Randomized, Placebo-Controlled Effectiveness Study of Quetiapine XR in Comorbid Depressive and Anxiety Disorders

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ABSTRACT

Objective: Quetiapine is approved as an adjunctive treatment for major depressive disorder (MDD) and as monotherapy for bipolar depression. It is often used off-label for treating anxiety conditions and as an augmentation agent for treatment-resistant depression. However, its benefit in depression with comorbid anxiety disorders has not been systematically evaluated. The current study evaluated the benefit and tolerability of quetiapine as augmentation to first-line antidepressants for MDD comorbid with anxiety disorders.

Methods: In this multicenter trial (June 2008–June 2013), 76 adults (aged 18–65 years) with a primary diagnosis of unipolar depression comorbid with at least 1 anxiety disorder (per *DSM-IV-TR* criteria) received flexible-dose quetiapine extended-release (XR) 50–300 mg/d or placebo as add-on for 12 weeks in a 2:1 ratio. Depression, anxiety, life satisfaction, and adverse events were assessed.

Results: Depression, anxiety, and function improved significantly in both groups. On primary outcome measures, quetiapine was superior to placebo in improving depression (17-item Hamilton Depression Rating Scale score: mean difference = –3.64; 95% CI, –7.01 to –0.27) and anxiety symptoms (Hamilton Anxiety Rating Scale score: mean difference = –4.02; 95% CI, –7.41 to –0.64), as well as Clinical Global Impressions–Severity of Illness scale score (mean difference = –0.64; 95% CI, –1.13 to –0.15). On secondary measures including the Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory, Penn State Worry Questionnaire, and Quality of Life Satisfaction and Enjoyment Questionnaire, quetiapine produced a greater degree of improvement compared to placebo, but group differences were not statistically significant. Quetiapine was well tolerated, with mostly minor and no serious adverse effects.

Conclusions: Quetiapine augmentation may be a useful intervention for MDD with comorbid anxiety.

Trial Registration: ClinicalTrials.gov Identifier: NCT00688818

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Depression and anxiety disorders are common mental illnesses that often occur comorbidly. The prevalence of depression is an estimated 10%–15%,[1,2] and that of anxiety disorders is between 3.8% and 25%.[3] Their co-occurrence is common, with approximately one-half to two-thirds of patients with MDD experiencing an anxiety disorder,[4,5] and often confers greater disease burden.[1,6] The most prevalent disorders comorbid with depression are social anxiety disorder (SAD) and generalized anxiety disorder (GAD).[1,7] Similarly, comorbid depression is common in patients with a primary diagnosis of an anxiety condition, in particular GAD, SAD, and panic disorder (PD).[7]

Comorbidity of anxiety and depression is associated with poorer outcomes for both illnesses including greater severity, protracted course, and more functional impairment than with either alone.[8] The presence of anxiety has been suggested to increase the likelihood of self-harm in patients with MDD.[9,10] Patients with the comorbidity tend to show poorer antidepressant response compared to those without[11] and are also more likely to report adverse effects, including agitation, nervousness, and worsening of somatic symptoms.[12]

Several atypical (second-generation) antipsychotics (eg, olanzapine, quetiapine, risperidone), as either monotherapy or augmentation, have been shown to improve symptoms of MDD,[13–15] GAD, SAD, PD, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder to varying degrees.[16,17] Among them, quetiapine is approved as adjunct therapy for MDD and is frequently used off-label to treat anxiety. Its antidepressant effects have been attributed to the down-regulation of 5-hydroxytryptamine 2A (5-HT_{2A}) receptors, 5-HT reuptake inhibition, and up-regulation of 5-HT_{1A} receptors.[18,19] Epidemiologic studies have noted increased use of quetiapine in recent years for non-psychotic disorders,[20] specifically for bipolar depression[21] and treatment-resistant unipolar depression.[22] Similarly, randomized controlled trials (RCTs) have reported the benefit of quetiapine in several anxiety and related disorders.[16,23–25] The anti-anxiety effects of quetiapine have been attributed, at least in part, to α_2 receptor antagonism leading to the release of norepinephrine in the prefrontal cortex.

Pooled analysis of RCTs in MDD indicated that quetiapine monotherapy was superior to placebo in treating depressed patients with high levels of anxiety[26] and, as adjunct treatment, was efficacious in reducing

Clinical Points

- Depression and anxiety disorders frequently occur comorbidly, and they are harder to treat and require augmentation strategies when comorbid.
- Atypical agents, including quetiapine, may be useful as augmentation to antidepressants to improve response and achieve remission.

both depressive and anxiety symptoms.[27] Although large RCTs are lacking, early evidence suggests quetiapine to be superior to placebo as augmentation to selective serotonin reuptake inhibitors (SSRIs)[28] and that its combination with venlafaxine is superior to either alone.[29] In one small RCT,[30] patients with comorbid MDD and GAD who received quetiapine either as monotherapy or as adjunct to antidepressants exhibited significant reduction in both depressive and anxiety symptoms. However, there is at least one report of absence of benefit of add-on quetiapine,[31] suggesting the need for further investigation.

Current Study

The primary aim of the current study was to evaluate the efficacy and tolerability of quetiapine compared to placebo as augmentation to first-line antidepressants to improve symptoms of depression and anxiety in patients with this comorbidity. The secondary aim was to evaluate the benefit of such augmentation on function and quality of life.

METHODS

Study Design

This randomized, placebo-controlled, double-blind, parallel-group study was conducted from June 2008 to June 2013. It evaluated the efficacy and tolerability of add-on quetiapine extended-release (XR) compared to placebo in patients with MDD or dysthymic disorder[26] and who reported symptoms of one or more of the following: GAD, SAD, and PD. After providing informed consent, subjects were randomly assigned to receive either quetiapine XR or placebo as add on to current first-line antidepressants (SSRI, serotonin-norepinephrine reuptake inhibitor [SNRI], or bupropion) in a 2:1 ratio using a computer-generated 6-block randomization program. Research personnel and participants were blinded to randomization.

Sample size was determined based on the ability to detect a minimum critical difference of 3 points in primary outcome within treatment groups, with planned analyses at 80% power and 5% significance level. Assuming a dropout rate of 15%, and based on the randomization ratio of 2:1, 105 patients would need to be enrolled to have 90 evaluable patients (n = 60, treatment group; n = 30, placebo group).

This 12-week trial was conducted across 4 sites in Ontario, Canada. The study was approved by each site's local research ethics committee and was registered at ClinicalTrials.gov (identifier: NCT00688818).

Study Population

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) was used in the diagnosis of study participants. Adult patients (aged 18–65 years) who met *DSM-IV-TR* criteria for MDD (primary diagnosis) as well as for at least one comorbid anxiety disorder (GAD, PD, and/or SAD) were included in the study. Participants were also required to be receiving a first-line antidepressant at a stable therapeutic dose for a minimum of 2 weeks prior to entering the study. Only subjects with at least moderately severe depression (17-item Hamilton Depression Rating Scale [$HDRS_{17}$] score ≥ 17) were included. Key exclusion criteria included, among others, previous trial of quetiapine and history or presence of psychotic symptoms, bipolar disorder, substance use disorders, risk of suicide, and significant medical illness. None of the participants had previously used any atypical antipsychotics.

Dosing Regimen

Patients were initiated on 50 mg/d of quetiapine XR or placebo added to the current antidepressant. The dose was titrated by 50-mg increments once weekly to a maximum of 300 mg/d based on response and tolerability, up to the end of week 8. This dose was then maintained until the end of 12 weeks. At the end of treatment, participants entered a step-down period of 3 to 5 days, depending on dose received and the clinical need.

Concomitant Treatments

Antidepressant medication. Patients remained on the same antidepressant medications and dosage as they were on at time of enrollment through the 12-week treatment phase. Under exceptional circumstances related to safety and tolerability, antidepressant doses were reduced but never increased. The type of antidepressant and proportion of patients taking each one are presented in Table 1.

Other concomitant medications. Lorazepam up to 2 mg total daily dose as needed was permitted for a maximum of 7 days of total use for the entire study. The use of potent cytochrome P450 inhibitors and inducers was disallowed. Needed non-psychotropic medications were allowed at the discretion of the investigator(s) and documented.

Clinical Measurements

Diagnoses were confirmed using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-P).[32] The primary efficacy measures included the $HDRS_{17}$,[33] Hamilton Anxiety Rating Scale (HARS),[34] and Clinical Global Impressions–Severity of Illness scale (CGI-S).[35] The latter two were added as primary outcomes after early review of study measurements and expert consensus. The secondary efficacy measures included the Montgomery-Asberg Depression Rating Scale (MADRS),[36] Beck Depression Inventory (BDI),[37] and Quality of Life Satisfaction and Enjoyment Questionnaire (Q-LES-Q).[38]

As well, ratings of diagnosis-specific symptoms were administered according to the participants' comorbid

Table 1. Baseline Characteristics by Treatment Group[a]

Baseline Variable	Quetiapine (n = 48)	Placebo (n = 28)	*P* Value
Male/female, n (%)	18 (37.5)/30 (62.5)	10 (35.7)/18 (64.3)	.88[b]
Age, y	43.56 (10.65)	43.89 (11.84)	.90
Employment (currently working), n (%)	20 (41.67)	6 (21.43)	.07[b]
BMI, kg/m^2	30.93 (9.09)	30.00 (7.47)	.65
Weight, kg	84 (21.64)	83.29 (20.16)	.89
Duration of current episode of depression, wk	54.61 (77.69)	101.83 (228.78)	.27
No. of past antidepressant trials	1.19 (.92)	1.20 (.76)	.97
Questionnaire score			
$HDRS_{17}$	22.81 (4.21)	24.07 (4.15)	.21
HARS	25.48 (8.21)	26.21 (6.74)	.69
CGI-S	4.26 (0.44)	4.15 (0.36)	.27
MADRS	27.94 (5.86)	30.04 (5.61)	.14
BDI	35.11 (11.77)	34.85 (11.61)	.93
Q-LES-Q	36.41 (24.56)	30.56 (22.29)	.31
PSWQ	64.48 (9.63)	67.39 (7.84)	.22
Concomitant antidepressant medication, n (%)			
Escitalopram	12 (25.00)	5 (17.86)	.47[b]
Venlafaxine	9 (18.75)	5 (17.86)	.92[b]
Duloxetine	4 (8.33)	1 (3.57)	.42[b]
Citalopram	6 (12.50)	2 (7.14)	.46[b]
Fluoxetine	5 (10.42)	3 (10.71)	.97[b]
Buproprion	5 (10.42)	3 (10.71)	.97[b]
Paroxetine	1 (2.08)	1 (3.57)	.70[b]
Desvenlafaxine	2 (4.17)	1 (3.57)	.90[b]

[a]Values are shown as mean (SD) unless otherwise noted.
[b]χ^2 analysis employed to assess for difference in proportion between the study groups.
Abbreviations: BDI = Beck Depression Inventory, BMI = body mass index, CGI-S = Clinical Global Impressions–Severity of Illness scale, HARS = Hamilton Anxiety Rating Scale, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, PSWQ = Penn State Worry Questionnaire, Q-LES-Q = Quality of Life Satisfaction and Enjoyment Questionnaire.

Table 2. Mean Scores at 12 Weeks, Mean Change From Baseline to 12 Weeks, and Mean Difference Between Quetiapine Treatment and Placebo for All Participants

	Score at 12 Weeks, Mean (SD)		Change in Score From Baseline to 12 Weeks, Mean (95% CI)		Difference Between Quetiapine and Placebo at 12 Weeks, Mean (95% CI)	Effect Size of Mean Difference, η^2
Outcome	Quetiapine	Placebo	Quetiapine	Placebo		
$HDRS_{17}$	11.83 (5.97)	15.75 (8.60)	10.98 (8.95 to 13.01)***	8.32 (4.89 to 11.76)***	−3.64 (−7.01 to −0.27)*	0.06
HARS	13.81 (7.88)	18.21 (8.55)	11.67 (9.14 to 14.19)***	8.00 (5.42 to 10.58)***	−4.02 (−7.41 to −0.64)*	0.07
CGI-S	3.00 (1.07)	3.57 (0.92)	1.26 (0.94 to 1.58)***	0.59 (0.26 to 0.93)**	−0.64 (−1.13 to −0.15)*	0.09
MADRS	16.28 (8.85)	20.52 (10.58)	11.72 (9.28 to 14.16)***	9.62 (5.33 to 13.90)***	−2.99 (−7.46 to 1.48)	0.03
BDI	26.32 (13.34)	31.48 (13.02)	8.46 (5.11 to 11.80)***	4.04 (−0.84 to 8.92)	−4.37 (−9.67 to 0.94)	0.04
Q-LES-Q	42.39 (25.20)	36.00 (24.02)	−5.56 (−11.73 to 0.62)	−5.00 (−12.30 to 2.30)	2.10 (−7.09 to 11.29)	0.003
PSWQ	58.21 (14.03)	62.80 (11.21)	6.03 (3.02 to 9.03)***	4.61 (0.79 to 8.43)*	−1.44 (−6.35 to 3.47)	0.01

*P < .05. **P < .01. ***P < .001.
Abbreviations: BDI = Beck Depression Inventory, CGI-S = Clinical Global Impressions–Severity of Illness scale, HARS = Hamilton Anxiety Rating Scale, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, PSWQ = Penn State Worry Questionnaire, Q-LES-Q = Quality of Life Satisfaction and Enjoyment Questionnaire.

disorder(s) and the included Penn State Worry Questionnaire (PSWQ)[39] for GAD, the Liebowitz Social Anxiety Scale (LSAS)[40] for SAD, and the Panic Disorder Severity Scale (PDSS)[41] for PD.

Study Procedures

Initial screen included a SCID-P, medical safety assessment, and severity measures ($HDRS_{17}$, HARS, and CGI-S) to determine eligibility for participation. At baseline visit, the patients were randomized to one of two treatment groups using a computer-generated randomization code. Primary efficacy and secondary measures were administered at baseline, weeks 6 and 12, or time of early termination. During the treatment phase (weeks 1 to 12), vital signs, concomitant medications, and adverse events were recorded at each study visit. Laboratory measures were completed at baseline and week 12 and within 2 weeks of early termination. Rater training and interrater reliability measurements were conducted for raters from all 4 sites.

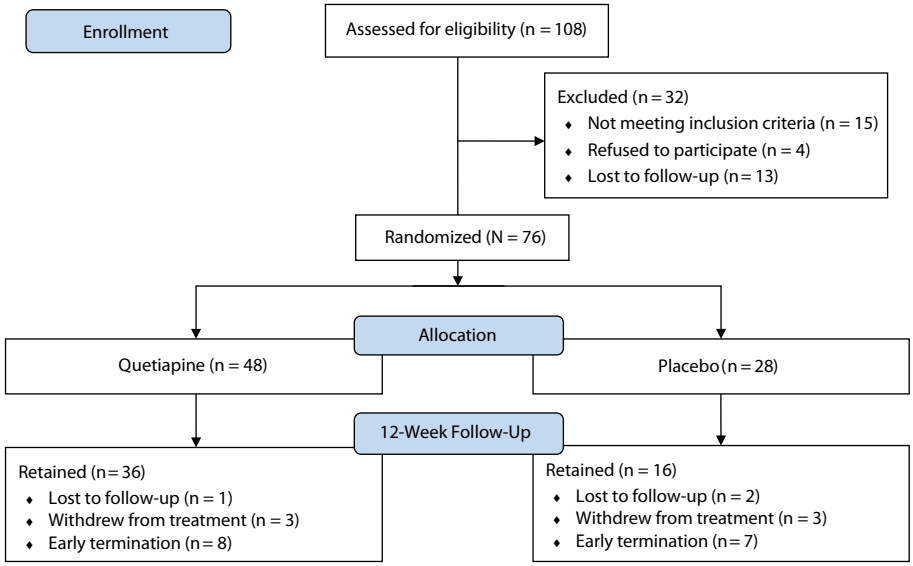
Definition of Treatment Response and Remission

Response was defined as an absolute score of 11 or less and/or a 50% decrease in $HDRS_{17}$ score (for depression) and HARS score (for anxiety disorders). Remission was defined as an $HDRS_{17}$ score of ≤ 7 (for depression) and an HARS score of ≤ 7 (for anxiety).

Statistical Analyses

The intent-to-treat population was analyzed using the last-observation-carried-forward method. *t* Tests were

Figure 1. Flowchart Depicting Patient Disposition Throughout the Study



conducted to assess mean changes from baseline to week 12 for primary and secondary measures for each intervention. Analyses of covariance (ANCOVAs) were also conducted to determine mean differences between groups at week 12 with Bonferroni-adjusted post hoc comparisons while controlling for baseline scores (95% confidence intervals [CIs] for all estimates, as well as mean scores at week 12, are shown in Table 2).

Mean demographic variables and baseline measures were compared between the quetiapine and placebo groups using independent-samples *t* tests and, when appropriate, non-parametric analysis such as χ^2.

RESULTS

Demographic Information for the Study Sample

The study recruitment pathway is depicted in Figure 1. Overall, 108 patients were assessed for eligibility and 76 were enrolled in the study (quetiapine, n = 48; placebo, n = 28). Mean demographic variables and baseline measures are presented in Table 1.

There were no significant differences in the demographic and clinical measures at baseline between the two groups. Mean $HDRS_{17}$ scores indicated moderate severity of depression, while the mean HARS scores indicated moderate to severe anxiety for both groups. The mean duration of the current episode was about 1 year with large standard deviations, reflecting the complex nature of the study population. Only 42% of the quetiapine group and 21% of the placebo group were currently working, with the majority either unemployed or on disability leave.

Comorbid Anxiety Disorders

In addition to depressive disorder, the majority of participants met criteria for GAD (n = 70). A smaller number of participants met criteria for SAD (n = 6), while none of the participants met criteria for PD.

Table 3. Doses of Study Drugs[a]

Drug	Week 2	Week 4	Week 6	Weeks 8–12 (Fixed)
Quetiapine	165.91 (70.52)	187.78 (85.38)	177.38 (84.25)	176.83 (88.10)
Placebo	213.04 (67.79)	227.27 (68.53)	234.21 (68.83)	240.63 (73.53)

[a]Doses are shown as mean (SD) mg/d.

Concomitant Antidepressant, and Study Medication

Participants were required to take a first-line antidepressant at a stable optimum dose for a minimum of 2 weeks prior to study enrollment. Most participants (79%) were on them for 8 weeks, while a minority had dose changes between 2 and 8 weeks from baseline. The type and frequency of antidepressant medication are presented in Table 1.

The mean dose of the study medications prescribed at each visit during the flexible treatment phase is presented in Table 3. At the end of week 8 (the start of the fixed dose phase), the mean (SD) dose for quetiapine (176.83 [88.10] mg/d) was significantly lower than the mean dose for placebo (240.63 [73.53] mg/d; $t_{55} = 2.57$, $P = .01$).

Primary Efficacy Measures

Observer-rated depression symptoms ($HDRS_{17}$). As shown in Table 2, analysis of $HDRS_{17}$ scores revealed that depressive symptoms declined following treatment for both quetiapine (MC = 10.98; 95% CI, 8.95 to 13.01) and placebo groups (MC = 8.32; 95% CI, 4.89 to 11.76). There was also a significant difference between the groups at week 12, indicating that mean $HDRS_{17}$ scores were lower in the quetiapine group in comparison to the placebo group (MD = −3.64; 95% CI, −7.01 to −0.27; $\eta^2 = 0.06$).

Observer-rated anxiety symptoms (HARS). Analysis of HARS scores revealed a significant decrease in anxiety scores following treatment for both quetiapine (MC = 11.67; 95% CI, 9.14 to 14.19) and placebo groups (MC = 8.00; 95% CI, 5.42 to 10.58). Furthermore, there was a significant difference between group scores at week 12, such that the quetiapine group had lower HARS scores compared to the placebo group (MD = −4.02; 95% CI, −7.41 to −0.64; $\eta^2 = 0.07$). The results are presented in Table 2.

While both HARS and $HDRS_{17}$ scores declined significantly over the study period, the absolute post-treatment scores were relatively high, indicating the presence of significant residual symptoms and absence of remission.

Observer-rated clinical severity (CGI-S). There were significant declines in CGI-S scores over the course of treatment for the quetiapine (MC = 1.26; 95% CI, 0.94 to 1.58) and placebo groups (MC = 0.59; 95% CI, 0.26 to 0.93). At week 12, the quetiapine group also had significantly lower CGI-S scores compared to the placebo group (MD = −0.64; 95% CI, −1.13 to −0.15; $\eta^2 = 0.09$). Results are shown in Table 2.

Treatment response and remission. Twenty-seven participants (56%) who received quetiapine and 11 participants (39%) in the placebo group fulfilled criteria for treatment response as measured by the $HDRS_{17}$. Among responders, 11 (23%) in the quetiapine and 6 (21%) in the placebo group were judged to be remitters. However, the proportions of responders ($\chi^2_1 = 2.04$, $P = .15$, n = 76) and remitters ($\chi^2 = 0.27$, $P = .60$) did not statistically differ between the two groups.

Treatment response as measured by reduction in HARS scores revealed that 27 participants (58%) in the quetiapine group and 9 (32%) in the placebo group were responders. Of these cohorts, 11 (23%) in the quetiapine group and 4 (14%) in the placebo group fulfilled criteria for remission. The proportion of responders ($\chi^2 = 3.45$, $P = .06$) and remitters ($\chi^2 = 0.83$, $P = .36$) did not differ between groups.

Secondary Efficacy Measures

The secondary efficacy measures included observer and self-report ratings of depression symptoms (MADRS, BDI) and quality of life (Q-LES-Q) as well as ratings of specific anxiety symptoms (PSWQ for GAD). There was an insufficient number of participants with SAD and none who met criteria for PD; therefore, those specific measures were not included in the analyses.

Analysis of MADRS scores revealed a significant decline in depressive symptoms over the treatment phase in the quetiapine (MC = 11.72; 95% CI, 9.28 to 14.16) and placebo groups (MC = 9.62; 95% CI, 5.33 to 13.90). BDI scores also decreased significantly after the 12-week period with quetiapine (MC = 8.46; 95% CI, 5.11 to 11.80) but not with placebo (MC = 4.04; 95% CI, −0.84 to 8.92). No significant differences in the two measures were seen between groups at week 12 (MADRS: MD = −2.99; 95% CI, −7.46 to 1.48; $\eta^2 = 0.03$; BDI: MD = −4.37; 95% CI, −9.67 to 0.94; $\eta^2 = 0.04$). These findings are shown in Table 2.

Table 4. Type of Adverse Events by Treatment Group[a]

Type of Adverse Event	Quetiapine (n = 48)	Placebo (n = 28)	Total (N = 76)
Somnolence	19 (39.58)	1 (3.57)	20 (26.32)
Dry mouth	19 (39.58)	6 (21.42)	25 (32.89)
Gastrointestinal	11 (22.92)	4 (14.29)	15 (19.74)
Fatigue	7 (14.58)	6 (21.42)	13 (17.11)
Dizziness	7 (14.58)	2 (7.14)	9 (11.84)
Appetite disturbance	6 (12.50)	3 (10.71)	9 (11.84)
Muscular (soreness, spasm)	4 (8.33)	3 (10.71)	7 (9.21)
Cardiac (tachycardia, palpitations)	3 (6.25)	0 (0.0)	3 (3.95)
Headache	3 (6.25)	2 (7.14)	5 (6.58)
Sexual dysfunction	3 (6.25)	1 (3.57)	4 (5.26)
Insomnia	1 (2.08)	3 (10.71)	4 (5.26)
Dermatologic (rash, pruritus)	2 (4.17)	3 (10.71)	5 (6.58)
Psychomotor agitation	2 (4.17)	2 (7.14)	4 (5.26)
Urinary (increased frequency, discoloration)	2 (4.17)	2 (7.14)	4 (5.26)
Weight change ≥ 7%[b]	7 (14.58)	2 (7.14)	9 (11.84)

[a]Values are shown as n (%).
[b]Clinically significant weight change defined by the US Food and Drug Administration.

Quality of life, as measured by the Q-LES-Q, improved modestly over time in both the quetiapine (MC = −5.56; 95% CI, −11.73 to 0.62; $P = .06$) and placebo groups (MC = −5.00; 95% CI, −12.30 to 2.30). The changes were not significant, and there was no difference in scores between groups at week 12 (MD = 2.10; 95% CI, −7.09 to 11.29; $\eta^2 = 0.003$). PSWQ scores declined significantly over time for both the quetiapine (MC = 6.03; 95% CI, 3.02 to 9.03) and placebo groups (MC = 4.61; 95% CI, 0.79 to 8.43). There was no statistically significant difference between groups (MD = −1.44; 95% CI, −6.35 to 3.47; $\eta^2 = 0.01$) (Table 2).

Adverse Events

At least 1 adverse event was reported by 46% of subjects in the placebo-treated group (n = 13) and 77% in the quetiapine group (n = 37). The frequencies based on total number of adverse events by medication group are reported in Table 4. Quetiapine-treated subjects reported a greater number of adverse events than those in the placebo group ($\chi^2_1 = 7.38$, $P < .01$, n = 76) that were judged to be possibly or probably related to study medication. Specifically, subjects in the quetiapine group experienced modest weight gain (MC = 2.76 kg; 95% CI, 1.57 to 3.95 kg; $P < .0001$; $\eta^2 = 0.11$), while those in the placebo group did not (MC = 0.33 kg; 95% CI, −1.41 to 2.06; $P = .70$; $\eta^2 = 0.02$). There was also a significant difference in weight between treatment groups at week 12 (MD = 3.10; 95% CI, 1.09 to 5.11; $\eta^2 = 0.12$). Seven subjects in the quetiapine and 2 in the placebo group experienced clinically significant weight change (defined as ≥ 7%) from baseline (Table 4). In general, the study medication was well tolerated. No participants withdrew from the study due to adverse reactions, and no serious events were reported.

DISCUSSION

Both quetiapine and placebo groups exhibited a significant decline in symptoms of depression and anxiety following treatment. Furthermore, those in the quetiapine-treated

group had significantly lower depression and anxiety scores compared to those who received placebo, suggesting the benefit of quetiapine as an add-on to first-line antidepressants as a useful therapeutic strategy for this population. Indeed, a review by McIntyre et al[42] suggests that the use of the combination of an antidepressant and quetiapine as first-line for MDD subjects with significant anxiety may have the benefit of accelerated response and increased likelihood of remission. Thase et al[26] previously reported the benefit of quetiapine in the treatment of anxious depression, and Maneeton et al[23] confirmed its benefit for GAD. Other studies have also found a reduction in anxiety symptoms following quetiapine treatment.[24,43] Our investigation extends the clinical utility of quetiapine to comorbid depressive and anxiety conditions.

The magnitude of change in depressive symptoms with quetiapine augmentation was moderate and thus in keeping with previous reports[13,26] and is comparable to that with risperidone and aripiprazole and similar to that with olanzapine-fluoxetine combination.[13] In a more recent meta-analysis,[44] quetiapine was found to have a large effect on anxiety symptoms, while in the current study, the benefit seen was more modest, probably due to the small sample size. Even with recent treatment advances, comorbid depression and anxiety remain clinically challenging to treat, which may also explain the relatively high posttreatment HARS and $HDRS_{17}$ scores in spite of significant decline. While many patients with this comorbidity appear to benefit from augmentation strategies, the degree of response is less robust than in those without the anxiety comorbidity.[45]

There were no significant differences in response or remission rates between groups. However, a numerical superiority for the quetiapine group was noted in 56% ($HDRS_{17}$) and 58% (HARS) of participants being responders compared to 39% ($HDRS_{17}$) and 32% (HARS) in the placebo group. There was also a trend for the quetiapine-treated patients to exhibit better response compared to the placebo group in several secondary measures. The cumulative benefit of ongoing antidepressants can improve symptoms and influence the course and severity of depression, and it likely further contributed to the placebo response. Placebo effects, as well as contribution of non-specific factors associated with participation in clinical trials, have been well documented.[46,47] Taken together, these findings suggested that quetiapine has clinically significant benefit.

In general, quetiapine was well tolerated with few significant adverse effects. However, subjects receiving quetiapine exhibited weight gain over the course of the study, though its magnitude was relatively modest ($\eta^2 = 0.11$). Among the study population, 9 participants (quetiapine, n = 7; placebo, n = 2) met criteria for significant weight change (defined as ≥ 7% from baseline). Weight gain is a well-documented consequence of many atypical antipsychotics and should be particularly monitored in those with metabolic syndrome receiving quetiapine longer term.

A key limitation of this study is that, in the majority of the subjects, the comorbid diagnosis was GAD, and as such, generalizability to other comorbid anxiety disorders is limited. It is noteworthy that quetiapine is approved in Canada for the treatment of GAD. Another significant limitation is the smaller-than-expected sample size, which warrants caution when interpreting the results. Inclusion criteria required all participants to have been on a stable dose of antidepressants for at least 2 weeks at baseline, and most (79%) were on them over 8 weeks. However, a small minority had dose changes between 2 and 8 weeks from baseline, possibly contributing to the placebo response by carryover effect, which is another limitation to consider in the interpretation of the findings. In addition, as with all placebo-controlled trials, inadequate blinding due to recognition of adverse effects that leads to rater bias is a further shortcoming.

With the aforementioned caveats, the findings of the study suggest that quetiapine augmentation to antidepressants is a useful and safe strategy to improve response in patients with depression and anxiety comorbidity. Evaluating this treatment strategy for other common comorbidities (eg, SAD, PTSD) to depression, both unipolar and bipolar, would be of benefit to these difficult-to-treat patients. Furthermore, quetiapine has been shown to reduce symptoms of bipolar depression[48–50] as well as comorbid anxiety,[51,52] suggesting its benefit to a broader cohort of patients with mood and anxiety conditions.

In conclusion, quetiapine augmentation may be a feasible and useful strategy for MDD patients with comorbid anxiety (in particular, comorbid GAD) who experience partial response to SSRI/SNRIs.

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