Efficacy and Safety of Quetiapine-XR as Monotherapy or Adjunctive Therapy to a Mood Stabilizer in Acute Bipolar Depression With Generalized Anxiety Disorder and Other Comorbidities: A Randomized, Placebo-Controlled Trial

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ABSTRACT

Objective: To study the efficacy and safety of quetiapine-XR as monotherapy or adjunctive therapy to a mood stabilizer in acute bipolar I or II depression with comorbid generalized anxiety disorder (GAD) and other comorbidities.

Method: The study was conducted from January 2007 to November 2011. The Mini-International Neuropsychiatric Interview was used to ascertain the diagnosis of *DSM-IV* bipolar disorder, GAD, and other Axis I disorders. Eligible patients were randomly assigned to quetiapine-XR or placebo for up to 8 weeks. The Hamilton Depression Rating Scale–17 items (HDRS-17) was used as a primary outcome to evaluate the difference between the 2 groups using the change from baseline to end of study. Last observation carried forward and mixed-effects modeling for repeated measures were used to analyze the primary and secondary outcome measures.

Results: Of the 120 patients screened, 100 patients were randomized to receive quetiapine-XR (n = 50) or placebo (n = 50). Twenty-six patients in the quetiapine-XR and 18 in the placebo group completed the study. The mean quetiapine-XR dose was 276 ± 50 mg/d (50–300 mg/d). There was no significant difference between the 2 groups in the change from baseline to end of study in HDRS-17 total score with an effect size of 0.19 favoring quetiapine-XR. There were also no significant differences between the 2 groups in secondary efficacy and safety outcome measures.

Conclusions: Quetiapine-XR was not significantly superior to placebo in bipolar I or II depression with GAD and other comorbidities, suggesting that data from relatively "pure" bipolar patients may not be generalizable to a highly comorbid population.

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Comorbidity in bipolar disorder is the rule rather than the exception, with comorbid anxiety disorders appearing to be the most prevalent.[1–4] Generalized anxiety disorder (GAD) is one of the most common comorbid anxiety disorders with bipolar disorder. Patients with bipolar disorder and comorbid anxiety disorders commonly have an earlier onset of illness, more rapid cycling, suicidal behavior, substance use disorder (SUD), poorer response to conventional agents, and worse prognosis.[5–7] However, comorbid anxiety disorders are often inadequately treated.[8] More importantly, there is no guideline or consensus on pharmacologic treatment for comorbid anxiety disorder like GAD in bipolar disorder, although cognitive-behavioral therapy was recommended by the Canadian Network for Mood and Anxiety Treatments (CANMAT) Comorbidity Task Force.[9]

Comorbid anxiety is associated with depressive relapses in bipolar disorder.[10] Antidepressants are the first-line agents for non-bipolar anxiety disorders and major depressive disorder. Their safety in bipolar disorder is still debatable, especially with regard to the risk for antidepressant-induced mania/hypomania and the destabilization of bipolar illness.[11,12] Meanwhile, there are no efficacy data to support their use in bipolar disorder with or without anxiety. Benzodiazepines, the second-line agents for some anxiety disorders, can be used in the treatment of anxiety in bipolar disorder without SUD, but may be riskier to prescribe for those with anxiety and SUD.[13] Undoubtedly, the use of benzodiazepines is inappropriate in a significant number of patients because of the potential risk of abuse or dependence.

Previous studies have shown that typical and atypical antipsychotics were superior to placebo and as effective as benzodiazepines in the treatment of primary GAD.[14,15] Quetiapine monotherapy was superior to placebo in the acute treatment of patients with "pure" GAD[16–18] and "pure" bipolar I or II depression.[19–23] More recently, Sheehan and colleagues[24] have shown that quetiapine-XR (extended release), but not divalproex-ER, was superior to placebo in reducing anxiety symptoms in patients with bipolar I or II and a lifetime history of panic disorder and/or GAD. In contrast, an early study of risperidone monotherapy in the treatment of bipolar I depression with GAD and/or panic disorder did not find any significant difference between risperidone and placebo in any outcome measure.[25]

However, there has never been a study focusing on bipolar patients with current GAD, especially one that includes patients with current SUD. For studying a broader spectrum of patients with bipolar disorder, this study was undertaken to assess the safety and efficacy of quetiapine-XR versus placebo in a cohort of patients with bipolar I or II depression and comorbid GAD with or without other comorbidities.

Clinical Points

- This is the first randomized, double-blind, placebo-controlled study in patients with bipolar depression and other comorbid psychiatric disorders.
- Quetiapine-XR monotherapy or adjunctive therapy to a mood stabilizer was not superior to placebo in reducing depression and/or anxiety symptoms in this highly comorbid bipolar population although quetiapine's efficacy has been demonstrated in "pure" population of patients with bipolar depression or generalized anxiety disorder.
- As in previous studies, quetiapine-XR was well tolerated, with dry mouth and sedation as the most common side effects.

METHOD

The study was conducted in the Mood and Anxiety Clinic within the Mood Disorders Program at Case Western Reserve University/University Hospitals Case Medical Center, Cleveland, Ohio, from January 2007 to November 2011 (NCT 00671853). The Institutional Review Board (IRB) at University Hospitals Case Medical Center approved all study procedures. Written informed consent was obtained from each subject before any study-related procedures were performed.

Study Design

This study was a randomized, double-blind, placebo-controlled, 8-week comparison of quetiapine-XR as monotherapy or adjunctive therapy to a mood stabilizer versus placebo as monotherapy or adjunctive therapy to a mood stabilizer in the acute treatment of bipolar I or II depression and comorbid GAD with or without current other comorbidity. All patients who discontinued the study due to any reason received 3 monthly routine clinical care gratis visits.

Study Subjects

Men and women from 18 to 65 years old who met *DSM-IV* criteria for bipolar I or II disorder, were currently depressed with a Hamilton Depression Rating Scale–17 items (HDRS-17)[26] total score ≥ 18 at screening and baseline visits, and had a current history of GAD with a Hamilton Anxiety Rating Scale (HARS)[27] total score ≥ 18 at screening and baseline visits were eligible. In addition, patients were required to be in good physical health. Patients were excluded if they had (1) severe medical or neurologic problems; (2) severe personality disorder; (3) current suicidal risk judged by a physician; (4) known history of intolerance or hypersensitivity to any of the medications involved in the study; (5) treatment with quetiapine ≥ 100 mg/d in the 6 months prior to randomization; (6) known lack of response to quetiapine in a dosage of ≥ 100 mg/d for 4 weeks at any time, as judged by the investigator; (7) dependence on an opiate, phencyclidine, and/or barbiturate; (8) concurrent obsessive-compulsive disorder; (9) use of any cytochrome P450 3A4 inhibitors or cytochrome P450 inducers in 14 days; (10) administration of a depot antipsychotic injection within 1 dosing interval (for the depot) before randomization; (11) unable to wean off benzodiazepines or other medication; (12) female patients who were pregnant, planning to be pregnant, or breastfeeding; and (13) Young Mania Rating Scale (YMRS)[28] total score ≥ 12.

Prescreening and Screening Phase

An Extensive Clinical Interview was performed to confirm the diagnosis of bipolar disorder and GAD and to determine if the inclusion and exclusion criteria were met.[3] During the screening visit, all Axis I disorders were ascertained with the Mini-International Neuropsychiatric Interview (MINI)[29] performed by a master's-level prepared research assistant. Substance use disorder was confirmed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders, Patient Version (SCID-P)[30] instead of the MINI. A *recent SUD* was defined as patients who had a diagnosis of substance dependence and continued to meet abuse or dependence criteria for a substance(s) in the past 6 months at the initial assessment or those who had a diagnosis of substance abuse and continued abusing a substance in the last 3 months.[3]

Eligible subjects were randomized within 28 days after the screening visit. With the exception of a mood stabilizer including lithium, valproic acid, and/or lamotrigine, all other medications were discontinued at least 5 half-lives prior to randomization. The permitted medication(s) was maintained at a stable dose for a minimal 2-week period.

Randomization and Double-Blind Treatment Phase

Random assignment to each arm was balanced for bipolar I versus bipolar II, male versus female, and with versus without recent SUD. The study medications were started at 50 mg for day 1 and day 2, increased to 150 mg at day 3 and day 4, and finally increased to 300 mg/d at day 5 and onward. For those who could not tolerate 300 mg/d, a 50-mg decrement per week was allowed to a minimum of 150 mg/d. Those who could not tolerate 150 mg/d were discontinued from the study. Assessments were performed at weeks 0, 1, 2, 4, 6, and 8.

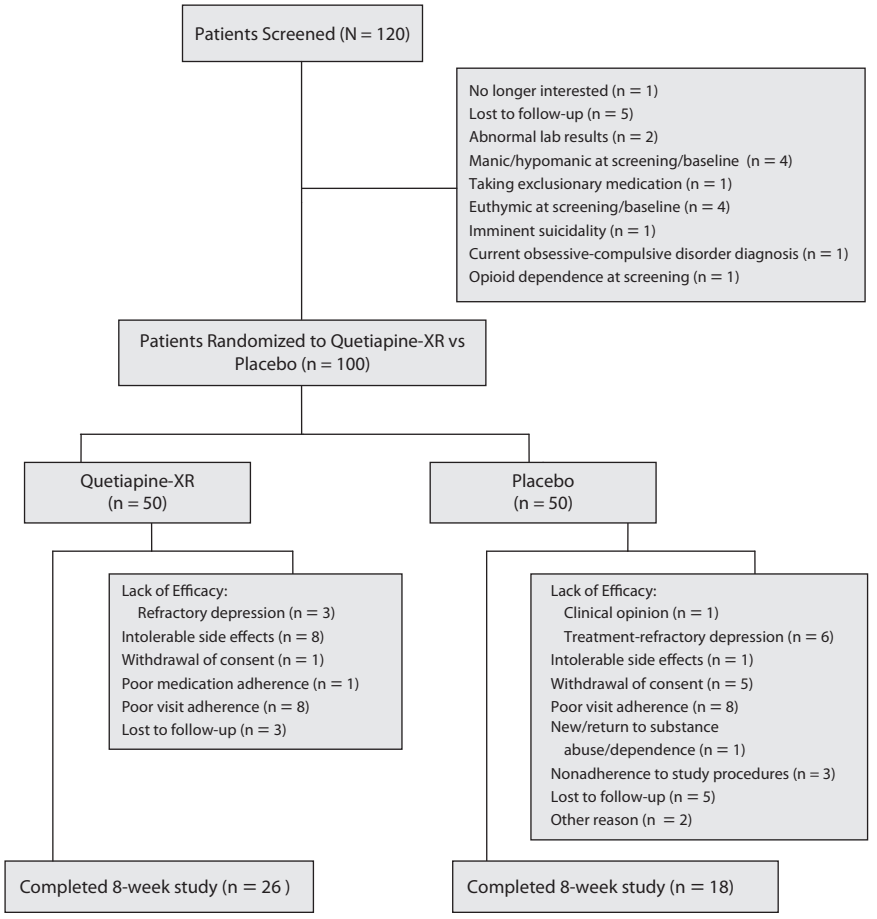
Concomitant Medications

Rescue medication for sleep such as zolpidem (Ambien 5–10 mg/d or Ambien-CR 6.25–12.5 mg/d) was permitted during the washout period and the double-blind phase. Except for the aforementioned mood stabilizers, no other medication was allowed.

Primary and Secondary Outcome Measures

The primary outcome was the change from baseline to end of study in HDRS-17 total score. Secondary outcome measures included mean changes from baseline to end of study in the HARS total score, Clinical Global Impression for Bipolar Disorder-Severity (CGI-S),[31] Quick Inventory for Depression–16 item self-report (QIDS-SR-16),[32] and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[33] response rate (≥ 50% reduction in HDRS-17 total score from baseline to end of study), and remission rate (HDRS-17 total score ≤ 7 at end of study).

Figure 1. Flowchart of the Study



Safety Monitoring

Safety was monitored by assessing adverse events (AEs), including extrapyramidal symptoms (parkinsonism) as measured by the Simpson Angus Scale (SAS)[34] and akathisia as measured by the Barnes Akathisia Scale (BARS),[35] the Frequency, Intensity, and Burden of Side Effects Rating scale (FIBSER),[36] and YMRS. In addition, clinical laboratory assessments and physical examinations were performed at baseline and repeated at the end point. For those with current SUD, monthly liver function tests were obtained if clinically indicated.

Statistical Analysis

Descriptive statistics, percentage, mean, and standard deviation were obtained for the patients' demographic and baseline clinical characteristics. The primary and secondary efficacy analyses were performed on the intent-to-treat (ITT) population, ie, all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline assessment. Treatment effects were tested using a 2-tailed α level of –.05. Data were analyzed using SAS software (SAS version 9.2, SAS Institute Inc, Cary, North Carolina).

As specified a priori of the primary outcome measure, the change in HDRS-17 score over the 8-week treatment period was performed using the last observation carried forward (LOCF) strategy and a mixed-effects model of repeated measures (MMRM). A first-order autoregressive, AR(1), variance-covariance structure was assumed in the MMRM model.

The effect size was calculated by the net changes in HDRS-17 score of quetiapine-XR from baseline to the end point over placebo divided by pooled standard deviation.[37] All secondary outcome measures were analyzed similarly. Analysis of variance (ANOVA) models were used to evaluate safety data, using mean change from baseline to end point based on a LOCF strategy. Chi-square/Fisher exact test was used to analyze treatment differences for categorical demographic and illness characteristics. Kaplan-Meier analysis and the log-rank test were used to compare treatment groups for time-to-event data.

RESULTS

Of the 120 patients screened, 100 were randomized, and 44 patients completed the 8-week study with 26 in quetiapine-XR group and 18 in placebo group (Figure 1). The common reasons for discontinuation are listed in Figure 1. The mean dose of quetiapine-XR was 276 ± 50 mg/d (50–300 mg/d).

Baseline Demographics and Clinical Characteristics

As shown in Table 1, there were no significant differences between quetiapine-XR and placebo groups in age, gender, race, bipolar subtypes, age of first onset of mania/hypomania, the number of depressive and mania/hypomania/mixed episodes in last 12 months, and baseline depression and anxiety severity. The lifetime and current history of comorbid anxiety disorders and SUDs were similar. The rate of past history of hospitalization, suicide attempt, psychosis, and early childhood trauma was also similar, as well as the proportion of patients who were on monotherapy or adjunctive therapy.

Primary Outcome

In an LOCF analysis, the change from baseline to end of study in HDRS-17 total score was not statistically significant with −9.91 ± 16.48 for the quetiapine-XR and −7.41 ± 8.13 for the placebo group (Table 2). An MMRM analysis of the change from baseline to end of study in HDRS-17 total scores with the adjustment for baseline HDRS-17 value plus the effect of week, treatment group, and week by treatment group interaction did not find a significant difference between the 2

Table 1. Demographic and Clinical Characteristics at Baseline

Characteristic	Quetiapine-XR (n = 46) n	%	Placebo (n = 45) n	%
Gender				
Male	24	52.2	24	53.3
Female	22	47.8	21	46.7
Race				
White	24	52.2	24	53.3
Black	21	45.7	21	46.7
Other	1	2.2	0	0.0
Bipolar subtype				
Bipolar I disorder	40	87.0	39	86.7
Bipolar II disorder	6	13.0	6	13.3
Lifetime other anxiety disorder[a]	43	93.5	38	84.4
Current other anxiety disorder[a]	41	89.1	34	75.6
Lifetime substance use disorder	38	82.6	37	82.2
Alcohol use disorder	32	69.6	32	71.1
Drug use disorder	30	65.2	30	66.7
Cannabis use disorder	22	47.8	28	62.2
Cocaine use disorder	14	30.4	13	28.9
Sedative/hypnotic/anxiolytic	2	4.3	3	6.7
Stimulant use disorder	5	10.9	3	6.7
Opioid use disorder	4	8.7	3	6.7
Hallucinogen use disorder	4	8.7	7	15.6
Polysubstance use disorder	2	4.3	3	6.7
Current substance use disorder	20	43.5	23	51.1
Alcohol use disorder	7	15.2	15	33.3
Drug use disorder	15	32.6	15	33.3
Cannabis use disorder	14	30.4	15	33.3
Opioid use disorder	1	2.2	0	0
Lifetime psychosis	12	26.1	15	33.3
Lifetime verbal abuse	23	50.0	26	57.8
Lifetime physical abuse	18	39.1	21	46.7
Lifetime sexual abuse	15	32.6	11	24.4
Rapid cycling in past 12 mo	39	84.8	41	91.1
Past suicide attempts	12	26.1	17	37.8
Hospitalizations	22	47.8	18	40.0
Pharmacologic treatment				
No medication	42	91.3	38	84.4
Adjunctive therapy	4	8.7	7	15.6
Lithium	2	4.3	0	0
Valproate/divalproex	0	0	3	6.7
Lamotrigine	2	4.3	3	6.7
Any combination of lithium, valproate, and/or lamotrigine	0	0	1	2.2
	Mean	SD	Mean	SD
Age at study entry, y	38.0	12.0	37.4	11.3
Age at first depressive episode, y	15.9	13.8	12.7	6.2
Age at first manic/hypomanic/mixed episode, y	18.0	13.3	17.9	15.3
Episode duration, d	248.6	621.8	171.4	275.1
Mean episode in last 12 mo				
Mania/hypomania/mixed	6.4	6.2	6.7	9.4
Depression	6.9	6.8	7.5	9.0
Total	13.2	11.6	14.4	18.2
Baseline				
HDRS-17	25.9	14.5	24.6	4.7
HARS	26.0	5.3	25.3	5.9
QIDS-SR-16	20.3	6.7	20.8	6.8
CGI-S	4.5	0.5	4.5	0.5

[a]Including panic disorder with or without agoraphobia, agoraphobia alone, social anxiety disorder, and posttraumatic stress disorder.
Abbreviations: CGI-S = Clinical Global Impression-Severity, HARS = Hamilton Anxiety Rating Scale, HDRS-17 = Hamilton Depression Rating Scale–17 items, QIDS-SR-16 = Quick Inventory of Depressive Symptomatology—Self-Report–16 items, SD = standard deviation.

Table 2. Comparison of Primary and Secondary Outcome Measures Between Quetiapine-XR and Placebo (LOCF)

Measure	Quetiapine-XR n	Mean	SD	Placebo n	Mean	SD	Quetiapine-XR vs Placebo *t* Value	*P* Value
HDRS-17								
Baseline	46	25.91	14.52	44	24.64	4.73	0.56	.574
End	46	16.00	6.70	44	17.23	8.57	−0.76	.451
Change	46	−9.91	16.48	44	−7.41	8.13	−0.92	.361
CGI-S								
Baseline	46	4.48	0.55	44	4.48	0.55	−0.01	.993
End	46	3.37	1.04	44	3.68	1.18	−1.34	.185
Change	46	−1.10	1.16	44	−0.80	1.21	−1.25	.213
Q-LES-Q								
Baseline	36	0.12	0.31	36	0.26	0.49	−1.44	.155
End	36	0.23	0.32	36	0.20	0.22	0.42	.672
Change	36	0.11	0.22	36	−0.06	0.52	1.77	.084
HARS								
Baseline	46	25.96	5.30	44	25.25	5.94	0.60	.553
End	46	16.41	7.67	44	17.00	9.31	−0.33	.744
Change	46	−9.54	7.58	44	−8.25	8.70	−0.75	.454
QIDS-SR-16								
Baseline	46	20.35	6.68	44	20.80	6.76	−0.32	.753
End	46	13.98	7.78	44	15.61	8.32	−0.96	.338
Change	46	−6.37	7.53	44	−5.18	9.17	−0.67	.503
HDRS-17	n	No	Yes	n	No	Yes	χ^2	*P* Value
Response[a]	46	34	12	44	33	11	0.906	1.000
Remission[b]	46	40	6	44	38	6	0.934	1.000

[a]Response defined as 50% decrease from baseline to end point in HDRS-17.
[b]Remission defined as ≤ 7 on HDRS-17 at the end of study.
Abbreviations: CGI-S = Clinical Global Impression-Severity Scale, HARS = Hamilton Anxiety Rating Scale, HDRS-17 = Hamilton Depression Rating Scale–17 items, LOCF = Last Observation Carried Forward, n = number of patients, QIDS-SR-16 = Quick Inventory of Depression Symptomatology–Self Report–16 items, Q-LES-Q = Quality Life Enjoyment and Satisfactory Questionnaire, SD = standard deviation.

groups (Table 3). The Cohen *d* effect size of the difference in HDRS-17 between quetiapine-XR and placebo was 0.19.

Kaplan-Meier analysis of the time to response based on ≥ 50% reduction in HDRS-17 total score yielded no significant difference between patients treated with quetiapine-XR and those given placebo (log-rank $\chi^2 = 0.147$, $P = .701$). Kaplan-Meier analysis of the time to remission based on HDRS-17 total score ≤ 7 between the 2 treatment groups showed similar results (log-rank $\chi^2 = 0.070$, $P = .791$). For both response and remission, the median times to event were not estimable due to the high degree of censoring in the data.

Secondary Outcomes

Response rates were virtually the same with quetiapine-XR of 26% (12 of 46) and placebo of 25% (11 of 44) (Table 2). Similarly, the remission rates were not significantly different with 13% (6 of 46) for quetiapine-XR and 14% (6 of 44) for placebo. There were also no significant differences in responder rates between those who were on monotherapy and those who were on adjunctive therapy within the treatment groups.

Based on ≥ 50% reduction in HARS total score, the response rates were 28% (13 of 46) for quetiapine-XR and 32% (14 of 44) for placebo. Based on a final HARS ≤ 7, remission rates were 11% (5 of 46) for quetiapine-XR and 16% (7 of 44) for placebo. Differences among these rates were not

Table 3. Comparison of Primary and Secondary Outcome Measures Between Quetiapine-XR and Placebo (MMRM)

Change From Baseline to End Point	Quetiapine-XR Least Squares n	Mean	SE	Placebo Least Squares n	Mean	SE	Quetiapine-XR vs Placebo *F* Value	*P* Value
HDRS-17	46	−8.59	1.35	44	−9.14	1.58	0.07	.790
CGI-S	46	−1.28	0.17	44	−1.11	0.20	0.41	.524
Q-LES-Q	36	0.05	0.05	36	−0.01	0.06	1.12	.297
HARS	46	−10.07	1.33	44	−9.45	1.60	0.09	.766
QIDS-SR-16	46	−6.97	1.24	44	−6.08	1.46	0.22	.641

Abbreviations: CGI-S = Clinical Global Impression-Severity Scale, HARS = Hamilton Anxiety Rating Scale, HDRS-17 = Hamilton Depression Rating Scale–17 items, LOCF = Last Observation Carried Forward, MMRM = mixed-effects model of repeated measures, n = number of patients, QIDS-SR-16 = Quick Inventory of Depression Symptomatology–Self Report–16 items, Q-LES-Q = Quality Life Enjoyment and Satisfactory Questionnaire, SE = standard error.

Table 4. Adverse Events With Incidence of ≥ 5% in Either Group

Adverse Event	Quetiapine-XR (n = 46) n	%	Placebo (n = 45) n	%
Sedation	21	45.7	14	31.1
Dry mouth	27	58.7	9	20.0
Stomach upset	5	10.9	3	6.7
Dizziness	5	10.9	6	13.3
Increased appetite	4	8.7	1	2.2
Diarrhea	3	6.5	1	2.2
Headache	7	15.2	3	6.7
Light-headedness	3	6.5	2	4.4
Nausea	2	4.3	3	6.7

statistically significant. No statistically significant differences between the 2 groups in the time to HARS response (log-rank $\chi^2 = 0.377$, $P = .539$) or the time to HARS remission (log-rank $\chi^2 = 0.919$, $P = .338$) were observed. Median times to event were not estimable for either response or remission.

LOCF and MMRM analyses of the other secondary assessments did not show statistically significant differences between quetiapine-XR and placebo (Table 2). The MMRM analysis of each of these secondary outcomes used baseline value as a covariate and included the week of treatment, treatment group, and the interaction of the week and treatment group in the model with an assumed AR(1) variance-covariance matrix structure (Table 3). Cohen *d* effect sizes for these measures were 0.26 for CGI-S, 0.42 for Q-LES-Q, 0.16 for HARS, and 0.14 for QIDS-SR-16.

Adverse Events

Adverse events experienced by ≥ 5% of patients during the double-blind treatment phase are summarized in Table 4. The rate of reported sedation was significantly higher in the quetiapine-XR group than that of the placebo, 30.4% versus 8.6%. The rate for dry mouth was also significantly higher in the quetiapine-XR group than that of the placebo, 60% versus 19.6%. Eight patients in the quetiapine-XR group and 1 patient in the placebo group discontinued the study due to intolerable adverse events.

Analysis of variance of FIBSER indicated no statistically significant difference between the 2 groups with respect to frequency, intensity, or impairment. There was no significant difference in the change of total SAS, BARS, and YMRS (−3.8 ± 6.4 vs −4.0 ± 7.1, $P = .88$) scores between the 2 groups. The laboratory results including fasting glucose, fasting lipids, thyroid functions, and vital signs were also not significantly different.

DISCUSSION

In this first study of enrolled patients with bipolar I or II depression and current GAD with or without other current comorbidity, quetiapine-XR monotherapy or adjunctive therapy to a mood stabilizer(s) was not superior to placebo monotherapy or adjunctive therapy to a mood stabilizer(s) in reducing depressive and anxiety symptoms. This finding is inconsistent with the results of quetiapine in the acute treatment of "pure" bipolar I or II depression[19–23] and "pure" GAD[16–18] and bipolar I or II depression with a lifetime history of panic disorder and/or GAD without an SUD.[24]

The negative finding in the present study suggests that the pivotal data of psychotropic drugs from "pure" populations may not be applied to comorbid populations. In other words, patients with multiple comorbidities may be more difficult to treat and may not respond to any currently available pharmacologic treatments, as reflected by very low response and remission rates in both groups. As shown in Table 2, the response rate was 26% for quetiapine-XR and 25% placebo, and the remission rate was 13% for quetiapine-XR and 14% for placebo. In contrast, in a pivotal study of quetiapine-IR monotherapy in the acute treatment of bipolar I and II depression, the response rate (≥ 50% reduction in MADRS total score) was 58.2% for quetiapine-IR 600 mg/d, 57.6% for quetiapine-IR 300 mg/d, and 36.1% for placebo.[19]

Quetiapine was less effective in this highly comorbid bipolar population than in relatively "pure" bipolar populations as reflected by a smaller effect size of quetiapine relative to placebo in the present study compared to previous studies of "pure" bipolar populations. The effect sizes of quetiapine-IR 300 mg/d in "pure" bipolar I or II depression ranged from 0.61 to 0.67.[19,20] The effect size of quetiapine-XR 300 mg was 0.61.[23] In the present study, the effect size of quetiapine-XR in reducing depressive symptoms was 0.19. If using an effect size of 0.20 to power a study, the sample size is estimated to be 394 to 400 patients per arm to detect a significant difference between quetiapine and placebo with 80% of power. Clearly, the sample size in the present study was much smaller than that needed to find a significant difference between quetiapine and placebo. However, such a study may be less clinically relevant because the magnitude of difference was too small.

Previous studies have shown that patients with bipolar disorder and SUDs were less likely to respond to any treatment.[38–42] In patients with rapid cycling bipolar disorder and a recent history of SUDs, lamotrigine adjunctive to lithium and/or valproate did not show superiority

over placebo adjunctive therapy in reducing depressive symptoms.[42] It is quite possible that the inclusion of patients with SUDs might decrease the power to detect the difference between quetiapine-XR and placebo in patients with bipolar and current GAD. However, in subgroup analyses of patients with and those without a recent SUD, there were also no significant differences between quetiapine-XR and placebo in these subgroups (data not shown).

Previous studies have also shown that bipolar patients with comorbid anxiety were less likely to respond to the same pharmacologic treatment than those without comorbid anxiety.[43,44] A more recent study from the STEP-BD (the Systematic Treatment Enhancement Program for Bipolar Disorders) found that bipolar patients with a lifetime anxiety disorder were more likely to recover with psychotherapy than with collaborative care (a 3-session comparison treatment plus pharmacotherapy).[45] However, patients with multiple anxiety disorders did not exhibit significant difference in response to 2 treatments. The results from our current study appear consistent with this finding. In our study, about 89% of patients had at least 2 lifetime anxiety disorders;, and 82% had at least 2 current anxiety disorders (Table 1).

The low response and low remission rates and very small effect sizes on both clinician and self-assessed measures in this study may be a reflection of the severity of illness in this group (Table 1). More than 65% of patients had history of childhood trauma. A previous study of major depressive disorder found that patients with history of childhood trauma responded better to psychotherapy than to medication.[46] It is also quite possible that in this study the placebo effect from the interaction with study staff overpowered the effect of quetiapine-XR although the placebo effect from this study was quite small. Similarly, studies have shown that patients with early onset bipolar disorder had a poorer response to treatment compared to those with late onset of bipolar disorder.[47,48] In our present study, the mean age at the first onset of depressive episode was younger than 16 years old, and the mean age at the first onset of manic episode was about 18 years old (Table 1). These factors might predetermine the poor response to treatment in this group of patients with highly comorbid conditions.

Limitations

Although this was the first double-blind, randomized, placebo-controlled clinical trial in patients with *DSM-IV* diagnoses with bipolar I or II depression and current GAD with or without a recent SUD, this study was limited by enrolling a relatively small number of patients. Using GAD as an index comorbid anxiety disorder may limit the generalizability of this study to patients with other comorbid anxiety disorder(s), although about 82% of patients had at least 1 current other anxiety disorder. Social phobia is the most common comorbid anxiety disorder in bipolar disorder.[1] Future studies focusing on comorbid social phobia in bipolar disorder are warranted. Undoubtedly, the initial calculation of sample size was overly optimistic to estimate the efficacy of quetiapine in this population. It was further limited by even lower numbers of patients completing the study. Poor visit adherence as the most common reason for premature discontinuation from the study suggests that future study in this population may need extra procedures in place to minimize such incidences.

CONCLUSION

In this study of highly comorbid patients with bipolar disorder and GAD, quetiapine-XR monotherapy or adjunctive therapy to a mood stabilizer was not superior to placebo in reducing depressive and anxiety symptoms. Quetiapine-XR was as relatively well tolerated as placebo in this population. Large studies are warranted to support or refute these findings. More importantly, there is an urgent need to conduct randomized, controlled studies in bipolar patients with comorbid anxiety disorder(s) and with or without an SUD to identify effective treatments for this highly comorbid population.

Drug names: divalproex (Depakote and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), quetiapine (Seroquel), risperidone (Risperdal and others), valproic acid (Depakene, Stavzor, and others), zolpidem (Ambien, Edluar, and others).

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