DOI: 10.1111/bdi.13378

ORIGINAL ARTICLE

BIPOLAR DISORDERS WILEY

Multi-trial, aggregated, individual participant data mega-analysis of short-term antidepressant versus mood stabilizer monotherapy of bipolar type II major depressive episode

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Funding information
Eli Lilly and Company; National Institute of Mental Health; Stanley Medical Research Institute

Abstract

Background: Few studies have systematically examined the safety and effectiveness of antidepressant versus mood stabilizer monotherapy of bipolar II depression. To date, there are no aggregated or mega-analyses of prospective trials of individual participant-level data (IPD) to inform future treatment guidelines on the relative safety and effectiveness of antidepressant or lithium monotherapy.

Methods: Data from a series of four independent, similarly designed trials of antidepressant or lithium monotherapy (where longitudinal IPD were available) ($n = 393$) were aggregated into an IPD dataset (i.e., mega-analysis). Hierarchical log-linear growth models were used to analyze primary outcome of change over time in Hamilton Rating Scale for Depression (HRSD) scores; while secondary outcomes examined Clinical Global Impressions severity (CGI/S) and change (CGI/C) scores, and change over time in Young Mania Rating (YMR) scores.

Results: Relative to lithium monotherapy, antidepressant monotherapy demonstrated significantly greater symptom reduction on HRSD scores across time ($b = -2.33$, $t = -6.68$, $p < 0.0001$), significantly greater symptom reduction on the CGI/S across time ($b = -0.414$, $t = -6.32$, $p < 0.001$), and a significant improvement in CGI/C across time ($b = -0.47$, $t = -7.43$, $p < 0.0001$). No differences were observed in change over time for YMR scores between antidepressant and lithium monotherapy ($b = 0.06$, $t = 0.49$, $p = 0.62$).

Conclusion: Findings from this IPD mega-analysis of bipolar II depression trials suggest a divergence from current evidence-based guidelines recommending combined mood stabilizer plus antidepressant therapy. The current mega-analysis suggests that antidepressant monotherapy may provide superior short-term effectiveness without clinically meaningful increase in treatment-emergent hypomanic symptoms compared to lithium monotherapy.

KEYWORDS
bipolar type II disorder, antidepressant monotherapy, bipolar depression, fluoxetine, hypomania, individual participant data, mega-analysis, lithium carbonate, mania, venlafaxine

1 | INTRODUCTION

Bipolar II disorder is the most common phenotypic expression of bipolar illness, affecting at least 1.1% of the adult population.[1] It is diagnostically stable over time and rarely evolves into bipolar I disorder.[2,3] Because bipolar II disorder is characterized by a high recurrence of depressive episodes and an absence of mania, putative antidepressant treatment approaches for bipolar II depression may differ from that of bipolar I disorder.[4]

The use of antidepressant drugs for initial treatment of bipolar II depression has been controversial.[5] Practice guidelines for the treatment of bipolar II depression have been based largely upon expert consensus panels[6–12] and often contradict one another.[11] In general, practice guidelines have been predicated upon treatment approaches for bipolar I disorder, which prioritize the use of lithium (or other mood stabilizers), and eschew the use of antidepressants which may promote treatment-emergent manic symptoms.[13–15]

Thus, the majority of current practice guidelines for treating bipolar II depression have followed the treatment recommendations for those of bipolar I depression, by recommending lithium monotherapy as first-line treatment, and only recommending the judicious use of antidepressant therapy in combination with a mood stabilizer for more severe bipolar II depression that is unresponsive or partially responsive to lithium alone.[12]

In contrast, few guidelines have recommended the use of antidepressant monotherapy for treating bipolar II depression.[12] One recent task force consensus recommended the cautious use of selective serotonin reuptake inhibitor (SSRI) antidepressants or bupropion monotherapy for the short-term treatment of mild bipolar II depression; although combined use of SSRI plus mood stabilizer therapy is still recommended for moderate to severe bipolar II depression.[12]

Consequently, there have been few prospective, controlled trials of antidepressant versus mood stabilizer monotherapy for short-term treatment of bipolar II depression. Several controlled clinical trials of bipolar II depression[4,16,17] have shown good effectiveness of SSRI monotherapy with a low propensity for manic induction. One investigator has even suggested that some SSRI antidepressants may function as mood stabilizer therapy in bipolar II depression.[16]

The paucity of data aggregating information from multiple treatment trials of bipolar II depression to inform future evidence-based treatment guidelines suggests that such analyses would be helpful in clarifying the relative safety and effectiveness of antidepressant versus mood stabilizer monotherapy for bipolar II depression.

Thus, we conducted a mega-analysis[18–23] of individual participant data (IPD) from four independent, prospective treatment trials of bipolar II major depressive episode.

Of the prior published bipolar II depression trials that were available for possible inclusion, we selected trials that included prospective, longitudinal trials where IPD were available and a treatment duration of 12 weeks was employed. This selection permitted us to then analyze the IPD by aggregating the available datasets for mega-analysis.[20,21,23]

In contrast to conventional meta-analyses which aggregate treatment main effects, mega-analyses with IPD datasets allowed the aggregation of the longitudinal effects of treatments across IPD points over time, allowing more precise estimates of safety and effectiveness measurements, while also reducing sources of error by controlling for covariates at the individual participant level.[18–23] In this regard, mega-analyses have been extensively employed previously for pooling aggregating IPD datasets from antidepressants treatment trials for unipolar depression,[23–26] although to our knowledge, no IPD mega-analyses have been conducted to compare safety and effectiveness of various pharmacotherapies for bipolar II depression.

2 | MATERIALS AND METHODS

2.1 | Selection of data for mega-analysis

We identified eight prior published reports of prospective, controlled clinical trials of antidepressant monotherapy of bipolar II depression.[16,17,27–36] Of these, we were able to acquire access to the safety and effectiveness IPD datasets from six of the trials.[27–36] Of these, one trial[34] was excluded because the data on efficacy of fluoxetine monotherapy were retrospectively, and not prospectively obtained. Of the remaining five trials, four were 12-week treatment trials, while one was only an 8-week treatment trial. After consideration, the latter trial[35,36] was excluded from IPD mega-analyses, because inclusion of the shorter 8-week duration into the planned mega-analysis would have required an extrapolation of treatment effectiveness data beyond 8 weeks in order to match the other 12-week trials. Inclusion of this shorter trial would have then resulted in an inaccurate estimation of treatment response; or would have restricted our statistical analysis to only an analysis of covariance of end-of-treatment (EOT) scores, as opposed to being able to examine continuous rates of symptom change over time. Thus, data from four 12-week trials were included in our final aggregated IPD mega-analysis dataset.[27–33]

All trials included in the current mega-analysis were prospective and longitudinal in design, and all tracked safety and effectiveness outcomes for at least 12 weeks. Trial 1[27,28] was a prospective, two-phase study, of which Study phase I examined the safety and effectiveness of fluoxetine monotherapy ($N=167$). Trial 2[29,30] ($N=80$) was a prospective comparison of the safety and effectiveness of variable-dose venlafaxine ($n=42$) versus lithium monotherapy ($n=38$). Trial 3[31] was a prospective cross-over comparison of venlafaxine versus lithium monotherapy for non-responders of either prior venlafaxine or lithium monotherapy ($N=17$). Trial 4[32,33] ($N=129$) was a prospective safety and effectiveness comparison of venlafaxine ($n=65$) versus lithium monotherapy ($n=64$). Thus, four trials[27,29,31,32] contributed data to the mega-analysis of antidepressant

monotherapy, and two trials contributed to the mega-analysis of lithium monotherapy.[31,32]

A total of 393 patients were included in the IPD mega-analysis dataset. All four trials utilized similar protocol designs and were conducted under Good Clinical Practice guidelines.[37] For example, all patients were outpatients ≥18 years old with a DSM-IV-TR Axis I diagnosis of bipolar II disorder and current major depressive episode with a 17-item Hamilton Rating Scale for Depression (HRSD)[38] score ≥ 16. The frequency of all safety and effectiveness outcome measurements were similar among trials.[37] Clinical diagnoses was verified via the *Structured Clinical Interview for DSM-IV* (SCID) Axis I disorder.[39]

The following IPD outcome measures were obtained at each study visit: 17-item HRSD score, Clinical Global Impression[40] Severity (CGI/S) score, Clinical Global Impression change (CGI/C) score, and Young Mania Rating (YMR)[41] score. HRSD score was the primary effectiveness outcomes, with CGI/S and CGI/C as secondary effectiveness outcomes. YMR scores over time was the secondary, safety outcome. All outcome measures were obtained at baseline and after treatment weeks 1, 2, 4, 6, 8, 10, and 12, respectively, for all trials included in our mega-analysis. Demographics (e.g., age, gender, race, etc.) were also collected at baseline, and missing baseline characteristics were imputed separately for each trial using random forest imputation with the missForest procedure in R version 3.4.0.[42]

2.2 | Statistical analysis procedure

In order to first understand how symptoms changed over the course of lithium or antidepressant, we constructed two separate hierarchical log-linear growth models[43] for lithium and antidepressant monotherapy. For each model, the 17-item HRSD total score was defined as the dependent variable, and time, defined in weeks, from baseline ($t=0$) through week 12 was entered as a fixed effect predictor. A random intercept and random slope of time was then modeled for each patient, and patients were nested within trial. The model also included baseline demographics of age, gender, race, rapid cycling status, duration of current depressive episode, number of prior major depressive episodes, and baseline YMR scores entered as fixed effects covariates.

To further compare the rates of symptom change over the course of lithium versus antidepressant monotherapies, treatment condition was coded as either lithium monotherapy or antidepressant monotherapy treatment (effect coded as lithium = −0.5 and antidepressant = 0.5). Time, treatment, and the treatment-by-time interaction were entered as fixed effect predictors.

The specification of this comparison model is as follows:

$$y_i = \beta_{0i} + \beta_{1ij}\left(\log(time+1)_i\right) + \beta_{2ij}\left(treatment_i\right) + \beta_{3ij}\left(\log(time+1)_i \times treatment_i\right) + \ldots + e_{ij}$$

where: time = weeks of treatment, and time = 0 represents baseline. Treatment is an effect-coded factor, where lithium is the reference group. Thus, where Time = 0, β_2 represents the differences in baseline 17-item HRSD total scores observed between lithium and antidepressants. β_3 represents the time-by-treatment interaction; that is, the difference in rate of symptom change per week between lithium monotherapy and antidepressant monotherapy. Thus, we are able to model both the mega-analytic regression curves of the aggregated IPD data for lithium monotherapy the aggregated IPD data for antidepressant monotherapy; and further, compare how the rates of symptom change over the 12 weeks between the two curves differ.

This process of constructing a separate lithium model, a separate antidepressant model, and a model comparing the rates of symptom change between the two was repeated using similar hierarchical models for the secondary outcomes of CGI/S, CGI/C, and YMR. The same predictors of time, treatment, the time-by-treatment interaction, and the baseline demographic covariates were entered as fixed effects for these models. A random intercept and random slope of time were also modeled for each patient, and patients were nested within trial. The only change in model specification was the outcome variable to CGI/S, CGI/C, or YMR, respectively. Statistical analyses were conducted in R version 4.1.2 using the package lme4.[44]

3 | RESULTS

3.1 | Clinical and demographic characteristics

Table 1 displays some statistically significant differences among treatment conditions for baseline demographic and clinical variables (e.g., age of illness onset; age at first depressive episode, number of prior hypomanic episodes, and baseline mean CGI/S score). For example, there occurred a greater proportion of rapid cycling patients in the lithium (48.0%) and antidepressant (34.7%) (during randomization $\chi^2 = 5.14$, $p = 0.023$) conditions. Analyses of variance also showed statistically significant randomization differences in several clinical and demographic baseline variables among the three individual treatment conditions (see Table 1). As previously reported, mean serum lithium concentrations were 0.64 mmol/L (SD = 0.265, range: 0.29–1.50) in trial 2,[29] and 0.94 mmol/L (SD = 0.38, range: 0.30–2.40) in trial 4.[32]

3.2 | Primary outcome measures

3.2.1 | HRSD scores

Controlling for baseline covariates, patients treated with antidepressant monotherapy showed a significant reduction in HRSD scores over time ($b = -5.08$, $t = -29.56$, $p < 0.0001$). Controlling for baseline covariates, patients treated with lithium monotherapy showed a significant reduction in HRSD scores over time ($b = -2.72$, $t = -8.47$, $p < 0.0001$).

In the comparison model between antidepressants and lithium monotherapy, after controlling for baseline covariates, antidepressant-treated patients had higher baseline HRSD scores

TABLE 1 Baseline demographic characteristics and tests of significant differences.

Mean (SD)	All patients ($n=393$)	Lithium ($n=102$)	Antidepressants ($n=291$)	Fluoxetine ($n=167$)	Venlafaxine ($n=124$)	Antidepressant versus lithium		Fluoxetine versus venlafaxine versus lithium	
						t	*p*	*F*	*p*
Age	39.39 (13.32)	40.82 (14.11)	38.88 (13.02)	37.1 (12.41)	41.29 (13.48)	−1.22	0.226	4.40	0.013*
Age of onset	17.7 (6.92)	16.48 (6.16)	18.13 (7.13)	18.25 (7.05)	17.98 (7.25)	2.24	0.026*	2.24	0.108
Age first MDE	18.78 (7.92)	17.22 (6.37)	19.33 (8.33)	19.35 (8.06)	19.29 (8.72)	2.64	0.009*	2.70	0.069
Age first hypomanic	21.34 (8.02)	21.05 (8.56)	21.44 (7.83)	21.53 (7.98)	21.33 (7.66)	0.41	0.684	0.11	0.894
# prior MDE	14.01 (26.03)	18.83 (26.88)	12.32 (25.56)	8.88 (18.85)	16.95 (31.98)	−2.13	0.034	5.93	0.003*
# prior hypomanic	26.28 (53.93)	37 (80.43)	22.52 (40.29)	15.62 (28.88)	31.81 (50.49)	−1.74	0.084	6.09	0.002*
# prior hypothermic	46.58 (60.21)	60.86 (72.77)	41.58 (54.4)	34.18 (45.52)	51.54 (63.31)	−2.45	0.016*	7.04	0.001*
Intake HAMD-17	20.45 (4.13)	20.64 (4.51)	20.39 (4)	20.61 (3.74)	20.09 (4.31)	−0.50	0.616	0.70	0.496
Intake YMAR	0.54 (1.58)	0.67 (1.67)	0.49 (1.55)	0.49 (1.67)	0.49 (1.38)	−0.92	0.361	0.45	0.639
Intake CGI/S	4.21 (0.45)	4.3 (0.48)	4.17 (0.44)	4.16 (0.38)	4.19 (0.5)	−2.40	0.017*	3.39	0.035*
Count (%)	**All Patients ($n=393$)**	**Lithium ($n=102$)**	**Antidepressants ($n=291$)**	**Fluoxetine ($n=167$)**	**Venlafaxine ($n=124$)**	**ADM versus lithium**		**Fluoxetine versus lithium versus lithium**	
						χ^2	*p*	χ^2	*p*
Sex, Male	176 (44.8)	42 (41.2)	134 (46)	79 (47.3)	55 (44.4)	0.54	0.462	0.98	0.614
Minority Race	83 (21.1)	25 (24.5)	58 (19.9)	42 (25.2)	16 (12.9)	0.70	0.404	7.36	0.025
Rapid cycling	150 (38.2)	49 (48)	101 (34.7)	48 (28.7)	53 (42.7)	5.14	0.023*	11.60	0.003*

Note: Asterisk signifies significant at $p<0.05$ level; t = Fisher's two-tailed t-test; F, analysis of variance F-Statistic; χ^2, Chi-square test.

relative to lithium-treated patients ($b=1.23$, $t=2.25$, $p=0$ 0.025). There was a significant effect of time ($b=-3.91$, $t=-22.41$, $p<0.0001$), reflecting symptom improvement over time in both treatment conditions. There was a significant time-by-treatment condition interaction ($b=-2.33$, $t=-6.68$, $p<0.0001$), indicating that patients receiving antidepressant monotherapy experienced a significantly greater reduction in HRSD score over time relative to lithium monotherapy (see Figures 1 and 2).

3.2.2 | CGI/S scores

Controlling for baseline covariates, patients treated with antidepressant monotherapy showed a significant reduction in CGI/S scores over time ($b=-0.81$, $t=-24.98$, $p<0.0001$). Controlling for baseline covariates, patients treated with lithium monotherapy showed a significant reduction in CGI/S scores over time ($b=-0.39$, $t=-6.08$, $p<0.0001$).

In the comparison model between antidepressant and lithium, after controlling for baseline covariates, there was no difference in baseline CGI/S scores for antidepressant-treated patients relative to lithium-treated patients ($b=0.076$, $t=1.081$, $p=0.28$). There was, however, a significant effect of time ($b=-0.388$, $t=-6.90$, $p<0.001$), reflecting symptom improvement over time in both treatments. There was also a significant time-by-treatment condition interaction ($b=-0.414$, $t=-6.32$, $p<0.001$), indicating that patients receiving antidepressant monotherapy experienced a significantly greater reduction in CGI/S scores over time versus lithium monotherapy.

3.2.3 | CGI/C scores

Controlling for baseline covariates, patients treated with antidepressant monotherapy showed a significant reduction in CGI/C scores over time ($b=-1.01$, $t=-22.76$, $p<0.0001$). Controlling for baseline covariates, patients treated with lithium monotherapy showed a significant reduction in CGI/C scores over time ($b=-0.43$, $t=-4.80$, $p<0.0001$).

In the comparison model between antidepressant and lithium, after controlling for baseline covariates, antidepressant-treated patients had higher CGI/C scores relative to lithium-treated patients at study baseline ($b=0.244$, $t=2.833$, $p=0.004$). There was a significant effect of time ($b=-0.29$, $t=-5.29$, $p<0.0001$), reflecting symptom improvement over time in both treatments. There was also a significant time-by-treatment condition interaction ($b=-0.47$, $t=-7.43$, $p<0.0001$), indicating that antidepressant monotherapy produced significantly higher CGI/C scores over time versus lithium monotherapy.

3.2.4 | YMR scores

Controlling for baseline covariates, patients treated with antidepressant monotherapy showed no significant change over time in YMR scores ($b=0.09$, $t=1.42$, $p=0.16$). Controlling for baseline covariates, patients treated with lithium monotherapy showed no significant change in YMR scores over time ($b=0.037$, $t=0.24$, $p=0.81$).

In the comparison model between antidepressant and lithium, after controlling for baseline covariates, there was no main effect of treatment condition ($b=-0.027$, $t=-0.22$, $p=00.82$), indicating there was no difference between antidepressant-treated and lithium-treated patients at study baseline. There was no main effect of time ($b=0.06$, $t=0.97$, $p=0.332$), indicating that YMR scores did not change over the course of treatment. Neither was there a time-by-treatment interaction ($b=0.06$, $t=0.49$, $p=0.62$), indicating that there were no differences in the change over time in YMR-rated manic symptom scores between antidepressant monotherapy and lithium monotherapy (see Figure 3).

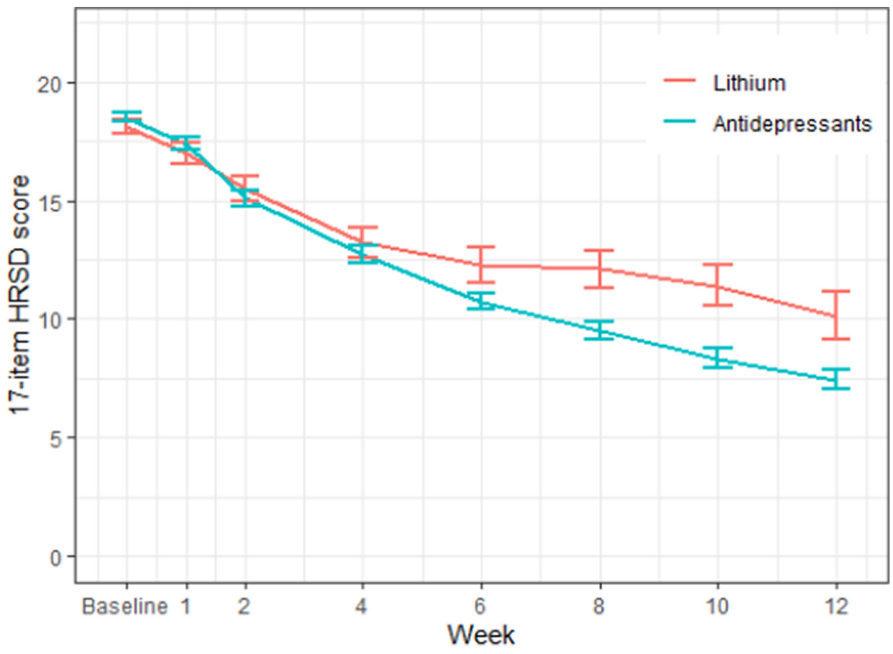

FIGURE 1 Change in HRSD scores over a 12-week period by treatment condition (lithium vs. antidepressants). Error bars represent standard error.

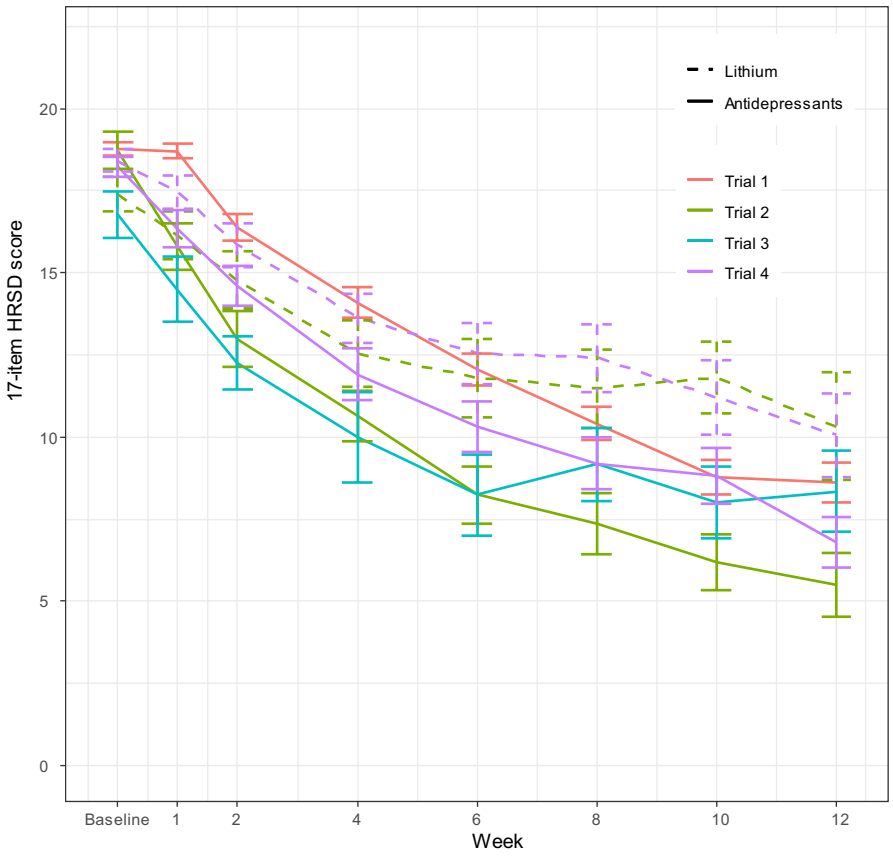

FIGURE 2 Change in HRSD scores over a 12-week period by study treatment arm. Error bars represent standard error.

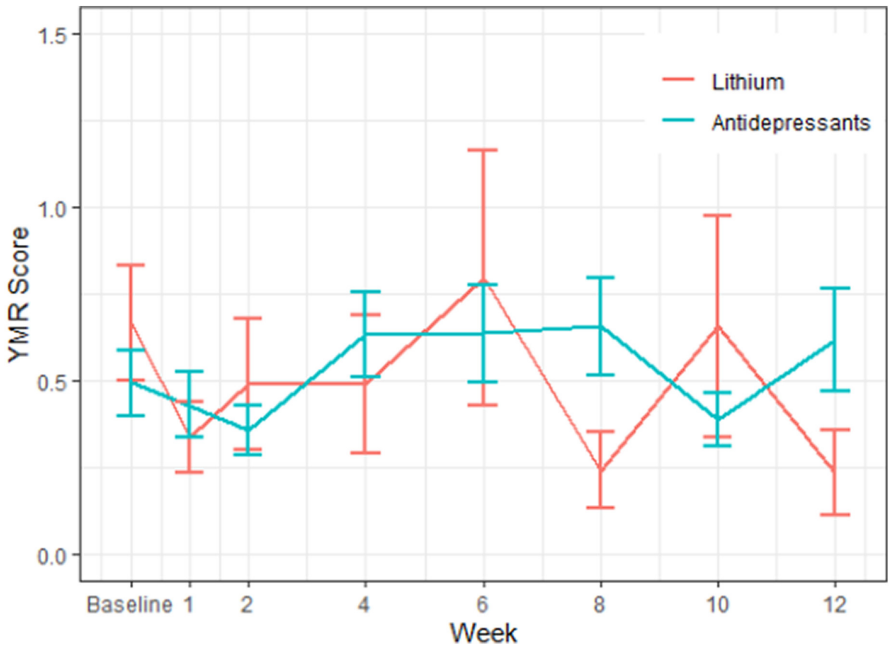

FIGURE 3 YMR scores over a 12-week period by treatment condition (lithium vs. antidepressants). Error bars represent standard error.

4 | DISCUSSION

We believe that this study represents the first mega-analysis aggregating individual participant data on the relative safety and effectiveness of two divergent short-term treatment approaches for bipolar II depression. It also explores current practice guideline recommendations favoring lithium monotherapy, relative to antidepressant monotherapy as first-line treatment for bipolar II depression.

By aggregating the longitudinal IPD treatment data from four separate, prospective trials, we were able to model the longitudinal trajectories of patients across either antidepressant monotherapy or lithium monotherapy. This mega-analytic approach has multiple advantages over traditional meta-analyses. For example, it allowed us

to expand our ability to model EOT differences and rate of symptom and hypomania change over time at a finer granularity, as well as to better control for patient-level variation in pre-treatment characteristics such as demographics.[18–23]

Specifically, through the use of aggregated IPD mega-analysis across multiple treatment trials, we found that bipolar II patients receiving both antidepressant monotherapy and lithium monotherapy improved over in depressive symptoms over time. Furthermore, we found that patients receiving antidepressant monotherapy improved at a significantly faster rate than patients receiving lithium monotherapy. Furthermore, these effectiveness findings occurred in the relative absence of significant differences in hypomanic symptoms across time between antidepressant and lithium monotherapies (as measured by the YMR), suggesting that there were no differences in the safety risk of antidepressant-induced hypomania between treatment conditions.

The results of the current bipolar II depression IPD mega-analysis appear to diverge from the consensus recommendations of many practice guidelines. In contrast to the earlier recommendations that antidepressant monotherapy be avoided in bipolar II depression, the current mega-analysis suggests that several antidepressant monotherapies may provide superior short-term benefit for bipolar II depression (relative to lithium monotherapy), with little or no clinically meaningful difference in treatment-emergent hypomania between treatments.

The reluctance to use antidepressant monotherapy in patients with bipolar II depression is most likely due to concerns over the precipitation of treatment-emergent manic symptoms. However, most reports of antidepressant-induced mania in bipolar II depression derive from older studies of tricyclic antidepressant monotherapy in bipolar I depression, or from studies of bipolar depressed patients that allowed for the inclusion of both bipolar I and bipolar II depressed subjects.[13–15,45,46]

In contrast, observations from the current aggregated IPD mega-analysis project comport with results from more recent, individual randomized controlled trials of antidepressant monotherapy that have focused exclusively on bipolar II depression.[4,16,17,34,35,47] For example, Kupfer et al.[47] reported that patients with bipolar II depression were no more likely than patients with unipolar depression to develop hypomania during acute imipramine monotherapy. Similar findings were subsequently reported by Amsterdam et al.[34] Moreover, studies containing exclusively bipolar II depressed patients have shown good antidepressant effectiveness for escitalopram monotherapy,[16] fluoxetine monotherapy,[27] sertraline monotherapy,[17] and venlafaxine monotherapy,[29–32,48] with a relatively low frequency of drug-induced hypomanic symptom. Finally, Altshuler et al.[17] prospectively examined 142 bipolar II depressed patients receiving either lithium monotherapy ($n=49$), sertraline monotherapy ($n=45$), or combination lithium plus sertraline ($n=48$). Only 14% of patients experienced a treatment-emergent hypomanic symptom: mild hypomania ($n=17$); and severe hypomania ($n=3$). Hypomanic switch rates did not differ between the antidepressant or lithium monotherapy conditions, and these rates were similar to the combined drug condition.

Several caveats should be considered in the interpretation of the current mega-analysis findings. The current IPD mega-analysis was ultimately limited to the inclusion of data from four independent trials conducted at a single, university-based research site (as the inclusion of IPD results from other sites was unavailable for inclusion). We acknowledge that the exclusion of trials from a diversity of sites may have resulted in biased observations in the current mega-analysis. On the other hand, we would also note that the inclusion of aggregated IPD mega-analyses is only possible where IPD datasets are available, and we were unable to obtain useable prospective IPD data from three known antidepressant treatment trials for bipolar II depression.[16,17,34,48] Furthermore, inclusion of trials with substantially shorter treatment durations[35,36] may have altered the current findings, and would have also limited our ability to examine relative safety and effectiveness outcomes over time. In this regard, the inclusion into the current mega-analysis of trials with treatment durations of at least 12 weeks, uniquely allowed us to analyze the aggregated rate of change of depressive symptoms over time, relative to the rate of treatment-emergent hypomanic symptoms occurring over time. If we had included trials with shorter windows of observation, we would have had to extrapolate these data in order to accurately compare their change over time with those of the longer treatment duration datasets. This procedure may have introduced a bias that could have misrepresented the rate of symptom change in the shorter duration trials as being slower than that of the longer duration trials. We would also have had to change the unit of analysis to EOT score for the 12-week trials with the resulting analysis of covariance used to examined only baseline and EOT scores for all trials (with the assumption that trials of varying lengths are similar in outcome to one another). In this case, however, we could no longer comment on the rate of symptom change over time—which we believe would provide a richer observation of antidepressant monotherapy.

Although lithium monotherapy appears to be less effective than antidepressant monotherapy in the current mega-analysis, we acknowledge that other mood stabilizers (e.g., lamotrigine) may have produced different outcomes than lithium.[49]

It is also possible that the relatively low treatment-emergent hypomanic symptom rates seen among all treatment conditions represent a background frequency of manic symptoms due to the illness rather than true drug-induced phenomena. Additionally, it is possible that the lack of difference among treatment conditions in the rate of hypomanic symptoms may be the result of relatively small sample sizes within the mega-analysis dataset, and that there is insufficient statistical power to detect group differences. Nevertheless, we would note that the estimated change in YMR scores by the end of week 12 was modest and not clinically meaningful for all treatment conditions. We would further note that failure to detect significant differences in YMR change scores between treatment conditions is not proof that such differences do not exist.

It is also possible that the frequency and severity of hypomanic symptoms may have been greater in the antidepressant conditions had a longer treatment duration been proposed. However,

observations from other bipolar II depression trials suggest that the majority of treatment-emergent hypomanic symptoms occur early in therapy, if they occur at all, and do not generally interfere with treatment outcome.[16,17]

We would also note that the low detection rate of hypomanic symptoms in the current mega-analysis may have resulted from the inclusion of patients with more mild illness recruited from only a single investigative site, whereby the patients had a generally lower propensity for treatment-emergent hypomania. In contrast, however, we note that the estimated frequencies of hypomanic symptoms at baseline were similar for all treatment conditions and did not differ substantially from hypomanic symptom rates reported by other bipolar II depression studies that were not included in the current aggregated IPD mega-analysis.[17]

It is possible that certain types of bipolar individuals (e.g., those with a prior history of antidepressant-induced hypomania) may be more vulnerable to treatment-emergent hypomania[46]; however, this factor would have been accounted for by the moderator analyses within the current mega-analysis.

Finally, we acknowledge that the results of this aggregated IPD mega-analysis should be interpreted as preliminary, and limited by the modest study number and sample size. For instance, while this mega-analysis is the first to aggregate IPD data from multiple trials of bipolar II disorder, all the data included were obtained from previous trials run by the principal author. While this introduces the possibility for investigator biases, we point out that our IPD mega-analysis findings are consistent with the results of two other trials for which we were unable to obtain IPD data.[16,17] Thus, findings from the current IPD mega-analysis should not be construed as endorsing a change in existing clinical practice guidelines for treating bipolar II depression. Rather, this study represents the first aggregated IPD mega-analysis of antidepressant versus mood stabilizer monotherapy for acute bipolar II depression.

While our current mega-analysis findings suggest that some antidepressant medications may be more effective than lithium carbonate therapy at resolving acute bipolar II depression, this should not imply that antidepressants may also act as mood stabilizer drugs during long-term therapy. Rather, our mega-analysis findings may suggest that bipolar II disorder may share neurobiological mechanisms closer to recurrent major depressive disorder than with bipolar I disorder. Further studies will be needed to assess a possible mood stabilizer effect of long-term antidepressant therapy on the prevention of hypomania in bipolar II disorder.

In conclusion, the recommendations drawn from this series of evidence-based bipolar II studies would appear to diverge from earlier bipolar practice guidelines. Antidepressant monotherapy may provide superior short-term benefit for bipolar II depression, with no clinically meaningful, treatment-emergent increase in hypomanic symptoms (relative to lithium monotherapy).

AUTHOR CONTRIBUTIONS

Dr. Amsterdam wrote and served as principal investigator for all individual grant studies and compiled and had access to the individual patient study datasets for all aggregated mega-analyses. He wrote and edited the first and all subsequent manuscript drafts.

Dr. Xu implemented and conducted the statistical mega-analyses; and co-wrote and edited the first and all subsequent manuscript drafts.

ACKNOWLEDGMENTS

None.

FUNDING INFORMATION

This research was originally funded by NIMH grant MH060353 and from Investigator Initiated grants from The Stanley Medical Research Institute (Chicago, IL) and Lilly Research Laboratories (Indianapolis, IN).

CONFLICT OF INTEREST STATEMENT

Dr. Amsterdam: Myrtelle, Inc. - Data Safety Monitoring Board (DSMB member): Gene Therapy for Treatment of Canavan Disease.

National Institute of Mental Health (NIMH) - Data Safety Monitoring Board (DSMB member): Ketamine for reduction of suicidal ideation R01 MH125155-01).

Neurawell Therapeutics, Inc. - Advisory Board Member.

Dr. Xu: None.

DATA AVAILABILITY STATEMENT

The individual participant data and aggregated datasets that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL STATEMENT

The purpose and procedures of this study were reviewed and approved in accordance with the ethical standards of the Institutional Review Board (IRB) at the University of Pennsylvania. Informed consent by subject participants was waived by the university IRB for this retrospective study of previously collected data; and all data identification and database storage conformed with Good Clinical Practice guidelines for human research, with oversight by the local Office of Human Research.

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How to cite this article: Amsterdam JD, Xu C. Multi-trial, aggregated, individual participant data mega-analysis of short-term antidepressant versus mood stabilizer monotherapy of bipolar type II major depressive episode. *Bipolar Disord*. 2023;00:1-10. doi:10.1111/bdi.13378