Sedation intensity during dose escalation of quetiapine XR or IR in bipolar depression: a multicenter, double-blind, randomized, phase IV study

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Abstract

Background/aims: This study examined the hypothesis that the profile of initial tolerability, including somnolence and sedation, differs between quetiapine extended-release (XR) and immediate-release (IR) formulations in patients with bipolar depression.

Methods: In a double-blind, double-dummy, randomized, parallel-group study, male or female patients aged 18 to 50 years with a *DSM-IV-TR* diagnosis of bipolar I or II depression were randomized, after washout, to receive placebo on Day 1 and quetiapine XR or IR at escalating doses of 50, 100, 200, 300, and 300 mg once daily on the evenings of Days 2 to 6, with discharge on Day 7. Sedation intensity was assessed by a self-reported Modified Bond-Lader Visual Analog Scale (VAS) score.

Results: Of 139 randomized patients, 134 completed the study. Sedation intensity at 1 hour after the 50 mg dose (the primary study measure) was significantly lower with quetiapine XR than IR (mean [SD] VAS score: 33.4 [26.92] vs 44.0 [31.76]; least squares mean difference: 12.55, P=0.009; modified intent-to-treat population). Sedation intensity was shown in secondary analyses to be significantly lower with quetiapine XR than IR at 1, 2, and 3 hours after each dose on Days 2 to 6 ($P \leq 0.05$), with similar sedation intensity between treatment groups at 4 to 14 hours post-dose. Overall tolerability for both formulations was consistent with the known profile of quetiapine.

Conclusions: This study demonstrated that, over the initial dose-escalation period studied, patients with bipolar depression reported significantly lower sedation intensity in the 1 to 3 hours after taking the quetiapine XR compared to IR formulation.

Background

- Quetiapine XR has demonstrated a broad range of efficacy in clinical trials, including schizophrenia, bipolar mania, bipolar depression, major depressive disorder, and generalized anxiety disorder[1-6]
- Quetiapine XR was developed to provide convenient, once-daily dosing and rapid dose escalation when compared with the IR formulation
- Quetiapine XR results in a longer time to peak quetiapine concentration than IR, allowing attainment of more stable plasma concentrations[7,8]
- In a healthy volunteer study, quetiapine XR and IR demonstrated differences in tolerability during initial dose escalation. Sedation intensity at 1 hour after the first dose (50 mg) in the morning – the primary study outcome – was significantly lower with quetiapine XR than IR[9]

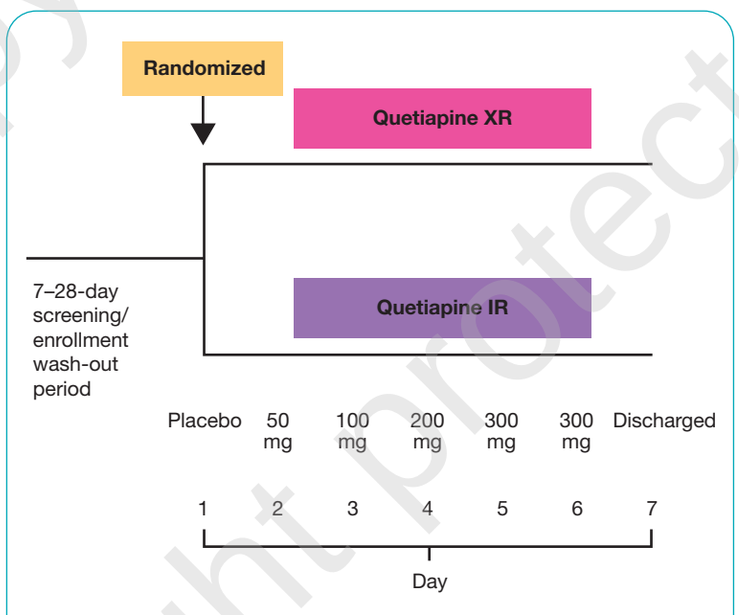
Aims

- To examine the hypothesis that the profile of tolerability, including somnolence and sedation, differs between quetiapine XR and IR during initial dose escalation in patients with bipolar depression

Methods

- A multicenter, double-blind, double-dummy, randomized, parallel-group, Phase IV study of male or female inpatients aged 18 to 50 years with a *DSM-IV-TR* diagnosis of bipolar I or II disorder, most recent episode depressed (Study D1443C00040)
- Exclusion criteria included: >8 mood episodes during the past 12 months, current episode of depression >12 months or <4 weeks from enrollment, current serious suicidal or homicidal risk, alcohol or other substance dependence or abuse, pregnancy or lactation
- Washout periods for prohibited psychotropic medications ranged from 7 to 28 days
- Inpatients were randomized to receive placebo on Day 1 and either quetiapine XR or IR at escalating doses of 50 mg on Day 2, 100 mg on Day 3, 200 mg on Day 4, and 300 mg on Days 5 and 6, with discharge on Day 7 (**Figure 1**)

Figure 1. Study design



- Quetiapine was administered in the evenings (7 PM), consistent with label recommendations for the XR formulation
- The Modified Bond-Lader VAS[10] was self-reported at –30 minutes pre-dose and 1, 2, 3, 4, 5, 12, 13, and 14 hours post-dose on Day 1 through Day 6. The Bond-Lader VAS (scale 0–100 mm) is a validated tool for self-assessment of sedation

Primary study outcome

- Sedation intensity with quetiapine XR versus IR at 1 hour after the first dose (50 mg) on Day 2, assessed by Modified Bond-Lader VAS score

Secondary study outcomes

- Sedation intensity with quetiapine XR versus IR at 1, 2, and 3 hours after each dose on Days 2 to 6
- Time to maximum sedation intensity after each dose (Days 1 to 6)
- Total amount of sedation, assessed by area under the VAS score–time curve (VAS AUC [0–14 hours])
- Safety and tolerability (adverse events, clinical assessments, and laboratory parameters)

Statistical analyses

- Primary and secondary analyses of sedation intensity used ANCOVA models with contrasts within models for LS mean differences between quetiapine XR and IR groups
- Analyses of sedation intensity were based on the MITT population, including patients who received study medication and provided sedation intensity VAS scores at baseline and at least 1 hour after the 50 mg dose
- Safety analyses were based on the safety population, including patients who received at least 1 dose of study medication
- Statistical comparisons were based on a 2-sided test using a significance level of 5%

Results

Study patients

- 139 patients were randomized and 134 (96.4%) completed the study
- The MITT population included 134 patients (n=69, XR group; n=65, IR group) and the safety population 139 patients (n=70, XR; n=69, IR)
- Patient demographics and disease characteristics are shown in **Table 1**. Psychiatric histories were similar between quetiapine XR and IR groups
- Rates of use of permitted concomitant psychoactive medication (ie, zolpidem tartrate, zaleplon, or zopiclone) were similar during the trial (62.9%, XR; 60.9%, IR)

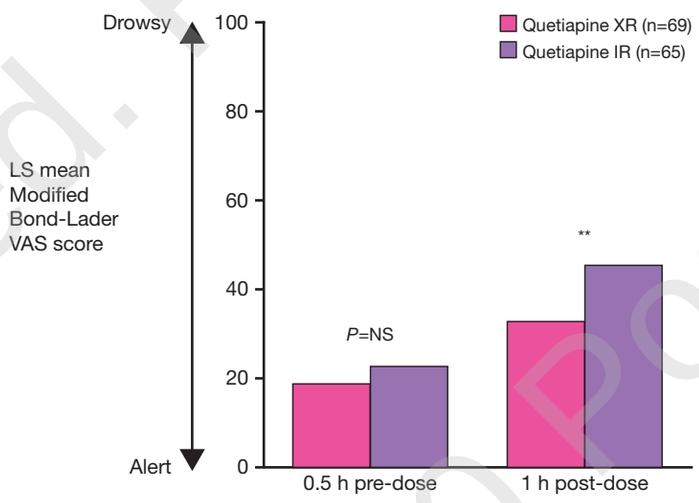
Table 1. Patient demographics and disease characteristics at baseline (randomized patients)

Patient parameter	Quetiapine XR (n=70)	Quetiapine IR (n=69)
Gender (n, %)		
Male	36 (51.4)	37 (53.6)
Female	34 (48.6)	32 (46.4)
Age (y)		
Mean (SD)	38.74 (8.52)	39.17 (8.55)
Range	18 – 50	19 – 50
Race (n, %)		
Black/African American	43 (61.4)	40 (58.0)
Caucasian	26 (37.1)	27 (39.1)
Other	1 (1.4)	2 (2.9)
BMI (kg/m^2)		
Mean (SD)	31.32 (7.81)	30.67 (6.90)
Range	19 – 58	17 – 49
Weight (kg)		
Mean (SD)	92.97 (23.19)	89.57 (20.62)
Range	49 – 183	48 – 151
Disease characteristics		
Bipolar I (n, %)	65 (92.9)	66 (95.7)
Bipolar II (n, %)	5 (7.1)	3 (4.3)
Mean MADRS total score	25.8	26.1

Primary study outcome

- Sedation intensity was significantly lower with quetiapine XR than IR at 1 hour after the 50 mg dose on Day 2
- Mean (SD) VAS score was 33.4 (26.92) with quetiapine XR versus 44.0 (31.76) with IR; LS mean difference: 12.55 (P=0.009; MITT) (**Figure 2**)

Figure 2. Primary study outcome: sedation intensity (mean VAS score) with quetiapine XR vs IR at 1 hour after 50 mg dose on Day 2 (MITT population, n=134)



MITT analysis set (n=134)
**P<0.01, quetiapine XR vs IR
P values based on ANCOVA model including treatment as a fixed effect, center as a random effect and Modified Bond-Lader VAS score at baseline as a covariate

Secondary study outcomes

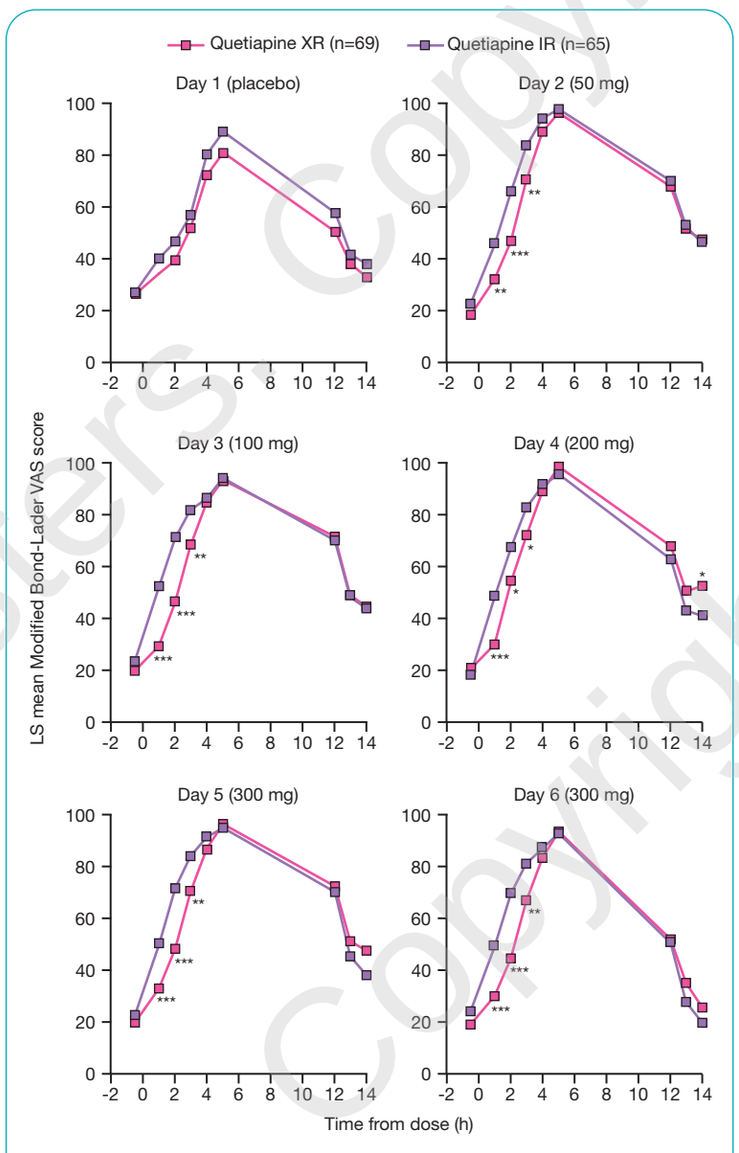
Sedation intensity

- Sedation intensity was significantly lower with quetiapine XR than IR at 1, 2, and 3 hours after each dose on Days 2 to 6 ($P \leq 0.05$). Sedation intensity was similar between XR and IR groups at 4 to 14 hours post-dose on each day (**Figure 3**)
- Mean time to maximum sedation intensity was numerically greater with quetiapine XR than IR after each dose, but differences were not statistically significant
- Total amount of sedation (VAS AUC [0–14 hours]) was numerically lower with quetiapine XR than IR after each dose, but differences were not statistically significant

Tolerability

- Overall tolerability of both formulations was consistent with the known profile of quetiapine (**Table 2**)
- Adverse events leading to study discontinuation were reported in 1 patient (1.4%; convulsion) in the quetiapine XR group and 2 patients (2.9%; agitation and tachycardia) in the IR group
- Adverse events potentially associated with extrapyramidal symptoms occurred in 2 (2.9%) patients in the quetiapine XR group and 8 (11.6%) patients in the IR group
- Potentially clinically significant orthostatic changes (pulse, systolic blood pressure, and diastolic blood pressure) occurred in 17.1% of the quetiapine group and 26.5% of the quetiapine IR group (combined parameters)

Figure 3. Secondary study outcomes: sedation intensities (mean VAS scores) with quetiapine XR vs IR over study duration (MITT population, n=134)



MITT analysis set (n=134)
*P<0.05; **P<0.01; ***P<0.001 vs quetiapine IR

Table 2. Commonly reported adverse events (≥5%) either with quetiapine XR or IR (safety population, n=139)[a]

MedDRA preferred term	Quetiapine XR (n=70)	Quetiapine IR (n=69)
Any adverse event, n (%)	40 (57.1)	49 (71.0)
Dry mouth	15 (21.4)	9 (13.0)
Increased appetite	11 (15.7)	11 (15.9)
Somnolence	7 (10.0)	5 (7.2)
Fatigue	6 (8.6)	3 (4.3)
Sedation	5 (7.1)	4 (5.8)
Dizziness	4 (5.7)	11 (15.9)
Headache	4 (5.7)	8 (11.6)
Nausea	4 (5.7)	1 (1.4)
Tachycardia	3 (4.3)	6 (8.7)
Akathisia	1 (1.4)	4 (5.8)

[a]Patients with multiple events are counted only once

Conclusions

- Patients with bipolar depression reported significantly lower sedation intensity with quetiapine XR than IR in the first 1 to 3 hours of each dose over the initial dose-escalation period
- These results are consistent with a volunteer study comparing sedation intensity with quetiapine XR and IR[9]
- Tolerability was consistent with the known profile of quetiapine. The overall incidence of adverse events was lower with quetiapine XR than IR

References

1. Kahn RS, Schulz SC, Palazov VD, et al. Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2007;68:832-842.
2. Bauer M, El-Khalili N, Datto C, et al. A pooled analysis of two randomised, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. *J Affect Disord.* 2010;127:19-30.
3. Bandelow B, Chouinard G, Bobes J, et al. Extended-release quetiapine fumarate (quetiapine XR): a once-daily monotherapy effective in generalized anxiety disorder. Data from a randomized, double-blind, placebo- and active-controlled study. *Int J Neuropsychopharmacol.* 2010;13:305-320.
4. Suppes T, Datto C, Minkwitz M, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. *J Affect Disord.* 2010;121:106-115.
5. Cutler AJ, Datto C, Nordenhem A. Randomized, double-blind, 3-week trial of the extended-release formulation of quetiapine as monotherapy for the treatment of adults with acute mania. *Clin Ther.* 2011; in press.
6. Weisler R, Joyce M, McGill L, et al. Extended release quetiapine fumarate monotherapy for major depressive disorder: results of a double-blind, randomized, placebo-controlled study. *CNS Spectr.* 2009;14:299-313.
7. Figueroa C, Brecher M, Hamer-Maansson JE, Winter H. Pharmacokinetic profiles of extended release quetiapine fumarate compared with quetiapine immediate release. *Prog Neuropsychopharmacol Biol Psychiatry.* 2009;33:199-204.
8. Nord M, Nyberg S, Brogren J, et al. Comparison of D2 dopamine receptor occupancy after oral administration of quetiapine fumarate immediate-release and extended-release formulations in healthy subjects. *Int J Neuropsychopharmacol.* 2011 Apr 11:1-10. [Epub ahead of print]
9. Datto C, Berggren L, Patel JB, Eriksson H. Self-reported sedation profile of immediate-release quetiapine fumarate compared with extended-release quetiapine fumarate during dose initiation: a randomized, double-blind, crossover study in healthy adult subjects. *Clin Ther.* 2009;31:492-502.
10. Bond A, Lader M. The use of analogue scales in rating subjective feelings. *Br J Med Psychol.* 1974;47:211-218.

ANCOVA, analysis of covariance; AUC, area under the curve; BMI, body mass index; *DSM-IV-TR, Diagnostic and Statistical Manual, Fourth Edition, Text Revision*; IR, immediate-release; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MITT, modified intention-to-treat; NS, not significant; VAS, visual analog scale; XR, extended-release

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