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Quetiapine extended-release vs olanzapine for Japanese patients with bipolar depression: A Bayesian analysis

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Abstract

Objective: It is unknown whether there are differences in efficacy and safety between quetiapine extended-release, 300 mg/d (QUEXR300), and olanzapine, 5-20 mg/d (OLA), for Japanese patients with bipolar depression.

Methods: We conducted a Bayesian analysis of data from phase 3 studies in Japan of QUEXR300 and OLA. Outcomes were remission rate (primary), response rate, improvement on the Montgomery-Åsberg Depression Rating Scale and 17-item Hamilton Depression Rating Scale scores, discontinuation rate, and incidence of individual adverse events. We calculated the standardized mean difference (SMD) and the risk ratio (RR) and 95% credible interval (95% CrI) for continuous and dichotomous data, respectively.

Results: There were no significant differences between QUEXR300 and OLA for any of the efficacy outcomes. QUEXR300 was associated with a higher incidence of somnolence than OLA (RR = 5.517; 95% CrI = 1.563, 19.787), while OLA was associated with greater increase body weight (SMD = −0.488; 95% CrI = −0.881, −0.089) and blood prolactin levels (SMD = −0.642; 95% CrI = −1.073, −0.213) than QUEXR300, and a greater decrease in high-density lipoprotein cholesterol levels (SMD = −0.408; 95% CrI = −0.785, −0.030) than QUEXR300.

Conclusion: Although the two drugs' efficacy did not differ, OLA increased the risk of metabolic syndrome and QUEXR300 the risk of somnolence. A large scale, long-term, head-to-head comparison study of QUEXR300 vs OLA for Japanese patients with bipolar depression is needed to confirm the results of the current study.

KEYWORDS

Bayesian analysis, bipolar depression, Japanese, olanzapine, quetiapine extended-release

1 | INTRODUCTION

In Japan, olanzapine (OLA) and quetiapine extended-release (QUEXR) are approved for the treatment of bipolar depression.[1] It is unknown, however, if one or the other antipsychotic is superior in terms of the risk-benefit ratio for Japanese patients with this disorder. We reviewed phase 3 studies of each antipsychotic for bipolar depression in Japan.

For OLA, a 6-week, double-blind, randomized, placebo-controlled phase 3 trial (OLA, n = 343; placebo, n = 171) was conducted in Japan, China, Taiwan, Korea, and the United States of America.[2] This was a flexible-dose study (5-20 mg/d). Patients aged 18 to

64 years with bipolar I disorder who were acutely depressed were recruited. Inclusion criteria were as follows: a depressive episode for ≤ 90 days at the time of randomization, a total score ≥ 18 on the 17-item Hamilton Rating Scale for Depression (HAMD-17),[3] and a history of ≥ 1 manic or mixed episode in the previous 6 years, but not currently having a manic episode (Young Mania Rating Scale [YMRS][4] total score ≤ 8 at randomization). The primary outcome of the study was the change from mean baseline to study endpoint in the Montgomery-Åsberg Depression Rating Scale (MADRS)[5] score. Although OLA was superior to placebo in terms of improved MADRS score and response (defined as a ≥ 50% reduction in MADRS at endpoint) rate, there was no significant difference in remission (defined as a MADRS total score ≤ 12) rate between the groups. Compared with placebo, OLA was associated with a higher incidence of somnolence, sedation, significant weight gain (≥7% body weight), and increased appetite. Patients taking OLA also had significantly increased total cholesterol, triglyceride, and low-density lipoprotein (LDL) cholesterol levels. An analysis was also conducted of the Japanese subpopulation in this study (OLA, n = 104; placebo, n = 52).[6] Although OLA was superior to placebo in terms of an improved MADRS score, there were no significant differences in rates of response (same definition as the primary analysis) or remission (same definition as the primary analysis) between OLA and placebo. In the Japanese subgroup, compared with placebo, OLA was associated with a higher incidence of somnolence and significant weight gain (≥7% body weight) and significantly increased total cholesterol, triglyceride, and LDL cholesterol levels, along with significantly decreased high-density lipoprotein (HDL) cholesterol levels. Thus, there were differences in some of the efficacy and safety outcomes between the primary and the Japanese subpopulation analyses.

An 8-week, double-blind, randomized, placebo-controlled phase 3 trial of QUEXR was conducted in Japan.[7] This was a fixed-dose study comparing QUEXR at 300 mg/d (QUEXR300, n = 179), at 150 mg/d (QUEXR150, n = 74), and placebo (n = 177). The investigators discontinued recruitment to the QUEXR150 arm because of difficulty in finding enough patients. Therefore, efficacy outcomes for QUEXR150 were not reported. Patients 20 to 64 years old with bipolar I disorder or bipolar II disorder who were acutely depressed were recruited. Inclusion criteria were a HAMD-17 total score ≥20, a HAMD-17 depressed mood score ≥2 points, a YMRS total score <13, and <9 mood episodes within 12 months prior to informed consent. The primary outcome of the study was the mean change from baseline to study endpoint in the MADRS score. QUEXR300 was superior to placebo in improving the MADRS score and rates of response (same definition as the OLA study) and remission (same definition as the OLA study). QUEXR300 was associated with a higher incidence of somnolence and dry mouth than placebo.

No head-to-head study of QUEXR300 vs OLA has been conducted to assess efficacy and safety among Japanese patients with bipolar depression. Therefore, we conducted a Bayesian analysis of data from both the Japan OLA and QUEXR phase 3 studies to compare the efficacy and safety of the two drugs in Japanese patients with bipolar depression (Appendix S1).

2 | METHODS

2.1 | PICO

Patients with bipolar depression who were not being treated with any mood stabilizers or antipsychotics at baseline were eligible. The intervention groups were given OLA or QUEXR300, and the control group was given placebo. The outcomes were efficacy and safety/tolerability (detailed information in the following section).

2.2 | Data synthesis

Two authors (T.K. and Y.M.) extracted data from the articles and entered it into a spreadsheet. The primary outcome of remission was defined as a MADRS score ≤12. The secondary outcomes included response (≥50% reduction in the MADRS score from baseline to endpoint) rate, an improvement in MADRS and HAMD-17 total scores from baseline, all-cause discontinuation, discontinuation due to adverse events, and individual adverse events. Only intention-to-treat population data were used in the analysis. For the OLA study, we used only data from the Japanese patients. The algebraic signs of the values of HDL cholesterol were reversed, as a decrease in the HDL cholesterol level indicates a worse response.

2.3 | Statistical analysis

A Bayesian analysis was conducted using the GeMTC package in R Statistics software.[8] We used a fixed effects model for this study because a random effects model might be too conservative for this small a Bayesian analysis. We calculated the standardized mean difference (SMD) and the risk ratio (RR) and 95% credible interval (95% CrI) for continuous and dichotomous data, respectively. The number of burn-in iterations, the number of interface iterations, and thinning factor were set at 5000, 20 000, and 10, respectively.

3 | RESULTS

3.1 | Study characteristics

The two studies were double-blind, randomized, placebo-controlled trials sponsored by pharmaceutical companies and were published in English. The methodological quality of both studies was high as assessed with the Cochrane Risk of Bias Tool.

3.2 | Results of Bayesian analysis

There were no significant differences between QUEXR300 and OLA in any of the efficacy outcomes (Table 1). Although QUEXR300 was associated with a higher incidence of somnolence than OLA

TABLE 1 Bayesian analysis: QUEXR300 vs OLA

	RR (95% CrI)[a]
Remission rate	0.786 (0.478, 1.257)
Response rate	1.109 (0.769, 1.577)
All-cause discontinuation	1.044 (0.476, 2.276)
Discontinuation due to adverse events	1.089 (0.277, 3.654)
Significant weight gain (≥7% body weight)	0.251 (0.009, 2.573)
Somnolence	5.517 (1.563, 19.787)
	SMD (95% CrI)[b]
MADRS	0.189 (−0.245, 0.626)
HAMD-17	0.283 (−0.114, 0.681)
Body weight	−0.488 (−0.881, −0.089)
Fasting blood sugar	−0.114 (−0.517, 0.291)
Serum triglycerides	−0.011 (−0.407, 0.390)
Serum total cholesterol	−0.086 (−0.483, 0.314)
Serum HDL cholesterol	−0.408 (−0.785, −0.030)
Serum LDL cholesterol	−0.172 (−0.575, 0.230)
Blood prolactin	−0.642 (−1.073, −0.213)

Abbreviations: 95% CrI, 95% credible interval; HAMD-17, 17-item Hamilton Rating Scale for Depression; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; MADRS, Montgomery-Åsberg Depression Rating Scale; RR, risk ratio; SMD, standardized mean differences.
[a]RR < 1 favors QUEXR300; RR > 1 favors OLA.
[b]Negative SMD values favor QUEXR300; positive SMD values favor OLA.

(RR = 5.517; 95% CrI = 1.563, 19.787), OLA was associated with greater increase body weight (SMD = −0.488; 95% CrI = −0.881, −0.089) and blood prolactin levels (SMD = −0.642; 95% CrI = −1.073, −0.213) than QUEXR300, and a greater decrease in HDL cholesterol levels (SMD = −0.408; 95% CrIs = −0.785, −0.030) than QUEXR300.

4 | DISCUSSION

We conducted a Bayesian analysis of QUEXR300 compared with OLA in terms of efficacy and safety outcomes for Japanese patients with bipolar depression. We did not detect any differences in efficacy between the two drugs. However, OLA had a greater risk than QUEXR300 of weight gain and decreased HDL cholesterol levels compared with QUEXR300. On the other hand, QUEXR300 had a greater risk of somnolence than OLA. A recent systematic review noted that if patients took QUEXR300 orally once daily in the evening rather than at bedtime, the incidence of somnolence would decrease.[9]

The study has several limitations. First, the differences in the characteristics of the patients (diagnosis: OLA = bipolar I disorder, QUEXR300 = bipolar I disorder or bipolar II disorder) and the studies (duration of study [6 weeks study vs 8 weeks study] and dosing effect [flexible-dose study vs fixed-dose study]) included in this study might influence the results of our study. However, we did not examine whether those clinical factors were associated with the results of the study (for example, somnolence) because the number of studies and of patients analyzed was small. Secondly, both studies included in the analysis were industry sponsored, so the possibility of sponsorship bias should be considered when interpreting our results.[10] Thirdly, this study did not evaluate several common adverse events such as extrapyramidal symptoms, constipation, or dry mouth because there were insufficient data for analysis. Finally, both trials had a short duration. A large scale, long-term, head-to-head comparison of QUEXR300 vs OLA for Japanese patients with bipolar depression is needed to confirm the results of the current study.

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CONFLICT OF INTEREST

The authors have declared that there are no conflicts of interest in relation to the subject of this study. We have had the following interests within the past 3 years. Dr. Kishi has received speaker's honoraria from Daiichi Sankyo, Dainippon Sumitomo, Eisai, Janssen, Otsuka, Meiji, MSD, Yoshitomi, and Tanabe-Mitsubishi and has received a Health Labour Sciences Research Grant, Grant-in-Aid for Scientific Research (C) and a Fujita Health University School of Medicine research grant. Dr. Ikuta received speaker's honoraria from Eli Lilly, Daiichi Sankyo, and Dainippon Sumitomo and is a consultant for Dainippon Sumitomo. Dr. Matsuda has received speaker's honoraria from Dainippon Sumitomo, Eisai, Otsuka, Tanabe-Mitsubishi, and Pfizer and has received a grant-in-aid for Young Scientists (B). Dr. Iwata has received speaker's honoraria from Astellas, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Shionogi, Novartis, and Pfizer and has had research grants from Daiichi Sankyo, Dainippon Sumitomo, Meiji, and Otsuka.

AUTHOR CONTRIBUTIONS

Dr. Kishi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design, Analysis and interpretation of data: Kishi. Statistical analysis: Kishi and Ikuta. Acquisition of data: Kishi and Matsuda. Drafting of the manuscript: All authors. Study supervision: Iwata.

DATA AVAILABILITY

Data used for the current study are reported in the Katagiri et al[6] and Murasaki et al[7].

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SUPPORTING INFORMATION

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