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Neuroleptic malignant syndrome associated with long-acting injectable versus oral second-generation antipsychotics: Analyses based on a spontaneous reporting system database in Japan

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ABSTRACT

Long-acting injectable antipsychotics (LAI-APs) remain underutilized. One reason is the concern that LAI-APs might cause serious adverse events such as neuroleptic malignant syndrome (NMS) and lead to prolonged symptoms compared with oral treatment. Because the risk of NMS associated with LAI second-generation antipsychotics (LAI-SGAs) remains unclear, we compared reporting frequency, time to onset, and mortality of NMS between LAI- and oral SGAs using data from a Japanese spontaneous adverse event reporting database between April 2004 and September 2019. Of 5791 patients reporting adverse events due to LAI-SGAs or the equivalent oral SGAs, 768 (13%) developed NMS. LAI aripiprazole and LAI paliperidone were associated with a significantly lower reporting frequency of NMS than the equivalent oral SGAs (adjusted reporting odds ratio [95% confidence interval]: 0.35 [0.19–0.63] and 0.40 [0.27–0.59], respectively). Between 42% and 62% of the NMS associated with LAI- and oral SGAs other than LAI risperidone occurred within 30 days after initiation. The proportion of mortality due to NMS associated with oral aripiprazole was 13.1% and no deaths occurred in patients with NMS associated with LAI aripiprazole. The proportions of mortality due to NMS associated with oral risperidone/paliperidone, LAI risperidone, and LAI paliperidone were 8.8%, 4.2%, and 3.4%, respectively. Our findings showed that LAI-SGAs were not associated with a higher reporting frequency and mortality of NMS compared with oral SGAs, although clinicians need to closely monitor the occurrence of NMS not only during oral SGA treatment, but also, and in particular, in the early stage of LAI-SGA treatment.

1. Introduction

Long-acting injectable antipsychotics (LAI-APs) are a valuable option in the maintenance treatment of schizophrenia (Kane and Garcia-Ribera, 2009) because of their potent ability to prevent relapse (Kishimoto et al., 2018, 2013). There are now several types of long-acting injectable second-generation antipsychotics (LAI-SGAs) available in clinical practice (Rauch and Fleischhacker, 2013).

Nonetheless, LAI-APs remain underutilized in most countries (Kane and Garcia-Ribera, 2009; Tang et al., 2020) for various reasons, including pain, fear of needles, and cost. In addition, there are concerns that LAI-APs might cause severe adverse events such as neuroleptic malignant syndrome (NMS), tardive dyskinesia, and cardiovascular events and lead to prolonged symptoms compared with oral antipsychotics (OAPs) (Glazer and Kane, 1992; Nasrallah, 2007). This is because LAI-APs cannot be rapidly removed from the body once they are initiated with a high dose (Misawa et al., 2016). NMS, characterized by rigidity, abrupt onset of fever, autonomic dysregulation, and altered mental status (Ananth et al., 2004), is one of the most serious and potentially fatal adverse events associated with antipsychotic treatment.

It remains controversial whether LAI-APs are associated with a higher risk of NMS compared with OAPs. A case-control study using health care registers reported that LAIs could be a risk factor for NMS (Nielsen et al., 2012). On the other hand, another case-control study using electronic health record data found that the risk depended on the type of LAI (Su et al., 2014). In addition, studies based on adverse event databases determined that LAI use did not increase the risk of NMS (Hatano et al., 2020; Kane et al., 2019). In particular, the risk of NMS associated with LAI-SGAs is unclear because few reports are available on the association of NMS with LAI-SGAs, which are newer than LAI first-generation antipsychotics (LAI-FGAs).

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In this study, we compared reporting frequency, time to onset, and mortality of NMS between LAI-SGAs and oral SGAs using a large spontaneous reporting database in Japan.

2. Methods

2.1. Database

This study used data from the Japanese Adverse Drug Event Report (JADER). JADER is a large database established in 2004 by the Pharmaceuticals and Medical Devices Agency (PMDA), which is a Japanese regulatory agency. It comprises spontaneous reports of adverse events from physicians, pharmacists, other health care professionals, and patients and is available from the website of the PMDA (Pharmaceuticals and Medical Devices Agency, 2004). Using the JADER database, studies investigating possible associations between specific drugs and adverse drug reactions have been proposed from the viewpoint of signal detection (Fujiwara et al., 2016). Data from JADER, which contains over 600,000 patients, comprise four component tables: 1) demographic information, 2) drug information, 3) adverse reactions, and 4) medical history. The data listed in each table are shown in Supplemental Table 1. These tables can be connected using the patient ID number. Adverse events in the adverse reaction table are coded according to the terminology in the Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J) (Pharmaceutical and Medical Device Regulatory Science Society of Japan, 2010).

2.2. Inclusion and exclusion criteria

We extracted data reported from April 2004 to September 2019 from JADER. We included patients who received any of three LAI-SGAs (LAI aripiprazole, LAI risperidone, and LAI paliperidone) and the equivalent oral SGAs (oral aripiprazole, oral risperidone, and oral paliperidone) in the "suspected medicine" list. In JADER, the contribution of the medication to adverse events is classified into three 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 excluded patients younger than 10 years old and older than 79 years old, because it is likely that patients in these age groups received antipsychotics for disorders other than schizophrenia. In addition, we excluded patients who could not be classified into a specific age group (e.g., patients described with the following: "unknown", "elderly", "adult", or "young adult") and patients lacking age information.

2.3. Definition of antipsychotic exposure

LAI aripiprazole, LAI risperidone, and LAI paliperidone are all LAI-SGAs available in Japan and were launched in Japan in May 2015, June 2009, and November 2013, respectively.

The name of each SGA was described in JADER as the following: "aripiprazole hydrate" for LAI aripiprazole; "risperidone" for LAI risperidone; "paliperidone palmitate" for LAI paliperidone; "aripiprazole" for oral aripiprazole; "risperidone" for oral risperidone; and "paliperidone" for oral paliperidone. Because both LAI and oral risperidone were described as "risperidone", we distinguished between the LAI and oral formulations by the administration route and/or dose. However, we excluded 88 patients for whom it was unclear whether LAI or oral risperidone was used.

Oral risperidone and paliperidone were considered the equivalent antipsychotics in this study because paliperidone is the main active metabolite of risperidone. On the other hand, we distinguished between LAI risperidone and LAI paliperidone because of the difference in the injection interval (2 weeks and 4 weeks, respectively).

Some patients received concomitant treatment with antipsychotics that were targeted in the "suspected" list. Patients treated with an LAI-SGA plus an oral SGA were categorized in the LAI-SGA group. Patients treated with an LAI-SGA plus another LAI-SGA or an oral SGA plus another oral SGA were considered as one patient but were included in each antipsychotic group when they were being compared with each different formulation of the equivalent antipsychotic (e.g., patients treated with oral risperidone and oral aripiprazole were included in the oral risperidone/paliperidone group when they were being compared with LAI risperidone or LAI paliperidone and in the oral aripiprazole group when they were being compared with LAI aripiprazole).

We regarded patients who received two or more antipsychotics in the "suspected medicine" list, which included not only the three LAI-SGAs and three oral SGAs targeted in this study, but also other antipsychotics, or those who received antipsychotics in the "concomitant medicine" list as concomitant use of antipsychotics.

2.4. Outcome

We detected patients with NMS by searching for "neuroleptic malignant syndrome", which is the preferred term used in the MedDRA/J (PT 10029282).

2.5. Analyses

2.5.1. Reporting odds ratio

The reporting odds ratio (ROR) is a validated effect measure for safety signal detection (Montastruc et al., 2011) that has frequently been used in spontaneous reporting databases as the safety signal index (Niinomi et al., 2019). It is calculated using a two-by-two contingency table (Rothman et al., 2004). In this study, the ROR was the ratio of the odds of reported NMS versus all other adverse events associated with an LAI-SGA compared with the equivalent oral SGA, except for adverse events related to injection, as mentioned below. We calculated adjusted RORs (aRORs) with the 95% confidence interval (CI) of NMS associated with each LAI-SGA using a logistic regression model adjusted for age group, sex, and the concomitant use of antipsychotics and/or lithium.

An aROR < 1 indicated that NMS was considered to be less reported after the use of an LAI-SGA compared with the equivalent oral SGA.

We excluded patients with unknown sex from the ROR analyses. In addition, because injection site induration, injection site pain, and post-injection delirium/sedation syndrome are not caused by oral SGAs, we excluded patients with such adverse events.

To match analysis periods between each of the equivalent LAI- and oral SGAs in the ROR analyses, we limited the time period to that after each specific LAI-SGA was launched in Japan: from the second quarter of 2015 for LAI aripiprazole; from the second quarter of 2009 for LAI risperidone; and from the fourth quarter of 2013 for LAI paliperidone.

2.5.2. Time to onset of NMS

We calculated the time to onset of NMS by using the initiation dates of each antipsychotic and of NMS onset. Therefore, we excluded patients with no date data from the analyses. If the date had only the month and year and not the day, we regarded the day as the 15th. If the date of initiation of the antipsychotic was after the date of NMS onset with this procedure, we considered the time to onset to be 0 days (i.e., the day of initiation of the antipsychotic was unknown and the date of onset of NMS was described as the day before the 15th).

2.5.3. NMS mortality

In the JADER database, clinical course is classified into six categories: "remission", "recovery", "death", "unrecovered", "sequelae", and "unclear". We calculated the proportion of death due to NMS associated with each LAI-SGA and oral SGA. We excluded patients with an

unknown clinical course from the mortality analysis: 23 patients (8.1%) receiving oral aripiprazole, 2 (11.8%) receiving LAI aripiprazole, 64 (14.6%) receiving oral risperidone/paliperidone, 5 (17.2%) receiving LAI risperidone, and 5 (14.7%) receiving LAI paliperidone.

2.5.4. Study approval and statistical software

This study did not require 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).

3. Results

3.1. Clinicodemographic characteristics

The present study included 5791 patients. The number of patients in each analysis is displayed in Supplemental Table 2. Patient characteristics are shown in Table 1. In the group aged less than 30 years, fewer patients received LAI-SGAs than oral SGAs. More patients concomitantly received antipsychotics in all LAI-SGA groups than in the equivalent oral SGA groups.

3.2. Adjusted RORs of NMS

NMS was significantly less reported with LAI aripiprazole or LAI paliperidone than with the equivalent oral SGA (LAI aripiprazole, aROR [95% CI] = 0.35 [0.19–0.63]; LAI paliperidone, aROR [95% CI] = 0.40 [0.27–0.59]) (Table 2). The reporting frequency of NMS associated with LAI risperidone was numerically lower than that associated with oral risperidone/paliperidone (aROR [95% CI] = 0.69 [0.45–1.06]), although the difference did not reach statistical significance (Table 2).

None of the confounding factors entered into the logistic models, such as age group, sex, and the concomitant use of antipsychotics and/or lithium, were significantly associated with the reporting frequency of NMS.

3.3. Time to onset of NMS

The median times to onset of NMS associated with LAI risperidone, LAI aripiprazole, and LAI paliperidone were about 15 weeks, 3 weeks, and 5 weeks, respectively. The time to onset of NMS associated with oral SGAs was within 1 month.

Although only about 30% of NMS associated with LAI risperidone occurred within 30 days after initiation, about half of patients treated with the other LAIs and oral SGAs had NMS within 30 days after initiation.

In patients with concurrent use of LAI-SGAs and other antipsychotics, the median times were longer than in those who received only LAI-SGAs. Moreover, the times were longer in patients who started receiving other antipsychotics after the initiation of LAI-SGAs than in those who did so before the initiation (Supplemental Table 3).

In a subgroup of patients who concomitantly received equivalent LAI- and oral SGAs, which is common in the early stage of LAI-SGA administration, the median times were as follows: 104 days for LAI risperidone (n = 13), 53 days for LAI aripiprazole (n = 7), and 34 days for LAI paliperidone (n = 11).

In short, NMS appeared to occur at a relatively early stage of both LAI- and oral SGA treatment (Table 3).

3.4. NMS mortality

In total, 13.1% of patients with NMS associated with oral aripiprazole died. On the other hand, no patients died of NMS associated with LAI aripiprazole. The proportion of death due to NMS associated with oral risperidone/paliperidone was 8.8%, whereas the proportions for LAI risperidone and LAI paliperidone were both about 4% (Table 4).

None of the patients with concomitant use of equivalent LAI- and oral SGAs died of NMS.

4. Discussion

To our knowledge, this is the largest study to compare LAI- and oral SGAs in terms of occurrence of NMS. Furthermore, the present study examined the time to onset of NMS, an aspect that had scarcely been investigated. We found that LAI-SGAs were not associated with a high reporting frequency and mortality of NMS compared with oral SGAs. In addition, NMS associated with both LAI- and oral SGAs was possible in the relatively early stage of antipsychotic administration.

In the present study, there were fewer reports of NMS associated with LAI-SGAs than with oral SGAs. Given that LAI-APs are used with a large single dose and cannot be rapidly removed from the body, LAI-APs may be expected to have a higher risk of NMS. Some studies suggested that LAI-FGAs could be considered a risk factor for NMS (Deng et al., 1990). In a longitudinal register linkage case-control study (Nielsen et al., 2012), treatment with LAI-APs, including five LAI-FGAs and LAI risperidone, increased the risk of NMS. However, another case-control study showed that the use of LAI flupentixol was significantly associated with NMS, unlike LAI risperidone (Su et al., 2014). In the Janssen clinical trial database, the occurrence of NMS associated with LAI paliperidone 1-monthly and 3-monthly was very rare (4/10,000 patient-years) (Kane et al., 2019). These and our findings indicate that at least LAI-SGAs might not have a high risk of NMS. Besides

Table 1
Patients' characteristics.

	All (n = 5791)	Oral aripiprazole (n = 2116)	LAI aripiprazole (n = 333)	Oral risperidone/paliperidone (n = 2711)	LAI risperidone (n = 255)	LAI paliperidone (n = 553)
Sex, n (%)						
Male	3010 (52.3)	1062 (50.5)	156 (47.1)	1425 (52.9)	143 (57.2)	313 (56.9)
Unknown	38 (0.7)	12 (0.6)	2 (0.6)	18 (0.7)	5 (2.0)	3 (0.5)
Age, n (%)						
10–19 years	271 (4.7)	109 (5.2)	4 (1.2)	160 (5.9)	3 (1.2)	7 (1.3)
20–29 years	625 (10.8)	270 (12.8)	27 (8.1)	311 (11.5)	17 (6.7)	31 (5.6)
30–39 years	1055 (18.2)	406 (19.2)	55 (16.5)	490 (18.1)	42 (16.5)	89 (16.1)
40–49 years	1150 (19.9)	408 (19.3)	100 (30.0)	465 (17.2)	67 (26.3)	145 (26.2)
50–59 years	1064 (18.4)	406 (19.2)	54 (16.2)	474(17.5)	47 (18.4)	115 (20.8)
60–69 years	1020 (17.6)	344 (16.3)	63 (18.9)	463 (17.1)	59 (23.1)	116 (21.0)
70–79 years	606 (10.5)	173 (8.2)	30 (9.0)	348 (12.8)	20 (7.8)	50 (9.0)
Concomitant use, n (%)						
Antipsychotics	2255 (38.9)	854 (40.4)	260 (78.1)	861 (31.8)	161 (63.1)	294 (53.2)
Lithium	205 (3.5)	97 (4.6)	8 (2.4)	79 (2.9)	10 (3.9)	19 (3.4)

Abbreviation: LAI, long-acting injectable.

Table 2
Reporting odds ratios of NMS.

	n	NMS, n (%)	Crude ROR (95% CI)	Adjusted ROR (95% CI)[c]
Oral aripiprazole	707	98 (13.9)	0.33 (0.20–0.57)[a]	0.35 (0.19–0.63)[a]
LAI aripiprazole	331	17 (5.1)		
Oral risperidone/paliperidone	1976	280 (14.2)	0.78 (0.52–1.17)[b]	0.69 (0.45–1.06)[b]
LAI risperidone	250	28 (11.2)		
Oral risperidone/paliperidone	1211	166 (13.7)	0.41 (0.28–0.61)[b]	0.40 (0.27–0.59)[b]
LAI paliperidone	550	34 (6.2)		

Abbreviations: LAI, long-acting injectable; NMS, neuroleptic malignant syndrome; ROR, reporting odds ratio.
[a] Versus oral aripiprazole.
[b] Versus oral risperidone/paliperidone.
[c] Adjusted for age group, sex, and the concomitant use of antipsychotics and/or lithium.

the characteristics of SGAs, this may be because the equivalent oral SGAs are used before the initiation of LAI-SGAs to evaluate the tolerability of the SGA, as required by the package inserts. On the other hand, tolerability assessment with OAP treatment is not required for LAI-FGAs. If NMS occurs in the OAP period, the agent in question is generally switched to a different oral drug, not to the equivalent LAI. Accordingly, tolerability assessment with the equivalent oral SGAs may have contributed to the lower risk of NMS associated with LAI-SGAs than with oral SGAs.

Furthermore, if NMS does tend to occur in the relatively early stage of antipsychotic administration, as found in the present study, tolerability assessment becomes more important to prevent the development of NMS associated with LAI-SGAs. In a review of 115 cases of NMS associated with FGAs, NMS occurred within the first 2 weeks of treatment in 66% of the cases, although NMS could occur at any time in the course of neuroleptic treatment (Addonizio et al., 1987). In another review of 68 cases of NMS associated with SGAs (Ananth et al., 2004), NMS occurred within 2 weeks in 62% of cases, although the mean duration from the initiation or last major change of SGA to the onset of NMS was 120 days. In the present study, the median durations from the start of oral and LAI-SGA treatment before the onset of NMS were less than 1 month and from 3 weeks to 3 months, respectively. Accordingly, NMS probably occurs in the relatively early stage of antipsychotic administration. When LAI-SGAs are initiated, clinicians should assess tolerability with oral SGAs for more than 1 month and monitor the development of NMS, especially in the early stage of LAI-AP administration.

The present study found that LAI-SGAs were not associated with higher mortality of NMS compared with oral SGAs. Because LAI-APs cannot be removed from the body even after adverse effects occur, they can be expected to be associated with a more severe clinical course after the occurrence of NMS than OAPs. While few studies have investigated the differences in the clinical course of NMS between LAI-APs and OAPs, a review of LAI-FGAs reported that there was no evidence that mortality due to NMS was higher with LAI-APs than with OAPs (Glazer and Kane, 1992). A case report described that NMS associated with LAI risperidone improved relatively quickly and completely, although the serum level of the risperidone active moiety was maintained at a steady-state level (Yamashita et al., 2013). Slow elimination of LAI-APs and the serum concentration of antipsychotics may not affect the clinical course of NMS. However, because the long-term effect of LAI-APs, including LAI-SGAs, can theoretically increase the risk of a severe clinical course, clinicians should closely monitor the development of NMS during LAI-AP treatment.

The findings of this study need to be interpreted in the context of several limitations. First, because JADER is a spontaneous reporting database, the results may have been affected by a reporting bias, although severe adverse events such as NMS tend to be reported. In addition, serious adverse events including NMS associated with LAI-SGAs might be more likely to be reported in Japan because a safety advisory was issued in 2014 after the reporting of fatal cases associated with LAI paliperidone. Second, we were unable to calculate accurate risks of the development of NMS associated with LAI-SGAs. Rothman et al. (2004) reported that the ROR can be used to estimate the relative risk by treating the spontaneous report database as source data for a case-control study and then by eliminating adverse events that might be subject to a difference in reporting frequency. Although we excluded adverse events related to injection, many other such adverse events could not be eliminated because severe adverse events associated with LAI-SGAs are probably more likely to be reported than those associated with oral SGAs after the issuing of the safety advisory on LAI paliperidone, as described above. Third, although a rapid dose escalation or high dose of antipsychotics may be associated with risk of NMS (Keck et al., 1989), we were not able to obtain such data from JADER. Fourth, because there were not enough data on psychiatric diagnoses in JADER, we did not include them in the analyses. Psychiatric diagnoses may have influenced the results of this study, given that oral SGAs are used more frequently for patients with non-schizophrenia conditions such as mood disorders than LAI-SGAs and patients with mood disorders are more vulnerable to the development of antipsychotic-induced extrapyramidal symptoms than those with schizophrenia (Gao et al., 2008). Fifth, we could not sufficiently evaluate the influence of combined antipsychotics. Although they were not associated with the reporting frequency of NMS in the logistic models, these models may not have been adjusted for enough confounding factors. For instance, we did not distinguish between FGAs and SGAs for combined antipsychotics because we could not obtain detailed data on antipsychotic doses from the JADER. Without this information, it would not be clinically useful to evaluate the risk (e.g., it is difficult to compare the risk

Table 3
Time to onset of NMS.

	n[a]	Median duration (interquartile range), days	NMS occurrence within 30 days, n (%)
Oral aripiprazole	190	21.5 (8–58.25)	118 (62)
LAI aripiprazole	12	19 (3–101.75)	7 (58)
Oral risperidone/paliperidone	210	27.5 (5–157)	110 (52)
LAI risperidone	25	104 (16–185)	7 (28)
LAI paliperidone	24	34.5 (4.25–117.75)	10 (42)

Abbreviations: LAI, long-acting injectable; NMS, neuroleptic malignant syndrome.
[a] Number of patients with NMS with date data.

Table 4
Death due to NMS.

	n[a]	Death, n (%)
Oral aripiprazole	260	34 (13.1)
LAI aripiprazole	15	0 (0)
Oral risperidone/paliperidone	374	33 (8.8)
LAI risperidone	24	1 (4.2)
LAI paliperidone	29	1 (3.4)

LAI, long-acting injectable; NMS, neuroleptic malignant syndrome.
[a] Number of patients with NMS with clinical course data.

between haloperidol 1 mg/day and risperidone 10 mg/day). In addition, it is difficult to determine whether or not antipsychotics combined with LAI-SGAs triggered NMS because we could not obtain data on the risk factors for NMS. Combined antipsychotics may be a trigger for NMS, given that the times to onset of NMS were longer in patients who started receiving other antipsychotics after the initiation of LAI-SGAs than in those who did so before the initiation. On the other hand, patients with risk factors for NMS could be more likely to discontinue combined antipsychotics quickly and not to start receiving other antipsychotics after the initiation of LAI-SGAs; thus, NMS may have occurred earlier in patients who received only LAI-SGAs than in those who received LAI-SGAs plus other antipsychotics or in patients who started receiving other antipsychotics before the initiation of LAI-SGAs than in those who did so after the initiation. Sixth, NMS was diagnosed in each case based on clinical judgment without the specific criteria, which may have resulted in the inconsistency in the occurrences and times to onset of NMS. Lastly, there may be duplicated reports in the JADER database because the same case could have been reported by different persons (e.g., by a physician and a patient), but we were unable to identify them because these is no key code to identify overlapping patients in the database.

5. Conclusion

These findings suggest that LAI-SGAs may not be associated with a higher frequency and mortality of NMS compared with oral SGAs. Nonetheless, clinicians need to closely monitor the development of NMS during LAI-AP treatment to recognize it as early as possible. Because of the limitations related to a spontaneous reporting database, further studies are warranted to investigate the risk of NMS associated with LAI-SGAs.

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There is no funding source to declare.

CRediT authorship contribution statement

All authors contributed to the study design and interpretation of the results. FM contributed to the statistical analysis and the writing of the report. All authors participated in the critical revision of manuscript drafts and approved the final version.

Declaration of competing interest

FM has received speaker's honoraria from Sumitomo Dainippon, Eli Lilly, Janssen, Novartis, Otsuka, and Pfizer.

YO has received personal fees from MSD K.K., Otsuka Pharmaceutical, Cando, Japan Medical Data Center, and Japan Medical Research Institute. He is also an employee of the Real World Data, Co., Ltd. and a president of the Initiative for Clinical Epidemiological Research.

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Appendix A. Supplementary data

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