Increasing Versus Maintaining the Dose of Olanzapine or Risperidone in Schizophrenia Patients Who Did Not Respond to a Modest Dosage:
A Double-Blind Randomized Controlled Trial

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ABSTRACT

Objective: While doctors often increase the dose of an antipsychotic when there is insufficient response, there is limited evidence that this intervention is any better than waiting longer on the lower dose. We put the proposition to test.

Method: In this 4-week, double-blind, randomized controlled trial conducted in psychiatric care from September 2012 to March 2015, 103 patients with schizophrenia (*ICD-10*) who did not respond to olanzapine 10 mg/d or risperidone 3 mg/d were randomly allocated to a dose-increment or -continuation group. In the increment group, antipsychotic doses were doubled for 4 weeks, whereas in the continuation group, doses were not changed. Completion rate (primary outcome measure); changes in psychopathology, function, and extrapyramidal symptoms; and response rate were compared between the groups. The relationship between baseline plasma antipsychotic concentrations and changes in psychopathology was examined.

Results: The completion rate was significantly lower in the increment group than in the continuation group (69.2% [36/52] vs 86.3% [44/51], *P* = .038). No significant superiority was observed in any of the outcome measures in the increment group compared to the continuation group, except the Positive and Negative Syndrome Scale (PANSS) positive subscale score change in intention-to-treat analysis. Those with lower plasma concentrations of olanzapine on their initial treatment showed a greater improvement on the PANSS positive subscale when their dose was increased (*P* = .042).

Conclusions: As a general strategy, patients with schizophrenia failing to respond to moderate antipsychotic doses may not benefit from an increase in dose. The possibility of benefit in those whose plasma antipsychotic concentrations at baseline are still low cannot be ruled out.

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Clinical Points

- It remains unclear as to whether antipsychotic doses should be increased or not in cases of insufficient treatment response to moderate doses.
- Patients with schizophrenia failing to respond to moderate antipsychotic doses may not benefit from dose increment in general.
- Therapeutic drug monitoring on an individual basis seems necessary for better treatment of schizophrenia.

Antipsychotic drugs play an indispensable role in the treatment of schizophrenia.[1] Based on clinical trials and brain-imaging data, recommended doses for these drugs are now available but often span a 100% range or more (eg, 10–20 mg/d for olanzapine and 2–6 mg for risperidone).[2] These ranges are derived from some fixed-dose trials,[3–5] and while all doses within the range usually show efficacy, there is little evidence to suggest that moving from a low dose within the recommended range to a higher dose brings any further clinical benefit. Yet, the question is of critical importance, as increasing dose is the most commonly undertaken clinical maneuver upon suboptimal response to a modest dosage.

Few studies[6–10] thus far have systematically addressed this question. In general, these trials suggest that dose increment does not yield any additional clinical gain compared to continuation of the standard doses.[11] However, the data are limited to fluphenazine, haloperidol, quetiapine, and ziprasidone, and more frequently prescribed antipsychotics such as olanzapine and risperidone have not yet been tested. Moreover, the dose ranges used in those studies were too high and do not represent current clinical practice (ie, fluphenazine 80 mg/d, haloperidol 12 mg/d, quetiapine 1,144 and 1,200 mg/d, and ziprasidone 320 mg/d). In addition, except for one ziprasidone study,[10] clinical outcomes have not been explored in terms of blood antipsychotic concentrations, which more precisely reflect the exposure to antipsychotic drugs than oral dosage given wide interindividual differences in pharmacokinetic parameters.[12] Thus, such a paucity of data still limits our dosing strategies for the treatment of schizophrenia.[13]

We therefore conducted a double-blind, randomized controlled trial to compare the efficacies between increasing antipsychotic dose and staying on the same dose in patients with schizophrenia who did not respond to moderate doses of olanzapine or risperidone. Furthermore, we evaluated the impact of baseline plasma antipsychotic concentrations on treatment outcomes.

METHOD

Study Design and Setting

This 4-week, double-blind, randomized controlled trial was conducted at Inokashira Hospital in Japan from September 2012 to March 2015. This trial was approved by the institutional review board of the hospital and registered

at UMIN Clinical Trials Registry in August 2012 (UMIN. ac.jp/ctr/index.htm identifier: UMIN000008667). Written informed consent was obtained from all of the participants after a full explanation of the study was provided.

Participants

Inclusion criteria of participants were as follows: (1) inpatients or outpatients who met the criteria for schizophrenia, schizoaffective disorder, or persistent delusional disorder according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*),[14] which is widely used in Japan; (2) patients who had been receiving olanzapine 10 mg/d or risperidone 3 mg/d for ≥4 weeks in clinical settings; (3) a total score of ≥60 on the Positive and Negative Syndrome Scale (PANSS),[15] ≥3 on the Clinical Global Impressions-Severity of Illness scale (CGI-S),[16] and ≤70 on the Global Assessment of Functioning (GAF),[17] (4) age of 20 years or older, and (5) ability to provide informed consent. Exclusion criteria were (1) concomitant use of another antipsychotic drug within the past 4 weeks, (2) history of nonresponse or intolerability to olanzapine 20 mg/d or risperidone 6 mg/d, (3) presence of active suicidal ideations or past suicide attempts, and (4) presence of severe physical diseases.

Procedures

Enrolled participants were randomly allocated to 1 of the 2 treatment groups in a 1:1 ratio by simple randomization stratified by their antipsychotic type (ie, olanzapine or risperidone) and treatment setting (ie, inpatient or outpatient). The person who was independent of this study in the central office prepared a piece of paper on which 1 of the assigned group was designated according to a computer-generated randomization list, inserted it into an envelope on which a participant ID number was written, and sealed it. Upon registration of each participant, 1 of the investigators opened the envelope that corresponded to the participant's ID, and the person who prepared the envelopes confirmed that the envelopes were appropriately opened. In the dose-increment group, the ongoing antipsychotic dose was increased to 20 mg/d for olanzapine or 6 mg/d for risperidone followed by a 4-week observation, whereas in the dose-continuation group, the ongoing antipsychotic drug dose (ie, olanzapine 10 mg/d or risperidone 3 mg/d) was kept the same for 4 weeks. These doses were selected with a reference to the upper limit of the suggested dose ranges in the Texas Medication Algorithm Project (ie, 10–20 mg/d for olanzapine and 2–6 mg/d for risperidone).[2] During the 4-week observation, all antipsychotic drugs were provided in identical powder form in amount and color with lactose added (ie, white powder of 0.6 g for participants receiving risperidone or its placebo and yellow powder of 2.5 g for those receiving olanzapine or its placebo). Thus, the participants were blinded to their allocated intervention. Other psychotropic drugs prescribed at baseline were kept constant or only reduced as clinically appropriate. When clinically indicated, lorazepam, zolpidem (for anxiety and

insomnia), and biperiden (for extrapyramidal symptoms) were allowed.

Assessment Measures

The following assessments were performed by assessors who were blinded to the allocation: PANSS, CGI-S, GAF, Simpson-Angus Scale (SAS),[18] Barnes Akathisia Rating Scale (BARS),[19] and Abnormal Involuntary Movement Scale (AIMS)[18] at baseline and week 4, and Clinical Global Impressions-Improvement scale (CGI-I)[16] at week 4. Plasma samples were collected for the measurement of concentrations of olanzapine or risperidone active moiety (risperidone plus 9-hydroxyrisperidone) more than 12 hours' postdose at baseline and week 4. Plasma concentrations of olanzapine and risperidone and 9-hydroxyrisperidone were assayed in heparinized plasma using LC/MS/MS (liquid chromatography with tandem mass spectrometry detection) at the Centre for Addiction and Mental Health in Toronto, with a limit of quantitation of 2.3 ng/mL, 0.82 ng/mL, and 2.13 ng/mL, respectively. The following information was also collected: concomitant medications, intervals between the last dose and blood draw, and demographic and clinical information including age, diagnosis, sex, race, weight, and duration of illness. Medication adherence was confirmed by plasma antipsychotic concentrations.

Population Pharmacokinetic Analysis

In case baseline plasma samples were taken before 12 hours postdose, plasma antipsychotic concentrations at trough were estimated for each individual with 2 samples taken at different points in time (ie, the sample taken before 12 hours postdose at baseline and the sample taken at week 4) using the established population pharmacokinetic models.[20,21] The precision and reliability of this estimation has recently been confirmed in our population pharmacokinetic studies.[22,23] The nonlinear mixed-effect models for olanzapine and risperidone active moiety were previously established using the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) data.[24,25] These original studies used to establish the population pharmacokinetic models comprised 1,527 olanzapine concentrations from 523 participants and 1,236 risperidone and 9-hydroxyrisperidone concentrations from 490 participants. Both compounds were adequately described using a 1-compartment linear model with first-order absorption. The previously established models utilized exponentiated or log-normal interindividual variability on each pharmacokinetic parameter; a mixture distribution to assign the trimodal distribution of clearance, as cytochrome P450 2D6 genotype was not available for risperidone; an age effect on clearance of the 9-hydroxyrisperidone moiety; and sex, race, and age effects on olanzapine disposition.

Statistical Analysis

Baseline demographic and clinical characteristics were compared between the increment and continuation groups by the Pearson χ² test or the Fisher exact test for categorical variables and by the Student t test or the Mann-Whitney U test for continuous variables, as appropriate. The primary outcome measure was the rate of participants who completed the 4-week treatment, since our main interest was to confirm the feasibility of antipsychotic dose increment. The secondary outcome measures were PANSS total score changes from baseline to week 4 and proportions of participants who achieved response, defined as a ≥25% reduction in the PANSS total score from baseline. Values of interests in treatment outcomes were compared between the 2 groups by the Pearson χ² test or the Fisher exact test for categorical variables and by the Student t test or the Mann-Whitney U test for continuous variables on intention-to-treat (ITT) or per-protocol basis. Baseline values were also used as end point values for dropouts in ITT analysis, whereas only completers were analyzed in per-protocol analysis. Logistic regression analysis was performed to evaluate associations between the successful study completion and the following variables: dose allocation, age (ie, < 51 years or ≥ 51 years), gender, duration of total antipsychotic treatment (ie, < 0.5 years or ≥ 0.5 years), baseline PANSS total score (ie, < 95 or ≥ 95), and antipsychotic drugs used. In completers in each group, Pearson or Spearman correlation coefficients were calculated to examine the relationship between the baseline plasma antipsychotic concentrations and reductions in the PANSS total, positive, negative, and general subscale scores. Those analyses conducted for the whole sample were also repeated for a subgroup of relatively "fresh" participants who had been treated with antipsychotic drugs for less than 6 months. In addition, those analyses were also conducted for a subgroup of participants with their baseline plasma antipsychotic concentrations below the optimal range recommended in the AGNP (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie) consensus guidelines[26] (ie, < 20 ng/mL for both olanzapine and risperidone). The Shapiro-Wilk test was used to assess whether the data had a normal distribution. A 2-tailed P value of < .05 was considered statistically significant for all tests. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 22.0, for Windows (IBM Corporation, Armonk, New York).

RESULTS

Patient Disposition and Characteristics

Of 113 eligible patients, 103 participants were enrolled and randomly assigned to either the increment group (n = 52) or the continuation group (n = 51) (Figure 1). Baseline demographic and clinical characteristics of the participants are shown in Table 1.

Outcome Measures

The completion rate was significantly higher in the continuation group than in the increment group (86.3% vs 69.2%) (Table 2). The logistic regression analysis found that only the same dose continuation was significantly associated with successful study completion (OR = 3.02; 95% CI, 1.08–8.47; P = .036; reference: dose increase) among the

Figure 1. Patient Flow


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                    ┌─────────────────────────────┐
                    │ Screened patients (N = 113) │
                    └─────────────────────────────┘
                                   │        ┌──────────────────────────────────────────┐
                                   │───────▶│ Ineligible patients                      │
                                   │        │   Patients who did not wish to            │
                                   │        │   participate (n = 9)                     │
                                   │        │   A score of < 60 on the Positive and     │
                                   │        │   Negative Syndrome Scale (n = 1)         │
                                   ▼        └──────────────────────────────────────────┘
                    ┌─────────────────────────────┐
                    │ Randomization (N = 103)     │
                    └─────────────────────────────┘
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Dose increment (n = 52) | Dose continuation (n = 51)

Adverse events (n = 12 [23.1%])
Consent withdrawal (n = 2 [3.8%])
Protocol violation (n = 2 [3.8%])

Protocol violation (n = 5 [9.8%])
Adverse events (n = 1 [2.0%])
Consent withdrawal (n = 1 [2.0%])

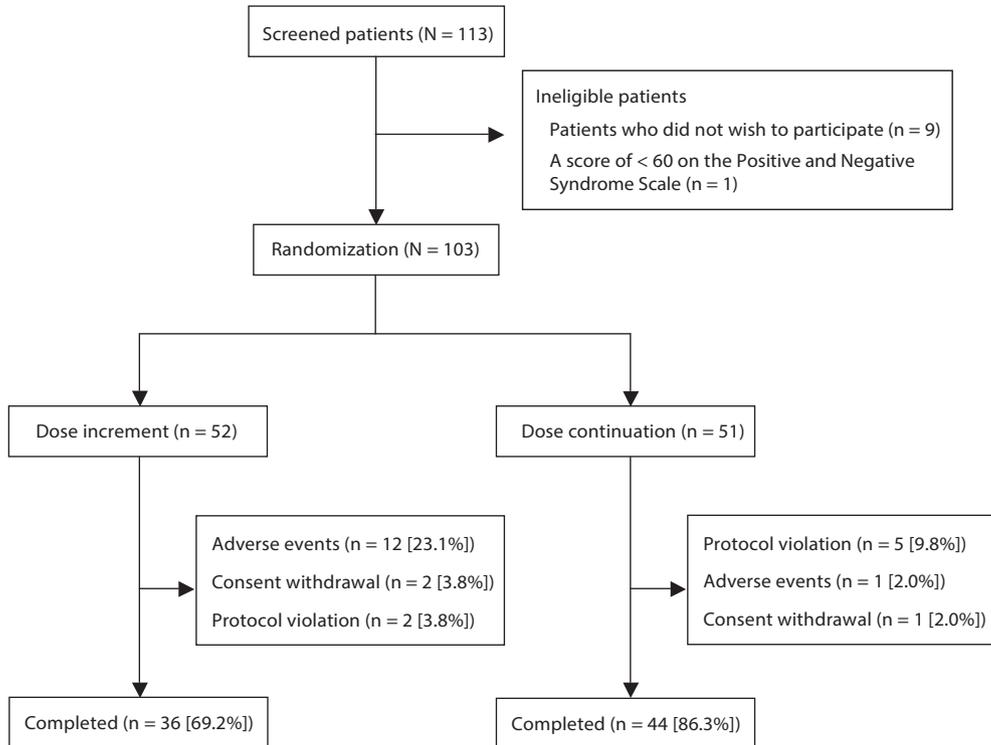Completed (n = 36 [69.2%]) | Completed (n = 44 [86.3%])

Table 1. Baseline Demographic and Clinical Characteristics of Participants

Characteristic	Increment (n = 52)	Continuation (n = 51)	Statistic	P Value
Age, mean (SD), y	51.1 (15.3)	50.3 (16.3)	$t_{101} = -0.23$	.82
Women, n (%)	32 (61.5)	33 (64.7)	$\chi^2_1 = 0.11$	.74
Asian race, n (%)	52 (100.0)	51 (100.0)	$z = 0.00$	1.00
Body weight, mean (SD), kg	60.4 (14.6)	58.3 (12.1)	$t_{101} = -0.79$	.43
Inpatient, n (%)	52 (100.0)	50 (98.0)	NA	.50[a]
Duration of illness, mean (SD, median), y	16.1 (14.4, 11.5)	16.0 (14.4, 12.0)	$z = -0.12$	.90
Duration of current episode, mean (SD, median), y	2.3 (6.2, 0.3)	1.9 (4.7, 0.4)	$z = -0.91$	.36
Total duration of antipsychotic treatment, mean (SD, median), y	11.3 (14.1, 3.8)	10.5 (13.9, 3.5)	$z = -0.58$	.56
Duration of current antipsychotic regimen, mean (SD, median), y	0.18 (0.38, 0.08)	0.15 (0.39, 0.08)	$z = -0.86$	.39
Medication, n (%)			$\chi^2_1 = 0.09$	.77
Olanzapine	25 (48.1)	26 (51.0)		
Risperidone	27 (51.9)	25 (49.0)		
Concomitant medication, n (%)				
Antidepressant	6 (11.5)	2 (3.9)	NA	.27[a]
Mood stabilizer	5 (9.6)	12 (23.5)	$\chi^2_1 = 3.62$	.057
PANSS score, mean (SD)				
Total	89.9 (14.6)	94.3 (16.1)	$t_{101} = 1.45$	.15
Positive	22.5 (5.5)	23.7 (4.4)	$t_{101} = 1.19$	.24
Negative	23.7 (5.1)	23.9 (5.2)	$t_{101} = 0.21$	.84
General	43.7 (7.3)	46.8 (8.4)	$t_{101} = 1.94$	.056
CGI-S score, mean (SD)	4.9 (0.8)	5.1 (0.9)	$z = -0.91$	.36
GAF score, mean (SD)	36.2 (9.7)	35.1 (9.3)	$z = -0.40$	.69
SAS total score, mean (SD)	1.9 (1.6)	2.3 (1.5)	$z = -1.41$	.16
BARS global clinical assessment score, mean (SD)	1.0 (0.8)	1.1 (0.8)	$z = -1.31$	.19
AIMS total score (1–7 items), mean (SD)	1.3 (1.2)	1.4 (1.4)	$z = -0.24$	.81
Plasma olanzapine concentration, mean (SD), ng/mL	30.7 (10.9)[b]	35.6 (15.5)[b]	$t_{46} = 1.23$	.22
Plasma risperidone concentration, mean (SD), ng/mL	30.1 (20.9)[c]	26.3 (12.1)[d]	$z = -0.33$	.74

[a]Fisher exact test.
[b]Data were available from 24 participants.
[c]Data were available from 26 participants.
[d]Data were available from 25 participants.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, NA = not available, PANSS = Positive and Negative Syndrome Scale, SAS = Simpson-Angus Scale.

Table 2. Changes in Outcome Measures and Plasma Antipsychotic Concentrations at 4 Weeks

Characteristic	Increment	Continuation	Statistic	P Value[a]
Completion rate, n/n (%)	36/52 (69.2%)	44/51 (86.3%)	$\chi^2_1 = 4.31$	**.038**
PANSS score change, mean (SD)				
Total (PP)	−8.1 (9.1)	−7.3 (7.3)	$z = -0.17$	.86
Total (ITT)	−5.6 (8.5)	−6.3 (7.2)	$z = -1.23$	.22
Positive (PP)	−2.7 (3.5)	−3.1 (2.5)	$z = -1.05$	.29
Positive (ITT)	−1.9 (3.2)	−2.7 (2.5)	$z = -2.09$	**.037**
Negative (PP)	−1.6 (2.8)	−1.1 (2.3)	$t_{78} = -0.80$	.43
Negative (ITT)	−1.1 (2.5)	−0.9 (2.2)	$z = -0.29$	.78
General (PP)	−3.8 (4.3)	−3.0 (4.5)	$t_{78} = -0.73$	.47
General (ITT)	−2.6 (4.0)	−2.6 (4.3)	$z = -0.51$	.61
Response rate, % (n/n) (PP)	22.2 (8/36)	15.9 (7/44)	$\chi^2_1 = 0.52$	.47
Response rate, % (n/n) (ITT)	15.4 (8/52)	13.7 (7/51)	$\chi^2_1 = 0.06$	.81
CGI-I, mean (SD)	3.1 (1.0)	3.1 (0.8)	$z = -0.40$	.69
GAF score change, mean (SD) (PP)	6.2 (8.3)	5.7 (4.5)	$z = -0.42$	.67
GAF score change, mean (SD) (ITT)	4.3 (7.5)	4.9 (4.6)	$z = -1.60$	.11
SAS total score change, mean (SD) (PP)	0.4 (0.8)	0.6 (1.5)	$z = -0.13$	.90
SAS total score change, mean (SD) (ITT)	0.3 (0.7)	0.5 (1.4)	$z = -0.59$	.56
BARS global clinical assessment score change, mean (SD) (PP)	0.1 (0.6)	0.2 (0.6)	$z = -0.83$	.41
BARS global clinical assessment score change, mean (SD) (ITT)	0.0 (0.3)	0.3 (0.6)	$z = -1.10$	.27
AIMS total score change (1–7 items), mean (SD) (PP)	0.3 (0.8)	0.4 (0.8)	$z = -0.30$	.77
AIMS total score change (1–7 items), mean (SD) (ITT)	0.0 (0.5)	0.3 (0.4)	$z = -0.82$	.41
Rescue drugs				
Lorazepam user, n (%)	14 (26.9)	15 (29.4)	$\chi^2_1 = 0.08$	.78
Lorazepam dose among users, mg/d, mean (SD)	0.9 (0.7)	0.7 (0.6)	$z = -1.13$	.26
Zolpidem user, n (%)	15 (28.8)	23 (45.1)	$\chi^2_1 = 2.92$	.087
Zolpidem dose among users, mg/d, mean (SD)	3.7 (2.7)	4.9 (2.9)	$z = -1.16$	.25
Biperiden user, n (%)	0 (0.0)	0 (0.0)	$z = 0.00$	1.00
Plasma olanzapine concentration, ng/mL, mean (SD) (PP)	67.7 (25.0)[b]	38.1 (16.8)[b]	$z = -3.72$	**<.001**
Plasma risperidone concentration, ng/mL, mean (SD) (PP)	57.8 (40.1)[c]	24.6 (11.9)[d]	$t_{18} = -3.20$	**.005**

[a]P values <.05 are shown in bold.
[b]Data were available from 19 participants.
[c]Data were available from 17 participants.
[d]Data were available from 22 participants.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, CGI-I = Clinical Global Impressions-Improvement scale, GAF = Global Assessment of Functioning, ITT = intention to treat, PANSS = Positive and Negative Syndrome Scale, PP = per protocol, SAS = Simpson-Angus Scale.

factors examined. Reasons for premature withdrawal are shown in Figure 1. Adverse events resulting in dropout were sedation (n = 8: olanzapine [n = 1] and risperidone [n = 7]), akathisia (n = 1, olanzapine), dysphagia (n = 1, risperidone), orthostatic hypotension (n = 1, olanzapine), and dyspnea (n = 1, olanzapine) in the increment group and akathisia (n = 1, olanzapine) in the continuation group. No serious adverse events were observed in both groups.

No statistically significant differences were found in any of the other outcome measures, including the response rate, between the 2 groups other than the PANSS positive subscale score change in ITT analysis (Table 2).

Plasma Concentrations and Outcome Measures

Thirty-five of 36 completers in the increment group provided blood samples both at baseline and at week 4, while 1 participant did not wish to provide the sample at baseline. Since 4 participants provided blood samples before 12 hours from the last dose, plasma drug concentrations at trough were individually estimated using the population pharmacokinetic models. Plasma antipsychotic concentrations at week 4 are shown in Table 2. In the increment group, there was a significant negative correlation between the baseline plasma antipsychotic concentration and score reduction in the PANSS positive subscale for olanzapine (Figure 2). In the continuation group, no statistically significant correlations

were found between baseline plasma antipsychotic concentrations and reductions in the PANSS total or any subscale score.
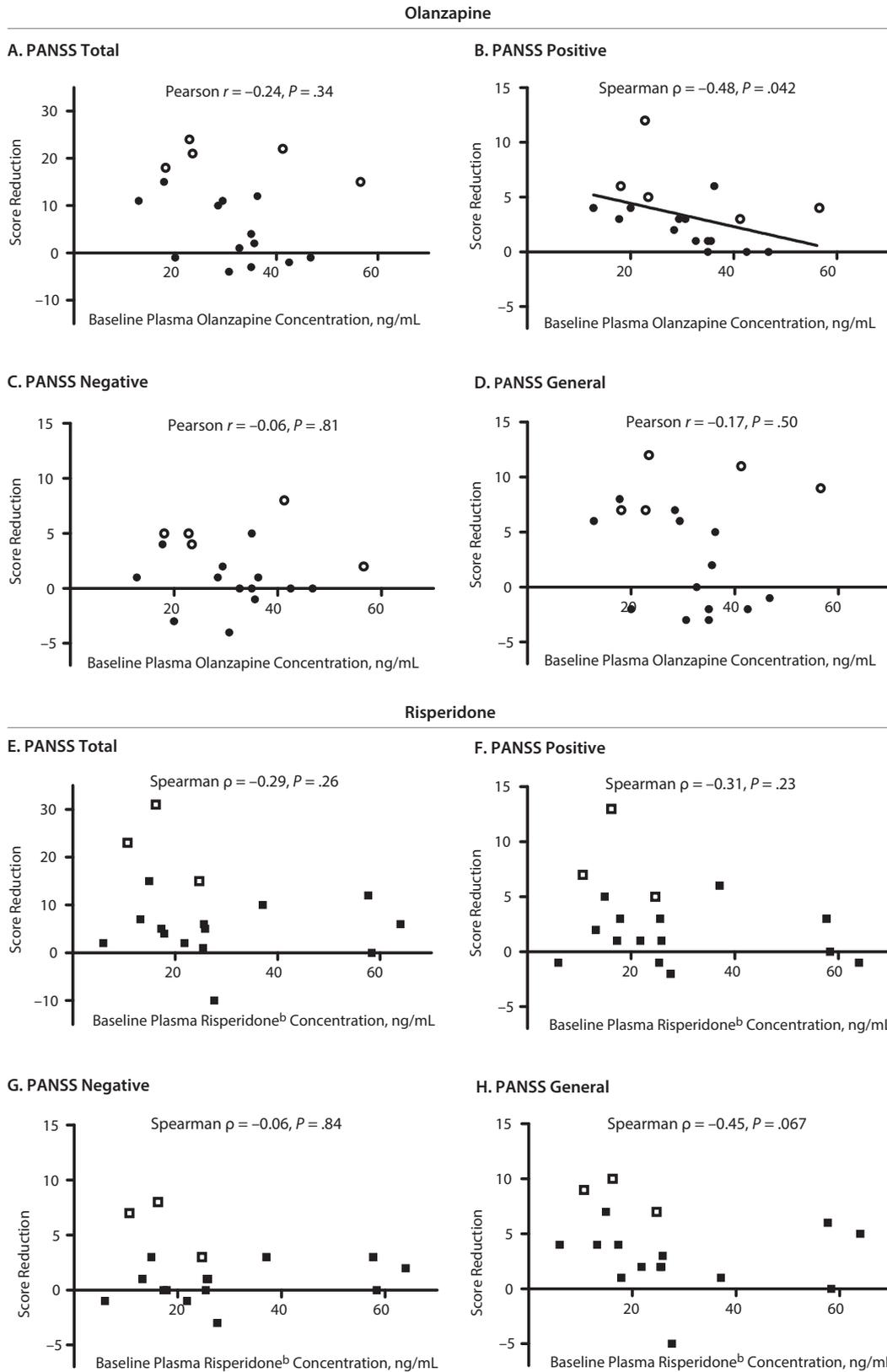
Outcomes in a Subgroup of Participants With <6 Months of Antipsychotic Treatment

Baseline demographic and clinical characteristics of the 38 participants who had been treated with antipsychotic drugs for less than 6 months are shown in Supplementary eTable 1 (available at PSYCHIATRIST.COM). Whereas the completion rate was significantly higher in the continuation group than in the increment group (95.0% vs 61.1%), the response rate was significantly higher in the increment group than in the continuation group in per-protocol analysis (54.5% vs 15.8%) (Table 3). There were no statistically significant differences in any of the other outcome measures between those 2 groups.

Outcomes in a Subgroup of Participants With Suboptimal Plasma Antipsychotic Concentrations at Baseline

Baseline demographic and clinical characteristics of the 29 participants with baseline plasma olanzapine or risperidone concentrations of <20 ng/mL are shown in Supplementary eTable 2. There were no statistically significant differences in any of the outcome measures between the 2 groups, although

Figure 2. Baseline Plasma Antipsychotic Concentrations and PANSS Score Reductions in the Increment Group[a]

Olanzapine

A. PANSS Total — Pearson $r = -0.24$, $P = .34$

B. PANSS Positive — Spearman $\rho = -0.48$, $P = .042$

C. PANSS Negative — Pearson $r = -0.06$, $P = .81$

D. PANSS General — Pearson $r = -0.17$, $P = .50$

Risperidone

E. PANSS Total — Spearman $\rho = -0.29$, $P = .26$

F. PANSS Positive — Spearman $\rho = -0.31$, $P = .23$

G. PANSS Negative — Spearman $\rho = -0.06$, $P = .84$

H. PANSS General — Spearman $\rho = -0.45$, $P = .067$

[a]Closed circles and squares indicate nonresponders and open circles and squares indicate responders. Spearman correlation analysis found a significant negative correlation between the baseline plasma olanzapine concentration and score reduction in the PANSS positive subscale ($\rho = -0.48$, $P = .042$).
[b]Active moiety.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Table 3. Outcome Measures in Participants With Total Duration of Antipsychotic Treatment of < 0.5 Years

Characteristic	Increment	Continuation	Statistic	P Value[a]
Completion rate, n/n (%)	11/18 (61.1)	19/20 (95.0)	NA	**.016**[b]
PANSS score change, mean (SD)				
Total (PP)	−12.1 (10.8)	−6.3 (8.0)	$z=-1.51$	.13
Total (ITT)	−7.4 (10.3)	−6.0 (7.9)	$z=-0.13$	.90
Positive (PP)	−4.5 (3.3)	−3.2 (2.5)	$t_{28}=-1.12$	.27
Positive (ITT)	−2.7 (3.4)	−3.1 (2.6)	$z=-0.85$	.41
Negative (PP)	−3.0 (3.9)	−1.0 (2.5)	$t_{28}=-1.65$	.11
Negative (ITT)	−1.8 (3.4)	−1.0 (2.4)	$z=-0.33$	.76
General (PP)	−4.6 (5.2)	−2.1 (4.5)	$z=-1.58$	.12
General (ITT)	−2.8 (4.7)	−2.0 (4.4)	$z=-0.40$	.70
Response rate, % (n/n) (PP)	54.5 (6/11)	15.8 (3/19)	NA	**.041**[b]
Response rate, % (n/n) (ITT)	33.3 (6/18)	15.0 (3/20)	NA	.26[b]
CGI-I, mean (SD)	2.6 (0.8)	3.2 (0.9)	$z=-1.25$	.23
GAF score change, mean (SD) (PP)	10.1 (10.0)	5.6 (4.7)	$z=-0.89$	.40
GAF score change, mean (SD) (ITT)	6.2 (9.2)	5.4 (4.7)	$z=-0.61$	.55
SAS total score change, mean (SD) (PP)	0.4 (0.9)	0.3 (1.0)	$z=-0.75$	.50
SAS total score change, mean (SD) (ITT)	0.2 (0.7)	0.3 (1.0)	$z=-0.15$	.90
BARS global clinical assessment score change, mean (SD) (PP)	0.0 (0.4)	0.3 (0.6)	$z=-1.49$	.29
BARS global clinical assessment score change, mean (SD) (ITT)	0.1 (0.5)	0.2 (0.5)	$z=-1.86$	.22
AIMS total score change (1–7 items), mean (SD) (PP)	0.0 (0.6)	0.3 (0.4)	$z=-1.21$	.35
AIMS total score change (1–7 items), mean (SD) (ITT)	0.2 (0.7)	0.3 (0.8)	$z=-1.58$	.25
Rescue drugs				
Lorazepam user, n (%)	5 (27.8)	3 (15.0)	NA	.44[b]
Lorazepam dose among users, mean (SD), mg/d	1.1 (0.6)	0.2 (0.1)	$z=-1.69$	.091
Zolpidem user, n (%)	5 (27.8)	9 (45.0)	$\chi^2_1=1.21$	.27
Zolpidem dose among users, mean (SD), mg/d	4.2 (3.9)	3.1 (1.5)	$z=-1.10$	.27
Biperiden user, n (%)	0 (0.0)	0 (0.0)	$z=0.00$	1.00

[a]P values < .05 are shown in bold.
[b]Fisher exact test.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, CGI-I = Clinical Global Impressions-Improvement scale, GAF = Global Assessment of Functioning, ITT = intention to treat, NA = not available, PANSS = Positive and Negative Syndrome Scale, PP = per protocol, SAS = Simpson-Angus Scale.

the dose-increment group demonstrated numerically greater score reductions in the PANSS (Supplementary eTable 3).

DISCUSSION

At a group level, dose increment was not superior to dose continuation with respect to any of the psychopathological and functional measures, and the former was even inferior in terms of the completion rate in patients who failed to respond to moderate dosage of olanzapine and risperidone. Additionally, lower plasma olanzapine concentrations at baseline were associated with a greater improvement in the PANSS positive symptom subscale in the increment group. These findings, overall, might argue against any additional benefit of increasing the dose in cases of nonresponse to a moderate dosage of olanzapine and risperidone, but they do point to the potential of dose increment to improve positive symptoms for patients whose antipsychotic exposure is still below the optimal range.

The antipsychotic dose increment failed to yield any additional clinical gains; rather, it resulted in more frequent dropouts. This observation may suggest that another strategy, including switching or augmenting antipsychotic drugs, should be considered in case of insufficient response to a moderate dosage of antipsychotic drug. However, it should be interpreted with caution in light of the greater improvement in positive symptoms that we observed in those whose baseline antipsychotic exposure was low. The

relationship between the oral dose of antipsychotic drugs and dopamine D_2 receptor occupancy usually fits a 1-site binding model. Baseline doses of olanzapine 10 mg/d and risperidone 3 mg/d correspond to the relatively flat part of the nonlinear curve.[27,28] Thus, dose increases would be expected to have a minimal impact on central occupancy and clinical response in general. In other words, the effectiveness of antipsychotic drugs may reach a plateau with those doses. On the other hand, a subgroup of patients whose antipsychotic exposure is still low due to their pharmacokinetic variations and who still fall on the steep part of the curve with the above-mentioned dosage may exhibit large changes in drug occupancy and therapeutic effects. These results are congruent with the finding from the ziprasidone study[10] in which serum drug concentration changes following dose increase were correlated with improvements in the PANSS positive symptom subscale at a trend level but not with other symptom domains.

In the present study, lower plasma olanzapine concentrations at baseline were associated with greater improvement, following antipsychotic dose increase in positive symptoms, but not in negative symptoms or general psychopathology. While antipsychotic effects for positive symptoms have been shown to be robust, their impact on other symptom domains appears relatively limited.[29,30] Moreover, antipsychotic treatment could result in secondary negative symptoms[31] and neuroleptic dysphoria[32] that are often difficult to be differentiated from the primary negative

symptoms. Furthermore, high doses of antipsychotic drugs can even be detrimental to negative and cognitive symptoms.[33,34] Our results may be interpreted as a ceiling effect of antipsychotic treatment for negative symptoms and general psychopathology.

In light of wide interindividual differences in responsiveness to antipsychotic drugs, we would like to refrain from simply stating, "Do not increase the dose in case of insufficient treatment response." Rather, our results underscore the importance of individualized dosing strategy with therapeutic drug monitoring. It appears fair to suggest that dose increment may be considered for patients who present with positive symptoms and whose plasma antipsychotic concentrations are still low. Furthermore, potential benefits of such a dose-increase strategy may be especially true for patients who recently started antipsychotic treatment, although it could also result in more dropouts. While these preliminary notions have to be confirmed in large prospective studies, the conventional dosing strategy may need to be revisited, as oral dose alone cannot be regarded as a reliable measure of antipsychotic exposure.[12]

This study has several limitations. First, the sample size was small. Moreover, no sample size calculation was performed since the trial was conducted as a hypothesis-generating study. Second, the duration of 4 weeks may have been too short to compare the effectiveness and the safety of the 2 dosing strategies, although it has been shown that this duration is adequate to evaluate antipsychotic response.[35] Third, since olanzapine and risperidone were the only drugs included, all participants were Japanese, 99.0% of the participants were inpatients, and the study sample included only patients who did not respond to moderate doses of olanzapine or risperidone, any extrapolation of these findings to other antipsychotic drugs or other populations must be made with caution. Fourth, heterogeneity of the sample should be taken into account. For example, the mean duration of current episode ranged from 0.03 years to 40 years, with a median of 0.4 years. Including both acute and chronic patients may have resulted in the overall low response rate as well as failure to find differences. Fifth, mixed-effect models for repeated measures were not used. They would have been ideal but were not employed in the present study since assessments were conducted only at the baseline and end point. Finally, corrections for multiple comparisons would have been ideal from a statistical perspective.

In conclusion, increasing the dose of an antipsychotic is a very common clinical intervention, especially when the dose is near the lower end of the standard range. We find no evidence to support this strategy in general. However, our findings do raise the possibility that the strategy may be a reasonable treatment option for those whose antipsychotic exposure is still insufficient. These findings emphasize the relevance of therapeutic drug monitoring to devise more effective dosing strategy on an individual basis for better management of schizophrenia.

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1. **Mr A is experiencing active symptoms of schizophrenia despite 4 weeks of treatment with olanzapine 10 mg/d. According to the results of this study, which measurement/assessment could you use to help determine whether to increase the dose?**

   a. Blood olanzapine concentration

   b. Electroencephalogram

   c. Blood brain-derived neurotrophic factor

   d. Blood C-reactive protein

2. **Mr A is experiencing active symptoms of schizophrenia despite 4 weeks of treatment with olanzapine 10 mg/d. According to the results of this study, which symptom cluster in the Positive and Negative Syndrome Scale might improve by increasing the dose?**

   a. Positive symptoms

   b. Negative symptoms

   c. General psychopathology

   d. All of them (total score)

3. **In this study, antipsychotic dose increase was associated with which outcome?**

   a. Worsening of negative symptoms

   b. Worsening of cognitive symptoms

   c. Neuroleptic dysphoria

   d. Significantly more treatment dropout than with continued dose
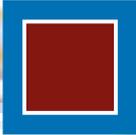
Supplementary Material

Article Title: Increasing Versus Maintaining the Dose of Olanzapine or Risperidone in Schizophrenia Patients Who Did Not Respond to a Modest Dosage: A Double-Blind Randomized Controlled Trial

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List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1. Baseline Demographic and Clinical Characteristics of Participants with Total Duration of Antipsychotic Treatment of <0.5 years

Characteristics	Increment (n=18)	Continuation (n=20)	Statistics	P-value
Age, years, mean (s.d.)	45.4 (12.4)	48.1 (18.0)	$t(36)=0.51$	0.61
Women, n (%)	12 (66.7%)	12 (60.0%)	$\chi^2(1)=0.18$	0.67
Race				
Asian, n (%)	18 (100.0%)	20 (100.0%)	$z=0.00$	1.00
Body weight, kg, mean (s.d.)	54.8 (10.7)	58.1 (13.3)	$t(36)=0.83$	0.42
Inpatient, n (%)	18 (100.0%)	19 (95.0%)	n.a.	1.00[a]
Duration of illness, years, mean (s.d., median)	5.4 (8.8, 3.0)	6.4 (7.6, 3.3)	$z=-0.16$	0.87
Duration of current episode, years, mean (s.d., median)	3.7 (9.0, 0.7)	1.9 (2.2, 0.9)	$z=-0.73$	0.48
Total duration of antipsychotic treatment, years, mean (s.d.)	0.17 (0.09)	0.15 (0.09)	$z=-1.10$	0.29
Duration of current antipsychotic regimen, years, mean (s.d.)	0.10 (0.03)	0.08 (0.01)	$z=-1.45$	0.21
Medication			$\chi^2(1)=3.71$	0.054
Olanzapine, n (%)	11 (61.1%)	6 (30.0%)		
Risperidone, n (%)	7 (38.9%)	14 (70.0%)		
Concomitant medications				
Antidepressant, n (%)	4 (22.2%)	0 (0.0%)	n.a.	**0.041**[a]
Mood stabilizer, n (%)	1 (5.6%)	1 (5.0%)	n.a.	1.00[a]
PANSS total score, mean (s.d.)	85.3 (13.9)	88.3 (11.6)	$t(36)=0.69$	0.50
PANSS positive score, mean (s.d.)	20.6 (4.2)	22.1 (3.6)	$t(36)=1.15$	0.26
PANSS negative score, mean (s.d.)	22.6 (5.4)	22.1 (4.3)	$t(36)=-0.32$	0.75
PANSS general score, mean (s.d.)	42.1 (7.4)	44.1 (6.1)	$t(36)=0.86$	0.40
CGI-S score, mean (s.d.)	4.7 (0.8)	4.8 (0.8)	$z=-1.29$	0.78
GAF score, mean (s.d.)	38.4 (11.4)	37.4 (9.4)	$t(36)=-0.30$	0.76
SAS total score, mean (s.d.)	1.2 (1.5)	2.2 (1.6)	$z=-2.05$	**0.048**
BARS global clinical assessment score, mean (s.d.)	0.7 (0.7)	0.8 (0.5)	$z=-0.52$	0.65
AIMS total score (1-7 items), mean (s.d.)	0.8 (1.2)	1.2 (1.1)	$z=-1.26$	0.25

[a.] Fisher's exact test.

P-values of <0.05 are shown in bold.

s.d., standard deviation; PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impression-Severity of Illness; GAF, Global Assessment of Functioning; SAS, Simpson-Angus Scale; BARS, Barnes Akathisia Rating Scale; AIMS, Abnormal Involuntary Movement Scale; n.a., not available

Supplementary eTable 2. Baseline Demographic and Clinical Characteristics of Participants with Baseline Plasma Olanzapine or Risperidone Concentrations of <20 ng/mL

Characteristics	Increment (n=13)	Continuation (n=16)	Statistics	P-value
Age, years, mean (s.d.)	44.6 (12.4)	44.9 (18.0)	$t(27)=0.05$	0.96
Women, n (%)	6 (46.2%)	9 (56.3%)	$\chi^2(1)=0.29$	0.59
Race				
Asian, n (%)	13 (100.0%)	16 (100.0%)	$z=0.00$	1.00
Body weight, kg, mean (s.d.)	66.7 (15.4)	57.8 (8.8)	$t(18)=-1.79$	0.09
Inpatient, n (%)	13 (100.0%)	16 (100.0%)	n.a.	1.00[a]
Duration of illness, years, mean (s.d.)	15.6 (12.6)	15.6 (14.2)	$t(27)=-0.00$	1.00
Duration of current episode, years, mean (s.d.)	0.9 (2.1)	0.8 (1.2)	$z=-0.05$	0.96
Total duration of antipsychotic treatment, years, mean (s.d.)	11.7 (13.9)	13.3 (14.4)	$z=-0.18$	0.86
Duration of current antipsychotic regimen, years, mean (s.d.)	0.08 (0.01)	0.10 (0.03)	$z=-1.57$	0.12
Medication			n.a.	0.71[a]
Olanzapine, n (%)	5 (38.5%)	5 (31.3%)		
Risperidone, n (%)	8 (61.5%)	11 (68.7%)		
Concomitant medications				
Antidepressant, n (%)	2 (15.4%)	2 (12.5%)	n.a.	1.00[a]
Mood stabilizer, n (%)	4 (30.8%)	8 (50.0%)	$\chi^2(1)=1.09$	0.30
PANSS total score, mean (s.d.)	86.8 (16.7)	97.3 (15.9)	$t(27)=1.67$	0.11
PANSS positive score, mean (s.d.)	22.4 (5.3)	24.3 (3.3)	$t(27)=1.12$	0.27
PANSS negative score, mean (s.d.)	21.6 (4.0)	24.3 (5.1)	$t(27)=1.50$	0.14
PANSS general score, mean (s.d.)	42.8 (8.8)	48.8 (9.1)	$t(27)=1.71$	0.65
CGI-S score, mean (s.d.)	4.8 (0.9)	5.2 (0.7)	$z=-0.85$	0.39
GAF score, mean (s.d.)	38.7 (12.2)	33.4 (8.5)	$t(27)=-1.33$	0.20
SAS total score, mean (s.d.)	1.5 (1.3)	2.1 (1.3)	$z=-0.93$	0.35
BARS global clinical assessment score, mean (s.d.)	0.6 (0.6)	1.2 (0.9)	$z=-1.63$	0.10
AIMS total score (1-7 items), mean (s.d.)	1.2 (1.1)	1.3 (1.7)	$z=-0.37$	0.71

[a.] Fisher's exact test.

P-values of <0.05 are shown in bold.

s.d., standard deviation; PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impression-Severity of Illness; GAF, Global Assessment of Functioning; SAS, Simpson-Angus Scale; BARS, Barnes Akathisia Rating Scale; AIMS, Abnormal Involuntary Movement Scale; n.a., not available

Supplementary eTable 3. Outcome Measures in Participants with Baseline Plasma Olanzapine or Risperidone Concentrations of <20 ng/mL

Characteristics	Increment	Continuation	Statistics	P-value
Completion rate, (%)	11/13 (84.6%)	12/16 (75.0%)	n.a.	0.66[a]
PANSS total score change, mean (s.d.) (PP)	-11.8 (9.3)	-7.0 (6.5)	$t(21)$=-1.39	0.18
PANSS total score change, mean (s.d.) (ITT)	-10.0 (9.5)	-5.3 (6.4)	$t(27)$=-1.55	0.13
PANSS positive score change, mean (s.d.) (PP)	-4.3 (3.5)	-3.1 (2.5)	$t(21)$=-0.90	0.38
PANSS positive score change, mean (s.d.) (ITT)	-3.6 (3.6)	-2.3 (2.6)	$t(27)$=-1.10	0.28
PANSS negative score change, mean (s.d.) (PP)	-2.3 (3.3)	-1.3 (1.7)	z=-0.38	0.71
PANSS negative score change, mean (s.d.) (ITT)	-1.9 (3.1)	-1.0 (1.6)	$t(17)$=-0.93	0.37
PANSS general score change, mean (s.d.) (PP)	-5.3 (3.4)	-2.6 (4.8)	$t(21)$=-1.47	0.16
PANSS general score change, mean (s.d.) (ITT)	-4.5 (3.7)	-1.9 (4.3)	$t(27)$=-1.62	0.12
Response rate, (%) (PP)	27.3% (3/11)	0.0% (0/12)	n.a.	0.09[a]
Response rate, (%) (ITT)	23.1% (3/13)	0.0% (0/16)	n.a.	0.08[a]
CGI-GI, mean (s.d.)	2.7 (0.9)	3.1 (0.6)	z=-0.97	0.33
GAF score change, mean (s.d.) (PP)	9.8 (9.0)	5.8 (3.5)	z=-1.24	0.22
GAF score change, mean (s.d.) (ITT)	8.3 (9.0)	4.4 (3.9)	z=-1.20	0.23
SAS total score change, mean (s.d.) (PP)	0.4 (0.5)	0.7 (2.4)	z=-0.74	0.46
SAS total score change, mean (s.d.) (ITT)	0.3 (0.5)	0.5 (2.1)	z=-0.94	0.35
BARS global clinical assessment score change, mean (s.d.) (PP)	0.1 (0.7)	-0.2 (0.4)	z=-0.93	0.35
BARS global clinical assessment score change, mean (s.d.) (ITT)	0.1 (0.6)	-0.3 (0.6)	z=-1.52	0.13
AIMS total score change (1-7 items), mean (s.d.) (PP)	0.5 (0.5)	0.3 (0.6)	z=-0.78	0.44
AIMS total score change (1-7 items), mean (s.d.) (ITT)	0.4 (0.5)	0.2 (0.5)	z=-0.95	0.34
Rescue drugs				
Lorazepam user, n (%)	4 (30.8%)	9 (56.3%)	$\chi^2(1)$=1.88	0.17
Lorazepam dose among users, mg/day, mean (s.d.)	0.3 (0.5)	0.4 (0.6)	z=-1.18	0.24
Zolpidem user, n (%)	4 (30.8%)	10 (62.5%)	$\chi^2(1)$=2.89	0.09
Zolpidem dose among users, mg/day, mean (s.d.)	1.4 (2.8)	3.3 (3.2)	z=-1.76	0.08
Biperiden user, n (%)	0 (0.0%)	0 (0.0%)	n.a.	1.00[a]

[a.] Fisher's exact test.

PANSS, Positive and Negative Syndrome Scale; s.d., standard deviation; PP, per-protocol; ITT, intention-to-treat; CGI-GI,

Clinical Global Impression-Global Improvement; GAF, Global Assessment of Functioning; SAS, Simpson-Angus Scale;

BARS, Barnes Akathisia Rating Scale; AIMS, Abnormal Involuntary Movement Scale; n.a., not available