Switching strategies for antipsychotic monotherapy in schizophrenia: a multi-center cohort study of aripiprazole

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Conflict of Interests

Acknowledgements

Running title: Switching to aripiprazole for schizophrenia

Abstract

Rationale

Changing antipsychotics of patients with chronic schizophrenia involves several risks. Switching to aripiprazole is especially difficult. We investigated switching methods and related factors for successful switching patients with chronic schizophrenia to aripiprazole.

Objectives

This study was a multicenter historical cohort study and approved by the research ethics committee of Okayama University Hospital and Okayama Psychiatric Medical Center. We compared survival proportions of 178 chronic schizophrenia patients who continued aripiprazole monotherapy for six months after non-direct switching (add-on switching (n=45), cross switching (n=62)), or direct switching (n=71). We adjusted possible confounders using a Cox proportional hazards model.

Results

Of patients with chronic schizophrenia, 56.7% (101/178) were switched to aripiprazole monotherapy, and 55.0% (98/178) showed improvement in symptoms as demonstrated by the Clinical Global Impression Severity score. Kaplan-Meier survival curves showed that non-direct switching had a higher survival proportion than direct

switching (log-rank test, p=0.012). Even after adjusting for several variables using a Cox proportional hazards model, add-on switching had a significantly lower hazard at 6 months than direct switching (hazard ratio: 0.42, 95% confidence interval: 0.21–0.82, P=0.01). In cases of switching to aripiprazole for psychiatric symptoms, non-direct switching had a lower hazard than direct switching (hazard ratio: 0.41, 95% confidence interval: 0.21–0.81, P=0.01), but was not significant for adverse reaction. When aripiprazole was switched from olanzapine, add-on switch showed the lowest hazard ratio for continuation (hazard ratio: 0.29, 95% confidence interval: 0.07–1.11, P=0.07).

Conclusions

Flexibility in strategies when switching to aripiprazole may induce a better outcome for patients with chronic schizophrenia.

Introduction

Schizophrenia is one of the most severe psychiatric disorders, with a lifetime prevalence of about 1% of the population in all cultures (Mueser and McGurk 2004). Though schizophrenia has a low prevalence, the burden of the disease is substantial (Charlson et al. 2018). The onset of schizophrenia is early, and the prevalence of a refractory clinical course is relatively high (McGrath et al. 2008). The quality of life of patients with schizophrenia is decreased, and their families may be devastated (Caqueo-Urízar et al. 2009). The mortality risk among patients with schizophrenia is about 5% (Hor and Taylor 2010) and has increased recently (Oakley et al. 2018).

The main treatment for schizophrenia is a combination of antipsychotic medication, counselling, psychosocial treatments, and self-help groups for social rehabilitation (Owen et al. 2016). Except for clozapine, antipsychotics have similar efficacies against psychotic symptoms, but the frequency of side effects is different (Leucht et al. 2013). A number of studies have suggested that patients with chronic schizophrenia are not as responsive to antipsychotics as drug-naive first-episode patients (Robinson et al. 2005; Haddad and Correll 2018). Leucht et al. (2009) reported that second-generation antipsychotics are more effective than placebo, and the effect size for overall symptoms is moderate (-0.51), but the response rate is not very high and only 41% of patients with schizophrenia respond to antipsychotics compared with the

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24% that respond to placebo. When patients with chronic schizophrenia need to switch antipsychotics, changing treatments is more complicated because the pharmacological profiles of frequently used second-generation antipsychotics are substantially different despite their similarities (Cerovecki et al. 2013).

Aripiprazole is a dopamine D2 receptor partial agonist, 5-hydroxytryptamine 2A (5-HT2A) receptor antagonist, and 5-HT1A receptor partial agonist (Lawler et al. 1999; Burris et al. 2002; Jordan et al. 2002). Aripiprazole has the same efficacy as risperidone (Potkin et al. 2003) or olanzapine (McQuade et al. 2004) and several advantages compared with the other second-generation antipsychotics, such as low risk of weight gain, QT prolongation, or extra-pyramidal side effects (Potkin et al. 2003; McQuade et al. 2004; Robinson et al. 2005; Newcomer 2007; Leucht et al. 2013). Aripiprazole is one of the most frequently administered antipsychotics in patients with schizophrenia in Japan, and we have good experience in switching from previous antipsychotics to aripiprazole in clinical settings. Switching patients with chronic schizophrenia to aripiprazole is especially difficult when they have been administered high dosages of antipsychotic drugs for long periods and are supposed to have acquired dopamine supersensitivity (Takase et al. 2015). Though there are several studies on the strategies of switching previous antipsychotics to aripiprazole, the reported protocols

were different and the results were not consistent (Casey et al. 2003; Takeuchi et al. 2008; Pae et al. 2009; Ryckmans et al. 2009; Hwang et al. 2015). In this study, we tried to assess three methods of switching and to elucidate the factors that make switching from previous antipsychotics to aripiprazole successful in patients with chronic schizophrenia in real clinical practice.

Materials and methods

Subjects

This study was a multicenter historical cohort study. Patients with chronic schizophrenia who had been switched from other antipsychotics to aripiprazole monotherapy were included. Patients with first-episode schizophrenia, patients who had discontinued previous antipsychotics, and patients taking a combination of aripiprazole and other antipsychotics, mood stabilizers, or antidepressants at six months after starting aripiprazole were excluded.

The subjects included 527 patients with schizophrenia, 100 patients at Okayama University Hospital and 427 patients at Okayama Psychiatric Medical Center. Of these, 74 patients with first-episode schizophrenia, 17 patients with a history of discontinuation of previous antipsychotics, and 258 patients taking combination

therapies were excluded. Finally, 45 of 178 patients with chronic schizophrenia were switched to aripiprazole monotherapy by add-on switching, 62 patients by cross switching, and 71 patients by direct switching.

A flow chart of the selection of subjects is shown in Figure 1.

We compared the following three methods. (1) Add-on switching: aripiprazole was added to the previous antipsychotic regimen. Previously administered antipsychotics were not changed for at least one week. Then previous antipsychotics were tapered off, and only aripiprazole was administered within 6 months. (2) Cross switching: tapering off previous antipsychotics was started at the same time as starting aripiprazole, and only aripiprazole was administered within 6 months. (3) Direct switching: previous antipsychotics were completely stopped at the time of starting aripiprazole monotherapy. (4) When add-on switching and cross switching were combined, it was defined as non-direct switching. The starting, maximum, and target doses (the final 6 months or end of aripiprazole treatment doses) of aripiprazole administered were flexible according to the clinical symptoms of the patient.

This study was approved by the research ethics committee of Okayama University Hospital and Okayama Psychiatric Medical Center. The clinical records of patients with schizophrenia administered aripiprazole at Okayama University Hospital

between January 2009 and December 2010 and Okayama Psychiatric Medical Center from April 2005 and March 2010 were investigated. We carefully protected patient personal information in reports about this research on our homepage. The diagnosis was based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision criteria for schizophrenia.

Assessment

To assess clinical outcomes of patients with schizophrenia, we investigated survival proportions of aripiprazole at 6 months, adverse reactions, and the severity of illness according to the Clinical Global Impression Severity scale (1 point: normal, not at all ill to 7 points: the most extremely ill) (Busner and Targum 2007) at the time of starting to administer aripiprazole and six months later. To assess social outcomes in patients with schizophrenia, we investigated their social adjustment. "Social adjustment" was defined as functioning as a member of society, including employees, housewives, and students, and "Social maladjustment" was defined as being inpatients and unemployed except for housewives and students (Sakamoto et al. 2016). Each physician in charge and senior trained psychiatrists assessed all clinical records. The assessments were made independently, and the two scores were averaged. The two raters were blind

to each other's assessments.

Statistical analysis

We compared the survival proportions of aripiprazole at 6 months of non-direct (add-on and cross) and direct switching. The cumulative proportion of survival (aripiprazole continuation) was estimated by the Kaplan-Meier method. The log-rank test was used for univariate comparisons. Survival time was calculated from the discontinuation of aripiprazole for any cause or maximum survival time at the end of the study observation period (180 days). We had no cases lost to follow-up. In addition, we adjusted the following possible confounders using a Cox proportional hazards model (age, sex, outpatient or inpatient, prior treatment duration, chlorpromazine-equivalent dose (Inada and Inagaki 2015) of previous antipsychotics, starting dose of aripiprazole, the Clinical Global Impression Severity score at the time of starting to switch to aripiprazole, the difference between medical institutions (Okayama Psychiatric Medical Center and Okayama University Hospital), and previous antipsychotics prior to switching to aripiprazole). We conducted adjusted analyses in stratifications by the risk of treatment discontinuation due to exacerbation of psychiatric symptoms, unchanging symptoms, or side effects, among the three switching strategies. We conducted adjusted

analyses in stratifications by reasons for the switch (psychiatric symptoms, adverse reaction, or both). All statistical analyses were conducted by using STATA 14SE for Windows (Stata Corp., College Station, TX, USA).

Results

Clinical status at 6 months after switching to aripiprazole

Backgrounds of the subjects included in the analyses are shown in Table 1. The average duration of treatment was about 8.15 years. The starting dose of aripiprazole was 10.1/9.0 (mean/median) mg/day (distribution: 1 mg (1), 3 mg (35), 4.5 mg (1), 6 mg (48), 9 mg (5), 12 mg (58), 15 mg (1), 18 mg (14), 24 mg (11), 30 mg (4)). The target dose of aripiprazole was 16.6/18.0 (mean/ median) mg/day (distribution: 3 mg (13), 4.5 mg (1), 6 mg (25), 9 mg (7), 12 mg (33), 15 mg (1), 18 mg (33), 20 mg (1), 21 mg (2), 24 mg (39), 27 mg (1), 28 mg (1), 30 mg (20), 36 mg (1)). Duration until the achievement of aripiprazole monotherapy was 63.4/55.0 (mean/ median) days in add-on switching and 35.8/28.0 (mean/ median) days in cross switching. More than half (56.7%; 101/178) of patients with schizophrenia were able to switch to aripiprazole monotherapy from other previous antipsychotics, and 55.0% (98/178) of patients with schizophrenia showed an improved Clinical Global Impression Severity score. Most

(84.2%; 85/101) patients with schizophrenia who were successful in switching to aripiprazole were sociable at six months after switching to aripiprazole. In contrast, 14.6% (26/178); 12.7% (9/71) in direct switching, and 15.6% (7/45) in add-on switching, 16.1% (10/62) in cross switching patients experienced exacerbation of psychiatric symptoms, and administration of aripiprazole was stopped at 70.7/63.0 (mean/ median) days. Administration of aripiprazole was stopped to 28.7% (51/178); 40.8% (29/71) in direct switching, 13.3% (6/45) in add-on switching, and 25.8% (16/62) in cross switching of patients because of unchanging symptoms at 34.2/21.0 (mean/ median) days. About one-fifth, 21.3% (38/178), of patients experienced side effects, and 12.4% (22/178); 11.3% (8/71) in direct switching, 13.3% (6/45) in add-on switching, 12.9% (8/62) in cross switching of patients stopped taking aripiprazole at 35.1/21.5 (mean/ median) days because of side effects, e.g., extra-pyramidal side effects (9), insomnia (5), gastrointestinal symptoms (3), over-sedation (2), headache (2), or elevated liver enzymes (1).

Differences in survival proportions of switching strategies after switching to aripiprazole monotherapy at 6 months

Non-direct switching (63.6%; 68/107), which included add-on switching

(71.1%; 32/45) and cross switching (58.1%; 36/62)), had higher survival proportions of aripiprazole monotherapy at 6 months than direct switching (46.4%; 33/71) (Table 1). Kaplan-Meier survival curves showed that non-direct switching had a higher survival proportion than direct switching (log-rank test, p=0.012). Figure 2 shows Kaplan-Meier survival curves of add-on, cross, or direct switching. In direct switching, administration of aripiprazole was stopped at 38.7/21.0 (mean/ median) days: 64.4/49.0 (mean/ median) days by exacerbation of psychiatric symptoms, 30.8/14.0 (mean/ median) days by unchanging symptoms, 39.5/22.0 (mean/ median) days due to side effects. In add-on switching, administration of aripiprazole was stopped at 59.6/60.0 (mean/ median) days; 69.7/73.0 (mean/ median) days for exacerbation of psychiatric symptoms, 48.0/49.0 (mean/ median) days by unchanging symptoms, 40.2/49.0 (mean/ median) days by side effects. In cross switching, administration of aripiprazole was stopped at 51.5/54.5 (mean/ median) days; 77.0/73.5 (mean/ median) days for exacerbation of psychiatric symptoms, 35.5/28.5 (mean/ median) days for unchanging symptoms, 26.9/19.5 (mean/ median) days for side effects.

Even after adjusting several variables, add-on switching still showed a significantly low HR for continuation (HR 0.42; 95% CI: 0.21–0.82, P=0.01) (Table 2). On the other hand, those who underwent cross switching showed a marginally low HR

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estimate (HR 0.59; 95% CI: 0.35–1.00, P=0.13) (Table 2). In the additional analysis of the treatment discontinuation for each reason, add-on switching showed a significantly low HR for continuation (HR 0.27; 95% CI: 0.11–0.66, P=0.004) and cross switching showed a marginally low HR estimate (HR 0.57; 95% CI: 0.31–1.07, P=0.081) in patients who stopped administration of aripiprazole because of unchanging symptoms. On the other hand, there was no statistical significance between three switching strategies of the patients who stopped administration of aripiprazole due to exacerbation of psychiatric symptoms (add-on switching; HR 0.81; 95% CI: 0.30–2.18, P=0.68 and cross switching; HR 0.99; 95% CI: 0.40–2.44, P=0.99) and side effects (add-on switching; HR 0.89; 95% CI: 0.30–2.65, P=0.84 and cross switching; HR 1.06; 95% CI: 0.38–2.91, P=0.92).

Effect on survival proportions after switching to aripiprazole by reason for the switch

We stratified patients by reasons for the switch (psychiatric symptoms, adverse reaction, or both) (Table 3). When switching to aripiprazole because of psychiatric symptoms, non-direct switching (57.4%; 27/47) (add-on switching and cross switching) had higher proportion of continuation of aripiprazole monotherapy at 6 months than direct switching (40.9%: 17/43). After adjusting several variables, it was still

statistically significant (HR 0.41, 95% CI: 0.21–0.81, P=0.01). On the other hand, when switching to aripiprazole because of adverse reaction, non-direct switching (67.6%: 25/37) had a higher survival proportion of continuation of aripiprazole monotherapy than direct switching (46.2%: 6/13) at 6 months, although there was no statistical significance after adjusting several variables (HR 0.53, 95% CI: 0.16–1.74, P=0.29).

Comparison of previous antipsychotics prior to switching

Previous antipsychotics prior to switching to aripiprazole were monotherapy with risperidone (n=72), olanzapine (n=51), perospirone (n=14), quetiapine (n=12), blonanserin (n=3), typical antipsychotics (n=14), or combination therapy (n=12). When aripiprazole was switched from olanzapine, add-on switching showed a lower point estimates of HR for continuation (HR 0.29, 95% CI: 0.07–1.11, P=0.07) compared to switching from risperidone (HR 0.35, 95% CI: 0.11–1.12, P=0.08), although neither HR estimate was statistically significant (Table 4).

Discussion

Switching from previous anti-psychotics to aripiprazole monotherapy was effective and safe in patients with chronic schizophrenia. We also demonstrated for the

first time that switching strategies and the reason for switching were related to the survival proportions in real clinical practice. Non-direct switching and especially add-on switching have higher survival proportions of aripiprazole monotherapy at 6 months than direct switching. In addition, when aripiprazole replaced olanzapine, add-on switch has the better chance to induce the continuation of aripiprazole.

The mean elimination half-life of aripiprazole is about 75 hours after oral administration, and that of dehydroaripiprazole, its active metabolite (U.S. Food and Drug Administration), is 9 hours. Because steady-state concentrations are known to be related to the mean elimination half-life, steady-state concentrations of aripiprazole are attained within 14 days of initiation (Koue et al. 2007). This is longer than with other antipsychotics, e.g., risperidone is four hours and olanzapine is about 30 hours (U.S. Food and Drug Administration). An early response to risperidone or olanzapine at two weeks is reported to be a clinical marker of subsequent response at 12 weeks in the treatment of schizophrenia (Kinon et al. 2010). On the other hand, aripiprazole needs one more week, and the advantage of using three weeks data is that it is reported to predict the response to aripiprazole at six weeks in first-episode psychosis (Park et al. 2014). In this study, administration of aripiprazole was stopped in about 30% of patients because of unchanging symptoms or side effects at about 35 days on average, which

may be not enough.

Aripiprazole has 25% to 30% intrinsic activity (Burris et al. 2002; Kegeles et al. 2008). It is effective for treatment of both positive and negative symptoms of schizophrenia without extra-pyramidal side effects, even at more than 90% dopamine D2 receptor occupancy in the striatum (Yokoi et al. 2002; Hamamura and Harada 2007). When patients with schizophrenia are administered mean doses of 20+/-8 mg/day aripiprazole, serum levels of aripiprazole are 214+/-140 ng/ml (Kirschbaum et al. 2008). Because dopamine D2/D3 receptor occupancy in the putamen and the inferior temporal cortex is almost 85% when the serum concentration of aripiprazole is 228 ng/ml (Gründer et al. 2008), a high dose of aripiprazole and high rate of dopamine D2 receptor occupancy may be necessary in clinical conditions. In this study, the starting dose (about 10 mg/day on average) and target dose (about 16 mg/day on average) of aripiprazole were relatively low. If we reduce the dose of previous antipsychotics when concentrations of aripiprazole are not adequate, the symptoms of patients with chronic schizophrenia may become worse.

The receptor-binding profile of aripiprazole shows a lower affinity for muscarinic M1, histamine H1, and adrenergic α1 receptors than the other antipsychotics (Lawler et al. 1999; Burris et al. 2002; Jordan et al. 2002). Cholinergic withdrawal

symptoms induce nausea, diarrhea, abdominal pain, headache, irritation, anxiety, insomnia, and other psychiatric symptoms, and withdrawal of clozapine, which has a high affinity to muscarinic M1 receptors, is reported to induce cholinergic rebound and rapid onset psychosis (Shiovitz et al. 1996). Olanzapine also has higher affinity to muscarinic M1 receptors than risperidone and aripiprazole (Shahid et al. 2009). Due to changing receptor affinities, switching or discontinuing antipsychotics induces withdrawal and rebound syndromes (Cerovecki et al. 2013). Direct switching is generally considered to be disadvantageous (Cerovecki et al. 2013). Thus, the receptor binding profile of aripiprazole may affect the difference between direct and non-direct switching.

There are five previous studies of aripiprazole switching strategies. The methods of these studies are summarized and compared to our method in Supplemental Figure 1. Pae et al. (2009) compared direct switching and cross switching, and showed that cross switching had a better tendency than direct switching. This result is similar to ours. The other studies showed no difference between the switching strategies. A meta-analysis including the studies of Pae et al. (2009) and Casey et al. (2003) shows that there was no difference in the switching strategies between abrupt and gradual discontinuation of antipsychotics (Takeuchi et al. 2017). One reason is that the methods

were different. The study of Casey et al. (2003) is more similar to our study, and their results did not differ between these strategies. The difference from our study is that the doses of previous antipsychotics were reduced in the case of add-on switching. Takeuchi et al. (2008) and Hwang et al. (2015) did not investigate direct switching. Rickman et al. (2009) did not investigate direct switching, and the previous antipsychotics were limited to risperidone. The other reason is that previous studies did not indicate the reason for switching.

Add-on switching is reported to have several disadvantages. When multidrug combination therapy is performed, the additive pharmacological effect may cause unexpected side effects or may controvert the original pharmacological effect (Kishimoto et al. 2013). The antipsychotic polypharmacy rate in Japan is reported to be rather high (Ito et al. 1999). Immediate discontinuation may be advantageous for simplicity because cross-titration of antipsychotics tends to constitute antipsychotic polypharmacy (Takeuchi et al. 2017). Though the rates of side effects in the three strategies were same in this study, when we switch the previous antipsychotics to aripiprazole because of side effects, we should select direct switching.

There are several limitations to be noted in this study. First, the sample size was not large enough to achieve significant results for comparison of cross switching with

direct switching. However, the sample size is relatively large compared with other previous studies, and we showed potentially better outcomes with the non-direct method and also add-on switching. Second, we excluded cases of combinations of antipsychotics, although the rate of combination therapy is high. Thus, our results may not reflect the tendency of all actual cases, and some caution in generalization is appropriate. Third, the rate of sociable patients at six months after switching to aripiprazole may be very high because the rate of outpatients included in this study is high (about 70%). Lastly, this study is a historical cohort study in a solely observational setting (real clinical practice). As a future study, we need to confirm the results with prospective/interventional research using a large sample.

When switching from other psychotics, aripiprazole monotherapy is relatively effective and safe in patients with schizophrenia. Non-direct switching, especially add-on switching to aripiprazole, induced higher survival rates than direct switching, especially when the previous antipsychotics were changed to aripiprazole due to their insufficient effect. Flexibility in switching to aripiprazole may produce a better clinical outcome for patients with chronic schizophrenia.

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Figure and table legends

Figure 1: Selection of subjects

A total of 527 patients with schizophrenia, 100 patients at Okayama University Hospital and 427 patients at Okayama Psychiatric Medical Center, were included. Of these, 74 patients with first-episode schizophrenia, 17 patients with discontinuation of previous antipsychotics, and 258 patients with combination therapy were excluded. Finally, of 178 patients with chronic schizophrenia, aripiprazole monotherapy was administered to 45 patients by add-on switching, 62 patients by cross switching, and 71 patients by direct switching.

Figure 2: Kaplan-Meier survival curves of aripiprazole monotherapy at 6 months

Cumulative proportion of survival (continuation of aripiprazole) between add-on, cross, or direct switching was calculated by the Kaplan-Meier method.

Treatment discontinuation in direct switching at 38.7/21.0 (mean/ median) days; 64.4/49.0 (mean/ median) days due to exacerbation of psychiatric symptoms, 30.8/14.0 (mean/ median) days due to unchanging symptoms, 39.5/22.0 (mean/ median) days due to side effects. Treatment discontinuation in add-on switching at 59.6/60.0 (mean/ median) days; 69.7/73.0 (mean/ median) days for exacerbation of psychiatric

symptoms, 48.0/49.0 (mean/ median) days for unchanging symptoms, 40.2/49.0 (mean/ median) days for side effects. Treatment discontinuation in cross switching at 51.5/54.5 (mean/ median) days; 77.0/73.5 (mean/ median) days for exacerbation of psychiatric symptoms, 35.5/28.5 (mean/ median) days for unchanging symptoms, 26.9/19.5 (mean/ median) days for side effects.

Supplemental Figure 1: Schematic diagram of this and previous studies

There were five previous studies of switching strategies of aripiprazole. The methods of these are summarized and compared to our method. Our study (upper left), Pae et al. 2009 (upper middle), Casey et al., 2003 (upper right), Takeuchi et al., 2008 (lower left), Hwang et al., 2015 (lower middle), and Ryckmans et al., 2009 (lower right).

Table 1: Background of subjects and clinical outcome at 6 months after switching to aripiprazole monotherapy

To assess clinical outcomes in patients with schizophrenia, we investigated proportions continuing aripiprazole at 6 months, adverse reactions, and the severity of illness according to the Clinical Global Impression Severity scale (1 point: normal, not

at all ill to 7 points: the most extremely ill) (Busner and Targum, 2007) at the time of starting aripiprazole and 6 months later. To assess social outcomes in patients with schizophrenia, we investigated their social adjustment (Sakamoto et al., 2016).

Table 2: Cox proportional hazards model of survival of aripiprazole monotherapy on three strategies

We compared three switching strategies (add-on, cross, and direct switching). In addition to the crude model, we adjusted the results by the possible confounders using a Cox proportional hazards model. All statistical analyses were conducted by using STATA 14SE for Windows (Stata Corp.).

Table 3: Effects on survival of aripiprazole monotherapy by reason for switching

Reasons for switching from other previous antipsychotics to aripiprazole were classified into the following three groups: (1) psychiatric symptoms, (2) occurrence of adverse reaction, or (3) both. We repeated analyses adjusted by the possible confounders using the Cox proportional hazards model. All statistical analyses were conducted by using STATA 14SE for Windows (Stata Corp.).

Table 4: Comparison of previous antipsychotics prior to switching to aripiprazole

Prior antipsychotics, risperidone (A) or olanzapine (B), were switched to aripiprazole monotherapy. We adjusted by the possible confounders using a Cox proportional hazards model. All statistical analyses were conducted by using STATA 14SE for Windows (Stata Corp.).

Figure 1: Selection of subjects
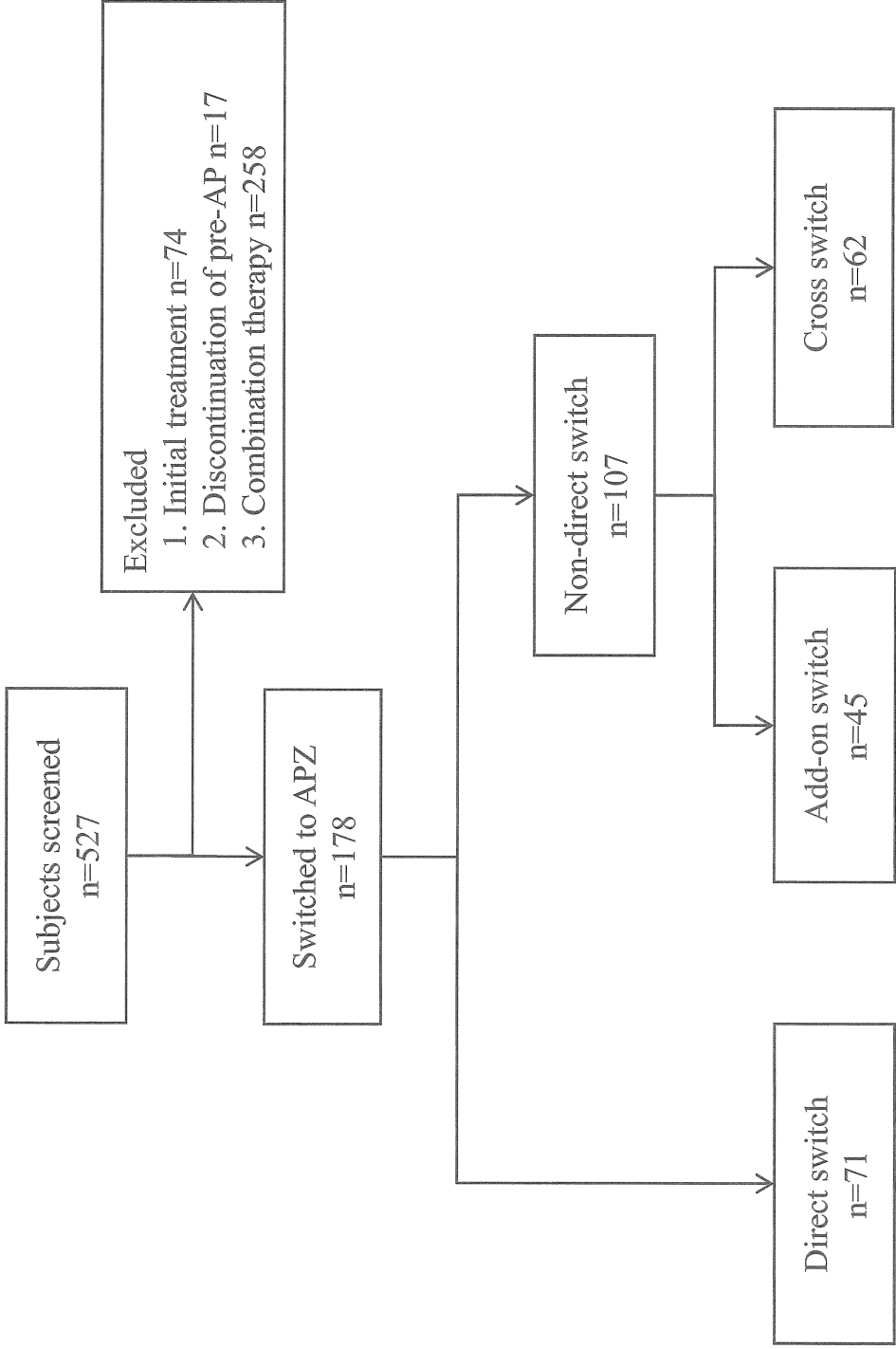
APZ: aripiprazole; Pre-AP: previous antipsychotics, Combination therapy: Patients with combination of APZ with the other antipsychotics, mood stabilizers, or antidepressants at 6 months after starting APZ

Figure 2: Kaplan-Meier survival curves of aripiprazole monotherapy at six months

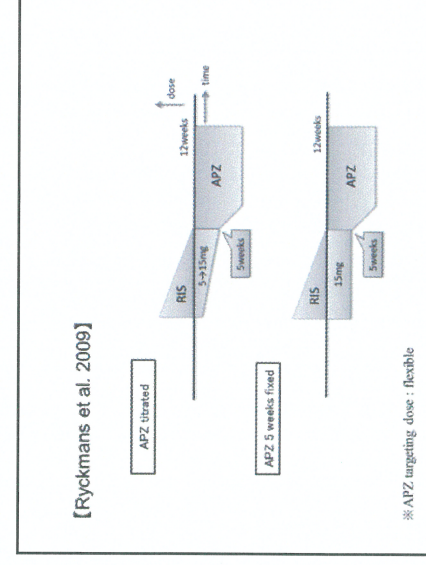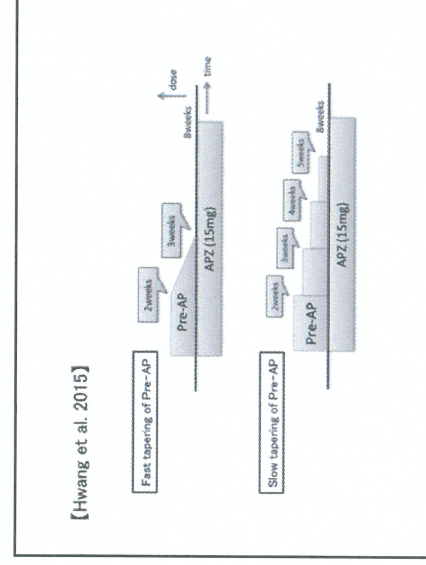# Supplemental Figure 1: Schematic diagram of this and previous studies
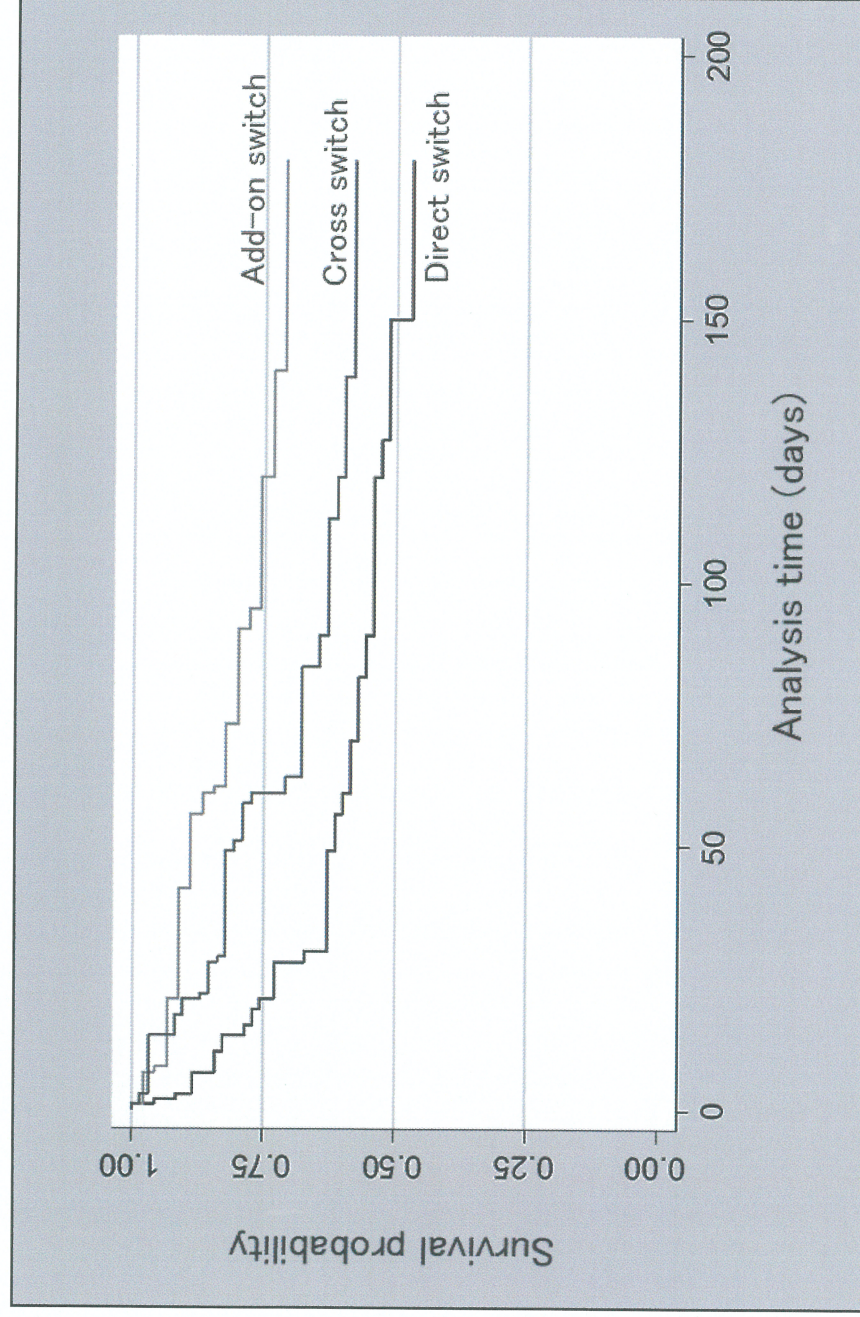
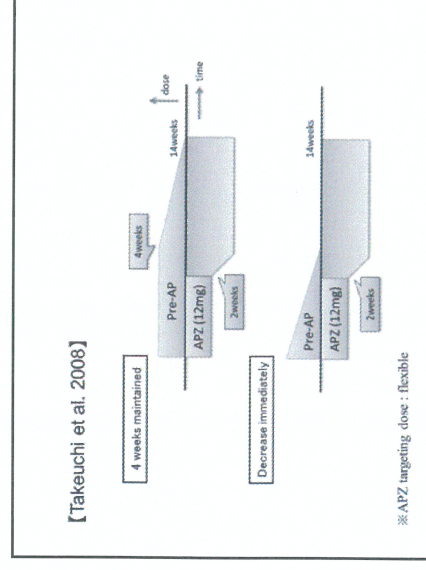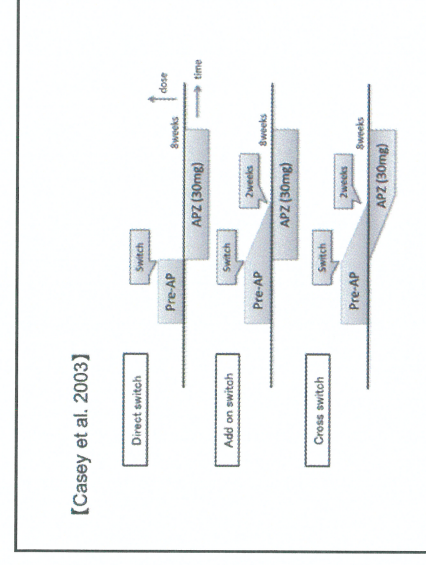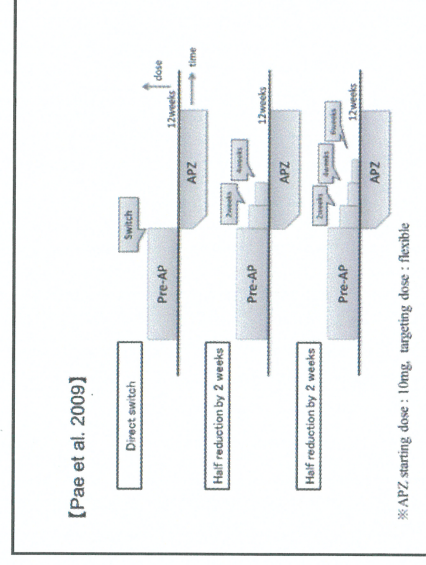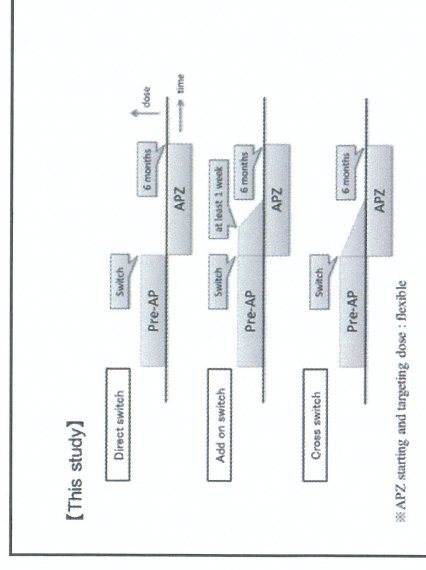APZ: aripiprazole, Pre-AP: previous antipsychotics

TABLE 1. Background of subjects and clinical outcome at six months after switching to aripiprazole monotherapy

Characteristics	Direct switch (n=71)				Add-on switch (n=45)				Cross switch (n=62)			
	Mean	SD	n	%	Mean	SD	n	%	Mean	SD	n	%
Continuation of APZ at 6 months			33	46.4			32	71.1			36	58.1
CGI-S score												
Starting	4.11	1.08			4.13	1.04			4.24	1.22		
Final	3.52	1.61			3.29	1.46			3.35	1.78		
Change of CGI-S score												
No change			28	39.4			8	17.8			18	29.0
Improvement			33	46.5			30	66.7			35	56.5
Exacerbation			10	14.1			7	15.6			9	14.5
Adverse reaction			12	16.9			13	28.9			13	21.0
Extrapyramidal symptoms			5	7.0			9	20.0			8	12.9
Gastrointestinal symptoms			3	4.23			0	0			1	1.61
Insomnia			2	2.82			2	4.44			1	1.61
Over sedation			0	0			2	4.44			1	1.61
Headache			2	2.82			0	0			1	1.61
Liver injury			0	0			0	0			1	1.61
Sociality at 6M from switching APZ			32	45.1			20	44.4			33	53.2
Age (year)	40.8	18.1			40.2	14.7			38.8	15.0		
Sex, Female			33	46.5			27	60.0			36	58.1
Outpatients			53	74.6			37	82.2			39	62.9
Prior treatment time (year)	8.54	10.33			8.53	10.84			7.44	9.24		
Previous antipsychotics												
First generation cases			9	12.7			7	15.6			4	6.5
Second generation cases			63	88.9			40	88.9			58	93.5
CP equivalent dose (mg)	292	264			433	282			472	306		
Switching to aripiprazole												
Starting dose of APZ (mg)	9.99	6.55			8.62	6.42			11.2	6.43		
Maximum dose of APZ (mg)	14.9	9.39			19.6	6.57			19.8	7.95		
Target dose of APZ (mg)	13.4	8.70			19.5	6.67			18.1	8.32		
Cases beyond 18mg dose of APZ			28	39.4			33	73.3			45	72.6

SD: standard deviation, APZ: aripiprazole, CP: chlorpromazine, CGI-S: Clinical Global Impression Severity

TABLE 2. Cox proportional hazards model of survival of aripiprazole monotherapy on three strategies

	Crude model			Model 1		
	HR	(95%CI)	P-value	HR	(95%CI)	P-value
Add-on switch	0.43	(0.23-0.81)	0.01	0.42	(0.21-0.82)	0.01
Cross switch	0.68	(0.41-1.12)	0.13	0.59	(0.35-1.00)	0.13
Direct switch	1.00	(Reference)		1.00	(Reference)	
Age (per 1 year increment)				0.98	(0.97-1.00)	0.09
Sex (male vs. female)				0.83	(0.50-1.39)	0.49
Out-Inpatient (inpatients vs. outpatients)				1.61	(0.89-2.89)	0.11
Prior treatment time (per 1 year increment)				1.04	(1.02-1.07)	0.00
CP equivalent dose of previous antipsychotics (per 100mg increment)				1.00	(1.00-1.00)	0.88
CGI-S score (per 1 increment)				0.96	(0.76-1.22)	0.73
Starting dose of APZ (per 1mg increment)				1.04	(1.00-1.08)	0.06
Medical institution (OUH vs. OPMC)				0.57	(0.30-1.12)	0.10
Previous antipsychotics (RIS(72), OLZ(51), PES(14), QTP(12), BNS(3), FGA(14), combination therapy(12))				0.95	(0.84-1.08)	0.43

CI : confidence interval, HR : hazard ratio, CP : chlorpromazine, CGI-S : Clinical Global Impression Severity, APZ: aripiprazole, OUH : Okayama University Hospital, OPMC : Okayama Psychiatric Medical Center, RIS : risperidone, OLZ : olanzapine, PES : perospirone, QTP : quetiapine, BNS : blonanserin, FGA : first-generation antipsychotic, Model 1 : adjusted for age, sex, out-inpatient, prior treatment time, CP equivalent dose of previous antipsychotics, CGI-S score at the time of starting APZ, starting dose of APZ, medical institution, previous antipsychotics

TABLE 3. Effects on survival of aripiprazole monotherapy by reasons for the switch

	HR	(95%CI)	P-value
Psychiatric symptoms (n=90)	0.41	(0.21-0.81)	0.01
Non-direct switch (vs. Direct switch)			
Adverse reaction (n=50)	0.53	(0.16-1.74)	0.29
Non-direct switch (vs. Direct switch)			
Psychiatric symptoms + Adverse reaction (n=38)	3.79	(0.47-30.56)	0.21
Non-direct switch (vs. Direct switch)			

Adjusted for age, sex, out-inpatient, prior treatment time, chlorpromazine equivalent dose, Clinical Global Impression Severity score at the time of starting aripiprazole, starting dose of aripiprazole, medical institution, previous antipsychotics

TABLE 4. Comparison of previous antipsychotics prior to switching to aripiprazole

A) Risperidone n=72

	Crude model			Model 1		
	HR	(95%CI)	P-value	HR	(95%CI)	P-value
Add-on switch	0.39	(0.14-1.07)	0.07	0.35	(0.11-1.12)	0.08
Cross switch	0.69	(0.31-1.51)	0.35	0.65	(0.27-1.58)	0.35
Direct switch	1	(Reference)		1	(Reference)	

B) Olanzapine n=51

	Crude model			Model 1		
	HR	(95%CI)	P-value	HR	(95%CI)	P-value
Add-on switch	0.19	(0.05-0.65)	0.01	0.29	(0.07-1.11)	0.07
Cross switch	0.63	(0.26-1.51)	0.30	0.80	(0.29-2.26)	0.68
Direct switch	1	(Reference)		1	(Reference)	

CI: confidence interval, HR: hazard ratio, Model 1: adjusted for age, sex, out-inpatient, prior treatment time, chlorpromazine equivalent dose, Clinical Global Impression Severity score at the time of starting aripiprazole, starting dose of aripiprazole, medical institution