Switching and augmentation strategies for antipsychotic medications in acute-phase schizophrenia: latest evidence and place in therapy

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Abstract: In terms of effectiveness of antipsychotics in schizophrenia, discrepancy often exists between results from double-blind randomized controlled trials and observations in emergency or acute-phase clinical practice. For instance, the antipsychotic switching strategy is not always applicable in emergency or acute-phase situations, and augmentation of another antipsychotic is occasionally done instead. In this review, we discuss strategies for early nonresponse to an antipsychotic drug such as switching and augmentation from the perspective of emergency and acute-phase treatment. We searched PubMed for the latest evidence on switching and augmentation strategies of antipsychotics for an emergency or acute-phase period. For risperidone and olanzapine, there is some evidence on switching and augmentation strategies in the management of acute-phase schizophrenia. There may be responders to olanzapine alone among early nonresponders to risperidone, whereas there may be few responders to risperidone alone among early nonresponders to olanzapine. However, there is still insufficient evidence at this time for application of these findings to routine clinical practice. For other antipsychotics, there is little evidence for their augmentation in acute-phase practice. We should be wary of polypharmacy, as multiple agents are too often prescribed by clinicians when not warranted. Considering current evidence, we propose how to switch antipsychotics in the acute phase of schizophrenia in routine practice.

Keywords: acute-phase schizophrenia, antipsychotic, augmentation, schizophrenia, switching

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Introduction

As a strategy for antipsychotic treatment of schizophrenia, monotherapy is clearly optimal when both effective and tolerated.^{1,2} When a patient fails to respond to an adequate dose and duration of an initial antipsychotic, switching to an antipsychotic other than clozapine is generally recommended. These recommendations are based primarily on double-blind randomized controlled trials (RCTs), which are not easily conducted for acute psychotic episodes requiring involuntary emergency admission because enrolling acute psychotic and agitated patients in RCTs is challenging, particularly when using a double-blind

design. Therefore, discrepancy often exists between results from double-blind RCTs and observations in emergency or acute-phase practice. For instance, the switching strategy is not always applicable in emergency or acute-phase situations, and augmentation of another antipsychotic is occasionally done for an emergency or acute-phase period instead. The frequency of antipsychotic polypharmacy among patients with schizophrenia in Denmark in 2012 was reportedly 24.6%, and independent correlates of antipsychotic polypharmacy included higher antipsychotic defined daily doses (odds ratio 3.05).³ Higher antipsychotic doses are associated with

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Figure 1. Flowchart of the systematic literature search of switching strategy of antipsychotics for an emergency and acute-phase period.

illness severity, and were reportedly required in some cases of psychiatric emergency admission.⁴ As high doses of antipsychotic above a licensed dose are not recommended, a second antipsychotic within a licensed dose is occasionally added to an initial antipsychotic administered at the upper limit of the licensed dose, particularly in psychotic patients with severe excitement and aggression. From the perspective of emergency and acute-phase treatment, strategies for early nonresponse to an antipsychotic drug such as switching and augmentation are discussed.

The latest evidence on switching strategy of antipsychotics for an emergency or acute-phase period

We conducted a computerized PubMed literature search of articles up to 28 February 2017 using the search words ‘antipsychotic’, ‘schizophrenia’ and ‘switching’ along with the filters ‘clinical trial’, ‘observational study’, ‘humans’ and ‘English’. Of the 173 articles identified, 158 were excluded on the basis of title and abstract (Figure 1). Reasons for exclusion were as follows: 62 studies were not

conducted in the acute phase, which is defined by an acute psychotic episode lasting weeks to months.⁵ In such situations, well organized clinical guidelines of pharmacotherapy for schizophrenia are the landmarks of clinical practice, and sufficiently applicable.^{1,2} Thirty-eight studies were associated primarily with side effects, which have been well described in a recent meta-analysis.⁶ Twenty-six studies were about long-acting injectable antipsychotics, which are not a strategy in an emergency and the acute phase. Twenty studies were not associated with switching from an antipsychotic to another antipsychotic. Seven articles were not reports on trials or observational studies. Three articles were only descriptions of study design. Two studies were conducted with unnecessary switching design. Thus, 15 full-text articles were assessed for eligibility, and four articles were excluded due to nonacute phase ($n = 2$) and a small number of case series ($n = 2$). According to subsequent searches for the reference list of already identified studies to retrieve additional articles, one article was included. As the number of eligible studies was small, any measures such as ‘significant improvement’ in Positive and Negative

Syndrome Scale (PANSS) total and subscale scores, 'response rate' and 'positive results' as well as 'time to discontinuation for any cause' were included as the definition of failure to respond. Thus, 12 studies were included in the final analysis.

Table 1 shows characteristics of the included clinical trials investigating the switching strategy in acute schizophrenia patients with insufficient response to an initial antipsychotic. There are six RCTs and six observational studies, with different purposes and a variety of primary outcome measures. There was not a robust difference in response rate between switching from olanzapine to risperidone and switching from risperidone to olanzapine in observational studies by Takahashi and colleagues^{7,8} and by Suzuki and colleagues,⁹ whereas switching from risperidone to olanzapine showed a higher response rate than switching from olanzapine to risperidone in an observational study by Agid and colleagues.¹⁰

Significant improvement of scores on the total and positive symptom subscale of PANSS in switching from aripiprazole to ziprasidone was not observed in an observational study with a small number of participants by Kim and colleagues¹³ whereas PANSS and Clinical Global Impression Severity scale (CGI-S) scores significantly decreased in switching from a previous antipsychotic to ziprasidone in an observational study by Mencacci and colleagues¹⁵ that was funded by the pharmaceutical company. In an observational study of switching from a previous antipsychotic to paliperidone extended release by Na and colleagues¹⁶ and an open-label RCT of switching from risperidone, olanzapine or aripiprazole to iloperidone by Weiden and colleagues,¹⁷ positive results were reported. Both studies were funded by the pharmaceutical companies.

In emergency and acute-phase practice, watchful waiting for several weeks despite the insufficient effects of an initial antipsychotic is not practical from the perspective primarily of safety management. Remarkably, a recent meta-analysis of 34 studies ($n = 9,460$) revealed that patients not even minimally improved by week 2 of antipsychotic treatment are unlikely to respond later and may benefit from a treatment change.¹⁹ The prediction of subsequent response from early response to an initial antipsychotic at 2 weeks is useful in emergency and acute-phase practice. With respect to the concept of early nonresponse to an initial

antipsychotic, three RCTs were identified. Kinon and colleagues¹² reported that switching from risperidone to olanzapine at week 2 resulted in a small but significantly greater reduction in PANSS total score and in depressive symptoms. However, the significant difference in the PANSS total score at the endpoint mean change at week 12 was reportedly 3.49, which was unexpectedly small. In the first period of our first study on switching strategy, early responders to risperidone ($n = 47$) continued with risperidone therapy, whereas early nonresponders to risperidone were randomized to either continue on risperidone (RIS-RIS, $n = 11$) or switch to olanzapine (RIS-OLZ, $n = 9$) for the next 2 weeks. Unfortunately, the numbers of patients in the RIS-RIS and RIS-OLZ groups were below the numbers required according to power analysis, although no significant differences were identified in efficacy outcomes or safety and tolerability outcomes at 4 weeks. In the second period of the study, early responders to olanzapine ($n = 33$) continued with olanzapine therapy, whereas early nonresponders to olanzapine were randomized to either continue on olanzapine (OLZ-OLZ, $n = 8$) or switch to risperidone (OLZ-RIS, $n = 6$) for the next 2 weeks. Similarly, the numbers of patients in the OLZ-OLZ and OLZ-RIS groups were below the numbers required according to power analysis, although no significant differences were apparent in not only efficacy outcomes, but also safety and tolerability outcomes at 4 weeks.¹⁴ In our second study on switching strategy in comparison with augmentation strategy, the following findings were obtained.¹⁸ Although time to treatment discontinuation for any cause was significantly shorter in early nonresponders to risperidone assigned to augmentation with olanzapine than in early responders to risperidone, it was not significantly shorter in early nonresponders to risperidone assigned to switching to olanzapine than in early responders to risperidone. In contrast, although time to treatment discontinuation for any cause was significantly shorter in early nonresponders to olanzapine assigned to switching to risperidone than in early responders to olanzapine, it was not significantly shorter in early nonresponders to olanzapine assigned to augmentation with risperidone than in early responders to olanzapine. These findings are consistent with the observational study by Agid and colleagues,¹⁰ in which switching from risperidone to olanzapine showed a higher response rate than switching from olanzapine to risperidone. Also, they are consistent with the finding of a double-blind RCT by Kinon

Table 1. Characteristics of the included clinical trials investigating the switching strategy in acute schizophrenia patients with insufficient response to an initial antipsychotic.

Study	Participants (n)	Trial duration (weeks)	Treatment (intervention group; control group)	Study design	Main findings/comments
Takahashi and colleagues ⁷	51, first episode	12	From OLZ to RIS; no control group	Observational	Responder rate (at least 20% decrease in BPRS total score plus final CGI score of 3 or less) was 35.3%
Takahashi and colleagues ⁸	58, first episode	12	From RIS to OLZ; no control group	Observational	Responder rate (at least 20% decrease in BPRS total score plus final CGI score of 3 or less) was 29.3%
Suzuki and colleagues ⁹	78	16	OLZ→QTP→RIS, OLZ→RIS→QTP, QTP→OLZ→RIS, QTP→RIS→OLZ, RIS→OLZ→QTP, or RIS→QTP→OLZ	Open-label RCT	39 [50%] responded to the first agent [OLZ, 16; QTP, 9; RIS, 14], and 14 responded to the second. Only 2 showed response to the third, and 16 failed to respond to all three antipsychotics, with only 7 dropouts. Overall, there were 22 OLZ, 14 QTP and 19 RIS responders
Ganguli and colleagues ¹¹ Pharmaceutical funded	123	6	Switch strategies [common RIS initiation scheme; varying OLZ discontinuation]	Rating-blind RCT	All-cause treatment discontinuation was lowest (12%) in the group with the slowest OLZ dose reduction. After the medication was changed, improvements at endpoint were seen in PANSS total score (-7.3 ; $p < 0.0001$) and in PANSS positive (-3.0 ; $p < 0.0001$), negative (-0.9 ; $p = 0.171$) and anxiety/depression (-1.4 ; $p = 0.0005$) subscale scores
Kinon and colleagues ¹² Pharmaceutical funded	378 ENRs among 628 patients enrolled	12	From RIS to OLZ; staying on RIS	Double-blind RCT (outpatients)	Switching RIS ENRs to OLZ at week 2 resulted in a small but significantly greater reduction in PANSS total score (endpoint; $p = 0.020$) and in depressive symptoms (endpoint; $p = 0.004$)
Kim and colleagues ¹³	19	12	From ARP to ZIP	Observational	Significant improvement of scores on the negative symptom subscale of PANSS, SOFAS, CDSS and BDI were observed
Hatta and colleagues ¹⁴	34 ENRs among 125 patients enrolled	4 weeks	First study period: from RIS to OLZ; staying on RIS Second study period: from OLZ to RIS; staying on OLZ	Rating-blind RCT (inpatients)	Numbers of patients were below the numbers required according to power analysis, although no significant differences were identified
Mencacci and colleagues ¹⁵ Pharmaceutical funded	131	8	From a previous antipsychotic to ZIP	Observational	PANSS and CGI-S scores significantly decreased throughout the study (mean total PANSS score at baseline: 111.2 ± 18.7 ; week 1: 101.5 ± 20.1 ; week 8: 80.8 ± 23.0 ; $p < 0.0001$ for both week 1 and week 8 versus baseline)
Na and colleagues ¹⁶ Pharmaceutical funded	387	24	From a previous antipsychotic to paliperidone extended release	Observational	The severity on the total and most of the SCL-90-R subscales decreased continuously and significantly from baseline to 24 weeks

Table 1. (Continued)

Study	Participants (n)	Trial duration (weeks)	Treatment (intervention group; control group)	Study design	Main findings/comments
Agid and colleagues ¹⁰	60 patients with suboptimal response among 244 first-episode patients enrolled	24	From OLZ to RIS or from RIS to OLZ; each trial was divided into three stages based on increase dose	Observational, from a treatment algorithm	Percentage of response for subjects switched from OLZ to RIS was 4.0% (1/25) <i>versus</i> 25.7% (9/35) for those switched from RIS to OLZ
Weiden and colleagues ¹⁷ Pharmaceutical funded	500	12	From RIS, OLZ or ARP to iloperidone either gradually or immediately	Open-label RCT	Integrated CGI of change results confirmed improved outcomes at week 12, with scores that were similar between the gradual and immediate-switch groups, respectively; for RIS, 2.82 and 2.67 [95% CI -0.229 to 0.511]; OLZ, 2.87 and 3.03 [95% CI -0.548 to 0.235]; and ARP, 2.79 and 2.81 [95% CI -0.405 to 0.368]
Hatta and colleagues ¹⁸	51 ENRs among 120 patients enrolled	12	From RIS to OLZ (RIS-OLZ); add on OLZ (RIS+OLZ) From OLZ to RIS (OLZ-RIS); add on RIS (OLZ+RIS)	Rater-blind RCT (inpatients)	Although time to treatment discontinuation for any cause was significantly shorter in the RIS+OLZ group [54.1 days; 95% CI 41.3–67.0] than in the RIS early responder group [68.7; 61.2–76.2; $p = 0.050$], it was not significantly shorter in the RIS-OLZ group [58.5; 43.1–73.9] than in the RIS early responder group ($p = 0.19$). Although time to treatment discontinuation for any cause was significantly shorter in the OLZ-RIS group [56.1 days; 40.7–71.5] than in the OLZ early responder group [74.9; 68.5–81.3; $p = 0.008$], it was not significantly shorter in the OLZ+RIS group [64.6; 49.6–79.6] than in the OLZ early responder group ($p = 0.20$)

ARP, aripiprazole; BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI, Clinical Global Impression; CI, confidence interval; ENR, early nonresponder; OLZ, olanzapine; PANSS, Positive and Negative Syndrome Scale; QTP, quetiapine; RCT, randomized clinical trial; RIS, risperidone; SCL-90-R, Symptom Checklist-90-Revised version; SOFAS, Social and Occupational Functioning Assessment Scale; ZIP, ziprasidone.

Figure 2. Flowchart of the systematic literature search of augmentation strategy of antipsychotics for an emergency and acute-phase period.

and colleagues,¹² in which switching from risperidone to olanzapine at week 2 resulted in a small but significantly greater reduction in PANSS total score.

The latest evidence on augmentation strategy of antipsychotics for an emergency or acute-phase period

The definition of augmentation is adding an atypical antipsychotic due to insufficient efficacy of an initial antipsychotic. Consequently, a patient receives the combination of two antipsychotics. We conducted a computerized PubMed literature search of articles up to 28 February 2017 using the search words ‘antipsychotic’, ‘schizophrenia’ and ‘augmentation’ along with the filters ‘clinical trial’, ‘observational study’, ‘humans’ and ‘English’. Of the 137 articles identified, 133 were excluded on the basis of title and abstract (Figure 2). Reasons for exclusion were as follows. One hundred and two studies were not associated with augmentation of an antipsychotic to an initial antipsychotic. Twenty-nine studies were not conducted in the acute phase. In such situations, switching to clozapine is recommended with very strong evidence,² rather than antipsychotic polypharmacy. Augmentation of an antipsychotic to clozapine is a controversial issue not in the acute phase. One study was about

side effects. One article was neither a trial nor an observational study. One study was not associated with pharmacotherapy. Thus, four full-text articles were assessed for eligibility, and one article was excluded due to nonacute phase. As one article was included after a hand search, four studies were included in the final analysis.

Table 2 shows the characteristics of the included clinical trials investigating the augmentation strategy in acute schizophrenia patients who had an insufficient response to an initial antipsychotic. There are two RCTs and two observational studies. In observational studies of olanzapine augmented with amisulpiride,²⁰ and risperidone,²¹ the response rates (>20% reduction in Brief Psychiatric Rating Scale Score) were 75.51% and 63.26%, respectively. These rates are considerably higher than the response rates of switching strategies such as from olanzapine to risperidone (35.3%) and from risperidone to olanzapine (29.3%), as mentioned above.^{7,8}

In the first RCT of augmentation strategy in emergency and acute-phase practice, although time to treatment discontinuation for any cause was significantly shorter in early nonresponders to risperidone assigned to increased risperidone dose than in early responders to risperidone, there

Table 2. Characteristics of the included clinical trials investigating the augmentation strategy in acute schizophrenia patients with insufficient response to an initial antipsychotic.

Study	Participants (n)	Trial duration (week)	Treatment (intervention group; control group)	Study design	Main findings/comments
Molina and colleagues ²⁰	49	3 months	OLZ augmented with amisulpride	Observational	Significant improvement in mental status as measured by the BPRS, CGI and UKU scales. The response rate (>20% reduction in BPRS score) was 75.51%
Hatta and colleagues ²²	26 ENRs to RIS among 78 patients enrolled	10	Augmentation with OLZ (RIS+OLZ group); increased RIS dose (RIS+RIS group)	Rater-blind RCT (inpatients)	Although time to treatment discontinuation for any cause was significantly shorter in the RIS+RIS group (6.8 weeks; 95% CI 5.2–8.4) than in early responders to RIS (8.6 weeks; 7.9–9.3; $p = 0.018$), there was no significant difference between the RIS+OLZ group (7.9 weeks; 6.3–9.5) and early responders to risperidone
Hatta and colleagues ¹⁸	51 ENRs among 120 patients enrolled	12	From RIS to OLZ (RIS-OLZ); add on OLZ (RIS+OLZ) From OLZ to RIS (OLZ-RIS); add on RIS (OLZ+RIS)	Rater-blind RCT (inpatients)	Although time to treatment discontinuation for any cause was significantly shorter in the RIS+OLZ group (54.1 days; 95% CI 41.3–67.0) than in the RIS-early responder group (68.7; 61.2–76.2; $p = 0.050$), it was not significantly shorter in the RIS-OLZ group (58.5; 43.1–73.9) than in the RIS early responder group ($p = 0.19$) Although time to treatment discontinuation for any cause was significantly shorter in the OLZ-RIS group (56.1 days; 40.7–71.5) than in the OLZ early responder group (74.9; 68.5–81.3; $p = 0.008$), it was not significantly shorter in the OLZ+RIS group (64.6; 49.6–79.6) than in the OLZ early responder group ($p = 0.20$)
Toledo-Romero and colleagues ²¹	49	3 months	RIS augmented with amisulpride	Observational	Significant improvement in mental status as measured by the BPRS, CGI and UKU scales. The response rate (>20% reduction in BPRS score) was 63.26%

BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; CI, confidence interval; ENR, early nonresponder; OLZ, olanzapine; RCT, randomized clinical trial; RIS, risperidone; UKU, Udvalg for Kliniske Undersøgelser side effects rating scale.

was no significant difference between early nonresponders to risperidone assigned to augmentation with olanzapine and early responders to risperidone.²² However, a major limitation of this study was the lack of a switching arm for the olanzapine monotherapy; that is, it was difficult to distinguish the add-on effects of olanzapine from the switching effects of olanzapine. In our second study on augmentation strategy in comparison with switching strategy, the findings were obtained as mentioned in the switching strategy section.¹⁸ It is possible that switching to olanzapine among early nonresponders to risperidone might have a small advantage over augmentation with olanzapine, while augmentation with risperidone might have a small advantage over switching to risperidone among early nonresponders to olanzapine.

Role of the evidence on switching and augmentation strategies in the management of acute-phase schizophrenia

For risperidone and olanzapine, there is some evidence on switching and augmentation strategies in the management of acute-phase schizophrenia, as mentioned above. There may be responders to olanzapine alone among early nonresponders to risperidone, whereas there may be few responders to risperidone alone among early nonresponders to olanzapine. Furthermore, the rates of at least 40% improvement in PANSS total in early nonresponders to risperidone assigned to augmentation with olanzapine and those assigned to switching to olanzapine were 29% and 8%, respectively. The rates of at least 40% improvement in PANSS total in early nonresponders to olanzapine assigned to augmentation with risperidone and those assigned to switching to risperidone were 50% and 25%, respectively, in our study.¹⁸ Thus, adding a second antipsychotic for a while in early nonresponders to an initial antipsychotic might be allowed in acute-phase practice. However, there is still insufficient evidence at this time for application of these findings to routine clinical practice. For other antipsychotics, there is little evidence for their augmentation in acute-phase practice.

When augmentation with another antipsychotic is inevitable in acute-phase patients, it is important that the potential demerits of polypharmacy, especially the long-term side effects such as weight gain, glucose intolerance, hyperlipidaemia, extrapyramidal side effects, prolactin increase, QTc prolongation and sedation, should be taken into account. Since the available trials

that have been reported only include very short follow-up periods, these trials failed to sufficiently detect the potential side effects. It goes without saying that when starting pharmacotherapy, even in acute-phase patients, we need to carefully consider prognoses and the possible long-term side effects. In addition, during emergency situations, the first-step of establishing a good relationship between patients and clinicians also needs to be deeply engraved in our mind.

Dosing strategies

Van Putten and colleagues²³ reported that among 80 newly admitted or readmitted schizophrenia patients assigned to receive either 5, 10 or 20 mg/day of haloperidol for 4 weeks, the 20 mg dose appeared to be superior to both the 5 mg and 10 mg doses for the first 2 weeks of treatment in efficacy, but that by the second week of treatment, many more patients in the group receiving the 20 mg dose had side effects and insisted on leaving the hospital against medical advice than those given 5 mg or 10 mg/day of haloperidol. Thus, high-dose antipsychotics such as a 20 mg/day dose of haloperidol, the equivalent dose of 12 mg/day risperidone,²⁴ may have substantial neuropsychotoxic effects by the second week of treatment. Zimbroff and colleagues²⁵ reported that 12, 20 and 24 mg/day of sertindole were significantly more effective in the treatment of psychosis than placebo, but only 20 mg/day of sertindole was significantly more effective in the treatment of negative symptoms than placebo, suggesting the disadvantage of high-dose antipsychotics. Also, the efficacy of high-dose risperidone was not observed in early nonresponders to 6 mg/day, the upper limit of the ordinary dose.²² Sajatovic and colleagues²⁶ reported that a real-world analysis of 1114 bipolar patients indicated that 40 or 80 mg/day were the most common starting doses of lurasidone and 55.2 mg/day was the mean maintenance dose, and that higher doses of lurasidone were prescribed to patients with comorbidities or prior antipsychotic use. Thus, an increase in a dosage within the ordinary range may be necessary unless efficacy is not shown, but trying high doses above the ordinary range is not recommended before switching from an antipsychotic to another one.

How to switch antipsychotics in acute phase of schizophrenia in routine practice

Practical pharmacotherapy for acute schizophrenia patients should be discussed based not only

on RCTs but also on data from real clinical practice, such as observational studies without support from pharmaceutical companies. However, it should not be overlooked that data from clinical practice can be heavily influenced by both the physicians' educational as well as cultural backgrounds. This is in contrast to data from RCTs, which can minimize such bias. Thus, to balance evidence with practical reality, there should be an emphasis not only on double-blind RCTs but also on rater-blind RCTs and high-quality observational studies. From such a practical point of view, we propose how to switch antipsychotics in the acute phase of schizophrenia in routine practice:

1. An initial antipsychotic with high efficacy and low side effects should be chosen considering recent high-quality evidence.⁶ A point may be vulnerability for each patient, such as weight gain, extrapyramidal symptoms, prolactin increase, QT prolongation and sedation. In a psychiatric emergency, as patients are frequently brought in with no previous medical information, close monitoring of such side effects is important.
2. When the initial antipsychotic with an initial dose is not effective, the dose should be gradually increased to the upper limit of the licensed dose if it is tolerable.
3. Antipsychotic switching can be considered according to the treatment response at 2 weeks after the initial antipsychotic starts.¹⁹ Based on a small number of RCTs without support from pharmaceutical companies, switching from risperidone to olanzapine can be successful, but reverse switching cannot. For switching from an antipsychotic to ziprasidone, paliperidone or iloperidone, there is only evidence based on a small number of observational studies with support from pharmaceutical companies, so nothing is conclusive. There is no evidence about other antipsychotic switching in an acute phase.
4. For pace of antipsychotic switching, a meta-analysis demonstrated no significant differences in any clinical outcomes, including study discontinuation, psychopathology, extrapyramidal symptoms and treatment-emergent adverse events, between wait discontinuation (i.e. introducing the new antipsychotic while maintaining the first for a period before initiating

its discontinuation) and nonwait discontinuation (i.e. initiating the first antipsychotic's discontinuation when introducing the new antipsychotic), suggesting either strategy can be used in clinical practice.²⁷

5. In the process of antipsychotic switching, transient polypharmacy is inevitable, as mentioned above. When the mental condition after the completion of antipsychotic switching becomes worse than that during transient polypharmacy, returning to the state of transient polypharmacy is a choice if it is tolerable. After such a patient stabilizes, the secondary antipsychotic should be discontinued. Evidence shows that most individuals with schizophrenia or schizoaffective disorder currently receiving antipsychotic polypharmacy could be safely transitioned to antipsychotic monotherapy with no clinical deterioration, but that a minority of individuals benefit from antipsychotic polypharmacy.²⁸

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Conflict of interest statement

Dr Hatta has received lecture honoraria from Eisai, Eli Lilly, GlaxoSmithKlein, Janssen, Meiji Seika, MSD, Otsuka, Takeda, and Tanabe-Mitsubishi within the last 3 years. Dr Sugiyama has received lecture honoraria from Eli Lilly, Janssen, Meiji Seika, Otsuka, and Pfizer within the last 3 years. Dr Ito declares no potential conflict of interest.

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