patients; aripiprazole, 2 patients; haloperidol, 1 patient; and unknown, 4 patients. Unfortunately, data on exact dosages were not available. No significant differences between groups were seen according to the kinds of previous antipsychotics taken.

Between 2 and 10 weeks, among the early responders to risperidone, 5 patients were lost to follow-up, and 2 patients withdrew consent. In addition, 8 patients discontinued risperidone due to insufficient efficacy (n = 2) and side-effects (n = 6; extrapyramidal side effects, n = 4; hyperprolactinemia, n = 2). In the RIS+RIS group, 8 patients discontinued the allocated intervention due to insufficient efficacy (n = 5), extrapyramidal side effects (n = 1), and non-adherence (n = 2). In the RIS+OLZ group, 5 patients discontinued the allocated intervention due to insufficient efficacy (n = 4) and side-effects (n = 1, weight gain) (Fig. 1).

Scattergrams of changes in PANSS total score at 10 weeks from baseline are shown in Figure 2. At 10 weeks, early responders to risperidone showed a significantly higher percentage of improvement in PANSS total score than the RIS+RIS group (66.3% [SD, 23.9] vs. 26.6% [SD, 31.7]; t = 4.89, $P < 0.0001$). Meanwhile, no significant difference was observed between the RIS+RIS and RIS+OLZ groups (26.6% [SD, 31.7] vs. 35.7% [SD, 26.4]; t = 0.80, P = 0.43). A comparison of outcomes between the RIS+RIS and RIS+OLZ groups is shown in Table 3. Mean maximum dose of olanzapine in the RIS+OLZ group was 16.9 mg/day, equivalent to 5.1 mg/day of risperidone (Kane et al., 2003). The total dose of antipsychotics in the RIS+OLZ group was thus equivalent to 10.6 mg/day (5.5+5.1 mg) of risperidone, higher than that in the RIS+RIS group (8.5 mg/day). In the RIS+RIS group, adjunctive benzodiazepines were given to 9 patients: lorazepam, 3 patients, 1 mg; nitrazepam, 1 patient, 10 mg; flunitrazepam, 6 patients, mean 1.8 mg (SD, 0.4 mg). In the RIS+OLZ group, adjunctive benzodiazepines were given to 12 patients: lorazepam, 9 patients, mean 1.5 mg (SD, 0.9 mg); nitrazepam, 4 patients, mean 12.5 mg (SD, 5.0 mg); flunitrazepam, 1 patient, 1 mg. In the RIS+RIS group, adjunctive valproate was given to 4 patients with the mean dose of 750 mg (SD, 300 mg). In the RIS+OLZ group, adjunctive valproate was given to 5 patients, with a mean dose of 540 mg (SD, 195 mg).

Achievement rates of $\geq$ 20%, $\geq$ 30%, $\geq$ 40%, and $\geq$ 50% improvement in PANSS total score in the

RIS+OLZ group were 77%, 69%, 62% and 23%, respectively. Achievement rates of ≥ 20%, ≥ 30%, ≥ 40%, and ≥ 50% improvement in PANSS total score in the RIS+RIS group were 46%, 46%, 38% and 23%, respectively (Fig. 3). With respect to the primary outcome measure, no difference in the rate of achieving ≥ 50% improvement in PANSS total score was observed between groups (23% [*n/N* = 3/13] in each). There were no differences in the rate of achieving ≥ 20%, 30%, and 40% improvement in PANSS total score between the RIS+OLZ group and the RIS+RIS group (77% vs. 46%, *P*=0.23, 69% vs. 46%, *P*=0.43, 62% vs. 38%, *P*=0.43). These are post hoc, and no significant difference was found either with or without Bonferroni correction. Likewise, no significant differences in safety and tolerability outcomes were identified (Table 3). Among the 6 patients with akathisia in the RIS+RIS group, only 2 patients showed akathisia at the time of treatment discontinuation. Severity of akathisia in these two patients was just '1: minimal, questionable' (full score, 4), and the reasons for treatment discontinuation in both patients were insufficient efficacy. A trend-level difference in fasting glucose change from baseline was apparent between the RIS+RIS and RIS+OLZ groups.

Treatment discontinuation for any cause did not differ significantly between treatment groups (*P* = 0.060, Fig. 4). Comparisons by log-rank test showed that although time to treatment discontinuation was significantly shorter in the RIS+RIS group (6.8 weeks; 95%CI, 5.2-8.4 weeks) than in early responders to risperidone (8.6 weeks; 95%CI, 7.9-9.3; *P* = 0.018), it was not significantly shorter in the RIS+OLZ group (7.9 weeks; 95%CI, 6.3-9.5 weeks) than in early responders to risperidone (8.6 weeks; 95%CI, 7.9-9.3 weeks; *P* = 0.37).

4. Discussion

As the definitions of the outcomes adopted in a study represent a critical factor, the characteristics of the CGI classification to identify early non-response in this study require some discussion. Although we used CGI-I, another possibility may be to use a certain cutoff in the PANSS score to decide early non-response. However, such lengthy measures are not used in standard clinical practice. We have recently shown that early response/non-response to risperidone according to CGI-I at 2

weeks can predict subsequent clinical outcomes (Hatta et al., 2011). The negative likelihood ratio for the prediction of achieving ≥ 50% response at 4 weeks according to early response status to risperidone at 2 weeks was 0.057. This value was sufficiently small (< 0.1), meaning that early non-response to risperidone at 2 weeks can predict < 50% response at 4 weeks. The result was consistent with prospective findings by Kinon et al. (2010), in which the full 30-item PANSS had been used to assess early response and non-response. Furthermore, the present finding of a -11.7% mean improvement in PANSS total score between baseline and 2 weeks in early non-responders to risperidone is consistent with the linking of CGI-I to percentage PANSS reduction (Leucht et al., 2005). Using CGI-I (score ≥ 4 as a cutoff) to identify early non-response thus appears reliable.

In the present study, a predominance of early responders to early non-responders was observed, with 67% of patients identified as early responders to risperidone. This is consistent with the findings of our previous randomized clinical study on early prediction of antipsychotic response (Hatta et al., 2011), but inconsistent with the retrospective analysis and prospective studies by Kinon et al. (2008, 2010). The discrepancies can be explained by the following points. First, severity of symptoms differed between investigations. With respect to baseline PANSS, mean total scores were approximately 92 in the retrospective analysis (Kinon et al., 2008) and 99 in the prospective trial (Kinon et al., 2010), compared to 106.2 in the present investigation. Extremely high baseline PANSS scores were thus one characteristic of our study, as all patients required emergency admission. Agitation/excitement can be a particularly responsive domain during early treatment (Breier et al., 2002), and may be associated with the predominance of early responders to early non-responders in our emergency-based study. Another difference is that 40% of patients in the present study were drug-naïve, in contrast with the chronically ill patients investigated by Kinon et al. (2010). Since a substantial proportion of the patients in the present study were receiving treatment for the very first time, response times of such patients might have differed (Emsley et al., 2006). The tendency toward a higher rate of antipsychotic-naïve patients among early responders to risperidone compared to early non-responders (Table 1) may support this.

The objective of this study was to clarify whether augmentation with olanzapine would be

superior to increased risperidone dose among acute schizophrenia patients showing early non-response to risperidone at 2 weeks in a real-world setting. The present finding that a ≥ 50% improvement in PANSS total score at 10 weeks among early non-responders allocated to augmentation with olanzapine (RIS+OLZ group) was achieved by 23% is new. In addition, the finding that a ≥ 50% improvement in PANSS total score at 10 weeks among early non-responders allocated to receive an increased risperidone dose (RIS+RIS group) was achieved by 23% is informative. Although we assumed that the subsequent response rate in the RIS+RIS group was 9%, and that the subsequent response rate in the RIS+OLZ group was 60% as described in the Statistical analysis section (2.4.), we could not confirm our original hypothesis. This point requires further elaboration. A ≥ 50% improvement in PANSS total score was achieved by 23% in both groups. This rate was unexpectedly low for the RIS+OLZ group, and unexpectedly high for the RIS+RIS group. The assumption of 9% for the RIS+RIS group was based on our previous finding at 4 weeks, but the present study included a 10-week follow-up period. This prolonged follow-up period might have led to better outcomes than we had expected. Remarkably, rates of achieving a ≥ 40% improvement in PANSS total score in the RIS+OLZ and RIS+RIS groups were 62% and 38%, respectively (Fig. 3). If the primary outcome measure had been the achievement of ≥ 40% rather than ≥ 50%, yielding improvement in PANSS total score for a larger number of patients, a significant difference between groups might have been observed. Kinon et al. (2008) analyzed data from 5 randomized clinical trials in the treatment of chronically ill patients with schizophrenia, suggesting that the 40% cut-off may be a more appropriate criterion for subsequent improvement. Stauffer et al. (2011) reported that at a threshold for later response of ≥ 50% improvement in PANSS total score, early non-response most strongly predicted later non-response in the treatment of patients with first-episode psychosis. Kinon et al. (2010) reported that a comparison of the proportion of responders observed at end point between switching risperidone to olanzapine and continuing on risperidone in chronically ill schizophrenia patients showing early non-response to risperidone did not reveal significant between-group differences for categorical response criteria of 20, 30,or 40% reduction in PANSS total score at end point, although a significantly greater proportion of patients who switched to

olanzapine attained at least a 50% reduction in symptoms. Thus, what is the appropriate rate as a threshold for later response is still controversy.

Time to treatment discontinuation was significantly shorter in the RIS+RIS group than in early responders, but was not significantly shorter in the RIS+OLZ group than in early responders. In the case of increasing risperidone above a standard dose of 3-6 mg daily, many studies (in Caucasian populations) have shown this either has no benefit or may result in more extrapyramidal symptoms, less improvement in negative symtpoms, and longer hospital stays (Kopala et al., 1997; Emsley, 1999; Love et al., 1999; Lane et al., 2000; Volavka et al., 2002). However, only one treatment discontinuation due to side-effects was seen in the RIS+RIS group and in the RIS+OLZ group (Fig. 1). Among the 6 patients with akathisia in the RIS+RIS group (Table 3), only 2 patients showed akathisia at the time of treatment discontinuation. Furthermore, the severity of akathisia in these two patients was just '1: minimal, questionable' (full score, 4), and the reason for treatment discontinuation in both patients was insufficient efficacy. Flexible dose design and allowing use of anticholinergics and benzodiazepines as needed might have helped to prevent treatment discontinuations for side-effects. Toxicity from high-dose risperidone in the RIS+RIS group might not necessarily have been the primary cause for the disadvantage of the RIS+RIS group and the advantage of the RIS+OLZ group. In addition, the lack of significant difference in rates of discontinuation due to side effects between groups suggests that the combination of risperidone and olanzapine is not necessarily risky.

Kinon et al. (2010) recently reported that switching risperidone to olanzapine at week 2 resulted in a small but significantly greater reduction in PANSS total score than continuing on risperidone among early non-responders. Tenacious monotherapy with risperidone without increasing the dose may thus be inferior to switching to olanzapine. However, the clinical significance of the switching strategy appears to be slight during acute-phase treatment, because the difference in mean PANSS total score between switching to olanzapine and staying on risperidone at 10 weeks was only 3 points. Unfortunately, the present study lacked a switching arm to another antipsychotic monotherapy. We therefore cannot claim that some benefit of augmentation therapy in the present

study is superior to the small but significant effects of switching from risperidone to olanzapine reported by Kinon et al. (2010). Further studies comparing augmentation effects with switching effects seem justified.

To the best of our knowledge, this represents the first randomized clinical trial of olanzapine augmentation of risperidone in patients with acute-phase schizophrenia unresponsive to risperidone monotherapy. One strength of this study was that all participants were psychiatric emergency cases requiring admission, mirroring real clinical practice. The absence of support from pharmaceutical companies was also a key characteristic of this study. One limitation was that the sample size was relatively small. Obtaining informed consent in emergency situations is often difficult. Accordingly, the rate of participation in the study among eligible patients was 23%. This rate is not particularly low for emergency situations (Hatta et al., 2008, 2009, 2011). Second, the study used a single-blind design. Both clinicians and patients may have had expectations about individual antipsychotics in terms of therapeutic potency for acute psychotic episodes, dosage requirements, side-effect profile, and likely need for as-needed medication. Such expectations could influence the dosage prescribed, decisions to prescribe as-needed medications, and decisions to discontinue the assigned drug. However, obtaining informed consent for a double-blinded study of emergency situations may be extremely difficult, and the rate of participation in a double-blinded study among eligible patients could well be much lower than that in a single-blinded study. As excessively low participation rates cannot reflect real practice, this issue is of particular concern for research into emergency situations. Third, the time to all-cause discontinuation may be a more appropriate measure for double-blind trials in which both prescriber and patient expectations are controlled and both study conditions include newly started medications (Essock et al., 2011). In an open-label trial with blinded raters, patients and prescribers in the switch condition may be more inclined to attribute alterations in feelings, symptoms, or side effects to the change in medication compared to patients and prescribers in the stay condition, who may have experienced these same alterations as part of normal variations in illness and medication response. In the present study, neither randomized group represented a stay condition, using either augmentation or an increase in dose. As both groups were conditions with a

change in medication, the comparisons may have been more appropriate than a comparison between stay and switch conditions, with respect to the time to all-cause discontinuation. Fourth, an interval of $\geq$ 1 week after increasing the doses of risperidone to 6 mg may be needed when determining early non-response. If such an interval is not applied, delayed effects could be seen after the decision to randomize, and thus affect the results. We should be wary of polypharmacy, as multiple agents are too often prescribed by clinicians when not warranted. However, when patients fail to respond to an adequate dose of antipsychotic, it is incumbent upon us to test other options. There was not RIS+OLZ advantage over RIS+RIS in the primary outcome of the present study. However, secondary outcomes justify the inclusion of augmentation arms in additional, much larger studies comparing strategies for early non-responders. More studies performed in real clinical practice with minimal bias are required to assist clinicians in making rational treatment decisions.

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Figure legends

Figure 1: Trial profile

Figure 2: Scatterplot of change in PANSS total score at 10 weeks from baseline

Early responders to risperidone showed significantly higher percentage of improvement in PANSS total score than the RIS+RIS group (66.3% [SD, 23.9%] vs. 26.6% [SD, 31.7%]; t = 4.89, df = 56, $P < 0.0001$). No significant difference was observed between the RIS+RIS and RIS+OLZ groups (26.6% [SD, 31.7%] vs. 35.7% [SD, 26.4%]; t = 0.80, df = 24, $P = 0.43$).

Figure 3: Change in PANSS total score at 10 weeks from baseline among early non-responders to risperidone

Rates of achieving ≥ 20%, ≥ 30%, ≥ 40%, and ≥ 50% improvement in PANSS total score in the RIS+OLZ group were 77%, 69%, 62% and 23%, respectively. Rates of achieving ≥ 20%, ≥ 30%, ≥ 40%, and ≥ 50% improvement in PANSS total score in the RIS+RIS group were 46%, 46%, 38% and 23%, respectively.

Figure 4: Time to treatment discontinuation for any cause

Kaplan-Meier estimates of time to discontinuation were 8.6 weeks (95%CI, 7.9-9.3 weeks) for early responders to risperidone, 7.9 weeks (95%CI, 6.3-9.5 weeks) for the RIS+OLZ group, and 6.8 weeks (95%CI, 5.2-8.4 weeks) for the RIS+RIS group. Comparisons by log-rank test showed that time to treatment discontinuation was significantly shorter in the RIS+RIS group than in early responders to risperidone ($P = 0.018$), but was not significantly shorter in the RIS+OLZ group than in early responders to risperidone ($P = 0.37$).

Table 1: Baseline characteristics of early responders to risperidone and early non-responders

	Early responders to risperidone (*n*=52)	Early non-responders to risperidone (*n*=26)	*P*
Age (years)	39.6 (12.0)	39.4 (12.0)	0.94
Men	25/52 (48%)	13/26 (50%)	0.81
Asian	52/52 (100%)	26/26 (100%)	
Diagnosis			
Schizophrenia/schizophreniform	49/52 (94%)	24/26 (92%)	1.00
Schizoaffective	3/52 (6%)	2/26 (8%)	
Substance dependence	3/52 (6%)	3/26 (12%)	0.39
Antipsychotic-naïve	27/52 (52%)	8/26 (31%)	0.09
Haloperidol injection received before enrolment	14/52 (27%)	4/26 (15%)	0.39
CGI-S	5.5 (0.9)	5.8 (0.8)	0.26
PANSS			
Total	106.2 (24.2)	106.1 (24.9)	0.98

Positive scale	29.7 (6.8)	29.1 (8.3)	0.76
Negative scale	23.1 (9.1)	25.2 (9.0)	0.35
General psychopathology scale	53.5 (13.1)	51.8 (12.9)	0.61
PANSS-EC	17.6 (6.5)	18.6 (7.3)	0.58
GAF	20.0 (8.3)	21.6 (7.2)	0.41
BMI (kg/m^2)	22.5 (3.5)	22.3 (4.5)	0.84
Overweight (BMI ≥25)	13/52 (25%)	6/26 (23%)	1.00
Hyperglycemia	0/52 (0%)	0/26 (0%)	
Hypercholesterolemia	7/52 (13%)	4/26 (15%)	1.00
Hypertriglyceridemia	3/52 (6%)	5/26 (19%)	0.11
Median dose of risperidone at 2weeks (mg/day)	5.5	6.0	0.17

Data represent mean (SD) or *n/N* (%), unless otherwise indicated. Diagnosis was made at discharge according to DSM-IV-TR. All substance dependence was alcohol dependence. 'Haloperidol injection received before enrolment': the maximal duration until enrollment was 3 days. CGI-S, Clinical Global Impression Severity rating scale; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Excitement (item number P4), Hostility (P7), Tension (G4), Uncooperativeness (G8), Poor impulse control (G14); GAF, Global Assessment of Functioning; BMI, body mass index.

Hyperglycemia: ≥200 mg/dL or fasting glucose ≥126 mg/dL. Hypercholesterolemia: cholesterol concentration ≥220 mg/dL. Hypertriglyceridemia: triglyceride level ≥150 mg/dL. Differences in age, CGI-S, PANSS, GAF, and BMI were calculated using the unpaired t-test. Differences in sex, diagnosis, and frequencies of substance dependence, haloperidol injection received before enrolment, and hypertriglyceridemia were calculated using the Fisher's exact test.

Table 2: Baseline characteristics of early non-responders to risperidone

	RIS+RIS (*n*=13)	RIS+OLZ (*n*=13)	*P*
Age (years)	41.9 (10.6)	36.8 (13.1)	0.29
Men	9/13 (69%)	4/13 (31%)	0.12
Asian	13/13 (100%)	13/13 (100%)	
Diagnosis			
Schizophrenia/schizophreniform	13/13 (100%)	11/13 (85%)	0.48
Schizoaffective	0/13 (0%)	2/13 (15%)	
Substance dependence	2/13 (15%)	1/13 (8%)	1.00
Antipsychotic-naïve	4/13 (31%)	4/13 (31%)	
Haloperidol injection received before enrolment			
	3/13 (23%)	1/13 (8%)	0.59
CGI-S	6.0 (0.7)	5.5 (0.9)	0.15
PANSS			
Total	109.7 (26.8)	102.5 (23.4)	0.48
Positive scale	29.7 (9.5)	28.5 (7.2)	0.73

Negative scale	26.6 (9.8)	23.8 (8.3)	0.44
General psychopathology scale	53.4 (15.7)	50.2 (9.6)	0.53
PANSS-EC	19.4 (7.9)	17.8 (6.8)	0.58
GAF	21.9 (6.9)	21.4 (7.7)	0.86
BMI (kg/m^2)	22.4 (5.5)	22.2 (3.6)	0.92
Overweight (BMI ≥25)	3/13 (23%)	3/13 (23%)	
Hyperglycemia	0/13 (0%)	0/13 (0%)	
Hypercholesterolemia	2/13 (15%)	2/13 (15%)	
Hypertriglyceridemia	1/13 (8%)	4/13 (31%)	0.32

RIS+RIS, Allocated to continuing with risperidone alone (max. dose, 12mg/day); RIS+OLZ, Allocated to augmenting with olanzapine (max. doses, risperidone 6mg/day, olanzapine 20mg/day). Data represent mean (SD) or *n/N* (%). Diagnosis was made at discharge according to DSM-IV-TR. All substance dependence was alcohol dependence. 'Haloperidol injection received before enrolment': the maximal duration until enrollment was 3 days. CGI-S, Clinical Global Impression Severity rating scale; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Excitement (item number P4), Hostility (P7), Tension (G4), Uncooperativeness (G8), Poor impulse control (G14); GAF, Global Assessment of Functioning; BMI, body mass index. Hyperglycemia: ≥200 mg/dL or

fasting glucose ≥126 mg/dL. Hypercholesterolemia: cholesterol concentration ≥220 mg/dL. Hypertriglyceridemia: triglyceride level ≥150 mg/dL. Differences in age, CGI-S, PANSS, GAF, and BMI were calculated using the unpaired t-test. Differences in sex, diagnosis, and frequencies of substance dependence, haloperidol injection received before enrolment, and hypertriglyceridemia were calculated using the Fisher's exact test.