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Dopamine supersensitivity psychosis and dopamine partial agonist: A retrospective survey of failure of switching to aripiprazole in schizophrenia

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Abstract

The administration of aripiprazole (ARI), a dopamine partial agonist, could provoke abrupt psychotic worsening in patients with schizophrenia. We explored the relationship between this psychotic worsening and dopamine supersensitivity psychosis (DSP), which is a clinically vulnerable state. We conducted a retrospective investigation for 264 patients whose treatment medication was switched to ARI from other antipsychotics. We divided the patients into the DSP(+) group with a history of DSP episode(s) (N = 70) and the DSP(−) group without such a history (N = 194), and then compared the clinical factors relevant to the success or failure of the switch to ARI between them. The results revealed that patients in the DSP(+) group experienced psychotic worsening following the switch to ARI with a significant higher rate compared to the DSP(−) group (23% vs. 8%, P < 0.01). Moreover, the dosages of the drugs before the ARI introduction in the patients experiencing the psychotic worsening in the DSP (-) group were higher than those in other patients of the group. Our findings suggest that patients who receive high dosages of antipsychotic drugs form overt or covert DSP and such state is highly associated with psychotic worsening following ARI treatment.

Keywords

Antipsychotic, dopamine partial agonist, dopamine supersensitivity, schizophrenia, tardive dyskinesia

Introduction

Antipsychotics have been a mainstay in treating patients with schizophrenia for the past decades, but approximately 50% of patients are unable to attain symptomatic remission regardless of appropriate pharmacotherapy; this is known as treatment-resistant schizophrenia (TRS). Dopamine supersensitivity psychosis (DSP) (Chouinard, 1991; Chouinard et al., 1978) is characterized by the need for high antipsychotic dosages for the treatment of patients with schizophrenia (Kirkpatrick et al., 1992), tardive dyskinesia (TD) (Chouinard and Chouinard, 2008), and/or an abrupt relapse triggered by the reduction or discontinuation of antipsychotics (Moncrieff, 2006). Vulnerability to minor stress has been raised as an important element of DSP (Fallon et al., 2012). DSP develops with multiple relapses, and some patients with these episodes develop TRS. It has been speculated that approximately 50% of the cases of TRS are due to DSP (Chouinard and Chouinard, 2008). An up-regulation of dopamine D2 receptor (DRD2) caused by long-term treatment with antipsychotic(s) may contribute considerably to DSP (Iyo et al., 2013). It has been suggested that dopamine supersensitivity is potentially formed through an interaction between the etiology of schizophrenia and its long-term treatment with antipsychotic(s). Thus, DSP has an iatrogenic aspect, and the prevention and treatment of DSP could have a great impact on patients' long-term prognosis.

It was reported that patients with schizophrenia treated with aripiprazole (ARI), a DRD2 partial agonist (DPA), have lower rates of relapse of psychosis and treatment discontinuation compared to those treated with other antipsychotics, including several new atypical antipsychotics (Azekawa et al., 2011; Gorwood, 2006). We demonstrated in an animal model that a chronic administration of ARI did not induce a DRD2 up-regulation or behavioral supersensitivity, whereas equivalent doses of haloperidol, a full DRD2 antagonist, induced a prominent DRD2 up-regulation and behavioral supersensitivity (Tadokoro et al., 2012). ARI may induce little dopamine supersensitivity due to its unique DPA profile, which is different from those of other antipsychotics (Iyo et al., 2013). Taken together, the existing data suggest that treatment with ARI could provide a more stable clinical course and better prognosis for patients with schizophrenia compared to other antipsychotics.

However, it has been reported that ARI can provoke acute psychotic worsening, i.e. relapse or exacerbation, particularly when a patient's treatment is switched from another antipsychotic to ARI

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(Adan-Manes and Garcia-Parajua, 2009; DeQuardo, 2004). These switching failures were speculated to be attributable to its unique receptor profile of DPA (Takeuchi et al., 2009). Indeed several ARI trials suggested that a switching method of concomitant ARI initiation and tapering off of the current medication could cause a relapse of psychosis (Lin et al., 2009; Pae et al., 2009), although this result was not always confirmed in other trials (Casey et al., 2003; Kim et al., 2009). In addition, Pae and colleagues noticed a possible association between psychotic relapse following switching to ARI and DSP (Pae, 2009; Pae et al., 2010). We consider that ARI's agonistic effects may yield excessive dopaminergic effects via the high DRD2 density in patients with DSP, leading to psychotic worsening and switching failure. To date, however, there have been no clinical studies that investigated the relationship between switching to ARI and DSP.

Here we conducted a retrospective survey of patients with schizophrenia who experienced the switch from treatment with another antipsychotic to ARI, in order to explore the relationship between failure of switching to ARI and DSP. We hypothesized that patients with a DSP history would show clinical worsening of psychosis following the ARI introduction more frequently than those without such a history. The results may provide evidence that dopamine supersensitivity is closely related to switching failure with ARI. In addition, the clinical features of such failure cases may provide predictors of psychotic worsening evoked by switching to ARI.

Methods

Subjects and study design

We collected the medical records of all in-/out-patients who met the diagnostic criteria for schizophrenia according to the DSM-IV-TR who were treated at Chiba University Hospital in the period from 1 September 2006 to 31 December 2012. Among them, we selected all of the patients who received the switching process to ARI from any other antipsychotic(s). In the present study we did not select candidate subjects based on any a priori hypothesis. We then identified the clinical information of each patient, including the presence or absence of DSP history before ARI introduction and his/her clinical outcome following the introduction. The study protocol was approved by the Ethics Committee of the Graduate School of Medicine in Chiba University and was conducted in accord with the Helsinki Declaration.

Measurements

Dopamine supersensitivity psychosis. We evaluated the presence of DSP episode(s) within the five years prior to each patient's ARI adjunction. The DSP criteria in the present study were based on the original version by Chouinard (1991), but were slightly modified by our team as follows: (a) *withdrawal psychosis*: an acute relapse or exacerbation of psychosis appeared after a dose reduction or discontinuation of antipsychotics, within six weeks for oral medication or three months for long-acting intramuscular injection; or (b) *the development of tolerance to antipsychotic effects*: an acute relapse or exacerbation of psychosis that occurred independently of a dose reduction or discontinuation of antipsychotic therapy and could not be successfully controlled by a 20% increased titration of drug; or (c) *a mixed episode* meeting the criteria of both (a) and (b): psychotic symptoms which were new to the patient, or of greater severity, that occurred immediately after a decrease in drug dosage.

Based on available information from the medical records, if at least one of the three items above was met, the patient was classified as a member of the DSP(+) group, whereas the other patients were classified as the DSP(–) group. Since DSP was generally considered to be a secondary state which could be relevant to pharmacotherapy for some duration, we excluded the patients who received ARI for their first acute episode of psychosis. We also excluded the patients with comorbidities such as substance abuse/dependence, and the patients who were clearly judged to refuse treatment and take medication. Involuntary movement disorder including TD and exacerbation caused by minor stress, both of which are related to DSP (Fallon and Durson, 2011; Fallon et al., 2012), are not necessarily covered by the DSP criteria of the present study.

Clinical outcome following the switch to aripiprazole. Regarding the outcome after the switch to ARI, we categorized each case to one of the following three subgroups based on the patient's clinical course subsequent to the ARI introduction: continuation of ARI (CON), discontinuation of ARI due to worsening positive symptoms (D-POS), or discontinuation of ARI due to any other reason(s) (D-OTH).

CON was defined as the continuation of ARI treatment from its introduction to the present survey (December 2013) regardless of any clinical prognosis, i.e. improvement or not. D-POS was defined as the discontinuation of ARI due to the worsening of psychosis after the start of ARI treatment. The worsening of psychosis was defined as the exacerbation of positive symptoms, based on a 5 point or greater reduction in the patient's Global Assessment of Functioning (GAF) score and an increase of $\geqslant 1$ point on the Clinical Global Impression-Severity scale (CGI-S). D-OTH was defined as the discontinuation of ARI treatment due to any other reason(s) except for the worsening by ARI initiation, including lack of sufficient antipsychotic effects, discontinuation by the patient him/herself, any adverse effect such as extrapyramidal symptom, insomnia and nausea, and other reasons. If clinical information necessary for the above judgment was not available due to transference to another hospital or discontinuation of visits to our hospital, the patient's outcomes were judged by the state at the final visits.

We also examined the outcomes of the patients with the D-POS pattern in detail, to investigate whether the relevant worsening of psychosis met the criteria of a DSP episode: that is, whether the worsening episode was related to the introduction of ARI, particularly in the patients with a history of DSP episode(s).

Statistical analysis

We used SPSS ver. 19.0 (IBM, Armonk, NY) for the statistical analysis in this study. We applied Student's t-test and an analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. The statistical threshold level was set at $\alpha = 0.05$.

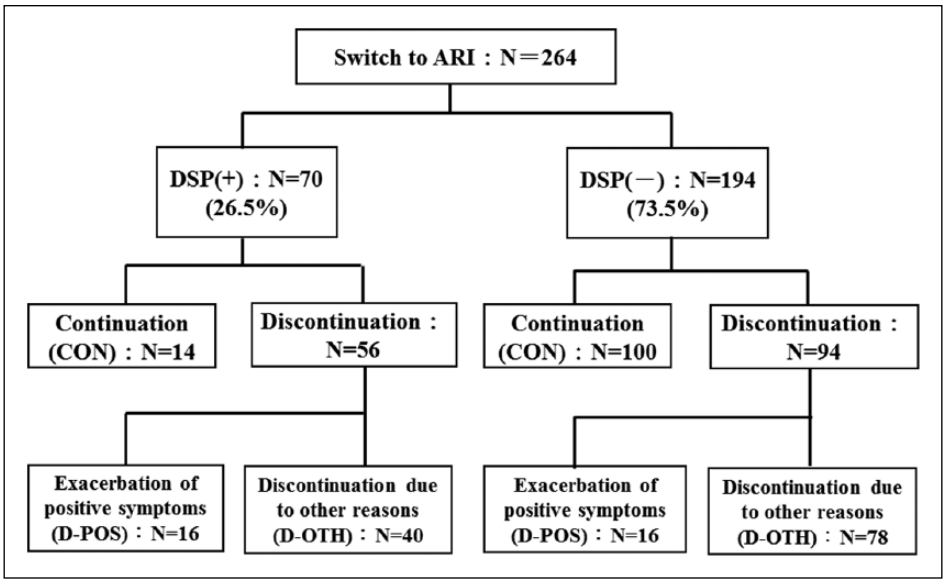

Figure 1. Overview of subject flow.

Results

We found that the treatment medication of 264 patients with schizophrenia (mean age, 40.5 yr; male/female ratio, 104/160) was switched to ARI from other antipsychotics during the surveyed period. None of these patients received ARI for the first-episode psychosis. Seventy patients (26.5%) were categorized in the DSP(+) group and 194 patients (73.5%) comprised the DSP(–) group (Figure 1). There was no significant between-group difference in any of the demographic factors, including the treatment indexes such as treatment duration and the distribution of antipsychotic class prior to the switch to ARI (Table 1).

Clinical course subsequent to aripiprazole switch and dopamine supersensitivity psychosis

In the DSP(+) group, the rates of CON, D-OTH and D-POS were 20%, 57% and 23%, respectively, whereas these values were 52%, 40% and 8% in the DSP(–) group (Figure 2), with a significant difference in the distribution between the two groups ($P < 0.01$). This result indicated that the discontinuation ratio of ARI and the worsening ratio in the DSP(+) group were significantly higher than those in the DSP(–) group.

The distributions of the primary reasons for D-OTH in the DSP(+) and DSP(–) groups were as follows: insufficient antipsychotic effects in 28.6% ($N = 20$) and 12.4% ($N = 24$), self-interruption in 8.6% ($N = 6$) and 5.7% ($N = 11$), insomnia in 0% ($N = 0$) and 6.2% ($N = 12$), nausea in 5.7% ($N = 4$) and 4.1% ($N = 8$), and extrapyramidal symptoms in 4.3% ($N = 3$) and 5.2% ($N = 10$), respectively.

Dosage of antipsychotics prior to aripiprazole introduction

The chlorpromazine-equivalent dose (CPZeq-dose) just prior to the start of ARI adjunction in the DSP(+) group (762.4 ± 376.0 mg) was significantly higher than that in the DSP(–) group (473.5 ± 373.3 mg) ($P < 0.01$, Table 1). There were no significant differences in the dosages among the CON (734.3 ± 344.9 mg), D-OTH (807.6 ± 413.9 mg) and D-POS (673.9 ± 269.2 mg) patterns within the DSP(+) group (Figure 3). However, there was a significant difference among the CON (425.2 ± 340.1 mg), D-OTH (496.6 ± 411.8 mg) and D-POS (662.7 ± 294.9 mg) patterns within the DSP(–) group ($P = 0.048$), and a post hoc Tukey test revealed that the dose in the D-POS subgroup was significantly higher than that of the CON subgroup within the DSP(–) group ($P = 0.048$) (Figure 3).

Effects of aripiprazole exposure and reduction of preceding antipsychotics on the worsening of psychosis

Among the D-POS patients, there were no significant differences between the DSP(+) group ($N = 16$) and the DSP(–) group ($N = 16$) in the CPZeq-dose just prior to ARI initiation, or in the duration from the initiation of ARI treatment to the exacerbation of psychosis (21.8 ± 53.5 wk and 16.3 ± 18.1 wk), or in the reduction rate of the preceding antipsychotic dosages (56.1 ± 39.1% and 33.9 ± 37.3%) or ARI dosage (21.8 ± 6.7 mg and 19.5 ± 9.1 mg) at the worsening (Table 2). The mean values for these patients (combined group of DSP(+) and DSP(–) groups) indicated that the worsening occurred at 19 weeks following the ARI initiation, and at the worsening, 20.6 mg ARI was being administered per day and there was a 45% reduction of the preceding antipsychotic dosage.

Lastly, we investigate whether or not the switching methodology influenced the worsening of psychosis. No patients with immediate ARI initiation and a simultaneous immediate discontinuation of previous antipsychotics (i.e. immediate suspension) experienced the D-POS pattern. The switching methods of all 32 patients with the D-POS pattern were up-titrating ARI and simultaneously tapering off previous antipsychotics over several weeks, or tapering off previous antipsychotics after several weeks following ARI adjunction (i.e. gradual suspension).

Table 1. Clinical characteristics and treatment state of the DSP(+) and (–) groups.

	DSP(+) (*N* = 70)	DSP(–) (*N* = 194)	*P*-value
Sex (male/female)	29/41	75/119	NS
Age (yr)	37.9 (12.6)	41.5 (14.7)	NS
(range)	(15–80)	(15–78)	
Duration of medication (yr)	13.0 (9.25)	11.6 (10.0)	NS
Follow-up duration following ARI initiation (yr)	1.26 (1.51)	1.71 (1.85)	NS
Antipsychotic before ARI initiation:			*P* < 0.01
Dosage (CPZeq: mg)	762.4 (376.0)	473.5 (373.3)	
Class of antipsychotic drug, *N* (%)			
Risperidone	32 (45.1%)	91 (47.2%)	
Olanzapine	18 (25.4%)	45 (23.3%)	
Quetiapine	8 (11.3%)	22 (11.4%)	
Perospirone	5 (7.0%)	15 (7.8%)	
Haloperidol	1 (1.4%)	9 (4.7%)	
Others	6 (8.5%)	12 (6.2%)	

Data are means (SD).
DSP: dopamine supersensitivity psychosis; ARI: aripiprazole; CPZeq: chlorpromazine-equivalent dose; NS: not significant.

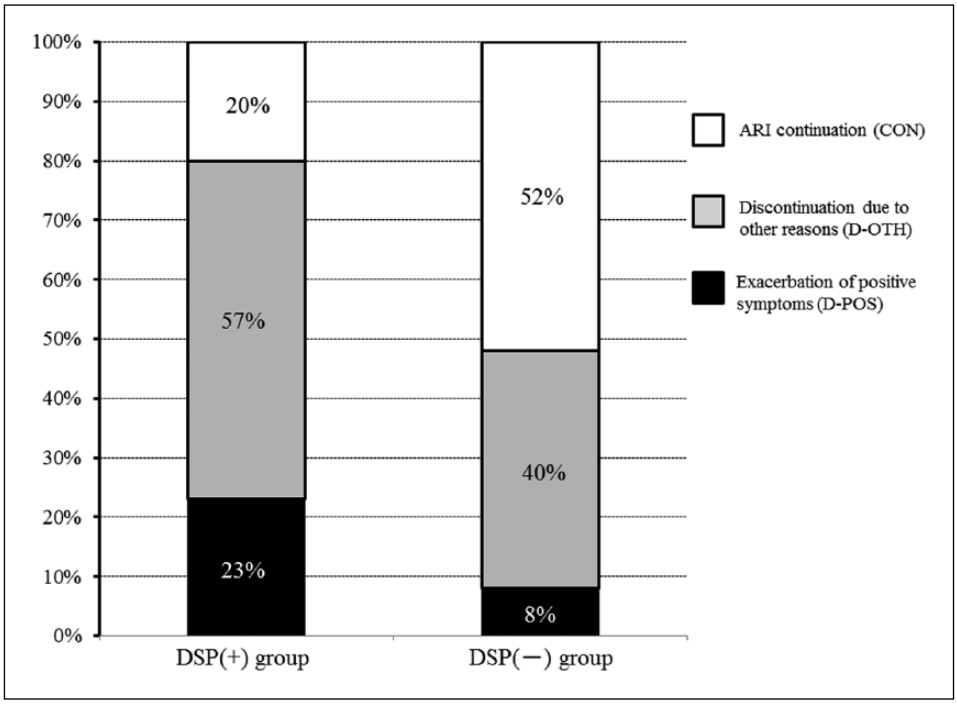

Figure 2. Distribution of clinical outcome following aripiprazole treatment in the DSP(+) and DSP(–) groups.

Discussion

The main finding in the present study is that the patients in the DSP(+) group showed a significantly higher rate of ARI discontinuation due to psychotic worsening compared to the DSP(–) group during the ARI switching process. In addition, even in the DSP(–) group, 8% of the patients experienced psychotic worsening during the switching process. We also found that the DSP(+) patients had significantly higher antipsychotic doses prior to ARI introduction, compared to the DSP(–) patients. The patients in the DSP(–) group who exhibited worsening during the switching process also had significantly higher prior antipsychotic doses, comparable to those in the DSP(+) group, compared to the other patients in the DSP(–) group. These results support our hypothesis that patients with a DSP history tend to suffer psychotic worsening during the process of switching to ARI. Our present findings also suggested that even the patients without a DSP history but treated with high antipsychotic doses also tended to suffer the worsening of symptoms, which may be a revelation of covert DSP. Overall, the present findings strongly suggest that a failure of switching to ARI in patients with schizophrenia treated with high antipsychotic doses could be closely associated with DSP.

We categorized the patients who had experienced the switching of antipsychotic medication to ARI into DSP(+) and DSP(–)

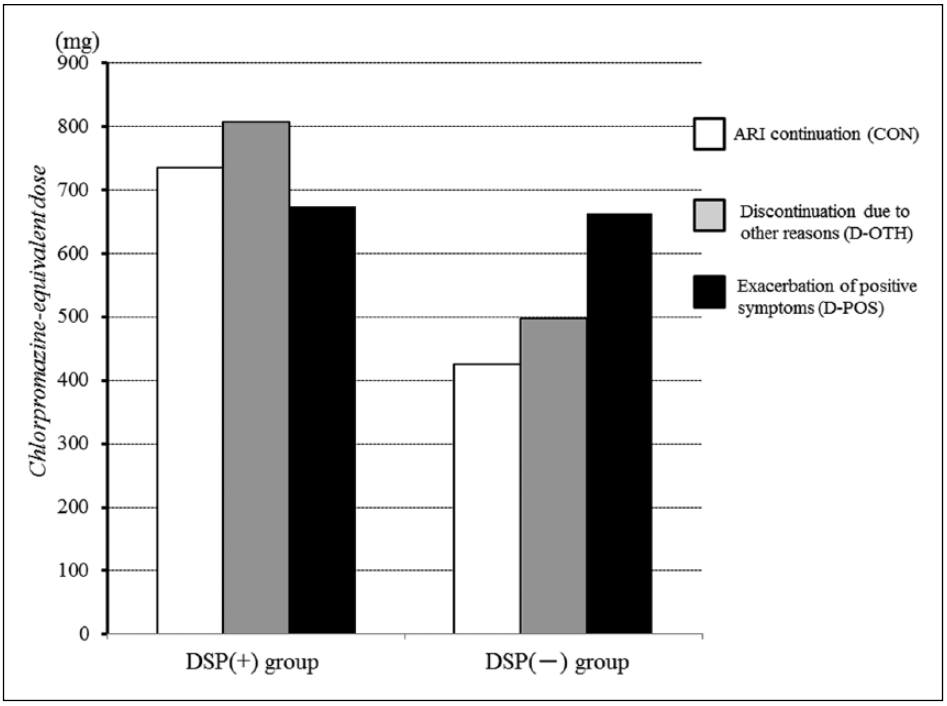

Figure 3. Chlorpromazine-equivalent dose of antipsychotic(s) just prior to the aripiprazole initiation in each subgroup.

Table 2. Worsened psychotic episodes relevant to the switch to ARI between the DSP(+) and DSP(–) groups.

	DSP(+) (*N* = 16)	DSP(–) (*N* = 16)	*P*-value
Index of clinical status prior to ARI switching:			
Dosage of antipsychotics (CPZeq: mg)	673.9 (269.2)	662.7 (294.9)	NS
GAF	41.6 (10.3)	41.3 (9.9)	NS
CGI-S	4.44 (0.70)	4.25 (0.90)	NS
Index of worsened psychosis following ARI switching:			
Duration from ARI switch to worsening (wk)	21.8 (53.5)	16.3 (18.1)	NS
Dosage of ARI (mg)	21.8 (6.7)	19.5 (9.1)	NS
Reduction rate of preceding antipsychotics (%)	56.1 (39.1)	33.9 (37.3)	NS
GAF	25.9 (9.6)	31.3 (10.7)	NS
CGI-S	6.00 (0.61)	5.44 (0.86)	NS

Data are means (SD).
DSP: dopamine supersensitivity psychosis; ARI: aripiprazole; CPZeq: chlorpromazine-equivalent dose; GAF: Global Assessment of Functioning; CGI-S: Clinical Global Impression-Severity scale; NS: not significant.

groups based on the retrospective clinical information of the presence or absence of a history of DSP, such as withdrawal psychosis and tolerance to antipsychotic effects within the five years before their ARI initiation. These episode(s) and/or clinical course are the core concept of DSP, as proposed by Chouinard (1991) and Kirkpatrick et al. (1992). On the other hand, the presence of TD and vulnerability to minor stress, which are important elements of DSP as well (Fallon and Durson, 2011; Fallon et al., 2012), were not required factors upon the diagnosis of DSP in the present study, since it is difficult to accurately identify these episodes from the viewpoint of study design. In the present study based on the former classification, the DSP(+) patients had a significantly higher rate, about 23%, of marked worsening of psychosis after the ARI initiation than the DSP(–) patients. The antipsychotic dosages prior to ARI initiation in the DSP(+) group were also significantly higher than those in the DSP(–) group, in agreement with our previous report that patients with DSP need high antipsychotic doses (Iyo et al., 2013). This finding suggests that a switch to ARI may greatly worsen the psychosis in patients with a history of DSP induced by previous treatment with high doses of antipsychotic drugs.

In the present DSP(–) group, 8% of the patients exhibited the D-POS pattern, i.e. worsening during the switching process and subsequent ARI discontinuation. Their preceding antipsychotic dosages were significantly higher compared to other patients within the DSP(–) group and comparable to those in the DSP(+) group. We speculate that the DSP had insidiously developed in these patients and was revealed by the switch to ARI, and we suspect that patients with high doses of preceding antipsychotic(s), regardless of the presence or absence of previous DSP episode(s),

may suffer psychotic worsening during the process of switching to ARI. It was reported that patients with abrupt psychotic relapses related to ARI switching had received high doses of antipsychotics, i.e. amisulpride 800mg/day (Adan-Manes and Garcia-Parajua, 2009) and olanzapine 60mg/day (DeQuardo, 2004). These patients might also experience a DSP episode with the introduction of ARI, in agreement with the present study's results.

In our DSP(+) group, 20% of the patients were able to continue ARI for a long period of time and 57% of the patients discontinued ARI due to reasons other than psychotic worsening (such as insufficient antipsychotic effects, 28%), although they had received high antipsychotic doses comparable to those of the patients showing psychotic worsening. We suspect that as the ARI dosage increases or the dosage of other antipsychotics is reduced following ARI initiation, the extent of ARI's binding to DRD2 increases, accompanied by an increase of ARI-induced dopaminergic effects due to a fixed ratio of intrinsic activity, approximately 17% (Tadori et al., 2009). In such a scenario, ARI-induced dopaminergic effects can exceed levels high enough to exacerbate psychosis in individuals with DSP, who have sufficiently high numbers of DRD2 for ARI binding, leading to psychotic worsening. When the increased ARI-induced dopaminergic effects are equivalent to pre-existing dopaminergic effects before the initiation of ARI, the severity of psychosis may not change between pre- and post-ARI initiation. This speculation may explain the reason of discontinuation due to insufficient antipsychotic effects of ARI in the D-OTH patients within the DSP(+) group.

In the D-POS patients, it is strongly suggested that the switch to ARI was a trigger for relapse, although several clinical factors such as a lack of insight into the disease and poor adherence are well-known predictors of a higher relapse rate in schizophrenia (Llorca, 2008; Masand et al., 2009; Valenstein et al., 2002) (Table 2). In the present study, the worsening occurred at 19 weeks on average following ARI initiation at the mean ARI dosage of 20.6mg and mean 45% reduction of preceding antipsychotic dosage, whereas Chouinard (1991) defined that psychotic worsening appears within six weeks after a dose reduction or discontinuation of oral antipsychotics in patients with DSP. These clinical index values upon relapse were relatively consistent with previous switching trials with ARI: one study showed immediate relapses following adjunction of ARI (Casey et al., 2003) and another study showed a higher drop-out rate in patients who received higher dosages of prior agents (Lin et al., 2009). In addition, all of the D-POS patients experienced the switching process of the gradual tapering-off regimen, whereas there was no patient with the immediate suspension of previous agents in the D-POS patients. This result supports the concept that the action of ARI contributes more to the worsening of psychosis than the discontinuation or the tapering off of previous antipsychotics. The extent of developed dopamine supersensitivity (i.e. the extent of an increase in the number of DRD2) in addition to the rates of ARI increase and the reduction of other drugs might differ among the patients. We thus suspect that the timing of the appearance of worsening psychosis following ARI initiation might have a wide range, and this might have occurred slightly later than the cases with a dose reduction or discontinuation of oral antipsychotics that showed worsening only two weeks after the initiation of ARI, which meets Chouinard's rebound psychosis criteria (i.e. within six weeks after the discontinuation of current agents) as reported by Pae et al. (2009).

The present study has several limitations, and thus caution is warranted when interpreting our findings. First, our sample size, particularly that of the patients with the D-POS pattern, was relatively small. If there were slight but significant differences in the distribution rate of the D-POS pattern among the switching cases, such differences would not be detected with only a small sample size presenting with the D-POS pattern. Second, a relapse episode of DSP might include relapse under treatment (i.e. not withdrawal psychosis), which leads to an overestimation of the number of DSP cases. Finally, with respect to the diagnosis of DSP, our study is in accord with both the criteria proposed by Chouinard (1991) and the concept described by Kirkpatrick et al. (1992), but it did not include the presence of involuntary movement disorder or vulnerability to minor stress as proposed by Fallon et al. (2012). This difference in the criteria used upon the diagnosis of DSP might have had some influence on the study results. However, DSP can present covertly with the dopamine supersensitivity state formed but without occurrence as DSP, and such a case was judged to belong in the DSP(–) group in this study. This may imply a limitation of the dichotomy of DSP.

In conclusion, this is the first study focusing on the possible relationship between the failure of a switch to ARI treatment and DSP. Our results strongly suggest that the abrupt worsening of psychosis following the initiation of ARI after treatment with other antipsychotics in patients with schizophrenia is associated with DSP.

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