Tardive Dyskinesia and Long-Acting Injectable Antipsychotics: Analyses Based on a Spontaneous Reporting System Database in Japan

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ABSTRACT

Objective: This study compared the reporting frequency of tardive dyskinesia (TD) between long-acting injectable antipsychotics (LAI-APs) and the equivalent oral antipsychotics (O-APs), LAI first-generation antipsychotics (LAI-FGAs) and LAI second-generation antipsychotics (LAI-SGAs), and individual LAI-APs.

Methods: The Japanese Adverse Drug Event Report was used in this study, and data were obtained from April 2004 to February 2021. Patients who received LAI-APs available in Japan (LAI haloperidol, LAI fluphenazine, LAI aripiprazole, LAI risperidone, and LAI paliperidone) or the equivalent O-APs were included in this study. We calculated the adjusted reporting odds ratios (aRORs) to compare the reporting frequency of TD.

Results: A total of 8,425 patients were included in the study. TD was reported significantly less frequently with LAI paliperidone than with oral paliperidone (aROR [95% confidence interval (CI)] = 0.13 [0.05–0.36]). Other LAI-APs were associated with a numerically lower reporting frequency of TD than the equivalent oral SGAs. The reporting frequency of TD associated with LAI-SGAs was significantly lower than that of LAI-FGAs (aROR [95% CI] = 0.18 [0.08–0.43]). All LAI-SGAs were significantly associated with a lower reporting frequency of TD than that of LAI fluphenazine (aROR [95% CI]: LAI aripiprazole, 0.11 [0.04–0.35]; LAI risperidone, 0.09 [0.03–0.32]; LAI paliperidone, 0.02 [0.005–0.09]). and LAI haloperidol, 8.58 [1.85–39.72]). LAI fluphenazine was significantly associated with a higher reporting frequency of TD than LAI haloperidol (aROR [95% CI] = 8.58 [1.85–39.72]). The reporting frequency of TD associated with LAI paliperidone was significantly lower than that with LAI aripiprazole (aROR [95% CI] = 0.18 [0.05–0.73]).

Conclusions: Compared to O-APs, LAI-APs, particularly LAI-SGAs, may be associated with a lower risk of TD.

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Long-acting injectable antipsychotics (LAI-APs) are an important option to prevent relapse in the maintenance treatment of schizophrenia.[1] However, despite their effectiveness, they remain underutilized in most countries worldwide.[2,3] The reasons for this underutilization are manifold: a possible one is the concern that LAI-APs might cause severe adverse events, compared with oral antipsychotics (O-APs), because LAI-APs cannot be promptly removed from the body when adverse events occur.[4–6]

Tardive dyskinesia (TD), characterized by abnormal involuntary movements of the face, torso, extremities, and respiratory system,[7] is one of the most severe and treatment refractory adverse events induced by antipsychotic treatment; it is associated with a poor quality of life[8] and increased mortality.[9] The pathophysiology of TD remains unclear, but the dopamine supersensitivity theory is the most widely accepted.[10] Long-term exposure to antipsychotics can result in postsynaptic dopamine D_2 receptor up-regulation, which leads to dopamine supersensitivity that can induce hyperkinetic movements such as TD.[10,11]

The relationship between TD, dopamine supersensitivity, and LAI-AP is controversial. Continuous blockade of dopamine D_2 receptors during LAI-AP treatment might likely evoke dopamine supersensitivity. In animal studies, rats continuously given antipsychotics demonstrated significantly greater vacuous chewing movement than those intermittently given antipsychotics.[12] Furthermore, a cross-sectional study found that the use of LAI-APs was a risk factor for TD.[13] In contrast, LAI-APs, which have a longer plasma half-life and a more stable blood concentration than O-APs, with a narrower difference between the peak and trough plasma levels, were considered to possibly prevent the development of dopamine supersensitivity.[14] Few studies have shown a low risk of TD with LAI-APs.[15,16] In addition, a prospective study showed that patients with dopamine supersensitivity responded more to LAI risperidone than those without dopamine supersensitivity.[17]

For safer and wider use of LAI-APs, it is important to examine the association between LAI-AP treatment and TD. Therefore, we conducted this study to compare the reporting frequency of TD between LAI-APs and the equivalent O-APs, LAI first-generation antipsychotics (LAI-FGAs) and LAI second-generation antipsychotics (LAI-SGAs), and individual LAI-APs, using a large spontaneous reporting database in Japan. Because the database included only spontaneously reported cases, we could not obtain incidence rates of TD and calculate the odds ratios. We therefore calculated the reporting odds ratios to compare the reporting frequency of TD.

Clinical Points

- The association between long-acting injectable (LAI) antipsychotics and tardive dyskinesia (TD) has not been well examined.
- LAI antipsychotics were associated with a lower reporting frequency of TD than the equivalent oral antipsychotics.
- Second-generation LAI antipsychotics were associated with a lower reporting frequency of TD than first-generation LAI antipsychotics.

METHODS

Database

The Japanese Adverse Drug Event Report (JADER) was used in this study. JADER is a large database established in 2004 by the Pharmaceuticals and Medical Devices Agency (PMDA), a Japanese regulatory agency. It is available from the website of the PMDA[18] and comprises spontaneous reports of adverse events from physicians, pharmacists, other health care professionals, and patients. Data from JADER, which contains over 650,000 patients, consist of 4 components: (1) demographic information, (2) drug information, (3) adverse reactions, and (4) medical history. Adverse events in the adverse reaction table are coded according to the terminology in the Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J). In the drug information table, the contribution of the medication to adverse events is classified into 3 categories based on the report: "suspected medicine," referring to medicine suspected to be related to an adverse event; "interaction," referring to medicine suspected of an interaction with a suspected medicine; and "concomitant medicine," referring to another medicine used at the occurrence of an adverse event. We obtained data from April 2004 to February 2021.

Inclusion and Exclusion Criteria

Patients who received LAI-APs available in Japan (LAI haloperidol, LAI fluphenazine, LAI aripiprazole, LAI risperidone, and LAI paliperidone) or the equivalent O-APs as the "suspected medicine" were included in this study. Because both LAI and oral risperidone are described as "risperidone," we distinguished between the LAI and oral formulations by the administration route and/or dose. We excluded patients for whom the administration route (ie, LAI or oral) of antipsychotics was not clear.

Antipsychotic Treatment

We classified patients into the LAI-AP and O-AP groups, while the patients receiving both LAI-AP(s) and O-AP(s) were classified in the LAI-AP group. If 2 or more LAI-APs or O-APs were listed as "suspected medicine" in 1 patient, the patient was categorized in each LAI-AP or O-AP group, respectively (eg, a patient receiving oral aripiprazole and oral risperidone was classified into both the oral aripiprazole and oral risperidone groups).

We regarded patients who received 2 or more antipsychotics in the "suspected medicine" list or those who received any antipsychotics in the "concomitant medicine" list as those receiving the concomitant use of antipsychotics. However, patients receiving LAI-AP(s) and the equivalent O-AP(s) (eg, LAI risperidone and oral risperidone) were not considered as those receiving the concomitant use of antipsychotics. Of the 32 cases, 2 or more LAI-APs were listed as the "suspected medicine" in 1 patient. Thus, we considered that those LAI-APs were used not concurrently, but separately, because the concurrent use of 2 or more LAI-APs is very rare.

Oral risperidone and paliperidone were considered equivalent antipsychotics in this study, because paliperidone is the main active metabolite of risperidone. Conversely, LAI risperidone was distinguished from LAI paliperidone because of the difference in the injection intervals.

Outcome

Patients with TD were identified by searching for "dyskinesia" and "tardive dyskinesia," which are the preferred terms used in the MedDRA/J.

Statistical Analyses

We calculated the reporting odds ratios (RORs) to compare the reporting frequency of TD between LAI-APs and the equivalent O-APs, LAI-FGAs and LAI-SGAs, and individual LAI-APs. When comparing LAI-FGAs and LAI-SGAs, and individual LAI-APs, we excluded patients in whom 2 or more LAI-APs were listed as "suspected medicine."

ROR is a validated effect measure for safety signal detection,[19] which has frequently been used in spontaneous reporting databases as the safety signal index.[20] It is calculated using a 2-by-2 contingency table.[21] In this study, the ROR is the ratio of the odds of reported TD versus all other adverse events. An ROR of < 1 indicates that TD was less frequently reported.

When comparing LAI-APs with the equivalent O-APs, we excluded patients with injection site induration, injection site pain, or post-injection delirium/sedation syndrome, each of which occurred in 1 patient treated with LAI paliperidone, because these adverse events are not caused by O-APs. We calculated adjusted RORs (aRORs) with the 95% confidence interval (CI) of TD using logistic regression models adjusting for age group, sex, and concomitant use of oral FGAs, oral SGAs, anticholinergics, and lithium.

Study Approval and Statistical Software

This study did not require an institutional review board review because it used only anonymized data from an existing source. All statistical analyses were performed using JMP 13.2.0 (SAS Institute, Cary, NC).

RESULTS

Clinicodemographic Characteristics

In the present study, 8,425 patients (8,911 reports) were included. Table 1 depicts the patient characteristics. Fewer

Table 1. Patient Characteristics

	Oral haloperidol (n = 770)	LAI haloperidol (n = 166)	Oral fluphenazine (n = 45)	LAI fluphenazine (n = 73)	Oral aripiprazole (n = 2,739)	LAI aripiprazole (n = 422)	Oral risperidone/ paliperidone (n = 3,633)	LAI risperidone (n = 346)	LAI paliperidone (n = 717)
Sex, n (%)									
Male	451 (58.6)	92 (55.4)	16 (35.6)	41 (56.2)	1,315 (48.0)	210 (49.8)	1,865 (51.3)	187 (54.0)	405 (56.5)
Female	307 (39.9)	70 (42.2)	29 (64.4)	31 (42.5)	1,377 (50.3)	206 (48.8)	1,695 (46.7)	152 (43.9)	303 (42.3)
Unknown	12 (1.6)	4 (2.4)	0 (0)	1 (1.4)	47 (1.7)	6 (1.4)	73 (2.0)	7 (2.0)	9 (1.3)
Age, n (%)									
≤ 10 y	7 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	25 (0.9)	0 (0.0)	49 (1.3)	0 (0.0)	0 (0.0)
10–19 y	22 (2.9)	3 (1.8)	0 (0.0)	0 (0.0)	131 (4.8)	4 (0.9)	178 (4.9)	3 (0.9)	9 (1.3)
20–29 y	55 (7.1)	5 (3.0)	1 (2.2)	4 (5.5)	289 (10.6)	29 (6.9)	336 (9.2)	20 (5.8)	36 (5.0)
30–39 y	90 (11.7)	30 (18.1)	10 (22.2)	13 (17.8)	453 (16.5)	58 (13.7)	507 (14.0)	51 (14.7)	106 (14.8)
40–49 y	151 (19.6)	33 (19.9)	9 (20.0)	20 (27.4)	428 (15.6)	116 (27.5)	506 (13.9)	77 (22.3)	165 (23.0)
50–59 y	154 (20.0)	36 (21.7)	11 (24.4)	16 (21.9)	444 (16.2)	65 (15.4)	521 (14.3)	63 (18.2)	142 (19.8)
60–69 y	140 (18.2)	30 (18.1)	3 (6.7)	11 (15.1)	387 (14.1)	78 (18.5)	493 (13.6)	65 (18.8)	133 (18.6)
70–79 y	98 (12.7)	15 (9.0)	7 (15.6)	0 (0)	197 (7.2)	34 (8.0)	382 (10.5)	27 (7.8)	56 (7.8)
80–89 y	26 (3.4)	1 (0.6)	0 (0.0)	1 (1.4)	108 (3.9)	5 (1.2)	291 (8.0)	5 (1.4)	8 (1.1)
90–99 y	5 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	16 (0.6)	1 (0.2)	64 (1.8)	0 (0.0)	0 (0.0)
≥ 100 y	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.03)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	22 (2.9)	13 (7.8)	4 (8.9)	8 (11.0)	260 (9.5)	32 (7.6)	305 (8.4)	35 (10.1)	62 (8.6)
Concomitant use, n (%)									
FGAs	448 (58.2)	70 (42.2)	25 (55.6)	42 (57.5)	680 (24.8)	119 (28.2)	1,209 (33.3)	90 (26.0)	164 (22.9)
SGAs	300 (39.0)	89 (53.6)	19 (42.2)	43 (58.9)	982 (35.8)	219 (51.9)	1,058 (29.1)	138 (39.9)	279 (38.9)
Anticholinergics	172 (22.3)	40 (24.1)	8 (17.8)	19 (26.0)	365 (13.3)	61 (14.5)	565 (15.6)	66 (19.1)	116 (16.2)
Lithium	17 (2.2)	3 (1.8)	0 (0.0)	6 (8.2)	106 (3.9)	12 (2.8)	91 (2.6)	15 (4.3)	23 (3.2)

Abbreviations: FGA = first-generation antipsychotic, LAI = long-acting injectable, SGA = second-generation antipsychotic.

patients received LAI-APs in the group under age 20 than in the other age groups. Patients receiving the FGAs had significantly more concurrent use of antipsychotics than those receiving SGAs.

LAI-APs vs the Equivalent O-APs

TD was reported significantly less frequently with LAI paliperidone than with oral paliperidone (aROR [95% CI] = 0.13 [0.05–0.36]) (Figure 1). LAI-APs other than LAI paliperidone were numerically associated with a lower reporting frequency of TD than the equivalent O-APs, although the differences were not statistically significant (Figure 1).

LAI-FGAs vs LAI-SGAs

The reporting frequency of TD associated with LAI-SGAs was significantly lower than that of LAI-FGAs (aROR [95% CI] = 0.18 [0.08–0.43]) (Figure 2).

Comparisons Between Individual LAI-APs

All LAI-SGAs were significantly associated with a lower reporting frequency of TD than LAI fluphenazine (aROR [95% CI]: LAI aripiprazole, 0.11 [0.04–0.35]; LAI risperidone, 0.09 [0.03–0.32]; and LAI paliperidone, 0.02 [0.005–0.09]). LAI fluphenazine was significantly associated with a higher reporting frequency of TD than LAI haloperidol (aROR [95% CI] = 8.58 [1.85–39.72]) (Figure 3).

The reporting frequency of TD associated with LAI paliperidone was significantly lower than that of LAI aripiprazole (aROR [95% CI] = 0.18 [0.05–0.73]) and LAI haloperidol (aROR [95% CI] = 0.18 [0.03–0.96]) (Figure 3).

DISCUSSION

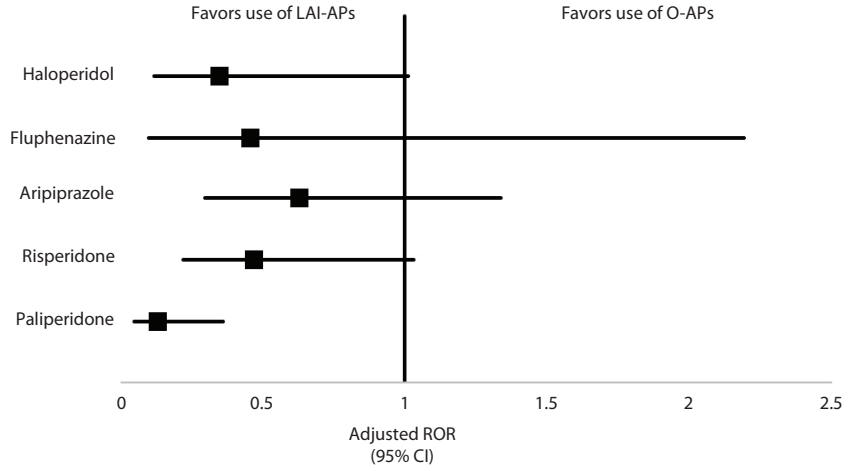
To the best of our knowledge, to date, this is the most detailed study to investigate the association between LAI-AP treatment and TD. In particular, few studies have compared the risk of TD between LAI-FGAs and LAI-SGAs or individual LAI-APs. We found that (1) LAI-APs were associated with a lower reporting frequency of TD than the equivalent O-APs; (2) LAI-SGAs were associated with a lower reporting frequency of TD than LAI-FGAs; and (3) LAI fluphenazine was associated with the highest reporting frequency of TD, while LAI aripiprazole was associated with a significantly higher reporting frequency of TD than LAI paliperidone.

This study did not show that LAI-APs were more highly associated with TD than O-APs. A previous study using the JADER data suggested that LAI-SGAs may not be associated with a higher frequency and mortality of neuroleptic malignant syndrome, which is the most concerning side effect of LAI-AP treatment, as well as TD.[22] Furthermore, a meta-analysis of randomized controlled trials showed few differences in the tolerability between LAI-APs and O-APs.[5] In light of these findings, clinicians should not hesitate to use LAI-APs because of the concerns about the related side effects.

The reporting frequency of TD was lower with LAI-APs than with the equivalent O-APs, and was also lower with LAI haloperidol than with LAI fluphenazine, which has a shorter plasma half-life.[23] These findings may support the hypothesis that a stable blood concentration with a narrower difference between the peak and trough could be beneficial for the prevention of TD. Antipsychotics with short plasma

Figure 1. Reporting Odds Ratios of Tardive Dyskinesia of LAIs vs the Equivalent Oral Antipsychotics[a]

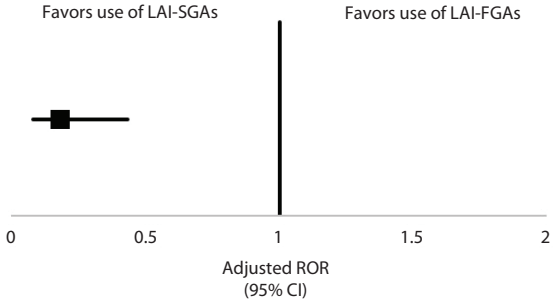
	n	Tardive dyskinesia, n (%)	Crude ROR	Adjusted ROR[b]
Oral haloperidol	770	47 (6.1)	Reference	Reference
LAI haloperidol	166	4 (2.4)	0.38 [0.13–1.07], $P=.067$	0.35 [0.12–1.01], $P=.053$
Oral fluphenazine	45	5 (11.1)	Reference	Reference
LAI fluphenazine	73	7 (9.6)	0.85 [0.25–2.85], $P=.791$	0.46 [0.10–2.19], $P=.338$
Oral aripiprazole	2,739	81 (3.0)	Reference	Reference
LAI aripiprazole	422	8 (1.9)	0.66 [0.31–1.38], $P=.224$	0.63 [0.30–1.34], $P=.232$
Oral risperidone/paliperidone	3,633	146 (4.0)	Reference	Reference
LAI risperidone	346	7 (2.0)	0.49 [0.23–1.06], $P=.071$	0.47 [0.22–1.03], $P=.058$
LAI paliperidone	717	4 (0.6)	**0.13 [0.05–0.36], $P<.001$**	**0.13 [0.05–0.36], $P<.001$**



[a]Bold type indicates statistically significant results.
[b]Adjusted for age group, sex, and use of oral first-generation antipsychotics, oral second-generation antipsychotics, anticholinergics, and lithium.
Abbreviations: AP = antipsychotic, LAI = long-acting injectable, O-AP = oral antipsychotic, ROR = reporting odds ratio.

Figure 2. Reporting Odds Ratios of Tardive Dyskinesia of LAI-FGAs vs LAI-SGAs[a]

	n	Tardive dyskinesia, n (%)	Crude ROR	Adjusted ROR[b]
LAI-FGAs	213	10 (4.7)	Reference	Reference
LAI-SGAs	1,393	16 (1.2)	**0.24 [0.11–0.53], $P<.001$**	**0.18 [0.08–0.43], $P<.001$**



[a]Bold type indicates statistically significant results.
[b]Adjusted for age group, sex, and use of oral first-generation antipsychotics, oral second-generation antipsychotics, anticholinergics, and lithium.
Abbreviations: FGA = first-generation antipsychotic, LAI = long-acting injectable, ROR = reporting odds ratio, SGA = second-generation antipsychotic.

half-lives, which can exceed an optimal level at peak, may be more likely to contribute to the development of dopamine supersensitivity, the pathophysiology of TD, than those with long plasma half-lives.[14,24] However, because it remains speculative that antipsychotics with long plasma half-lives including LAI-APs can prevent dopamine supersensitivity, further studies are warranted.

LAI-SGAs were associated with a lower reporting frequency of TD than LAI-FGAs. In addition, a meta-analysis[25] showed that the prevalence of TD was significantly lower with SGAs (20.7%) than with FGAs (30.0%). In summary, regardless of the formulation, SGAs may be associated with a lower risk of TD than FGAs. Although the reason is unclear, the difference may be due to the fact

Figure 3. Adjusted Reporting Odds Ratios of Tardive Dyskinesia in Comparisons Between Individual LAI Antipsychotics[a]

LAI haloperidol				
8.58 [1.86–39.72], P = .006	LAI fluphenazine			
0.98 [0.23–4.15], P = .975	**0.11 [0.04–0.35], P < .001**	LAI aripiprazole		
0.78 [0.17–3.66], P = .753	**0.09 [0.03–0.32], P < .001**	0.80 [0.25–2.53], P = .702	LAI risperidone	
0.18 [0.03–0.96], P = .045	**0.02 [0.005–0.09], P < .001**	**0.18 [0.05–0.73], P = .016**	0.23 [0.05–1.01], P = .051	LAI paliperidone

[a]Values in this table are adjusted reporting odds ratios[b] of each LAI antipsychotic in the row compared with individual ones in the column. Bold type indicates a statistically significant result.
[b]Adjusted for age group, sex, and use of oral first-generation antipsychotics, oral second-generation antipsychotics, anticholinergics, and lithium.
Abbreviation: LAI = long-acting injectable.

that FGAs are more likely than SGAs to block dopamine D_2 receptors.[10] However, because TD remains highly prevalent even during SGA treatment, further studies are needed to elucidate the prevention and treatment of TD.

The present study showed that the reporting frequency of TD associated with LAI aripiprazole was significantly higher than that with LAI paliperidone. This may be because cases with a high risk of TD may have been more likely to receive LAI aripiprazole than LAI paliperidone. Further, it could be attributed to the difficulty in adjusting the dose of LAI aripiprazole, which is dosed only at 400 mg, or 300 mg as an option in cases of intolerance. Therefore, some patients might have received excessive doses of aripiprazole during LAI aripiprazole treatment. In addition, LAI aripiprazole is indicated for the treatment of not only schizophrenia but also bipolar I disorder in Japan. Given that mood disorders are known to be a risk factor for TD,[7] patients with bipolar disorder receiving LAI aripiprazole might be more likely to have TD than patients receiving LAI paliperidone, all of whom were suspected to have schizophrenia. On the other hand, aripiprazole may prevent the development of TD because the partial agonism to dopamine D_2 receptors could not up-regulate the receptors.[26] Further studies are warranted to investigate the association between aripiprazole and TD.

The results of this study must be interpreted in the context of several limitations. First, there are inherent biases in studies using JADER. We could not accurately evaluate the risk of TD because of the non-randomized sample. As the cases in JADER had been spontaneously reported from physicians, pharmacists, other health care professionals, and patients, without any incentive, all relevant cases were not included in the database. A reporting bias could, therefore, have affected the results. In addition, this study could not evaluate the association between TD and LAI-APs in people who are not of Japanese origin, because JADER included cases only from Japan. Second, the RORs can estimate the relative risks of TD by treating the database as a case-control study and subsequently eliminating the adverse events that could make a difference in reporting frequency between LAI-APs and O-APs. However, we could not calculate the accurate risks of TD development. Third, TD was diagnosed in each patient based on clinical judgment without specific criteria such as Schooler-Kane criteria,[27] and we could not evaluate the severity and duration of TD. Fourth, we did not distinguish between tardive and withdrawal dyskinesia, because we could not obtain data on changes in antipsychotic doses. Fifth, we did not estimate sample size before starting this study, and the number of cases in some treatments (eg, oral fluphenazine and LAI fluphenazine) may have been insufficient with regard to statistical significance. Lastly, although we adjusted for some confounding factors, we

were not able to do so with important factors that could be risk factors for TD (eg, psychiatric diagnosis, alcohol or substance abuse, and physical comorbidities such as diabetes and HIV positivity),[7] because JADER did not include these data. Furthermore, we could not obtain detailed data on antipsychotic treatment, such as treatment duration, dose, and antipsychotics prescribed before the suspected antipsychotics; for example, the association of TD with LAI-SGAs was reported less frequently than that with LAI-FGAs, which might have been caused by a difference in treatment durations rather than the generation of antipsychotic. It should also be noted that the lack of antipsychotic dose data is a serious limitation.

In conclusion, our findings suggest that LAI-APs, particularly LAI-SGAs, may be associated with a lower risk of TD than O-APs, and clinicians need not hesitate to use LAI-APs because of concerns regarding TD. However, clear evidence about the association between LAI-APs and TD cannot be drawn from the results of this study because it has several limitations, including a reporting bias. Furthermore, it still remains unclear whether TD associated with LAI-APs is more severe than with O-APs. Thus, clinicians need to closely monitor the development of TD during LAI-AP treatment to detect and manage it as early as possible. Further studies are warranted to replicate these findings owing to the nature of the present study using a spontaneous reporting database.

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