Published in final edited form as:

J Clin Psychopharmacol. 2015 October ; 35(5): 605–608. doi:10.1097/JCP.0000000000000384.

Antidepressants in type II versus type I bipolar depression: A randomized discontinuation trial

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Abstract

Background—We sought to test the hypothesis that antidepressants (ADs) may show preferential efficacy and safety among type-II over type-I bipolar disorder (BD) patients.

Methods—DSM-IV BD-I (n=21) and -II patients (n=49) in acute major depressive episodes were treated with ADs plus mood-stabilizers to euthymia sustained for two months, and then randomized openly to continue or discontinue ADs for up to three years. Outcomes were episode-recurrences and changes in standardized symptom-ratings.

Results—In follow-up averaging 1.64 ± 0.98 years, both subgroups showed improvement in depressive episode frequency with AD continuation, but contrary to the hypothesis, more improvement was seen in type I than in type II bipolar depression (for type II, mean decrease in depressive episodes per year 0.21 ± 0.26 [CI:0.05, 0.37]; for type I: mean decrease 0.35 ± 0.15

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Disclosures: In the past 36 months, Dr. Ghaemi has had a research grant with Takeda and provided research consultation to Sunovion. All other authors declare no personal or immediate family business interests that might appear to represent conflicts of interest.

[CI:0.30, 0.41]). Type II subjects continued on ADs had slightly more depressive, but fewer manic/hypomanic, episodes than BD-I subjects. No notable differences were seen in either group in time to a recurrence of mood episodes or total time-in-remission.

Conclusions—The findings do not confirm the hypothesis that long-term AD treatment in BP-II has better outcomes than in BD-I patients, except somewhat lower risk of manic/hypomanic episodes.

Keywords

bipolar disorder; antidepressants; maintenance treatment

Introduction

The efficacy and safety of antidepressants (ADs) for short- and long-term treatment of bipolar disorder (BD) patients remain controversial,¹⁻⁴ and research pertaining to *long-term* effects of ADs in BD remains rare.^{2, 5} Short-term trials suggest that ADs may be particularly effective for depression in type-II bipolar disorder patients (BD-II), with a low risk of hypomania.^{2, 3} In addition, a one-year trial found fluoxetine-alone to be more effective against depressive recurrences in BD-II patients than either placebo or lithium, again with little risk of hypomania.⁶ Despite very limited research support and inconsistent findings,⁽²⁻⁴⁾ ADs continue to be among the most commonly prescribed drugs for treating BD patients, and they are often included in drug-combinations for long-term treatment.^{7, 8}

Given the severe paucity of research on effectiveness and safety of ADs in long-term treatment of BD patients, we now report a secondary analysis of findings from a long-term controlled trial comparing open-randomized treatment with mood-stabilizers, with or without continuation of ADs, following recovery from acute major depression.⁵ We aimed to test the hypothesis that ADs would be at least as effective, and less likely to induce hypomania or mania among BD-II (or BD-unspecified [NOS]) than BD-I patients.

Methods

In an unblinded, randomized trial within the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) project,⁵ following methods detailed previously,^{5, 9, 10} subjects (N=70) with DSM-IV (11) BD were identified who had recently recovered from an index episode of acute DSM-IV major depression after being treated clinically with an AD and a mood stabilizer. Thus, patients were preselected to be responders to antidepressants added to mood stabilizers for the acute bipolar depressive episode (the “enriched” or randomized discontinuation design).¹¹ Subjects were required to have 2 DSM-IV depressive symptoms for 2–4 months, and then were randomized, to continue or discontinue modern ADs, as mood stabilizers continued unchanged, for up to 3 years of prospective follow-up. After recovery from the acute bipolar depressive episode, those assigned to antidepressant discontinuation were gradually tapered over two weeks, not abruptly discontinued.

Subjects were recruited from Cambridge Health Alliance (Cambridge, MA), University of Pennsylvania Hospital (Philadelphia, PA), University of Kentucky Medical Center (Louisville, KY), and Massachusetts General Hospital (Boston, MA). Study procedures were approved by the Institutional Review Boards of the collaborating sites, and all participants provided written, informed consent. Clinical and demographic characteristics of the sample are provided in detail in the primary outcome publication.⁵ Briefly, the sample was 47% male, with mean 43.0 ± 13.4 years, age of onset 18.7 ± 9.7 years, 23% had prior psychosis, 43% prior substance abuse, 38.5% past antidepressant-induced mania, and 25% had a rapid-cycling course.

Mood stabilizers used were lithium carbonate, sodium divalproex, carbamazepine, or lamotrigine; second-generation antipsychotic drugs were allowed if mood-stabilizers had previously been ineffective or were poorly tolerated. Other initially prescribed psychotropic medicines (except other ADs) could continue or be adjusted clinically⁵.

The primary and secondary outcomes in the study have been described in detail elsewhere.⁵ Briefly, the primary outcome of the study was the Clinical Monitoring Form (CMF) used in the STEP-BD study in every clinical visit of every patient enrolled in that study. The CMF, a measure of symptom morbidity rather than episode frequency, was validated as having good correlation with standard mania and depression rating scales.¹² In addition, mood episodes were identified using DSM-IV criteria, and episode frequency and polarity were systematically recorded throughout follow-up. Time to the first mood episode was also recorded, as was time in remission in between DSM-IV defined mood episodes. In this secondary outcome report, mood episodes were prespecified as the main outcome of interest.

When the study was designed and before data-analyses, we proposed to evaluate whether the diagnostic subtype (BD-I vs. -II or -NOS ["BD-II"]) was related to outcome. Among outcomes assessed were numbers and types of recurrences of DSM-IV major affective episodes, latency to first new episode (by Kaplan-Meier survival analysis with Cox regression to generate Hazard Ratios [HR] to evaluate covariates including diagnosis and treatment), and percentage of weeks in euthymia or in subsyndromal symptom-states. Unless stated otherwise, data are reported as means $\pm$ standard deviation (SD) or as effect-estimates (absolute percentages, relative risks, or mean differences), with 95% confidence-intervals (CI). Statistical analyses employed standard commercial software (Stata 11; StataCorp, College Station, TX).

Data are presented as both *within-* and *between-*group comparisons. *Within-group* analyses assessed BD-II subjects separately and compared treatment with versus without ADs. *Between-group* comparisons included the whole sample, comparing BD-I and BD-II subjects, with versus without long-term AD treatment. We present both kinds of analyses. The between-group analyses have larger numbers of subjects and greater statistical power.

Diagnostic subtype (I versus II) groups were similar in age (42.9 ± 14.1 vs. 43.2 ± 10.6 years) and sex-distribution (49.0% vs. 62.0% women). All but four subjects (5.7%, all BD-II) were

Caucasian. Duration of follow-up during the study was similar between diagnoses (20.8 ± 13.0 vs. 20.2 ± 13.6 months).

Results

70% of the sample (49/70) had type I bipolar illness, and 30% type II (21/70). 45.7% (32/70) of the sample experienced at least one recurrence of a DSM-IV major affective episode. The first mood episode was depressive in 68.8% (22/32) and manic/hypomanic/ mixed in 31.2% (10/32). In continued follow-up over three years, there were a total of 110 new episodes, at recurrence rates of 7.1%/person-month (30/21/20.2) among BD-II cases (20 depressive and 10 hypomanic), and 7.9%/person-month (80/49/20.7) in BD-I patients (53 depressive and 27 manic/hypomanic/mixed).

The rate of episode recurrences/year was similar among BD-I and BD-II subjects not given ADs (Table). In those receiving ADs, frequency of depressive episodes was slightly higher in BD-II than BD-I subjects, but there were fewer manic/hypomanic episodes in BD-II subjects (mean difference: -0.20 [CI: $+0.03$ to -0.44], a 105% decreased recurrence rate). Overall, when examine within each type, there were numerically fewer depressive episodes with AD continuation over three years of follow-up, versus AD discontinuation (for type II: 0.76 ± 0.90 vs 0.97 ± 1.46 ; for type I: 0.59 ± 0.87 vs 0.94 ± 1.16). Despite the smaller subsamples in those analyses, these differences were statistically significant (for type II, mean difference 0.21 ± 0.26 [CI: 0.05 , 0.37]; for type I: mean difference 0.35 ± 0.15 [CI: 0.30 , 0.41]). The improvement seen in the type I subgroup was larger than the improvement seen in the type II subgroup (mean differences noted above). Dropout rates were somewhat higher in type I than type II illness (13/49, 26.5%, vs 4/21, 19.0%; RR = 1.39, 95% CIs 0.51, 3.78), but with wide confidence intervals.

For survival analysis and Cox regression modeling with stratification by diagnostic type (see figure), the apparent difference in recurrence rates for mania/hypomania was not statistically significant overall (Hazard Ratio [HR]: 1.55 [CI: 0.75–3.22]), nor were differences in weeks to a first major depressive (HR=0.60 [CI: 0.12–2.88]) or first manic/hypomanic episode (HR=1.47 [CI: 0.71–3.03]). The diagnostic groups also did not differ in percentage of time during follow-up without mood episodes (Table).

Discussion

This trial was a component of the longest randomized study of maintenance treatment in BD involving modern ADs as well as mood-stabilizers, with treatment-exposure averaging 1.64 years. With ADs continued, BD-II subjects did not have notably better outcomes than BD-I cases with respect to depressive episodes, although they had fewer manic/hypomanic episodes. In fact more benefit with AD continuation was seen in the direction of fewer depressive episodes in type I BD subjects, not type II BD subjects. Such differences between diagnostic groups were not found among subjects randomized to *discontinue* ADs. There was no notable benefit in latency to first episode-recurrences nor in the proportion of time in virtual euthymia.

In the primary analysis published elsewhere,⁵ the main finding was some mood morbidity benefit with AD continuation (measured by the STEP-BD Clinical Monitoring Form) as well as lengthened time to first mood episode relapse with AD continuation. At one year outcome, differences in overall frequency of mood episodes and time in remission were not seen in the overall sample when comparing AD continuation versus discontinuation. These type I versus type II secondary analyses involve three year outcomes, not one year outcomes, as in the primary analysis of this study. With three year follow-up, there was benefit with mood episode relapse, comparing AD continuation versus discontinuation within each subgroup, in this analysis.

The impression that ADs may be more effective in type II than in type I bipolar depression mainly come from studies that do not include head-to-head comparisons of type I versus type II subjects who receive or do not receive ADs. Rather, that impression appears to come from comparing different studies each of which are limited only, or mainly, to type I or type II samples. Thus, most RCTs of ADs in bipolar depression enroll mostly type I subjects, and the majority of those studies find no or little benefit with ADs in the acute bipolar depressive episode.³ In contrast, a number of studies of type II bipolar depression only report benefit with various ADs versus placebo (or versus lithium) in the acute bipolar depressive episode.^{6, 13, 14} The few studies that directly compared outcomes in type II versus type I patients, like some analyses from Stanley Network,¹⁵ are observational, rather than randomized. In the main randomized trial from the Stanley Network, comparing three antidepressant arms (but no placebo arm), no differences were seen between type II and type I patients in overall AD response over one year.¹⁶

These differences among studies may reflect the impact of the enriched, or randomized discontinuation, trial design. In this study, patients were selected to respond to a mood stabilizer plus an AD before maintenance treatment began. In previous studies, subjects also were selected only after responding to an AD, often alone, and sometimes added to a mood stabilizer. Such “enrichment” trial designs may be biased in favor of the initial treatment for which response is required. In our study and in previous studies this involved ADs, in contrast to a lack of preferential selection in previous long-term arms involving lithium. The only previous, randomized, controlled, long-term trial involving BD-II patients which did not use such an enrichment design to select initial AD-responders failed to find any benefit with ADs in type II bipolar depression (12). That study was a double-blind, randomized, controlled trial with enrollment of 22 BD-II patients over an average of 11 months, with direct randomization to long-term treatment with imipramine alone or with lithium. Risks of depressive recurrences were very similar in both arms, indicating no apparent advantage of including an AD (12).

It should be noted that in our study, as well as in other samples,¹⁶ there is replication of increased rates of manic relapses with AD continuation in type I BD, but less so in type II BD.

Limitations

The findings are constrained by the unblinded trial-design and pooling of BD-II and BD-NOS cases, as well as by limited statistical power. However, the number of subjects is

similar to the rare previous, long-term trials involving ADs for BD patients^{2,3}. Observed differences in any outcome measure between BD-I and BD-II patients, and during long-term treatment with or without ADs were modest (Table). The view that insufficient statistical power would account for lack of benefit with ADs in type II over type I BD is not supported by the fact that the direction of benefit was larger for type I than type II BD. Continued mood-stabilizing treatment may have dampened potential differences in outcomes between the diagnostic groups or effects of adjunctive AD treatment. Nevertheless, it would have been clinically and ethically challenging to continue ADs without mood-stabilizers, especially in BD-I patients.

Conclusions

When modern ADs were continued long-term with mood-stabilizers following an index episode of major depression, BD-II patients did not have fewer depressive recurrences than BD-I patients, but did have less risk of mania/hypomania.

Acknowledgments

Supported by NIMH grant MH-64189 (to SNG) and, in part by a grant from the Bruce J. Anderson Foundation and the McLean Private Donors Research Fund (to RJB).

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Figure. Survival in type I versus type II bipolar illness by antidepressant continuation versus discontinuation

No differences are statistically significant.

Table
Clinical outcomes during long-term treatment with antidepressants continued versus discontinued with mood-stabilizers in bipolar disorder patients following an index episode of major depression

Outcomes	<i>Antidepressants Continued</i>		<i>Antidepressants Discontinued</i>	
	Bipolar-II	Bipolar-I	Bipolar-II	Bipolar-I
Cases (n)	10	22	11	27
Exposure (months)	23.55 ± 12.1	20.95 ± 13.4	17.2 ± 14.6	20.7 ± 12.8
<i>Recurrences/year</i>				
Depressions	0.76±0.90	0.59±0.87	0.97±1.46	0.94±1.16
Manias/hypomanias	0.19±0.45	0.39±0.90	0.20±0.34	0.26±0.50
Total	0.95±1.05	0.98±1.31	1.17±1.40	1.14±1.22
% months no episodes	18.7 ± 5.5	20.0 ± 6.1	19.5 ± 4.4	17.3 ± 6.2

All data are means ± SD.