinical response was defined as a >50% reduction in the Hamilton Depression Rating Scale (HDRS)/Montgomery Asberg Depression Rating Scale (MADRS) or moderate-to-marked improvement in the Clinical Global Impression (CGI) scale. Of the 662 patients in those four trials, 213 were assigned to the experimental group and 449 to the placebo group. The results showed that patients treated with an antidepressant were more likely to respond by the end of the trial (risk ratio=1.86, 95% CI=1.49–2.30). The number needed to treat with antidepressants in the acute phase (4–10 weeks) of BPD was 4.2 (95% CI=3.2–6.4). Remission (defined as a HDRS≤7 and a MADRS≤12) was used as an outcome measure in only two studies (9, 13), but they are the two largest studies, with a total of 160 patients in the experimental group and 413 patients in the comparison group. All the patients in those two studies were taking a concurrent mood stabilizer or an atypical antipsychotic. It emerged that patients treated concomitantly with an antidepressant (paroxetine, imipramine or fluoxetine) were more likely to reach remission than those who were not taking an antidepressant (risk ratio=1.41, 95% CI=1.11–1.80). The number needed to treat with antidepressants in order to achieve remission in the acute phase of BPD was 8.4 (95% CI=4.8–33). The authors concluded that their data strongly support an average positive efficacy for antidepressants versus placebo in BPD in trials lasting up to 10 weeks.

Nemeroff et al.'s study (13) compared the efficacy and safety of paroxetine and imipramine with that of placebo in the treatment of BPD in adult outpatients stabilized on a regimen of lithium. Their results suggested that while antidepressants may not be useful as adjunctive therapy for bipolar depressed patients with high serum lithium levels, antidepressant therapy may be beneficial for patients who cannot tolerate high serum lithium levels or who have symptoms that are refractory to the antidepressant effects of lithium. In this double blind, placebo-controlled study, 117 outpatients with DSM-III-R bipolar disorder, depressive phase, were randomly assigned to

treatment with paroxetine (N=35), imipramine (N=39), or placebo (N=43) for 10 weeks. In addition to lithium monotherapy, the patients received either carbamazepine or valproate in combination with lithium for control of manic symptoms. They were stratified on the basis of serum lithium levels as determined at the screening visit (high: > 0.8 meq/liter; low: < 0.8 meq/liter). The differences in overall efficacy among the three groups were not statistically significant. The antidepressant response at endpoint also did not significantly differ from placebo for patients with high serum lithium levels, but both paroxetine and imipramine were superior to placebo for patients with low serum lithium levels.

Amsterdam and Brunswick (14) used post hoc subanalyses of data from studies of major depression that had been performed in the DSM-III era, when type II bipolar illness was diagnosed as major depression. They found that monotherapy with fluoxetine or venlafaxine was effective in treating depression associated with type II bipolar illness. The response rates (defined as > 50% improvement) in these studies were similar to those in studies of unipolar depression (63% for fluoxetine and 48% for venlafaxine).

In a retrospective study, Ghaemi et al. (15) compared antidepressant treatment in bipolar versus unipolar depressed patients and found less benefit and higher risk for antidepressants in the treatment of the former compared with the latter. The authors analyzed clinical records for outcomes of antidepressant trials for 41 patients with bipolar depression and 37 with unipolar depression, similar in age and sex distribution. Short-term non-response (lack of recovery after four weeks of antidepressant trial) was more frequent in bipolar (51.3%) than unipolar (31.6%) depression. Late response loss (i.e., re-emergence of major depression after one month or more of remission) was 3.4 times as frequent, and withdrawal relapse into depression (i.e., re-emergence of depression less than eight weeks after discontinuation of antidepressants) was 4.7 times less frequent in bipolar as in unipolar depression.

With the exception of the study by Nemeroff et al. (13), which showed lack of antidepressant efficacy under high levels of lithium, the data of the other above-cited studies support the efficacy of antidepressants for BPD. It is therefore assumed that the caveat to avoid the use of antidepressants for BPD (as implemented in the APA guidelines) is not based on lack of efficacy but rather on the need for caution derived from evidence on the associated adverse effects (discussed below).

The findings of a more recent study by Sachs et al. (16), which is part of a large effectiveness study, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), contradicted the previously described data. The STEP-BD is a collaboration sponsored by the National Institute of Mental Health designed to evaluate the effectiveness of treatments for BPD and to provide results that can be generalized to routine clinical practice. The STEP-BD collaboration is a multicenter, double blind, randomized, placebo-controlled, parallel-group study of standard antidepressants (either bupropion or paroxetine) as adjuncts to treatment with mood stabilizers (lithium, valproate, carbamazepine, or other FDA-approved antimanic agents) at 22 centers in the United States conducted between November 1999 and July 2005. Subjects with bipolar I or bipolar II disorder were treated for up to 26 weeks in order to evaluate the effectiveness, safety, and tolerability of the adjunctive use of antidepressant medication. The conclusion of this study was that mood stabilizer monotherapy provides as much benefit for the treatment of bipolar depression as treatment with mood stabilizers combined with a standard antidepressant. Patients in this study were randomly assigned to receive treatment with a mood stabilizer plus adjunctive antidepressant therapy or a mood stabilizer plus a matching placebo. The primary outcome was the percentage of subjects in each treatment group meeting the criterion for a durable recovery (eight consecutive weeks of euthymia). Secondary effectiveness outcomes and rates of treatment-emergent affective switch (i.e., a switch to mania or hypomania early in the course of treatment) were also examined. Forty-two of the 179 subjects (23.5%) who received a mood stabilizer plus adjunctive antidepressant therapy had a durable recovery, as did 51 of the 187 subjects (27.3%) who received a mood stabilizer plus a matching placebo (P=0.40). In that study, however, there was no "pure" placebo group (i.e., one in which no active psychotropic medication was administered) and so it cannot establish the effectiveness of treatment with a

mood stabilizer alone. The disparity between the findings of Sachs et al.'s (16) study and those of Gijsman et al. (8), which found standard antidepressants to be efficacious in the treatment of bipolar depression, may have resulted from several differences in study designs. The entry criteria of Sachs et al.'s study (16) permitted the recruitment of subjects with bipolar I or bipolar II disorder, including those with coexisting anxiety disorders, substance abuse disorders, or psychotic symptoms that are ubiquitous among most patients with BPD. Their study design also differed from that of most efficacy studies in that it featured equipoise randomization strata. By eliminating the possibility that the subjects would be randomly assigned to a treatment they did not want to receive, it allowed the entry of subjects who preferred to avoid one of the standard antidepressants. Finally, it is clinically meaningful that the primary outcome of durable recovery was met if the subjects had euthymia for eight consecutive weeks. In contrast, the primary outcome in most short-term efficacy studies is change from the baseline score on symptom-severity scales at a single visit. The results of Sachs et al. (16) are, therefore, likely to be more in accord with the expectations of clinicians and patients in the general population for treatment effectiveness than are the results of previous efficacy studies.

Adverse Effects of Antidepressants in the Treatment of Bipolar Depression

There are ample randomized data to support caution in the use of antidepressants in BPD and very little randomized evidence to the contrary. There are two distinct elements involved in this issue. The first involves the short-term acute manic switch following antidepressant use. The period of observation for a switch that might reasonably be considered as drug induced should probably be limited to the first two months after the initiation of the antidepressant. Manic "switches" that occur later are difficult to attribute to the initiation of an antidepressant as opposed to the natural history of the BPD. The second concerns the long-term risk of antidepressant-induced mood destabilization, or the association of antidepressants with more and more mood episodes (both mania and depression) over time. This long-term mood destabilization risk consists of two patterns: (a) cycle acceleration defined as an increase of two or more DSM-IV affective episodes while on antidepressants when compared with a similar exposure time immediately before such treatment, and (b) induction of de novo rapid cycling or exacerbation of pre-existing rapid cycling, applying the DSM-IV definition of rapid cycling, i.e., four or more mood episodes in one year.

Induction of Acute Mania/Hypomania by Antidepressants

Manic induction is a clinically known complication of antidepressant treatment in patients with bipolar illness. The above-mentioned study by Gijsman et al. (8) reviewed the evidence from randomized, controlled trials on the efficacy and safety of antidepressants in the short-term treatment of BPD. The main outcome measures were the proportion of patients who clinically responded to treatment and the rate of switching to mania. They found that antidepressants did not induce more switching to mania in the acute phase of treatment (up to 10 weeks) when antidepressants were compared with placebo in the five trials that were analyzed. Only two out of the five had predefined measures for detecting manic switch: the event rate was 3.8% for antidepressants and 4.7% for placebo. Six trials allowed comparison between two antidepressants. The rate of switching was 10% for tricyclic antidepressants and 3.2% for all other antidepressants combined. That review's data did not suggest that switching is a common early complication of treatment with antidepressants. Critics of Gijsman et al.'s (8) work stated that, since the analysis is post hoc, it does not represent a hypothesis-testing approach that establishes relationships, but rather represents hypothesis generation, which cannot be accepted without further prospective replication. Some of the studies in that review involved a post hoc exploratory pooled analysis from unipolar depression clinical trials. The data were re-analyzed for BPD by retrieving information on study patients diagnosed with type II bipolar disorder. Furthermore, no mania rating scales were performed, probably resulting in unreliable reporting of manic symptoms. In the Stanley Foundation Network Study (17), the authors examined the comparative risks of switches

in mood polarity into hypomania or mania during acute and continuation trials of adjunctive antidepressant treatment of BPD. They found that antidepressant augmentation, in general, is not likely to yield a high rate of sustained antidepressant response without a switch throughout both the acute and continuation treatment phases. Their BPD patients with depression that occurred in the context of ongoing treatment with at least one mood stabilizer at clinically therapeutic blood levels had been randomly assigned to receive bupropion, sertraline, or venlafaxine adjunctively. Life charts were available for 159 of the original 184 patients described in the cross-sectional evaluation of the acute clinical trial. Patients who did not respond acutely to the initial antidepressant were offered blind re-randomization to one of the other two drugs. In this fashion, 16 patients received bupropion in the second or third acute randomization, 26 received sertraline, and 27 received venlafaxine. The total number of drug exposures was 228, including 66 exposures to bupropion, 76 to sertraline, and 86 to venlafaxine. A total of 87 antidepressant continuation trials for up to one year — 24 for bupropion, 32 for sertraline, and 31 for venlafaxine — were assessed. Antidepressant response and the occurrence of sub-threshold brief hypomania (i.e., emergence of brief hypomania by at least one day but <7 days or recurrent brief hypomania) and threshold switches (emergence of full-duration hypomania [7 days] or mania) were blindly assessed by using clinician-rated daily reports of mood-associated dysfunction on the National Institute of Mental Health Life Chart Method. Threshold switches into full-duration hypomania and mania occurred in 11.4% and 7.9%, respectively, of the acute treatment trials and in 21.8% and 14.9%, respectively, of the continuation trials. In only 37 (16.2%) of the original 228 acute antidepressant trials, or in only 23.3% of the patients, was there a sustained antidepressant response in the continuation phase in the absence of a threshold switch. Subtracting the number of continuation trials associated with a switch from those with an antidepressant response yielded a 42.5% overall response rate (37 of 87) in the evaluable group that entered the continuation phase. Only these 37 patients (16.2%), however, remained from the original 228 acute intent-to-treat antidepressant trials: in other words, 23.3% of the patients had a long-term antidepressant response without a switch into hypomania or mania in both phases. The Stanley Foundation study also revealed a lower risk of switching in patients with bipolar II disorder than in patients with bipolar I disorder in the acute as well as in the continuation trials. The rate of threshold switches was higher in the 169 trials in patients with bipolar I disorder (30.8%) than the 59 trials in patients with bipolar II disorder (18.6%). In contrast to this line of evidence, the STEP-BD study (16) found no significant difference in the rates of prospectively observed treatment-emergent mania, hypomania, or mixed episodes between the patients receiving a mood stabilizer plus an antidepressant (10.1%) and those receiving a mood stabilizer plus placebo (10.7%) during the 26-week trial. Among the subjects reporting a treatment-emergent affective switch associated with one or more previous courses of treatment with antidepressants, response rates did not differ significantly between the ones who received a mood stabilizer plus an antidepressant and the ones who received a mood stabilizer plus placebo (13.6% and 25.4%, respectively; $p = 0.10$), nor did the prospectively observed rates of treatment emergent affective switch (10.2% and 17.9%, respectively; $P = 0.22$). These findings suggest that antidepressants induce higher switches to manic states when given in the depressive phase of BPD.

Long-term Risk of Mood Destabilization (Cycle Acceleration)

The absence of systematic or objective measures may account for the general under-recognition and lack of data on cycling. The results of three randomized controlled trials suggested an increased risk of cycle acceleration with antidepressants. In a study by Quitkin et al. (18), manic episodes were reported almost 2.5 times more frequently in bipolar type I patients who were on double-blind treatment of lithium plus imipramine (24%) compared with lithium alone (10%) over a mean 1.6-year follow-up ($n = 75$). These results were statistically significant in the female subgroup. Depressive relapse rates, on the other hand, were similar for lithium alone (10%) compared with lithium plus imipramine (8%). A small placebo-controlled study by Wehr and Goodwin (19) also demonstrated a pattern of in-

creased cycling with tricyclic antidepressants. Their study reported that the time between affective switches was almost four times shorter with desipramine compared with lithium monotherapy. The third controlled study, a later one by Wehr et al. (20), assessed 51 patients with rapid cycling admitted to the NIMH over one decade. Non-randomized assessments of treatment response history suggested antidepressants were associated with rapid cycling in 51% of patients. After prospective double blind randomized replacement of tricyclic antidepressants with placebo, the study concluded that 33% (17 of 51) of the patients experienced rapid cycling directly related to tricyclic antidepressants. The researchers further studied a subgroup of 17 patients in greater depth and determined that tricyclic antidepressant use was definitively associated with rapid cycling in 10 patients from the original sample (19.6%). Thus, this study, which probably represents the most rigorous examination of this issue, demonstrates with high likelihood a causative association between tricyclic antidepressants and rapid cycling that can be conservatively estimated at about 20%, at least in a highly refractory population such as that seen at the NIMH. The conclusions in the non-randomized observational literature on mood destabilization are mixed, but they suggest more of an association between antidepressant use and rapid cycling than the lack of such an association. If antidepressants are associated with a long-term risk of rapid cycling or worsening, then the recommendation to discontinue antidepressant treatment as soon as possible after remission of the acute episode would appear logical. Critics claim that there is an association between antidepressant discontinuation and relapse into depression. Altshuler et al. (21) prospectively followed for one year 84 subjects with BPD who achieved remission from a depressive episode with the addition of an antidepressant to an ongoing mood stabilizer regimen. The risk of depressive relapse among the 43 subjects who stopped antidepressant treatment within six months after remission ("discontinuation group") was compared with the risk among the 41 subjects who continued taking antidepressants beyond six months ("continuation group"). Shorter antidepressant exposure time following successful treatment was associated with a significantly shorter time to depressive relapse. Furthermore, patients who discontinued antidepressant treatment within the first six months after remission experienced a significantly shorter period of euthymia before depressive relapse over the length of a 1-year follow-up. One year after successful antidepressant response, 70% of the antidepressant discontinuation group experienced a depressive relapse compared with 36% of the continuation group. By the 1-year follow-up evaluation, 15 (18%) of the 84 subjects had experienced a manic relapse; only six of these subjects were taking an antidepressant at the time of manic relapse. The authors concluded that risk of depressive relapse in patients with bipolar illness was significantly associated with discontinuing antidepressants soon after remission. The risk of manic relapse was not significantly associated with continuing use of antidepressant medication and, overall, was substantially less than the risk of depressive relapse. To support their previous study, the same group carried out another retrospective study on 44 bipolar subjects (39 with bipolar I disorder, five with bipolar II disorder) treated for an acute depressive episode with the addition of an antidepressant to an ongoing adequate mood stabilizer regimen (22). The results of the later study indicated that termination (compared with continuation) of antidepressant treatment within the first year of remission significantly increased the risk of depressive relapse within that year. Moreover, other reports in the literature suggest that continuation of the antidepressant is not associated with a higher risk of relapse into mania.

Summary

The majority of standard randomized controlled trials indicate efficacy of antidepressants in the treatment of the acute phase of bipolar depression. This held true when given as monotherapy or as adjuncts to mood stabilizers. The position that advises caution in prescribing antidepressants in bipolar depression (as in the APA guidelines) is based on consistent, albeit limited, data that indicate higher switch rates and increased cycle acceleration. These adverse effects are lessened when adjunct mood stabilizers are added. At the same time, some data indicate higher rates of relapse into depression when antidepressants are discontinued early after remission. Surprisingly, a recent large effectiveness study,

the STEP-BD, found no benefit in efficacy and no risk of affective switch when antidepressants were added to a mood stabilizer. Since the STEP-BD study is better adjusted to "real life" clinical practice, it has relevance when clinical decisions are taken. A clinically oriented editorial was published by Belmaker (23) in the same issue of *The New England Journal of Medicine* in which the Sachs et al. (16) STEP-BD results were published. The editorial suggests epidemiological difference in the incidence of mania and depression between North America and Europe that can contribute to the earlier presented contradicting data. Moreover, Belmaker discusses the need to subcategorize the treatment groups in bipolar depression studies so that patients with mostly past manias will differ from those whose past episodes were mostly depression, assuming a different response to treatment. Future studies designed to elucidate the issues discussed in this paper are essential and may help establish better guidelines for the treatment of the complex clinical entity of BPD. Until then, factors such as history of severe manias (as stressed in Belmaker's editorial), past depression severity and length and rapid cycling will continue to play a role in the decision of clinicians in prescribing antidepressants for BPD in different phases of the disorder.

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