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Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness):

A Pragmatic 6-Month Trial of Lithium Versus Quetiapine for Bipolar Disorder

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ABSTRACT

Background: Bipolar disorder is among the 10 most disabling medical conditions worldwide. While lithium has been used extensively for bipolar disorder since the 1970s, second-generation antipsychotics (SGAs) have supplanted lithium since 1998. To date, no randomized comparative-effectiveness study has compared lithium and any SGA.

Method: Within the duration of the study (September 2010–September 2013), participants with bipolar I or II disorder (*DSM-IV-TR*) were randomized for 6 months to receive lithium (n = 240) or quetiapine (n = 242). Lithium and quetiapine were combined with other medications for bipolar disorder consistent with typical clinical practice (adjunctive personalized treatment [APT], excluding any SGA for the lithium + APT group and excluding lithium or any other SGA for the quetiapine + APT group). Coprimary outcome measures included Clinical Global Impressions-Efficacy Index (CGI-EI) and necessary clinical adjustments, which measured number of changes in adjunctive personalized treatment. Secondary measures included a full range of symptoms, cardiovascular risk, functioning, quality of life, suicidal ideation and behavior, and adverse events.

Results: Participants improved across all measures, and over 20% had a sustained response. Primary (CGI-EI, $P = .59$; necessary clinical adjustments, $P = .15$) and secondary outcome changes were not statistically significantly different between the 2 groups. For participants with greater manic/hypomanic symptoms, CGI-EI changes were significantly more favorable with quetiapine + APT ($P = .02$). Among those with anxiety, the lithium + APT group had fewer necessary clinical adjustments per month ($P = .02$). Lithium was better tolerated than quetiapine in terms of the burden of side effects frequency ($P = .05$), intensity ($P = .01$), and impairment ($P = .01$).

Conclusions: Despite adequate power to detect clinically meaningful differences, we found outcomes with lithium + APT and quetiapine + APT were not significantly different across 6 months of treatment for bipolar disorder.

Trial Registration: ClinicalTrials.gov identifier for the Bipolar CHOICE study: NCT01331304

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The full spectrum of bipolar disorder affects up to 4.5% of the US population,[1] with a total annual (direct plus indirect) cost in the United States of at least $151 billion.[2] Most people living with bipolar disorder have relapsing, recurrent, chronic condition, commonly with residual (subsyndromal) mood symptoms and related disability.[3] In addition, bipolar disorder is associated with multiple comorbid psychiatric and medical challenges.[4] Pharmacotherapy guidelines recommend mood stabilizers for both acute treatment of mood episodes and long-term maintenance treatment.[5] Clinicians and patients, however, frequently must choose between the classic antimanic mood stabilizers (ie, lithium or valproate) or second-generation antipsychotics (SGAs; eg, aripiprazole, asenapine, lurasidone, olanzapine, quetiapine, risperidone, or ziprasidone).

Among the classic antimanic mood stabilizers, lithium has the largest evidence base, is available as an inexpensive generic, and has a well-established but narrow therapeutic window that requires blood level monitoring.[6] Lithium, even at therapeutic levels, can cause tremor, polyuria, nausea, vomiting, and diarrhea. Longer term therapy with lithium can cause renal impairment and hypothyroidism.[6] Quetiapine is the most extensively studied, broadly efficacious, and the most widely prescribed SGA for bipolar disorder in the United States.[7,8] Quetiapine can cause clinically significant sedation/somnolence and weight gain, with the latter in turn increasing risks of cardiovascular disease, diabetes mellitus, and the metabolic syndrome in a patient population already at a higher risk than those in the general population.[9,10] Unlike lithium, the effects of years of exposure to quetiapine have not yet been systematically studied, although first-generation

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†Drs Leon and Singh, important contributors who provided energy and commitment to the project, are deceased.

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Clinical Points

- Quetiapine, along with other second-generation antipsychotics, has largely supplanted the use of lithium for bipolar disorder, but no pragmatic studies have ever examined whether quetiapine would result in better outcomes.
- Quetiapine and lithium, given along with other medications commonly used for bipolar disorder (adjunctive personalized treatment), resulted in 6-month outcomes that were not significantly different.
- Growing use of second-generation antipsychotics as a treatment for bipolar disorder over the past 2 decades, leading to a widespread shift away from lithium as the cornerstone of therapy for bipolar disorder, may not provide substantially better outcomes, safety, or tolerability.

antipsychotics and SGAs may increase the risk of cardiovascular death.[11]

In the past decade, clinicians have been prescribing more SGAs and less lithium to manage patients with bipolar disorder,[12] but no randomized comparative-effectiveness study has examined the standard clinical practice advantages and disadvantages of any SGA, including quetiapine, compared to lithium. Although efficacy studies have established quetiapine superiority over placebo and similarity to lithium using monotherapy or 2-drug combination therapy in bipolar disorder populations with minimal psychiatric comorbid conditions (ie, lacking clinical heterogeneity),[13] no randomized studies have evaluated the performance of quetiapine under standard clinical practice conditions (ie, using combination regimens to address all clinically significant symptoms in a diverse group of patients with bipolar disorder). The purpose of the Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness) study was to assess the benefits and harms of 6 months of lithium compared to quetiapine in a generalizable (heterogeneous) cohort of symptomatic outpatients with bipolar disorder who were also taking adjunctive personalized treatment (APT).

METHOD

Study Design

This was an 11-site, parallel group, randomized comparative-effectiveness study of participants with bipolar I or II disorder who were at least mildly ill, had not been treated with adequate doses of lithium or quetiapine in the past, and were willing to be randomized to lithium + APT or quetiapine + APT. Adjunctive personalized treatment, based on the Texas Implementation of Medication Algorithm,[14] was guideline-informed, evidence based, and personalized according to current symptoms, prior treatment history, and illness course.[14] The overall study was approved by the institutional review board (IRB) at the Massachusetts General Hospital-Partners HealthCare (coordinating center) as well as the IRBs at the other 10 sites. Patients signed approved informed consent forms in the presence of study clinicians prior to initiation of any study procedures. The study was conducted from September 2010 to September 2013. The study is registered on ClinicalTrials.gov (identifier: NCT01331304).

Study Participants

Participants were screened based on meeting 3 primary study criteria (over 18 years of age, bipolar I or II disorder [*DSM-IV-TR* criteria], and current symptomatic status). The primary exclusion criteria were any contraindication to lithium or quetiapine (eg, prior hypersensitivity to lithium or quetiapine, severe cardiovascular or renal disease, or pregnancy), being currently in crisis such that inpatient hospitalization or other crisis management should take priority, currently taking lithium or quetiapine, and unwillingness to comply with study requirements. The rationale and design of this study are described in detail elsewhere.[15]

Randomization and Treatment

Participants were randomized to lithium + APT or quetiapine + APT using an internet-based program with stratification. In the 11 clinical research sites, a research clinician provided the treatment and tracked treatments prescribed; treatment was monitored but not directed by the national coordinating center. For each site, randomization was stratified by provider and prior lifetime lithium use. Adjunctive personalized treatment allowed research clinicians to flexibly use the best evidence-based bipolar disorder treatment(s), personalized with respect to current symptoms and prior medication exposure, response, and tolerability.

However, treatment was restricted in that the lithium + APT group could not receive quetiapine or any other SGA and the quetiapine + APT group could not receive lithium or any other SGA.

Primary Outcomes

Clinical Global Impressions-Efficacy Index (CGI-EI). The CGI-EI[16,17] integrates benefit and harms to yield scores that can be compared across interventions. Benefit and harm were rated separately. The CGI-EI was generated by using the CGI-Bipolar Version (CGI-BP),[18] a modified version of the CGI designed specifically for use in assessing global illness severity in patients with bipolar disorder. This version assigns ratings for mania, depression, overall severity, and side effects. We defined the CGI-EI score as the difference between the rated benefit and harm; thus, CGI-EI spans ordinally (ie, the numbers assigned are ranked in order) from −3 (no benefit, significant harm) to +3 (significant benefit, no harm). To avoid the risk of concurrent knowledge of benefit and harm interfering with rater blinding, assessments of therapeutic effects and side effects were performed by raters who had no knowledge of treatment assignment.

Necessary clinical adjustments. The Medication Recommendation Tracking Form[19] was developed and successfully implemented in a previous study to capture

recommended medication changes at each study visit. Clinicians record dosage changes, missed doses, and new medications added or discontinued, and they specify the reason for each change. Any change in all psychotropic medications, or medications used to treat side effects, is coded along with the reason for the change. We calculated the necessary clinical adjustments from the raw data in the Medication Recommendation Tracking Form as described in detail elsewhere.[19] As stated in that article, "A medication change was defined as a [necessary clinical adjustment] if the primary or secondary reason was due to symptoms or side effects that were either new, persistent, or worsened (ie, improved symptoms/side effects did not qualify as a [necessary clinical adjustment]). If any medication change met this initial criterion, but it was also recorded as a planned dose titration or randomization, it was not counted as a [necessary clinical adjustment]. Changes that were made in between study visits (either by phone contact or unexpected office visit) were counted towards the nearest study visit."[19(p1689)] Necessary clinical adjustments were recorded for the full duration of the study.

Secondary Outcomes

The Framingham risk score[20] was used to assess the cardiovascular side effects. The Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT)[21] was used to assess functioning. The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[22] assessed subjective quality of life.

The Bipolar Inventory of Symptoms Scale (BISS),[23,24] which assesses a broad array of bipolar symptoms, was used to generate Montgomery-Asberg Depression Rating Scale (MADRS)[25] and Young Mania Rating Scale (YMRS)[26] scores. The Concise Health Risk Tracking[27] assessed cognitions, behaviors, and impulsivity associated with suicide. The Columbia-Suicide Severity Rating Scale (C-SSRS) baseline and follow-up versions[28] were used to assess lifetime and current/ongoing suicidal ideation and behavior. The Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) Scale[29] measured medication side effects and burden. The Intent to Attend Scale[30] measured participants' intent to attend the next study visit, or to complete the entire study, and was used to inform the extent to which attrition is ignorable.[31]

Our primary hypothesis was that participants randomized to lithium + APT would have, on average, more favorable overall benefit relative to harm, as assessed by CGI-EI scores over 6 months compared to those randomized to quetiapine + APT. For the coprimary hypothesis, we proposed that participants randomized to quetiapine + APT would have more necessary clinical adjustments in medications per month over the course of 6 months compared to those randomized to lithium + APT.

Raters

Consistent with the design of a comparative-effectiveness study, treatment was open for participants and study clinicians. Raters were, however, blind to treatment assignment and specific side effects. The blind was maintained by ensuring that raters did not have access to patient records. Raters had at least a bachelor's degree and completed rater training and certification on the assessments, and they were retrained every 12 months. As an additional check, blinded ratings were compared with unblinded ratings conducted by physicians to ensure reliability.

Statistical Analyses

Because this study had 2 coprimary outcomes (CGI-EI and necessary clinical adjustments), the analyses of the treatment effect in the 2 primary hypotheses (described below) each involved a 2-tailed α level of .025 (ie, .05/2). Other statistical tests used a 2-tailed α level of .05, not corrected for multiple comparisons. Sample size requirements for mixed-effects linear regression analyses were examined in a simulation study using SAS Proc Mixed (SAS Institute). We assumed that each subject would participate in approximately 6 (of the 9 planned) CGI-EI assessments and that the intraclass correlation coefficient over time for the CGI-EI would be 0.40, 0.50, or 0.60. One thousand data sets were generated for each combination of simulation specifications. A sample size of 216 participants per group was calculated to be necessary to provide power of at least 0.80 to detect an effect size of 0.30 SD units or larger.

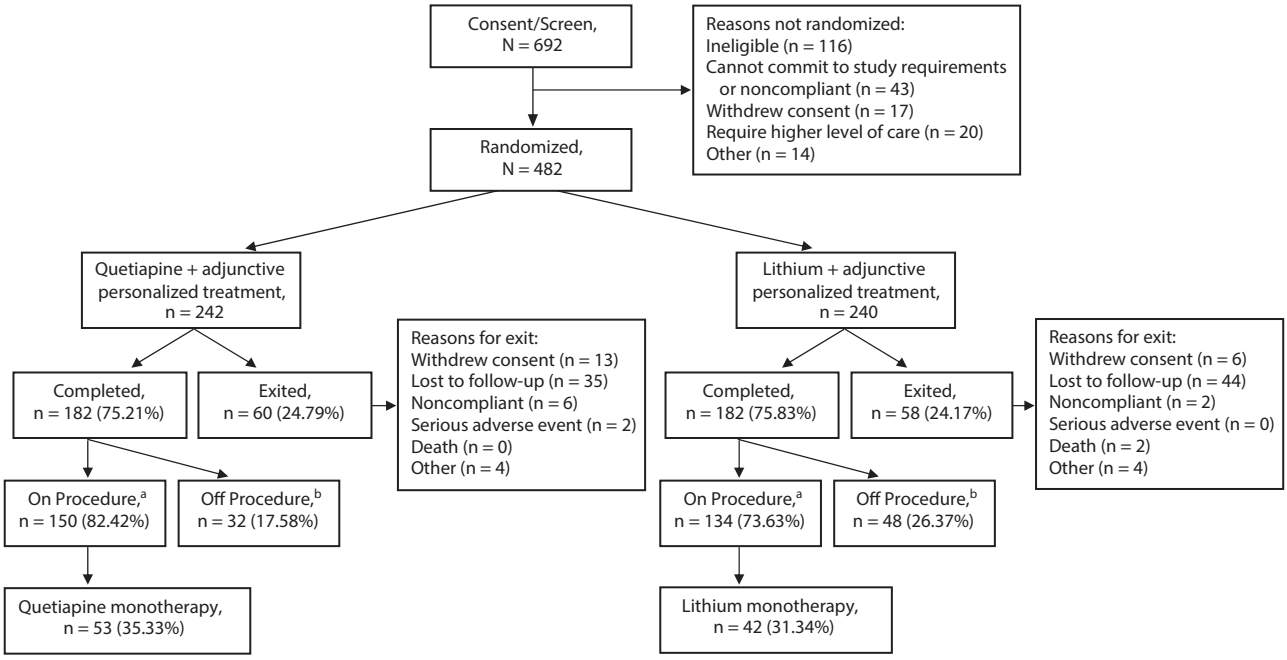
Primary hypotheses. For the first coprimary aim, mixed-effects linear regression analyses[32] compared the 2 intervention groups on the repeated assessments of the CGI-EI over 6 months. For the second coprimary, patient monthly rates of necessary clinical adjustments (determined by dividing total number of necessary clinical adjustments during follow-up by the length of follow-up—to account for attrition and resulting differential exposure time) for treatment groups were compared using a Wilcoxon rank sum test. For the secondary outcomes, mixed-effects linear regression analyses compared the 2 intervention groups on the repeated assessments.

Attrition. Data from all participants were incorporated into the mixed-effects model, including those who dropped out prematurely. To examine the assumption of ignorable attrition for the CGI-EI end point, we calculated the probability of a patient attending a visit using the recorded intent to attend variable[30] and then weighted each datum from the attended visit by the inverse of this probability. This adjusts for possible treatment effects on the patients' attendance.[33] The analysis of necessary clinical adjustments inherently took into account attrition by taking an average rate of necessary clinical adjustments over each patient-specific follow-up.

RESULTS

A total of 482 participants were enrolled. The CONSORT chart describing screening, randomization, early terminations, and completions is shown in Figure 1.

Figure 1. CONSORT Chart



[a]Completed study taking randomized treatment without deviating from study requirements.
[b]Completed study deviating from study requirements.

Demographics, clinical variables, and comorbid conditions overall and for each randomized group are shown in Table 1.

Participants randomized to lithium + APT (49.8%, n = 240) were dosed to maximum tolerability, with a mean maximum dose of 1,007.5 mg (median dose = 900 mg) and mean (SD) blood lithium levels at weeks 2, 16, and 24 of 0.5 (0.3), 0.6 (0.3), and 0.6 (0.4) mEq/L, respectively. Participants randomized to quetiapine + APT (50.2%, n = 242) took a mean maximum dose of quetiapine of 344.9 mg (170.6) (median dose = 300 mg). With regard to the other medications as a part of APT, participants took a mean of 1.2 other medications over the study (mean difference between treatment groups was not significant, $P = .10$). By the end of 6 months, 23.8% of the lithium + APT and 27.3% of the quetiapine + APT group completed the study ($P = .14$) on monotherapy.

Primary Outcomes

Both groups had significant improvement in CGI-EI over 6 months, with the majority of improvement occurring within the first 2 months of the study (Table 2 and Figure 2). Overall, participants had a mean of 0.9 necessary clinical adjustments per month.

As shown in Table 2 and Figure 2, changes in the CGI-EI did not differ between treatment groups. The sensitivity analysis provided nearly identical estimates (not shown), supporting the assumption of ignorable attrition. The monthly rates of necessary clinical adjustments did not differ between lithium + APT (mean = 0.8, SD = 0.8) and quetiapine + APT (mean = 0.9, SD = 1.0) ($P = .15$). We found similar nonsignificant findings for changes in all secondary measures. Notably, no statistically significant differences between groups were found for any measure of suicidal ideation, suicidal behavior, suicide attempts, or hospitalizations related to suicide. However, 1 participant died of suicide within a week of randomization to the lithium + APT arm.

We examined whether specific predetermined variables predicted better outcomes with either of the treatments by looking for a significant treatment-by-characteristic-by-time interaction. These variables included demographics; psychiatric and medical comorbid conditions; bipolar I or II disorder subtype; BISS depression, mania, or anxiety symptom severity; and suicide risk. The only significant moderator for CGI-EI was that the greater the baseline BISS mania severity, the greater the effect of quetiapine compared to lithium ($P = .02$). That is, the difference at 6 months on the CGI-EI between lithium and quetiapine decreased by 0.06 for each 10-point increase in BISS mania score at baseline. Moderators of differences in necessary clinical adjustments between lithium + APT and quetiapine + APT included comorbid anxiety conditions. Among those with anxiety (ie, patients with any of the following current diagnoses based on the Mini-International Neuropsychiatric Interview[34]: panic disorder, agoraphobia, social phobia, and generalized anxiety disorder), the lithium + APT group had fewer necessary clinical adjustments per month as compared to the quetiapine + APT group (0.83 vs 1.11, respectively; $P = .02$), while in those without comorbid anxiety, the lithium + APT and quetiapine + APT groups experienced similar rates of necessary clinical adjustments per month (0.78 and 0.69, respectively).

Table 1. Baseline Demographics, Clinical Features, and Comorbid Conditions in CHOICE[a]

Characteristic	Overall (N = 482)	Randomized Treatment Group: Lithium + Adjunctive Personalized Treatment (n = 240)	Randomized Treatment Group: Quetiapine + Adjunctive Personalized Treatment (n = 242)	*P* Value
Demographics				
Female	58.7 (283/482)	58.3 (140/240)	59.1 (143/242)	.87
Age, y	38.9 ± 12.1 (482)	38.6 ± 12.1 (240)	39.1 ± 12.2 (242)	.63
Race				
White	72.2 (348/482)	72.5 (174/240)	71.9 (174/242)	.83
Black	19.9 (96/482)	19.2 (46/240)	20.7 (50/242)	
Asian	3.3 (16/482)	3.8 (9/240)	2.9 (7/242)	
Other	4.6 (22/482)	4.6 (11/240)	4.5 (11/242)	
Ethnicity: Hispanic or Latino	11.0 (53/482)	13.3 (32/240)	8.7 (21/242)	.09
Education				
Less than high school	5.0 (24/482)	5.0 (12/240)	5.0 (12/242)	.85
High school or GED	20.3 (98/482)	18.3 (44/240)	22.3 (54/242)	
Some college	30.9 (149/482)	30.0 (72/240)	31.8 (77/242)	
Tech school or associates degree	12.0 (58/482)	12.9 (31/240)	11.2 (27/242)	
College diploma	24.3 (117/482)	25.8 (62/240)	22.7 (55/242)	
Graduate or professional degree	7.5 (36/482)	7.9 (19/240)	7.0 (17/242)	
Employment status				
Employed	36.3 (175/482)	39.2 (94/240)	33.5 (81/242)	.56
Unemployed	35.3 (170/482)	32.9 (79/240)	37.6 (91/242)	
Disability recipient	15.4 (74/482)	15.8 (38/240)	14.9 (36/242)	
Student	9.1 (44/482)	7.5 (18/240)	10.7 (26/242)	
Retired	1.7 (8/482)	2.1 (5/240)	1.2 (3/242)	
Other	2.3 (11/482)	2.5 (6/240)	2.1 (5/242)	
Clinical features				
Bipolar I disorder	68.3 (329/482)	66.7 (160/240)	69.8 (169/242)	.46
History of psychiatric hospitalizations	46.8 (225/482)	45.6 (109/240)	47.9 (116/242)	.61
History of suicide attempts[b]	36.1 (173/479)	36.3 (86/237)	36.0 (87/242)	.94
Age at first depressive episode, y	16.4 ± 8.0 (482)	16.0 ± 8.6 (240)	16.7 ± 7.5 (242)	.36
Age at first manic episode, y	19.8 ± 9.5 (478)	19.5 ± 9.8 (237)	20.1 ± 9.1 (241)	.47
Age at first mood episode, y	15.5 ± 7.7 (482)	15.1 ± 8.3 (240)	16.0 ± 7.1 (242)	.17
Duration of depression, y	22.5 ± 12.3 (482)	22.6 ± 12.3 (240)	22.4 ± 12.3 (242)	.90
Duration of mania, y	19.0 ± 12.2 (478)	19.1 ± 12.1 (237)	18.9 ± 12.3 (241)	.92
Illness duration, y	23.3 ± 12.4 (482)	23.6 ± 12.5 (240)	23.1 ± 12.4 (242)	.70
BISS total				
Overall	56.1 ± 18.8 (482)	55.7 ± 18.8 (240)	56.5 ± 19.0 (242)	.67
Depression	37.6 ± 14.0 (482)	38.0 ± 13.4 (240)	37.2 ± 14.6 (242)	.53
Mania	18.5 ± 12.1 (482)	17.8 ± 12.1 (240)	19.3 ± 12.1 (242)	.16
CGI-Severity of Illness score	4.5 ± 0.9 (482)	4.5 ± 0.8 (240)	4.5 ± 0.9 (242)	.83
MADRS	23.8 ± 10.3 (482)	24.2 ± 10.0 (240)	23.5 ± 10.6 (242)	.44
YMRS	13.4 ± 8.7 (482)	13.0 ± 8.9 (240)	13.8 ± 8.6 (242)	.33
MINI diagnoses				
Current manic episode	6.8 (33/482)	7.5 (18/240)	6.2 (15/242)	.57
Current hypomanic episode	4.8 (23/482)	3.8 (9/240)	5.8 (14/242)	
Current depressive episode	62.9 (303/482)	60.8 (146/240)	64.9 (157/242)	
Current mixed episode	10.0 (48/482)	10.4 (25/240)	9.5 (23/242)	
None of the above (subthreshold)	15.6 (75/482)	17.5 (42/240)	13.6 (33/242)	
Comorbid conditions				
Panic disorder (current)	23.2 (112/482)	18.8 (45/240)	27.7 (67/242)	.02
Agoraphobia (current)	36.5 (176/482)	37.1 (89/240)	36.0 (87/242)	.80
Social phobia (current)	24.7 (119/482)	21.3 (51/240)	28.1 (68/242)	.08
OCD (current)	10.6 (51/481)	10.4 (25/240)	10.8 (26/241)	.90
PTSD (current)	12.0 (58/482)	12.9 (31/240)	11.2 (27/242)	.55
GAD (current)	22.3 (107/480)	23.4 (56/239)	21.2 (51/241)	.55
Any anxiety disorder (current)[c]	57.5 (277/482)	55.4 (133/240)	59.5 (144/242)	.36
Any substance use disorder (lifetime)[d]	61.4 (296/482)	62.1 (149/240)	60.7 (147/242)	.76

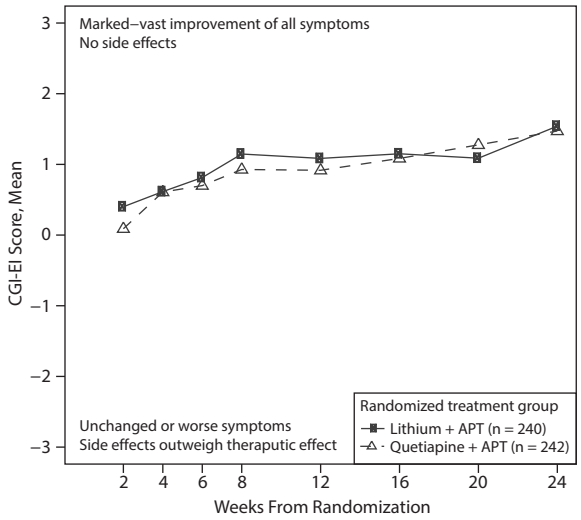
[a]Statistics reported are (n/N) for categorical variables and mean ± SD (n) for continuous variables. *P* values reported are based on χ^2 test for categorical variables and *t* test for continuous variables.
[b]Based on Columbia-Suicide Severity Rating Scale.
[c]Includes patients with any of the following current diagnoses (based on MINI): panic disorder, agoraphobia, social phobia, and generalized anxiety disorder.
[d]Includes patients with any current alcohol/drug abuse/dependence (based on MINI).
Abbreviations: BISS = Bipolar Inventory of Symptoms Scale, CGI = Clinical Global Impressions, CHOICE = Clinical Health Outcomes Initiative in Comparative Effectiveness, GAD = generalized anxiety disorder, GED = General Education Development, MADRS = Montgomery-Asberg Depression Rating Scale, MINI = Mini-International Neuropsychiatric Interview, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, YMRS = Young Mania Rating Scale.

Table 2. Model-Based Treatment Effects Over Primary and Secondary Outcomes[a]

Outcome	Estimated Change From Baseline, Lithium + APT		Estimated Change From Baseline, Quetiapine + APT		Estimated 6-mo Difference, (lithium + APT) – (quetiapine + APT)	
	Mean (95% CI)	*P* Value	Mean (95% CI)	*P* Value	Mean (95% CI)	*P* Value
Primary outcomes						
CGI-EI difference	1.58 (1.32 to 1.84)	<.0001	1.52 (1.26 to 1.78)	<.0001	0.06 (−0.16 to 0.29)	.59
Necessary clinical adjustments/mo	−0.93 (−1.10 to −0.75)	<.0001	−1.00 (−1.17 to −0.82)	<.0001	0.07 (−0.07 to 0.21)	.34
Secondary outcomes						
CGI-BP						
Severity	−1.51 (−1.67 to −1.36)	<.0001	−1.61 (−1.77 to −1.46)	<.0001	0.10 (−0.10 to 0.31)	.31
Depression	−1.43 (−1.59 to −1.27)	<.0001	−1.54 (−1.70 to −1.38)	<.0001	0.10 (−0.10 to 0.31)	.32
Mania	−0.90 (−1.04 to −0.76)	<.0001	−0.90 (−1.04 to −0.76)	<.0001	0.00 (−0.16 to 0.16)	.99
BISS						
Overall	−27.61 (−29.99 to −25.24)	<.0001	−28.56 (−30.91 to −26.21)	<.0001	0.94 (−2.10 to 3.99)	.54
Depression	−18.21 (−20.04 to −16.37)	<.0001	−18.92 (−20.73 to −17.11)	<.0001	0.71 (−1.60 to 3.01)	.55
Mania	−9.43 (−10.66 to −8.20)	<.0001	−9.21 (−10.43 to −7.99)	<.0001	−0.22 (−1.55 to 1.11)	.75
CHRT	−11.04 (−12.39 to −9.69)	<.0001	−10.43 (−11.75 to −9.11)	<.0001	−0.61 (−2.37 to 1.14)	.49
Framingham risk score	−0.26 (−0.66 to 0.14)	.20	0.17 (−0.21 to 0.54)	.19	−0.43 (−0.94 to 0.09)	.11
FIBSER						
Frequency	−1.41 (−1.78 to −1.04)	<.0001	−1.08 (−1.45 to −0.72)	<.0001	−0.33 (−0.65 to-0.00)	.05
Intensity	−1.48 (−1.80 to −1.15)	<.0001	−1.12 (−1.44 to −0.79)	<.0001	−0.36 (−0.65 to −0.07)	.01
Impairment	−1.13 (−1.43 to −0.82)	<.0001	−0.77 (−1.07 to −0.47)	<.0001	−0.36 (−0.61 to −0.11)	.01
Q-LES-Q[b]	15.19 (12.44 to 17.94)	<.0001	15.64 (12.94 to 18.35)	<.0001	−0.45 (−4.07 to 3.17)	.81
LIFE-RIFT	−3.74 (−4.29 to −3.19)	<.0001	−3.61 (−4.15 to −3.07)	<.0001	−0.14 (−0.84 to 0.57)	.70

[a]Results are based on mixed-effects regression.
[b]General activities score (short-form total).
Abbreviations: APT = adjunctive personalized treatment, BISS = Bipolar Inventory of Symptoms Scale, CGI-BP = Clinical Global Impressions-Bipolar Version, CGI-EI = Clinical Global Impressions-Efficacy Index, CHRT = Concise Health Risk Tracking, FIBSER = Frequency, Intensity, and Burden of Side Effects Rating, LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

Figure 2. Clinical Improvement Over Study Duration



Abbreviations: APT = adjunctive personalized treatment, CGI-EI = Clinical Global Impressions-Efficacy Index.

Table 3. Predictors of Overall Response[a]

Variable	Odds Ratio	95% CI	*P* Value
No current anxiety disorder (vs any[b])	1.81	1.11 to 2.96	.02
MADRS (10-point decrease)	1.76	1.35 to 2.30	<.01
YMRS (10-point decrease)	1.95	1.42 to 2.68	<.01
Employed/student (vs not[c])	1.67	1.03 to 2.72	.04
MINI suicide risk[d] (1-point decrease)	1.46	1.07 to 1.99	.02
Bipolar II (vs I) disorder	1.75	1.07 to 2.86	.03

[a]Results are based on stepwise logistic regression with entry and removal criteria of $P < .1$. Overall response is defined as Clinical Global Impressions-bipolar version severity score ≤ 2 for ≥ 8 weeks.
[b]Includes patients with any of the following current diagnoses (based on MINI): panic disorder, agoraphobia, social phobia, and generalized anxiety disorder.
[c]Includes unemployed, disability recipient, retired, and other.
[d]Defined as follows: none = 0, low = 1, moderate = 2, high = 3.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, MINI = Mini-International Neuropsychiatric Interview, YMRS = Young Mania Rating Scale.

As a part of our moderator analysis, we tested whether entry mood episode (MDD, hypomanic/manic, mixed, neither) moderated the treatment effect on the 2 coprimary outcomes—it proved nonsignificant for both CGI-EI and necessary clinical adjustments ($P > .05$). We did not include a table for the entire moderator analysis since most of the findings were nonsignificant and it was not the primary aim of the study.

The proportion of participants who experienced sustained response (CGI-BP severity ≤ 2 for at least 8 weeks) was 21.4% overall, with 24.2% in the lithium + APT group and 18.6% in the quetiapine + APT group (no statistically significant group difference; $P = .14$). Predictors of overall response with odds ratios are shown in Table 3.

About 60% of each group continued with their randomized medication for the entire 6-month study duration, without any differences in survival functions (log-rank test, $P = .97$). Quetiapine + APT resulted in modestly greater adverse effects over the 6 months of treatment on FIBSER frequency ($P = .05$), intensity ($P = .01$), and impairment ($P = .01$) compared to lithium + APT, with most of the differences occurring within the first 3 months.

DISCUSSION

We found that participants with bipolar disorder, regardless of treatment group, improved over 6 months, with the majority of improvement occurring within the first 8 weeks of treatment. For all outcome measures, lithium + APT and quetiapine + APT were not statistically significantly different between groups.

Moderators of CGI-EI changes between groups included baseline manic and hypomanic symptoms, with a greater difference in improvement favoring quetiapine + APT compared to lithium + APT, suggesting that quetiapine may be the more effective strategy for patients presenting with greater manic symptoms. This result should be considered preliminary, however, as it was not predicted and arose in the context of examining multiple moderators. We did not find that baseline depression or anxiety predicted a difference in response to lithium + APT or quetiapine + APT, contrary to our expectation that the quetiapine + APT group would have had a superior response given the evidence that quetiapine is efficacious for bipolar depression[7] and anxiety in the context of bipolar disorder,[35,36] whereas lithium is widely thought to yield benefits that are, at best, modest for bipolar depression and minimal for anxiety. In contrast, we found that the lithium + APT compared to quetiapine + APT group required fewer necessary clinical adjustments among those participants who had anxiety. Lithium has been reported to have distinctive antisuicidal properties, independent of its effects on depression,[37] but we did not find a difference in any suicidal measure between the lithium + APT and quetiapine + APT groups in a cohort with a substantial risk of suicidal outcomes. Thus, our findings contrast with heuristics about choosing lithium or quetiapine based on depression, anxiety, or suicidal risk. It is possible, however, that the 6-month design could have limited our ability to detect the differential benefits of the 2 regimens on suicidal behaviors; a longer study is needed.

The quetiapine group had a modestly greater side effect burden for the first few months of treatment; however, both groups had similar discontinuation rates. We thus conclude that the 2 strategies were both similarly effective and similarly tolerated. One implication of this study is that the growing use of SGAs as a treatment for bipolar disorder over the past 2 decades, leading to a widespread shift away from lithium as the cornerstone of therapy for bipolar disorder, may not provide substantially better outcomes, safety, or tolerability. Given the greater potential for adverse metabolic outcomes with the SGAs, studies of even longer duration are needed to determine whether lithium might actually have a more favorable risk benefit across years or even decades of preventive therapy.

One limitation of this study is a direct result of the decision to conduct a comparative-effectiveness study rather than a more restrictive efficacy study, namely, that our findings may have been influenced by the lack of blinding of participants and research physicians. With relatively low sustained response rates and no placebo group, it might be suggested that the study treatments were comparably ineffective rather than comparably effective. Placebo control groups and double-blind administration of study interventions can increase assay sensitivity and minimize some aspects of bias, but they can also introduce limitations on the generalizability of the results. For a comparative-effectiveness study, when the efficacy of readily available interventions has already been established and if the participants and clinicians are in reasonable equipoise about the study treatments, then neither a placebo group nor blinding are necessary to answer the question at hand, namely, is one treatment superior to the other under more generalizable standard clinical (or "real world") circumstances. By having the study clinicians unblinded, we allowed them to manage patients just as they would in clinical practice, thus maximizing ecological validity. Had we included a placebo comparison, it would have introduced limitation on the generalizability of the findings by excluding more severely ill participants who would most likely refuse to participate in a study involving chance of placebo assignment. We strove to mitigate bias in outcome assessments by having blinded raters.

Despite the instructions to clinicians to have their participants who were taking lithium get to levels of at least 0.6 mEq/L, lithium levels were, on average, low, with a mean of 0.6 ± 0.4 mEq/L. To address this concern, we reran our coprimary analyses on the subset of patients in the lithium + APT group who achieved at least 0.6 mEq/L lithium levels (n = 116) and those in quetiapine + APT who were prescribed a dose of quetiapine of at least 300 mg/d (n = 177). We found similar nonsignificant 6-month treatment effects on CGI-EI (estimated 6-month difference [lithium − quetiapine]: 0.06; 95% CI, −0.23 to 0.36; $P = .67$) and on necessary clinical adjustments (lithium vs quetiapine: mean [SD] = 0.9 [0.9] vs 0.9 [1.0], $P = .79$). To further assess this concern, we compared outcomes (CGI-EI and necessary clinical adjustments) between those who reached therapeutic levels and those who did not within each treatment group. Again, we found nonsignificant 6-month differences between these groups (all P values $> .05$). The validity of this subset analysis is conditional on the assumption that the 2 treatment groups remain comparable after being limited to only those patients who reach therapeutic levels of the study drug.

Another limitation is the complexity we introduced by including APT. One might argue that we should have compared lithium monotherapy to quetiapine monotherapy, but we rejected this option to facilitate recruitment, reduce bias, and, again, to maximize ecological validity (generalizability). The rules for choosing APT within the study, moreover, tried to make the 2 randomized groups as different as possible from one another, with any other SGA and lithium excluded from the quetiapine group and quetiapine and any other SGA excluded from the lithium group. Nonetheless, the APT medications used resulted in complex patterns of treatment that have been found in pharmacoepidemiologic studies[8,38,39] and will be analyzed in detail in future reports.

The study duration of 6 months could also be considered a limitation since the full effects of lithium may take 12 to 24 months to be apparent.[6] We chose 6 months for two practical reasons: (1) the study was funded for a total of 36 months without any option to continue the study longer. Six months was chosen because we could recruit and follow these participants within this time constraint; and (2) we wanted to minimize drop outs, and in conversations with patients, most said that they would be willing to remain with randomized treatment for 6 months, but not much longer.

Nevertheless, the results of Bipolar CHOICE can inform clinicians, patients, and policy makers. Given that standard clinical practice use of lithium or quetiapine resulted in 6-month outcomes that were not statistically different, clinicians and patients can base their decision on the acceptability, ease of use, and tolerability of short- and long-term adverse effects of each treatment, taking into account the burden of monitoring lithium blood levels and metabolic changes with quetiapine. Furthermore, for individuals experiencing greater severity of manic or hypomanic symptoms, quetiapine + APT may prove to have an efficacy advantage over lithium + APT. Although overall harms were comparable, some individuals may prefer to undertake the distinctive risks inherent with lithium, while others may prefer to face the different risks associated with quetiapine. Additionally, enriched efficacy studies suggest that, at least for those who respond initially to the *combination* of lithium and quetiapine, continuation with both medications could result in better outcomes than either treatment alone,[9] but the long-term benefits and harm of the combination would warrant confirmation in another comparative-effectiveness study. Further comparative-effectiveness studies should assess longer term outcomes. One method for a long-term study is to treat patients first with the combination of lithium and quetiapine and then randomize responders to continue with either the combination of lithium and quetiapine or monotherapy with lithium or monotherapy with quetiapine. Overall response in Bipolar CHOICE was consistent with the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)[40] and the Lithium Treatment Moderate-Dose Use Study (LiTMUS),[41] with most bipolar disorder symptoms improving over time, but, unfortunately, with only a minority of patients reaching and sustaining a satisfactory response, highlighting the limitations of currently available treatments and the need for novel drug development.

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REFERENCES

1. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*. 2007;64(5):543–552.
2. Dilsaver SC. An estimate of the minimum economic burden of bipolar I and II disorders in the United States: 2009. *J Affect Disord*. 2011;129(1–3):79–83.
3. Judd LL, Schettler PJ, Akiskal HS, et al. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. *Arch Gen Psychiatry*. 2008;65(4):386–394.
4. Leboyer M, Soreca I, Scott J, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? *J Affect Disord*. 2012;141(1):1–10.
5. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord*. 2013;15(1):1–44.
6. Malhi GS, Tanious M, Das P, et al. The science and practice of lithium therapy. *Aust N Z J Psychiatry*. 2012;46(3):192–211.
7. Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005;162(7):1351–1360.
8. Hayes J, Prah P, Nazareth I, et al. Prescribing trends in bipolar disorder: cohort study in the United Kingdom THIN primary care database 1995–2009. *PLoS ONE*. 2011;6(12):e28725.
9. Vieta E, Suppes T, Eggens I, et al. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *J Affect Disord*. 2008;109(3):251–263.
10. Sheehan DV, McElroy SL, Harnett-Sheehan K, et al. Randomized, placebo-controlled trial of risperidone for acute treatment of bipolar anxiety. *J Affect Disord*. 2009;115(3):376–385.
11. Ray WA, Chung CP, Murray KT, et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med*. 2009;360(3):225–235.
12. Pillarella J, Higashi A, Alexander GC, et al. Trends in use of second-generation antipsychotics for treatment of bipolar disorder in the United States, 1998–2009. *Psychiatr Serv*. 2012;63(1):83–86.
13. Weisler RH, Nolen WA, Neijber A, et al; Trial 144 Study Investigators. Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study). *J Clin Psychiatry*. 2011;72(11):1452–1464.
14. Suppes T, Dennehy EB, Hirschfeld RMA, et al; Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *J Clin Psychiatry*. 2005;66(7):870–886.
15. Nierenberg AA, Sylvia LG, Leon AC, et al; Bipolar CHOICE Study Group. Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder (Bipolar CHOICE): a pragmatic trial of complex treatment for a complex disorder. *Clin Trials*. 2014;11(1):114–127.
16. Guy W. *ECDEU Assessment Manuel for Psychopharmacology, Revised*. Washington, DC: US Government Printing Office; 1976.
17. Feighner JP, Jacobs RS, Jackson RE, et al. A double-blind comparative trial with mianserin and amitriptyline in outpatients with major depressive disorders. *Br J Clin Pharmacol*. 1983;15(suppl 2):227S–237S.
18. Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res*. 1997;73(3):159–171.
19. Reilly-Harrington NA, Sylvia LG, Leon AC, et al. The Medication Recommendation Tracking Form: a novel tool for tracking changes in prescribed medication, clinical decision making, and use in comparative effectiveness research. *J Psychiatr Res*. 2013;47(11):1686–1693.
20. Kagan A, Dawber TR, Kannel WB, et al. The Framingham study: a prospective study of coronary heart disease. *Fed Proc*. 1962;21(4):52–57.
21. Leon AC, Solomon DA, Mueller TI, et al. A brief assessment of psychosocial functioning of

subjects with bipolar I disorder: the LIFE-RIFT, Longitudinal Interval Follow-up Evaluation-Range Impaired Functioning Tool. *J Nerv Ment Dis*. 2000;188(12):805–812.
22. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull*. 1993;29(2):321–326.
23. Bowden CL, Singh V, Thompson P, et al. Development of the Bipolar Inventory of Symptoms Scale. *Acta Psychiatr Scand*. 2007;116(3):189–194.
24. Gonzalez JM, Bowden CL, Katz MM, et al. Development of the Bipolar Inventory of Symptoms Scale: concurrent validity, discriminant validity and retest reliability. *Int J Methods Psychiatr Res*. 2008;17(4):198–209.
25. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
26. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
27. Morris DW, Trivedi MH, Husain MM, et al. Indicators of pretreatment suicidal ideation in adults with major depressive disorder. *Acta Psychiatr Scand*. 2010;121(6):480–484.
28. Posner K, Brent D, Lucas C, et al. *Columbia-Suicide Severity Rating Scale (C-SSRS)*. New York, NY: New York State Psychiatric Institute; 2009.
29. Wisniewski SR, Rush AJ, Balasubramani GK, et al; STARD Investigators. Self-rated global measure of the frequency, intensity, and burden of side effects. *J Psychiatr Pract*. 2006;12(2):71–79.
30. Leon AC, Demirtas H, Hedeker D. Bias reduction with an adjustment for participants' intent to dropout of a randomized controlled clinical trial. *Clin Trials*. 2007;4(5):540–547.
31. Hedeker D, Gibbons RD. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychol Methods*. 1997;2(1):64–78.
32. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38(4):963–974.
33. Rabideau DJ, Nierenberg AA, Sylvia LG, et al. A novel application of the Intent to Attend assessment to reduce bias due to missing data in a randomized controlled clinical trial. *Clin Trials*. 2014;11(4):494–502.
34. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(Suppl 20):22–33, quiz 34–57.
35. Hirschfeld RM, Weisler RH, Raines SR, et al; BOLDER Study Group. Quetiapine in the treatment of anxiety in patients with bipolar I or II depression: a secondary analysis from a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2006;67(3):355–362.
36. Sheehan DV, Harnett-Sheehan K, Hidalgo RB, et al. Randomized, placebo-controlled trial of quetiapine XR and divalproex ER monotherapies in the treatment of the anxious bipolar patient. *J Affect Disord*. 2013;145(1):83–94.
37. Cipriani A, Hawton K, Stockton S, et al. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ*. 2013;346:f3646.
38. Baldessarini R, Henk H, Sklar A, et al. Psychotropic medications for patients with bipolar disorder in the United States: polytherapy and adherence. *Psychiatr Serv*. 2008;59(10):1175–1183.
39. Bauer M, Glenn T, Alda M, et al. Drug treatment patterns in bipolar disorder: analysis of long-term self-reported data. *Int J Bipolar Disord*. 2013;1(1):5.
40. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry*. 2006;163(2):217–224.
41. Nierenberg AA, Friedman ES, Bowden CL, et al. Lithium treatment moderate-dose use study (LiTMUS) for bipolar disorder: a randomized comparative effectiveness trial of optimized personalized treatment with and without lithium. *Am J Psychiatry*. 2013;170(1):102–110.