Discontinuation Rate of Lurasidone and Quetiapine Extended Release in Bipolar Depression

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Keywords
lurasidone, quetiapine extended release, bipolar depression

received 06.03.2024
revised 11.04.2024
accepted 13.05.2024
published online 2024

Bibliography
Pharmacopsychiatry
DOI 10.1055/a-2331-2300
ISSN 0176-3679

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Supplementary material is available at
https://doi.org/10.1055/a-2331-2300

ABSTRACT

Introduction Lurasidone (LUR) was compared with quetiapine extended release (QUE-ER) regarding 1-year discontinuation in patients with bipolar depression (n = 317).

Methods This is a retrospective cohort study.

Results Although the time to all-cause discontinuation was estimated using the Kaplan–Meier survival curve with log-rank tests to compare treatment groups, no difference was found ($p = 0.317$). The Cox proportional hazard model revealed that only the presence of adverse events (AEs) is associated with increased treatment discontinuation ($p < 0.0001$). The most common AEs were akathisia for LUR (17.7 %) and somnolence for QUE-ER (34.7 %). In other Cox models divided by LUR or QUE-ER, the presence of akathisia or somnolence was associated with increased LUR ($p = 0.0205$) or QUE-ER ($p < 0.0001$) discontinuation, respectively.

Discussion The acceptability of both antipsychotics to bipolar depression in clinical practice may be similar. However, specific AEs for each antipsychotic (LUR: akathisia and QUE-ER: somnolence) were associated with high treatment discontinuation.

Introduction

Bipolar disorder (BD), with a global prevalence of approximately 2 %, is characterized by periods of deep, prolonged, and profound depression that alternate with periods of excessively elevated or irritable mood, known as mania [1]. Our meta-analyses have consistently demonstrated that maintenance treatment with mood stabilizers (MSs) or second-generation antipsychotics (SGAs) can decrease the risk of BD recurrence [2, 3]. Treatment discontinuation is an important acceptability outcome in clinical trials not only for schizophrenia but also for BD treatments [2–4]. Several major reasons for discontinuation in such trials have been identified, including the lack of efficacy, adverse events (AEs), withdrawal of consent, loss to follow-up, and protocol violation. Thus, treatment discontinuation can be used to assess various aspects of a treatment's potential utility in clinical practice.

Recent meta-analyses have demonstrated that quetiapine (QUE) is effective for acute mania [5] and acute depression in individuals with BD [6], and QUE prevents manic and depressive recurrence in individuals with BD in the maintenance phase [2]. However, although another meta-analysis showed that lurasidone (LUR) is effective for acute depression in individuals with BD [6], no trial of LUR monotherapy has been conducted in individuals with acute mania. Moreover, combining LUR with MS therapy prevents depressive recurrence but not manic recurrence in patients with BD in the maintenance phase, as shown in a meta-analysis [2]. Therefore, in this study, the clinical utility of LUR and QUE extended release (QUE-

ER) was examined by comparing the 1-year discontinuation rates of both SGAs in patients with BD.

Methods

Study design

This study included adults with BD who started LUR or QUE-ER treatment between January 2017 and January 2024 at Fujita Health University Hospital in Toyoake, Japan. Patients with unknown start times while taking SGAs or who declined to participate were excluded. The final chart review was performed on January 6, 2024. This study was approved by the Institutional Review Board of Fujita Health University (HM22–342). Informed consent was obtained through an opt-out form on the website and in-hospital bulletin board. At least one experienced psychiatrists carefully diagnosed the patients with BD strictly on the basis of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [7].

Data collection

Data on age at which SGAs started, sex, SGA treatment duration, treatment status at which SGAs started, AEs, and the concomitant use of psychotropic medications (antipsychotics, MSs, antidepressant, and benzodiazepines) at which SGAs started were collected.

Statistical analysis

Pearson's chi-square test (categorical variables) and two-sample t-test (continuous variables) were used to compare demographic characteristics between the LUR and QUE-ER groups. Time to all-cause discontinuation was estimated using the Kaplan–Meier survival curve with log-rank tests to compare treatment groups (primary outcome). Individuals who were transferred to another hospital were considered censored cases. The Cox proportional hazard model was also used to examine the association between time to discontinuation and the following potential confounding factors: SGAs (LUR or QUE-ER), type of BD (I or II), age at which the SGAs started, sex (male or female), treatment status at which the SGAs started (in or outpatient), the presence of AEs during the SGA treatment (yes or no), and the concomitant use of psychotropic medications (yes or no, **Table S1**). The most common AEs were akathisia for LUR and somnolence for QUE-ER (**Table S2**). Moreover, another Cox proportional hazard model was performed to examine the association between time to discontinuation in each SGA and the following factors: type of BD, age at which the SGAs started, sex, treatment status at which the SGAs started, the initial dose of the SGA (the factor used only for the LUR group because the initial dose of QUE-ER was 50 mg/day for all participants), the presence of akathisia for LUR (or somnolence for QUE-ER), and the concomitant use of psychotropic medications. In addition, logistic regression was conducted to examine the association between the risk of akathisia for LUR and somnolence for QUE-ER and the following factors: type of BD, age at which the SGAs started, sex, treatment status at which the SGAs started, the initial dose of the SGA (the factor used only for LUR group because the initial dose of QUE-ER was 50 mg/day for all participants), the maximum dose during the SGA treatment, and the concomitant use of psychotropic medications. According to the Bayesian information criterion (BIC)[8], the best subset approaches were used to select the variables. After logistic regression, the BIC model was obtained using screened variables with minimal BIC. Moreover, sensitivity analysis was performed excluding the participants who received concomitant antipsychotics at baseline for all analyses. JMP software (JMP 14.2.0. SAS Institute Inc.) was used to perform all statistical analyses.

Results

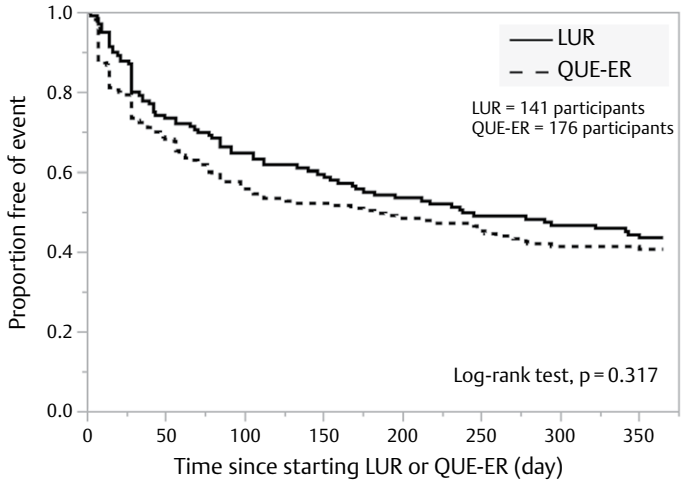
A total of 141 and 176 participants received LUR and QUE-ER, respectively, and the cohort of this study consisted of 317 individuals (**Table S1**). The mean age at which the SGAs started was 46.2 ± 14.6 years, and the proportion of females was 64.7 % (**Table S1**). The proportion of BD type I was 31.6 %, and 67 participants used different SGAs at various times. Significant differences in the treatment status at which the SGAs started and concomitant psychotropic drugs were found (especially benzodiazepine receptor agonists, **Table S1**). For the initial dose, although 14.2 % of participants in the LUR group used 10 mg/day, all participants in the QUE-ER group used 50 mg/day. The most common AEs were akathisia for LUR (17.7 %) and somnolence for QUE-ER (34.7 %, **Table S2**).

Kaplan–Meier analysis did not show a significant difference between the LUR and QUE-ER treatment groups (log-rank test, $p = 0.317$, ▶ **Fig. 1**). Another Kaplan–Meier analysis using only data from participants who did not receive concomitant antipsychotics at baseline showed no significant difference between the LUR and QUE-ER treatment groups (log-rank test, $p = 0.0988$, **Figure S1**).

The Cox proportional hazard model found that only the presence of AEs is associated with increased treatment discontinuation ($p < 0.0001$, **Table S3**). Sensitivity analysis of this model showed that the factors associated with increased treatment discontinuation include the presence of AEs ($p < 0.0001$) and the presence of concomitant antidepressants ($p < 0.0361$, **Table S3**).

Based on other Cox proportional hazard models divided by LUR or QUE-ER, the presence of akathisia was associated with increased LUR discontinuation ($p = 0.0205$, **Table S4**). The median treatment continuation in participants with or without akathisia was 84 or 238 days, respectively. Based on sensitivity analyses of the models, no factors were associated with LUR discontinuation (**Table S4**). The Cox model of QUE-ER showed the association of somnolence with increased QUE-ER discontinuation ($p < 0.0001$, **Table S5**). The median treatment continuation in participants with or without somnolence was 29 days or 278 days, respectively. Sensitivity analysis of this Cox model also showed the association of somnolence with increased QUE-ER discontinuation ($p < 0.0001$, **Table S5**). The median treatment continuation in participants with or without somnolence was 28 days or 215 days, respectively.

In multiple logistic regression for the LUR group, individuals who started LUR at an initial dose of 20 mg/day were associated with a higher incidence of akathisia compared to those who started LUR at an initial dose of 10 mg/day ($p = 0.00360$, **Table S6**). The proportion of akathisia in each group was 20.7 % in individuals who started LUR at 20 mg/day group and 0.00 % in individuals who started LUR at 10 mg/day. No patient remained at 10 mg/day during the study. The maximum dose during the study in individuals who started LUR at 10 mg/day was 40.0 ± 17.5 mg/day. In multiple logistic regression for the QUE-ER group, participants with low maximum



Number of participants at risk

LUR, n (%)	39 (27.7)	54 (38.3)	62 (44.0)	69 (48.9)	77 (54.6)	81 (57.5)	85 (60.3)
QUE-ER, n (%)	60 (34.1)	82 (46.6)	90 (51.1)	99 (56.3)	106 (60.2)	112 (63.6)	114 (64.8)
ORs (95 % CI)	0.739 (0.456, 1.20)	0.712 (0.453, 1.12)	0.750 (0.481, 1.17)	0.745 (0.478, 1.16)	0.795 (0.507, 1.24)	0.771 (0.490, 1.21)	0.826 (0.522, 1.31)

▶ **Fig. 1** Kaplan–Meier survival curve. LUR, lurasidone; QUE-ER, quetiapine extended release; ORs, odds ratios; 95% CI, 95% confidence interval.

doses of QUE-ER reported more somnolence compared to those with high maximum doses of QUE-ER ($p < 0.0001$, **Table S7**). The results of sensitivity analyses for these two models were similar to those of primary analyses (**Tables S6 and S7**).

Discussion

This retrospective cohort study is the first to investigate whether there was a difference in treatment discontinuation for Japanese adults with BD between the LUR and QUE treatment groups. The acceptability of both SGAs to BD in clinical practice may be similar. However, we found that specific AEs for each SGA (i. e., LUR: akathisia and QUE-ER: somnolence) were associated with high treatment discontinuation.

The risk of akathisia increases in a dose-dependent manner for some antipsychotics such as LUR [9]. Lurasidone is principally metabolized by cytochrome P450 (CYP) 3A4 [10]. Considering that the CYP3A4 gene is highly polymorphic, individuals exhibit varying degrees of CYP3A4 enzyme activity, which could affect the safety and efficacy of drugs cleared and activated by CYP3A4 [11]. A recent pharmacokinetic study reported that the plasma concentration of some antipsychotics, including LUR, metabolized by specific CYP enzymes, might be higher with the same daily dose in East Asian populations than in Western populations [11]. Therefore, akathisia may appear less frequently when the initial dose was 10 mg/day than when it was 20 mg/day.

The difference in the initial dose of LUR was not associated with the median treatment continuation days (10 mg/day, 365 days; 20 mg/day, 182 days) or the maximum dose during the LUR treatment (10 mg/day, 40.0 ± 17.5; 20 mg/day, 36.9 ± 16.4). Thus, 10 mg/day might be the suitable initial dose of LUR for Japanese adults with BD compared with 20 mg/day to reduce the risk of akathisia that causes early treatment discontinuation.

Our study had several limitations. First, the results of our retrospective study might be affected by selection bias. Second, our study had a small sample size and a short research period. Third, although we collected the data on adverse events written in their chart, we did not use a specific definition for diagnosing individual AEs. This study did not also limit the use of concomitant medications during the study. Various concomitant drugs might have affected our results. Since patients who took benzodiazepine receptor agonists at the baseline might have had anxiety-related symptoms, they might have exaggerated adverse events. Therefore, there might be differences in the incidence of individuals AEs between our study and the Phase III studies for each drug [12, 13]. Fourth, we have not been able to obtain the following information from a chart review: a history of the treatments, the number of psychiatrists involved in the treatment for each participant, psychiatric comorbidity (e. g., anxiety), a specific reason for treatment discontinuation (e. g., inefficacy), and details of concomitant medication during the trial.

Authors' Contributions

Dr. Kishi developed the study concept and design, had full access to all data, took full responsibility for the integrity of the data and accuracy of the data analysis, and performed the statistical analyses. Dr. Kishi, Dr. Sakuma, Dr. Hamanaka, and Dr. Nishii extracted the data from medical records. All authors acquired and interpreted the data and wrote the manuscript. Dr. Iwata supervised the review.

Data availability

The data are not publicly available because they contain information that could compromise the privacy of research participants.

Acknowledgment

We want to thank Maruzen-Yushodo Co., Ltd., for English language editing.

Conflict of Interest

All authors have no conflicts of interest to declare concerning this study. They also declare any potential competing interests that have arisen in the last 3 years. Dr. Kishi has received speaker honoraria from Eisai, Janssen, Meiji, Daiichisankyo, Otsuka, Sumitomo, Takeda, Tanabe-Mitsubishi, and Viatris and research grants from Eisai, Grant-in-Aid for Scientific Research (C) (19K08082 and 23K06998), Japan Agency for Medical Research and Development (JP22dk0307107 and JP22wm0525024), and the Japanese Ministry of Health, Labour, and Welfare (21GC1018). Dr. Sakuma has received speaker honoraria from Daiichisankyo, Eisai, Janssen, Kyowa, Meiji, Otsuka, Sumitomo, and Takeda, and a grant from the Japan Agency for Medical Research and Development (JP22dk0307107 and JP23dk0307122) a Fujita Health University School of Medicine Research Grant for Early-Career Scientists, a Grant-in-Aid for Young Scientists (B)(19K17099), a Grant-in-Aid for Scientific Research (C)(23K06998). Dr. Hamanaka has received speaker compensation from Sumitomo. Dr. Nishii has received speaker compensation from Sumitomo. Dr. Iwata has received speaker honoraria from Eisai, Janssen, Meiji, Otsuka, Sumitomo, Takeda, Tanabe-Mitsubishi, and Viatris and research grants from Daiichi Sankyo, Eisai, Meiji, Otsuka, Sumitomo, Takeda, Tanabe-Mitsubishi, Grant-in-Aid for Scientific Research (B)(22H03003), and Japan Agency for Medical Research and Development (JP-22wm0425008).

Funding

This study was supported by JSPS KAKENHI (grant number 23K06998).

References

[1] Nierenberg AA, Agustini B, Kohler-Forsberg O et al. Diagnosis and treatment of bipolar disorder: A Review. JAMA 2023; 330: 1370–1380. DOI: 10.1001/jama.2023.18588

[2] Kishi T, Ikuta T, Matsuda Y et al. Mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase: A systematic review and network meta-analysis of randomized controlled trials. Mol Psychiatry 2021; 26: 4146–4157. DOI: 10.1038/s41380-020-00946-6

[3] Kishi T, Sakuma K, Okuya M et al. Effects of a conventional mood stabilizer alone or in combination with second-generation antipsychotics on recurrence rate and discontinuation rate in bipolar I disorder in the maintenance phase: A systematic review and meta-analysis of randomized, placebo-controlled trials. Bipolar Disord 2021; 23: 789–800. DOI: 10.1111/bdi.13053

[4] Lieberman JA, Stroup TS, McEvoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353: 1209–1223. DOI: 10.1056/NEJMoa051688

[5] Kishi T, Ikuta T, Matsuda Y et al. Pharmacological treatment for bipolar mania: A systematic review and network meta-analysis of double-blind randomized controlled trials. Mol Psychiatry 2022; 27: 1136–1144. DOI: 10.1038/s41380-021-01334-4

[6] Yildiz A, Siafis S, Mavridis D et al. Comparative efficacy and tolerability of pharmacological interventions for acute bipolar depression in adults: A systematic review and network meta-analysis. Lancet Psychiatry 2023; 10: 693–705. DOI: 10.1016/S2215-0366(23)00199-2

[7] APA. Diagnostic and statistical manual of mental disorders, 5th ed. American Psychiatric Association: Arlington; 2013

[8] Zhang Z. Variable selection with stepwise and best subset approaches. Ann Transl Med 2016; 4: 136. DOI: 10.21037/atm.2016.03.35

[9] Wu H, Siafis S, Wang D et al. Antipsychotic-induced akathisia in adults with acute schizophrenia: A systematic review and dose-response meta-analysis. Eur Neuropsychopharmacol 2023; 72: 40–49. DOI: 10.1016/j.euroneuro.2023.03.015

[10] Li Q, Wang J, Wang ZL et al. The impacts of CYP3A4 genetic polymorphism and drug interactions on the metabolism of lurasidone. Biomed Pharmacother 2023; 168: 115833. DOI: 10.1016/j.biopha.2023.115833

[11] Lin SK. Racial/ethnic differences in the pharmacokinetics of antipsychotics: focusing on East Asians. J Pers Med 2022; 12. DOI: 10.3390/jpm12091362

[12] Kato T, Ishigooka J, Miyajima M et al. Double-blind, placebo-controlled study of lurasidone monotherapy for the treatment of bipolar I depression. Psychiatry Clin Neurosci 2020; 74: 635–644. DOI: 10.1111/pcn.13137

[13] Murasaki M, Koyama T, Kanba S et al. Multi-center, randomized, double-blind, placebo-controlled study of quetiapine extended-release formulation in Japanese patients with bipolar depression. Psychopharmacology (Berl) 2018; 235: 2859–2869. DOI: 10.1007/s00213-018-4977-6