Extended Release Quetiapine Fumarate in Patients With Major Depressive Disorder: Suicidality Data From Acute and Maintenance Studies

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ABSTRACT

Objective: To prospectively analyze effects of extended release quetiapine fumarate (quetiapine XR) on suicidality in major depressive disorder (MDD).

Method: Data were pooled from randomized, acute studies (4 monotherapy; 2 adjunct therapy) in adult patients with a *DSM-IV* diagnosis of MDD who were considered not to be at high risk of suicide at baseline and were receiving quetiapine XR 50 mg/d (n = 181), 150 mg/d (n = 910), or 300 mg/d (n = 685) or placebo (n = 957). Data from 1 acute monotherapy study in elderly patients receiving quetiapine XR (50–300 mg/d; n = 166) or placebo (n = 172) and maintenance data (up to 52 weeks) for patients receiving quetiapine XR (50–300 mg/d; n = 391) or placebo (n = 385) were also evaluated. Overall incidences and relative risks for suicidality (suicidal behavior/ideation) were assessed by Columbia-type review and classification. The proportion of patients with Montgomery-Asberg Depression Rating Scale (MADRS) item 10 (suicidal thoughts) score ≥ 4 was analyzed.

Results: Incidence of suicidality during acute treatment in adults was 1.1%, 0.7%, 0.7%, and 0.7% with quetiapine XR 50 mg/d, 150 mg/d, and 300 mg/d and placebo, respectively. The proportion of patients with MADRS item 10 score ≥ 4 during acute treatment in adults was 1.8% with quetiapine XR (all doses combined) and 2.4% with placebo. In elderly patients, the incidence of suicidality during acute treatment was 0.6% in both treatment groups; the proportion of patients with MADRS item 10 score ≥ 4 was 0% with quetiapine XR (all doses combined) and 1.2% with placebo. During maintenance treatment, the incidence of suicidality was 0.3% (n = 1) and 0.5% (n = 2) for quetiapine XR and placebo, respectively. The proportion of patients with MADRS item 10 score ≥ 4 was 4.1% with quetiapine XR in the open-label stabilization period and 0.3% with quetiapine XR and 0.5% with placebo during the randomized period.

Conclusions: This analysis suggests that there is no evidence of treatment-emergent suicidality with quetiapine XR therapy in patients with MDD considered not to be at high suicide risk at baseline.

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Suicidal ideation/behavior (suicidality) is a serious, common complication in patients with major depressive disorder (MDD).[1,2] The psychopathologic state of suicidality includes symptoms of severe depression, cognitive impairment, behavioral disturbances, and abnormal thought processes.

Consensus among MDD treatment guidelines is that first-line therapy options should include a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor.[3–5] On the basis of safety information from regulatory studies, published data, and observational studies, regulatory bodies in the United States[6] and Europe[7] have issued warnings highlighting the risk of suicide (suicide attempt, suicidal thoughts, and hostility) with all antidepressant treatments in younger adults. The warnings also highlight the need for close clinical monitoring similar to that used in clinical trials, especially for younger adults, adolescents, and children. However, findings from epidemiologic, long-term, and prospective studies on the risks of suicidality with antidepressant use are often inconsistent, and therefore the requirement for the box warning is subject to much debate. Data analysis from trials in pediatric and adolescent patients identified an increased risk versus placebo of suicidal behavior or ideation among patients receiving antidepressants.[8] In addition to adolescents, the elderly are at particular risk for suicide,[9,10] with those aged ≥ 75 years having the highest suicide rate of all age groups in most industrialized countries.[11]

Several clinical trial database reviews have evaluated the effect of SSRIs on suicidality. A meta-analysis of treatment-emergent suicidality data from double-blind, randomized, placebo-controlled studies of paroxetine in adults (N = 14,911) showed a higher incidence of suicidal behavior with paroxetine versus placebo in patients with MDD.[12] This was considered to be related to the higher incidence in younger adults (18–24 years). Analysis of longitudinal data on suicidal thoughts and behavior in randomized placebo-controlled studies showed no evidence for increased suicide risk with fluoxetine and venlafaxine, with a risk reduction over time.[13] In another meta-analysis of clinical trial data, no association with increased risk of suicidal acts or suicidal thoughts was found for fluoxetine versus placebo in patients with MDD.[14]

Analysis of the effect of citalopram on suicidality in placebo-controlled studies showed that citalopram was significantly more effective than placebo at reducing suicidal thoughts.[15] A review of efficacy and safety data from placebo-controlled studies of escitalopram reported no indication that escitalopram was associated with increased suicidal behavior versus placebo in patients with MDD.[16]

Clinical trial data support the antidepressant efficacy of atypical antipsychotics in MDD; however, there is a lack of published data

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Clinical Points

- Regulatory bodies in the United States and Europe have issued warnings highlighting the risk of suicide with all antidepressant treatments in younger adults.
- This prospectively planned analysis of pooled data showed no evidence of treatment-emergent suicidality compared with placebo following treatment with quetiapine XR in patients with major depressive disorder considered not at high risk of suicide at baseline.

describing suicidality risk in patients with MDD receiving atypical antipsychotics.

Extended release quetiapine fumarate (quetiapine XR) is indicated for use as adjunctive therapy to antidepressants for the treatment of MDD in the United States[17] and within the European Union as add-on treatment for major depressive episodes in patients with MDD who have shown suboptimal response to antidepressant monotherapy.[18] Quetiapine XR is also indicated as monotherapy for MDD in some countries, such as Australia and Canada. Quetiapine XR efficacy and tolerability data have been reported from 4 acute monotherapy studies in adults,[19–22] 1 acute monotherapy study in elderly patients,[23] 1 maintenance monotherapy study in adults,[24] and 2 acute adjunct therapy studies in adults.[25,26]

This prospectively planned pooled analysis evaluated the incidence of suicidal behavior/ideation during acute and maintenance treatment with once-daily quetiapine XR in patients with MDD who were considered not to be at high suicide risk at the time of screening or randomization.

METHOD

Details of study designs and methodologies used in the quetiapine XR clinical development program in adult patients with MDD (4 acute monotherapy studies: D1448C00001 [Study 1],[19] D1448C00002 [Study 2],[20] D1448C00003 [Study 3],[21] D1448C00004 [Study 4][22]; 2 acute adjunct therapy studies: D1448C00006 [Study 6],[25] D1448C00007 [Study 7][26]; a maintenance monotherapy study, D1448C00005 [Study 5][24]; and an acute monotherapy study in elderly patients with MDD, D1448C00014 [Study 14][23]) have been reported previously. Data were pooled from the 6 acute adult studies (4 acute monotherapy studies and 2 acute adjunct therapy studies) to ensure a large patient population and to increase the probability of detecting a difference in suicidality between quetiapine XR and placebo for acute treatment. A brief overview of study details is provided in eAppendix 1 at Psychiatrist.com.

Patients

Male and female patients aged 18–65 years in the adult studies and ≥ 66 years in the elderly study, with a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[27] diagnosis of MDD (single episode or recurrent) as confirmed by the Mini-International Neuropsychiatric Interview, were eligible for inclusion. Patients considered to be at high risk of suicide at screening or baseline (Hamilton Depression Rating Scale [HDRS] item 3 [suicide] score ≥ 3 or suicide attempt within 6 months prior to enrollment) were excluded from the studies. Patients with a history of psychosis were not excluded from the studies. Further details of inclusion/exclusion criteria are provided in eAppendix 1.

Statistical Analysis

Study population. All data analyses were performed using the safety populations from the acute and maintenance studies that comprised all patients who received ≥ 1 dose of quetiapine XR or placebo during randomized treatment periods. Additional analyses were conducted using the open-label safety population (all patients who received ≥ 1 dose of open-label quetiapine XR or placebo during open-label run-in or stabilization treatment periods) in the maintenance study.

Classification of suicidal behavior or ideation. All adverse events (AEs) and AEs classified as suicidal behavior/ideation across the 8 studies were reviewed. Patients in the safety populations with possible suicidal behavior/ideation were identified and assessed by Columbia-type review and classification analysis using the codes shown in Supplementary eTable 1.[28] Reviewers were trained in Columbia-type review and were not associated previously with any of the studies. All study data were blinded. The proportion of patients with Montgomery-Asberg Depression Rating Scale (MADRS) item 10 (suicidal thoughts) score ≥ 4 during the studies was also analyzed.

Data analysis. Suicidal behavior/ideation (Columbia codes 1, 2, 3, 4), suicidal behavior (1, 2, 3), suicidal ideation (4), and possible suicidal behavior/ideation (5, 6, 9) incidences and relative risks (RRs) were calculated using 3 sets of data: pooled data from the safety populations in 6 acute studies, data from the acute monotherapy study in elderly patients, and data from the open-label and randomized safety populations in the maintenance study. Patients with > 1 event classified by Columbia codes 1, 2, 3, or 4 were assigned the most serious classification. Patients without an event rated as Columbia codes 1, 2, 3, or 4 were evaluated for possible events classified as Columbia codes 5, 6, or 9, and, if an event was present, the most serious classification was applied. If events with these codes were absent, patients were assigned the most serious of the remaining classifications for their respective events. No events occurring in patients who were screen failures or events occurring more than 30 days after last dose of study medication were collected.

The proportion of patients with MADRS item 10 score ≥ 4 was calculated using the 3 populations described above. Patients with MADRS item 10 score ≥ 4 at randomization were excluded from the analysis.

In the adult studies, age subgroup analyses of suicidality incidence data (Columbia-type analysis; patients stratified into the following age categories: 18–24, 25–30, and 31–65 years) were conducted. Relative risk of suicidality for quetiapine XR versus placebo was adjusted for the study using Mantel-Haenszel stratification, and 95% confidence

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Table 1. Incidence of Suicidal Behavior/Ideation (Columbia-type analysis) and Proportion of Patients With MADRS Item 10 (suicidal thoughts) Score ≥ 4 Postrandomization in Acute Studies of Quetiapine XR as Monotherapy or Adjunct Therapy in Adult or Elderly Patients With MDD (randomized safety population)[a]

	Adult Patient Studies					Elderly Patient Studies	
			Quetiapine XR Dose Groups				
	Placebo	All Doses of Quetiapine XR	50 mg/d	150 mg/d	300 mg/d	Placebo	Quetiapine XR
Columbia-type analysis/classification code	n = 957	n = 1,776	n = 181	n = 910	n = 685	n = 172	n = 166
Suicidal behavior/ideation (1, 2, 3, 4)	7 (0.7)	13 (0.7)	2 (1.1)	6 (0.7)	5 (0.7)	1 (0.6)	1 (0.6)
Suicidal behavior (1, 2, 3)	2 (0.2)	3 (0.2)	0	1 (0.1)	2 (0.3)	1 (0.6)	1 (0.6)
Suicidal ideation (4)	5 (0.5)	10 (0.6)	2 (1.1)	5 (0.5)	3 (0.4)	0	0
Possible suicidal behavior/ideation (5, 6, 9)[b]	13 (1.4)	16 (0.9)	1 (0.6)	9 (1.0)	6 (0.9)	2 (1.2)	0
MADRS item 10 analysis[c]	n = 933	n = 1,740	n = 178	n = 890	n = 672	n = 166	n = 160
MADRS item 10 score ≥ 4	22 (2.4)	32 (1.8)	4 (2.2)	13 (1.5)	15 (2.2)	2 (1.2)	0

[a]Data expressed as n (%).
[b]Includes intent unknown and insufficient information ratings.
[c]Numbers of patients with MADRS Item 10 score < 4 at randomization.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, quetiapine XR = extended release quetiapine fumarate.

intervals (CIs) were calculated. If CIs for the comparisons between the quetiapine XR groups and placebo included 1, the difference between treatment groups was classed as not statistically significant.

RESULTS

Patient Population

Pooled acute monotherapy and acute adjunct adult studies. Patient characteristics in the 6 acute studies in adults (Studies 1, 2, 3, 4, 6, and 7) have been described previously.[19–22,25,26] A total of 2,733 patients were randomly assigned to receive quetiapine XR 50 mg/d (n = 181), 150 mg/d (n = 910), or 300 mg/d (n = 685) or placebo (n = 957) and comprised the pooled safety population. For these secondary analyses, only data for quetiapine XR and placebo were pooled (active control data excluded).

Acute monotherapy study in elderly patients. Patient characteristics in the acute monotherapy study in elderly patients (Study 14) have been reported previously.[23] A total of 166 patients were randomly assigned to receive quetiapine XR, and 172 were randomly assigned to receive placebo.

Maintenance monotherapy study. Patient characteristics in the maintenance monotherapy study (Study 5) have been reported previously.[24] Of the 1,854 patients who received quetiapine XR during the open-label treatment period, 776 patients were subsequently randomly assigned to quetiapine XR (n = 391) or placebo (n = 385).

Incidence of Suicidal Behavior/Ideation

Pooled acute monotherapy and acute adjunct studies. A review of all AEs and reported suicidal behavior/ideation during the randomized treatment period in the 6 acute studies in adults identified 105 events requiring Columbia-type review and classification recorded in 72 of 1,776 quetiapine XR–treated patients and 58 events recorded in 46 of 957 placebo-treated patients. In the acute studies in adults, no AEs were reported as completed suicide during randomized treatment.

Using Columbia-type analysis, the overall incidence of suicidality (behavior/ideation [Columbia codes 1, 2, 3, 4]) during acute randomized treatment was 0.7% in the quetiapine XR group (all doses combined) and 0.7% in the placebo group (Table 1). Similar incidences of each suicidality subtype were observed in each treatment group (suicidal behavior [Columbia codes 1, 2, 3], 0.2% in each treatment group; suicidal ideation [Columbia code 4], 0.6% vs 0.5% in the quetiapine XR and placebo groups, respectively). Incidences of possible suicidality (Columbia codes 5, 6, 9) were also low and similar in each treatment group (quetiapine XR, 0.9%; placebo, 1.4%). No dose-related effect of quetiapine XR on suicidality incidence was observed.

Suicidality incidences stratified by age are shown in Table 2. The overall incidence of events was low, and there was no imbalance in suicidal behavior/ideation across treatments or age cohorts.

Suicidality (behavior/ideation [Columbia codes 1, 2, 3, 4]) adjusted RR (95% CI) for quetiapine XR (all doses) compared with placebo during randomized treatment was 0.84 (0.36–1.97), indicating no statistically significant difference between treatment groups (ie, CI included 1). The suicidality (behavior/ideation) adjusted RR (95% CI) versus placebo for quetiapine XR 50, 150, and 300 mg/d also showed no evidence of increased risk of suicidality and the differences between treatment groups were not statistically significant (Figure 1). An analysis of combined confirmed and possible suicidal behavior/ideation (Columbia codes [1, 2, 3, 4] + [5, 6, 9]) data showed similar findings (adjusted RR [95% CI] of suicidality versus placebo: quetiapine XR [all doses], 0.85 [0.49–1.48]; 50 mg/d, 0.38 [0.10–1.39]; 150 mg/d, 0.80 [0.42–1.56]; 300 mg/d, 0.96 [0.46–2.04]).

The proportion of patients with MADRS item 10 score ≥ 4 was 1.8% (n = 32) in the quetiapine XR group (all doses combined) and 2.4% (n = 22) in the placebo group (Table 1).

Acute monotherapy study in elderly patients. A review of all AEs and reported suicidal behavior/ideation during the randomized treatment period in the acute monotherapy study in elderly patients identified 9 events requiring Columbia-type review and classification in 8 of

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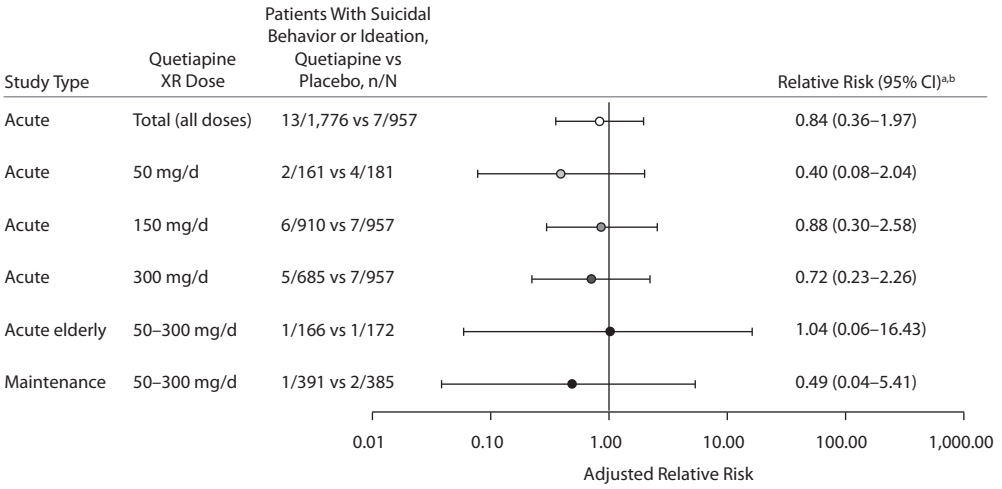
Table 2. Age-Stratified Incidence of Suicidal Behavior/Ideation (Columbia-type analysis) in Acute Studies of Quetiapine XR as Monotherapy or Adjunct Therapy in Adult Patients With MDD (randomized safety population)[a]

Classification Codes	Placebo (n = 957)	All Doses of Quetiapine XR (n = 1,776)	Quetiapine XR Dose Groups		
			50 mg/d (n = 181)	150 mg/d (n = 910)	300 mg/d (n = 685)
18–24 y age cohort	n = 75	n = 144	n = 17	n = 73	n = 54
Suicidal behavior/ideation (1, 2, 3, 4)	1 (1.3)	3 (2.1)	0	2 (2.7)	1 (1.9)
Suicidal behavior (1, 2, 3)	0	0	0	0	0
Suicidal ideation (4)	1 (1.3)	3 (2.1)	0	2 (2.7)	1 (1.9)
Possible suicidal behavior/ideation (5, 6, 9)[b]	0	2 (1.4)	0	1 (1.4)	1 (1.9)
25–30 y age cohort	n = 113	n = 180	n = 23	n = 84	n = 73
Suicidal behavior/ideation (1, 2, 3, 4)	4 (3.5)	3 (1.7)	1 (4.3)	0	2 (2.7)
Suicidal behavior (1, 2, 3)	2 (1.8)	0	0	0	0
Suicidal ideation (4)	2 (1.8)	3 (1.7)	1 (4.3)	0	2 (2.7)
Possible suicidal behavior/ideation (5, 6, 9)[b]	2 (1.8)	1 (0.6)	1 (4.3)	0	0
31–65 y age cohort	n = 769	n = 1,452	n = 141	n = 753	n = 558
Suicidal behavior/ideation (1, 2, 3, 4)	2 (0.3)	7 (0.5)	1 (0.7)	4 (0.5)	2 (0.4)
Suicidal behavior (1, 2, 3)	0	3 (0.2)	0	1 (0.1)	2 (0.4)
Suicidal ideation (4)	2 (0.3)	4 (0.3)	1 (0.7)	3 (0.4)	0
Possible suicidal behavior/ideation (5, 6, 9)[b]	11 (1.4)	13 (0.9)	0	8 (1.1)	5 (0.9)

[a]Data expressed as n (%).
[b]Includes intent unknown and insufficient information ratings.
Abbreviations: MDD = major depressive disorder, quetiapine XR = extended release quetiapine fumarate.

Figure 1. Relative Risk (95% CI) for Suicidal Behavior/Ideation (classification 1, 2, 3, 4) for Quetiapine XR Versus Placebo as Acute Monotherapy or Adjunct Therapy (pooled data) and Maintenance Monotherapy (randomized safety population)



[a]Relative risk < 1 indicated that suicidal behavior/ideation is less likely to occur in the quetiapine XR vs the placebo group (favors placebo). Relative risk > 1 indicated that suicidal behavior/ideation is more likely to occur in the quetiapine XR vs the placebo group (favors treatment).
[b]Adjusted relative risk for pooled acute monotherapy and adjunct studies; relative risk for acute elderly monotherapy study and maintenance monotherapy study.
Abbreviation: quetiapine XR = extended release quetiapine fumarate.

166 quetiapine XR–treated patients and 11 events in 10 of 172 placebo-treated patients. No completed suicides were recorded.

The overall incidence of suicidality (behavior/ideation) using Columbia-type analysis and the proportion of patients with MADRS item 10 score ≥ 4 are shown in Table 1. The incidence of suicidality (behavior/ideation) using Columbia-type analysis was 0.6% (1 event) in both the quetiapine XR and placebo groups.

The suicidality (behavior/ideation) RR (95% CI) for quetiapine XR versus placebo during randomized treatment was 1.04 (0.065–16.430), indicating that there was no statistically significant difference between treatment groups (CI included 1) (Figure 1). An analysis of combined confirmed and possible suicidal behavior/ideation (Columbia codes [1, 2, 3, 4] + [5, 6, 9]) data showed similar findings, with RR (95% CI) of suicidality versus placebo of 0.35 (0.03–3.29).

Maintenance monotherapy study. A review of all AEs and reported suicidal behavior/ideation during the randomized treatment period identified 31 events requiring Columbia-type review and classification in 28 of 391 quetiapine XR–treated patients and 18 events in 17 of 385 placebo-treated patients. No completed suicide was recorded during the open-label stabilization or randomized treatment periods of the maintenance study.

Using Columbia-type analysis, the overall incidence of suicidality during open-label stabilization treatment with

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Table 3. Incidence of Suicidal Behavior/Ideation (Columbia-type analysis) and Proportion of Patients With MADRS Item 10 (suicidal thoughts) Score ≥ 4 in a Maintenance Study of Quetiapine XR Monotherapy During the Open-Label Stabilization and Randomized Double-Blind Treatment Periods in Patients With MDD (randomized safety population)[a]

	Open-Label Stabilization Treatment Period: Quetiapine XR 50–300 mg/d	Randomized Double-Blind Treatment Period	
		Placebo	Quetiapine XR 50–300 mg/d
Columbia-type analysis/classification code	n = 1,854	n = 385	n = 391
Suicidal behavior/ideation (1, 2, 3, 4)	25 (1.3)	2 (0.5)	1 (0.3)
Suicidal behavior (1, 2, 3)	9 (0.5)	0	0
Suicidal ideation (4)	17 (0.9)	2 (0.5)	1 (0.3)
Possible suicidal behavior/ideation (5, 6, 9)[b]	10 (0.5)	0	2 (0.5)
MADRS item 10 analysis[c]	n = 1,854	n = 385	n = 391
MADRS item 10 score ≥ 4	76 (4.1)	2 (0.5)	1 (0.3)

[a]Data expressed as n (%).
[b]Includes intent unknown and insufficient information ratings.
[c]Numbers of patients with MADRS item 10 score < 4 at randomization.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, quetiapine XR = extended release quetiapine fumarate.

Table 4. Age-Stratified Incidence of Suicidal Behavior/Ideation (Columbia-type analysis) in Maintenance Study of Quetiapine XR as Monotherapy During the Open-Label Stabilization and Randomized Double-Blind Treatment Periods in Patients With MDD (randomized safety population)[a]

Classification Codes	Open-Label Stabilization Treatment Period: Quetiapine XR 50–300 mg/d (n = 1,854)	Randomized Double-Blind Treatment Period: Placebo (n = 385)	Randomized Double-Blind Treatment Period: Quetiapine XR 50–300 mg/d (n = 391)
18–24 y age cohort	n = 152	n = 26	n = 19
Suicidal behavior/ideation (1, 2, 3, 4)	7 (4.6)	0	0
Suicidal behavior (1, 2, 3)	2 (1.3)	0	0
Suicidal ideation (4)	5 (3.3)	0	0
Possible suicidal behavior/ideation (5, 6, 9)[b]	3 (2.0)	0	0
25–30 y age cohort	n = 203	n = 36	n = 31
Suicidal behavior/ideation (1, 2, 3, 4)	3 (1.5)	0	0
Suicidal behavior (1, 2, 3)	1 (0.5)	0	0
Suicidal ideation (4)	2 (1.0)	0	0
Possible suicidal behavior/ideation (5, 6, 9)[b]	0	0	1 (3.2)
31–65 y age cohort	n = 1,498	n = 323	n = 341
Suicidal behavior/ideation (1, 2, 3, 4)	15 (1.0)	2 (0.9)	1 (0.3)
Suicidal behavior (1, 2, 3)	6 (0.4)	0	0
Suicidal ideation (4)	10 (0.7)	2 (0.9)	1 (0.3)
Possible suicidal behavior/ideation (5, 6, 9)[b]	7 (0.5)	0	1 (0.3)

[a]Data expressed as n (%).
[b]Includes intent unknown and insufficient information ratings.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, quetiapine XR = extended release quetiapine fumarate.

quetiapine XR (n = 1,854) was 1.3% (Table 3). The incidences of suicidal behavior, suicidal ideation, and possible suicidal behavior/ideation during this stabilization treatment period were 0.5%, 0.9%, and 0.5%, respectively.

As assessed using Columbia-type analysis, overall incidences of suicidality in each cohort of patients during the randomized treatment period were 0.3% for quetiapine XR and 0.5% for placebo; all cases were suicidal ideation (Table 3). Possible suicidality was identified in 0.5% and 0% of patients in the quetiapine XR and placebo groups, respectively.

Age-stratified analyses of suicidality incidence were difficult to interpret during the open-label and randomized treatment periods because of the overall low incidence of events and the small numbers of patients in some age groups; however, these data showed no imbalance across treatment or age cohorts (Table 4).

The suicidality RR (95% CI) for quetiapine XR (50–300 mg/d) versus placebo during randomized treatment was 0.49 (0.04–5.41) and indicated no evidence of increased risk with quetiapine XR treatment compared with placebo (Figure 1).

The incidence of combined confirmed and possible suicidal behavior/ideation (Columbia codes [1, 2, 3, 4] + [5, 6, 9]) during randomized treatment was 0.8% (3 events) and 0.5% (2 events) for the quetiapine XR and placebo groups, respectively, with an RR (95% CI) of 1.48 [0.25–8.79] for quetiapine XR versus placebo.

The proportion of patients with MADRS item 10 score ≥ 4 during open-label stabilization treatment with quetiapine XR was 4.1%. During the randomized treatment period, the proportion of patients with MADRS item 10 score ≥ 4 was 0.3% for quetiapine XR and 0.5% for placebo (Table 3).

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DISCUSSION

Given the relatively high risk of suicide among patients with MDD, it is important to assess the potential of new agents to increase suicidality (suicidal ideation and behavior). This analysis is the first to report suicidality incidence and risk in randomized, placebo-controlled studies of quetiapine XR in patients with MDD.

Using Columbia-type review and classification, this prospectively planned analysis of pooled data in patients with MDD considered not at high risk of suicide at baseline showed no increased risk of suicidality compared with placebo following treatment with quetiapine XR as acute monotherapy, acute adjunct therapy, or maintenance monotherapy. This was consistent with previous studies in patients with bipolar depression treated with quetiapine or quetiapine XR.[29–33] Furthermore, in patients with MDD, similar incidences of suicidality were observed between quetiapine XR and placebo, and no dose-related effect of quetiapine XR on suicidality incidence was apparent. Of note, suicidality during the randomized treatment period of the quetiapine XR maintenance monotherapy study did not exceed incidences observed during the 12- to 18-week open-label stabilization period in either treatment group. Given the low incidence of suicidality across all the studies reported here and therefore the large confidence intervals associated with the relative risk of suicidality in these analyses, significantly larger patient populations would be required to detect any potential difference between treatment groups. However, MADRS item 10 data, collected systematically in all studies in the global quetiapine XR clinical program in MDD to assess suicidal thoughts, further supported the lack of increased risk of suicidal ideation with quetiapine XR.

In our analysis including patients with MDD aged 18–65 years, incidences of suicidality in patients receiving quetiapine XR or placebo were similar in all age groups assessed. Adjusted RR of suicidality for quetiapine XR was lower versus placebo, but no statistical difference between treatment groups was shown. It is important, however, to emphasize that interpretation of our age-stratified analyses is limited due to imbalance in patient numbers across age groups and the infrequency of suicidality events. Nevertheless, data from our pooled quetiapine XR acute therapy studies (6–8 weeks) showed that, although the overall incidence of suicidality in all groups was low, there was a trend toward a higher relative incidence of suicidality versus placebo in young adults (< 25 years). In addition, although a direct comparison of data should be viewed with caution, incidences of suicidality in patients receiving quetiapine XR or placebo in the elderly study were similar to those in the acute adult studies, with a trend toward the incidences shown in the 18–24 and 31–65 years age groups. In the current analysis of data from the quetiapine XR maintenance study, incidence of suicidality was also highest among 18- to 24-year-olds during the 12- to 18-week, open-label stabilization period (4.6%) compared with other age cohorts (1.5%, 25–30 years; 1.0%, 31–65 years). No incidences of suicidality were subsequently reported during the randomized treatment period in the 18–24 or 25–30 years age groups, and suicidality incidence remained low in the 31–65 years age group.

In the quetiapine XR acute studies in adult patients with MDD, adjusted RR of suicidality (behavior/ideation) versus placebo was approximately 50% lower in the quetiapine XR 50-mg/d group compared with the 150- and 300-mg/d groups (0.40 vs 0.88 and 0.72); however, it is important to note that the imbalance in patient numbers between dose groups (the 50 mg cohort was included in only 1 of 6 acute studies) may limit the conclusions that can be drawn from this.

Other atypical antipsychotics have been reported to show no increased risk of suicidality, although these findings are based on a small evidence base. No reports to date assess the incidence or risk of suicidality with olanzapine-fluoxetine combination (OFC) therapy versus placebo in patients with MDD; however, a 76-week, open-label, noncomparative trial in 560 patients with MDD noted that 1.3% of patients receiving OFC attempted suicide during the study.[34] A pooled analysis of data from two 6-week, double-blind, placebo-controlled studies evaluated the effect of adjunctive aripiprazole on suicidality in patients with MDD and an inadequate response to antidepressants in those not at significant risk of suicide. The results suggested that adjunctive aripiprazole was associated with decreased risk of suicidality in these patients.[35] Currently, there are no reports of long-term suicidality risk associated with aripiprazole in patients with MDD.

Strengths and limitations of the current analyses are described in eAppendix 1. In brief, key strengths are (1) use of pooled data to provide a more robust data set for analysis; (2) use of the Columbia-type classification method, which provides improved sensitivity for detecting safety AEs linked to suicide; and (3) inclusion of outcome measures in each study that enabled investigation of any quetiapine XR dose-related effects on suicidality. Limitations are (1) exclusion of patients considered to be of high suicide risk at baseline, resulting in a sample that is not fully generalizable to the wider patient population with MDD treated in clinical practice and preventing conclusions on the effects of treatment on active suicidal behavior; (2) unbalanced patient numbers across dose and age-stratified groups, which limit the statistical power of some analyses; and (3) inclusion of studies of different duration (6 or 8 weeks).

Practicing clinicians should be aware that individuals with untreated depressive disorders and known patients with unremitted depression as previously noted remain at greater risk for suicide. Ideally, all patients with affective disorders should be treated for their mood disorder with pharmacotherapy, psychotherapy, or a combination of both to obtain optimal response while being periodically monitored for suicidality.

In conclusion, the analysis reported here showed no evidence of treatment-emergent suicidality with quetiapine XR as acute monotherapy, adjunct therapy, or maintenance therapy compared with placebo in patients with MDD

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considered by investigators not to be at high suicide risk at baseline.

Drug names: aripiprazole (Abilify), citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), olanzapine (Zyprexa), olanzapine-fluoxetine combination (Symbyax and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), venlafaxine (Effexor and others).

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Supplementary Material

Article Title: Extended Release Quetiapine Fumarate in Patients With Major Depressive Disorder: Suicidality Data From Acute and Maintenance Studies

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List of Supplementary Material for the article

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eAppendix 1

Weisler et al , Extended release quetiapine fumarate (quetiapine XR) in patients with major depressive disorder: suicidality data from acute and maintenance studies

MATERIALS AND METHODS

Study Design and Treatment

Pooled data were analyzed from six multicenter, randomized, double-blind, placebo-controlled studies in adult patients: four acute monotherapy studies (D1448C00001 [Study 1];[1] D1448C00002 [Study 2];[2] D1448C00003 [Study 3];[3] D1448C00004 [Study 4][4]) and two acute adjunct therapy studies (D1448C00006 [Study 6];[5] D1448C00007 [Study 7][6]). Data from the acute monotherapy study in elderly patients (D1448C00014 [Study 14][7]) were analyzed separately due to the different patient population. Data from the maintenance monotherapy study (D1448C00005 [Study 5])[8] were also analyzed separately due to major design differences compared with the acute studies. To ensure blinding in each study, quetiapine XR tablets were identical in appearance, smell, and taste to their respective placebo tablets with identical packaging and labeling. Study medication was taken orally, once daily in the evening.

Acute Monotherapy Studies in Adult Patients

The four acute monotherapy studies in adult patients consisted of a 7–28-day enrollment/washout period, a 6–8-week randomization period (during which patients were randomized to treatment in an equal ratio using a computer-based randomization system), and a 2-week, posttreatment drug discontinuation/tapering period. Studies 1 and 2 were fixed-dose studies with patients randomized to 6 weeks' treatment with quetiapine XR 150 or

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300 mg/day or placebo. Additional cohorts of patients received 6 weeks' treatment with quetiapine XR 50 mg/day (Study 1) or duloxetine 60 mg/day as an active comparator (Study 2). Studies 3 and 4 were modified fixed-dose studies with patients randomized to 8 weeks' treatment with quetiapine XR 150 mg/day or placebo. An additional cohort of patients in Study 4 received escitalopram 10 mg/day as an active comparator. In Studies 3 and 4, patients with an inadequate response to treatment at week 2 (defined as failure to achieve a ≥20% improvement from randomization in Montgomery Åsberg Depression Rating Scale [MADRS] total score) had their treatment dose increased (quetiapine XR 300 mg/day [Studies 3 and 4] or escitalopram 20 mg/day [Study 4 only]).

Acute Adjunct Therapy Studies in Adult Patients

Studies 6 and 7 consisted of an enrollment/washout period of up to 14 days, a 6-week randomization period (during which patients were randomized to treatment in an equal ratio using a computer-based randomization system) and, in Study 6 only, a 2-week, posttreatment follow-up period. Patients with a history of inadequate response to antidepressant treatment (defined as continuing depressive symptoms despite ≥6 weeks of therapy at an adequate dose [minimum effective dose according to the product label and including at least one dose increase as permitted by the label]) were randomized to quetiapine XR 150 or 300 mg/day or placebo as adjunct to ongoing antidepressant therapy.

Acute Monotherapy Study in Elderly Patients

Study 14 consisted of an enrollment period of up to 28 days, a 9-week randomized treatment period, and a 2-week follow-up period. All quetiapine XR patients started on a 50 mg/day dose for 3 days, followed by up-titration to 100 mg/day on day 4, 150 mg/day on day 8, 200 mg/day on day 15, and 300 mg/day on day 22. From day 4, re-titration could take place at the judgment of the investigator if the dose was not tolerated. From day 8, dose reduction

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could take place if the dose was not tolerated, and up-titration continued if the patient's response to the dose was inadequate (defined as <20% reduction from baseline in MADRS total score). On days 29 to 63, all quetiapine XR patients were treated with flexible dosing, from 50 mg/day to 300 mg/day, based on efficacy and tolerability. Patients randomized to the placebo group received matched placebo according to the same treatment plan. At the end of 9 weeks of randomized treatment, all investigational product was discontinued and patients underwent a 2-week posttreatment follow-up period.

Maintenance Monotherapy Study in Adult Patients

Study 5 was a maintenance monotherapy study comprising an enrollment/washout period of up to 28 days, a 4–8-week open-label run-in treatment period, a 12–18-week open-label stabilization treatment period, and a double-blind, randomized treatment period of up to 52 weeks (during which patients were randomized to treatment in an equal ratio using a computer-based randomization system). During the open-label treatment periods, patients received quetiapine XR 50, 150, or 300 mg/day, based on the investigator's clinical judgment. Patients were randomized to quetiapine XR (at the same dose as the last open-label visit) or placebo.

Patients

Inclusion Criteria

Male and female patients aged 18–65 years in the adult studies and ≥66 years in the elderly study, with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[9] diagnosis of MDD (single episode or recurrent) as confirmed by the Mini-International Neuropsychiatric Interview, were eligible for inclusion.

For inclusion in the acute monotherapy studies, patients were required to have a Hamilton

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Rating Scale for Depression (HAM-D) total score ≥22 and a HAM-D Item 1 (depressed mood) score ≥2 at enrollment and randomization.

Eligible patients in the acute adjunct therapy studies had a HAM-D total score ≥20 and a HAM-D Item 1 score ≥2 at enrollment and randomization. Patients were also required to have a history of inadequate response to one of the following antidepressants during the current depressive episode: amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine.

In the maintenance monotherapy study, eligible patients were required to have a current episode of depression lasting <12 months and ≥4 weeks prior to enrollment, and a HAM-D total score of ≥20 and HAM-D Item 1 score ≥2 at enrollment. For the open-label stabilization and randomization treatment periods, patient were required to have a MADRS total score ≤12 and a Clinical Global Impressions-Severity of Illness total score ≤3.

Exclusion Criteria

Patients considered to be at high risk of suicide at screening or baseline (HAM-D Item 3 [suicide] score ≥3 or suicide attempt within 6 months prior to enrollment) were excluded from the studies. Other key exclusion criteria included: diagnosis of a DSM-IV Axis I disorder (other than MDD) within 6 months prior to enrollment; diagnosis of any DSM-IV Axis II disorder significantly impacting psychiatric status; duration of the current MDD episode >12 months or <4 weeks from enrollment; DSM-IV diagnosis of dementia or mild cognitive impairment; or current substance/alcohol abuse.

In the acute and maintenance monotherapy studies, patients with a history of an inadequate response to ≥6 weeks of treatment (during the current depressive episode) with ≥2 classes of antidepressant were also excluded.

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KEY STRENGTHS AND LIMITATIONS

Key strengths of the current analyses are: (1) use of pooled data from multiple clinical studies with similar methodological designs that provides a more robust data set (increased sample size and reduced sample variation) for analysis and also an opportunity for clinically meaningful interpretation of subgroup analyses that might otherwise be precluded due to low statistical power in the study-specific data sets; (2) use of the validated Columbia-type classification method that has demonstrated good inter-rater reliability and provides improved sensitivity for detecting safety AEs linked to suicide; (3) inclusion of outcome measures in each study, such as the use of MADRS Item 10 scores, that enabled investigation of any quetiapine XR dose-related effects on suicidality. Limitations of these analyses are: (1) exclusion of patients considered to be of high suicide risk at baseline including serious suicidal thoughts or plans, a history of a recent suicide attempt, drug and/or alcohol abuse and dependence (thus, this is not a fully representative sample of the wider patient population with MDD treated in clinical practice, and prevents conclusions on the effects of treatment on active suicidal behavior); (2) unbalanced patient numbers across dose groups (fewer patients in 50 mg/day cohort) and age-stratified groups (fewer patients in 18–24 and 25–30 years cohorts) that limits the statistical power of some analyses; and (3) inclusion of studies of different duration (6 or 8 weeks).

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Supplementary eTable 1. Columbia Suicidality Classification Codes

Code	Description
1	Completed suicide
2	Suicide attempt: self-injurious behavior associated with some intent to die. Intent can be stated or inferred by rater. No injury needed.
3	Preparatory acts towards imminent suicidal behavior: person takes steps to injure self but is stopped by self or other. Intent to die is either stated or inferred.
4	Suicidal ideation: passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior.
5	Self-injurious behavior, intent[a] unknown: self-injurious behavior where associated intent to die is unknown and cannot be inferred.
6	Not enough information, death: insufficient information to classify the event.
7	Self-injurious behavior, no intent[a]: self-injurious behavior associated with no intent to die – behavior is intended to effect change in others or the environment.
8	Other
9	Not enough information, non-death

[a]Intent inferred if the behavior was clinically impressive or there was more than one piece of evidence suggesting suicidal intent.

Based on Posner K, Oquendo MA, Gould M, et al. *Am J Psychiatry.* 2007;164(7):1035–1043.

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