Brief Report

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Time to onset of drug-induced parkinsonism: Analysis using a large Japanese adverse event self-reporting database

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SUMMARY Whether there are differences in the time to onset of drug-induced parkinsonism (DIP) depending on the type of drugs causing DIP remains uncertain, so that question was investigated here using a large real-world database. Fourteen DIP-related drug categories were defined to perform a disproportionality analysis using a large Japanese pharmacovigilance database containing more than 600,000 self-reported adverse events (AEs) recorded between April 2004 and September 2021 to identify AEs indicating "parkinsonism" in association with the defined drug categories. The time from drug administration to the onset of DIP was comparatively analyzed. Results indicated that the median time to onset was shorter than 1 month in more than half of the cases of DIP; it was shortest with peripheral dopamine antagonists (median: 0.1 weeks), followed by benzodiazepine (median: 0.5 weeks), butyrophenone (median: 0.7 weeks), novel antidepressants (median: 2.5 weeks), atypical antipsychotics (median: 3.3 weeks), other antidepressants (*e.g.*, lithium, median: 3.7 weeks), and benzamide (median: 4.5 weeks). In contrast, anti-dementia drugs, tricyclic antidepressants, and antiepileptic drugs resulted in a relatively longer time to onset (median: 9.9, 17.2, and 28.4 weeks, respectively). In addition, a maximum delay of even longer than 2 years was reported for benzamide (846 weeks), anti-Parkinsonism drugs (382 weeks), phenothiazine (232 weeks), atypical antipsychotics (167 weeks), anti-dementia drugs (161 weeks), and benzodiazepines (120 weeks). The current results suggested that the characteristics of the time to onset of DIP may substantially differ depending on the type of drug causing that DIP. This finding may help when diagnosing patients with parkinsonism.

Keywords drug-induced parkinsonism, real-world data, adverse events, pharmacovigilance

1. Introduction

Drug-induced parkinsonism (DIP) is a syndrome in which parkinsonian symptoms typically occur within a few months after receiving specific drugs (*1,2*), such as antipsychotics (*3*). Parkinson's disease (PD) is characterized by a faster clinical course, a higher frequency of a symmetrical distribution of symptoms, or a poorer response to levodopa therapy. Although dopamine antagonists are drugs that typically cause DIP (*1,2*), it can also be caused by various types of medications, including antidepressants (tricyclic antidepressants [TCAs], novel antidepressants, including selective serotonin reuptake inhibitors [SSRIs]), benzodiazepines, calcium channel blockers (CCBs), peripheral dopamine antagonists (metoclopramide or domperidone), antiepileptic drugs (valproate), or other miscellaneous drugs (*4*).

When diagnosing DIP, physicians suspect the drug that a patient recently started taking is the cause of acute-onset parkinsonian symptoms, so the drug is withdrawn to confirm the diagnosis of DIP. This is because the time from administration to the development of DIP is, in many cases, short. An earlier pharmacovigilance study based on a large number of self-reports from France (*4*) reported that approximately 70% of cases of DIP occurred within 3 months after receiving the drugs that caused DIP. An earlier study also reported that 20% of cases of DIP occurred up to 12 months after administration (*4*). CCBs were also reported to result in a longer time to onset than typical antipsychotics or benzamides (*4*). This means that the duration of the time to onset may need to be considered in order to correctly differentiate DIP from PD and to

identify the drug causing DIP. This is because DIP and subclinical dopaminergic dysfunction sometimes occur concurrently (*2,5*) and because patients with DIP are sometimes taking several types of potentially causative drugs simultaneously (*e.g.*, CCBs for hypertension and antidepressants for depression). To date, however, the details of the time to onset due to other potentially causative drugs or possibly a longer range of time remain unclear. If these details can be characterized in detail, then this might help clinicians determine the likelihood of a drug being the cause of their patients' parkinsonism.

To address these points, potential cases of DIP were analyzed using a large Japanese database of self-reported adverse events (AEs). This pharmacovigilance database provides structured data on a large number of cases of potentially drug-induced AEs, including dates of drug administration and AE onset. Despite its limitations due to the nature of self-reports, this database has been widely used to identify hypothetical associations between drugs and AEs (*6*). The current attempt might provide some useful suggestions regarding more detailed aspects of time to onset that are difficult to collect in sufficient numbers in conventional observational studies.

2. Materials and Methods

2.1. Data acquisition and preprocessing

This was a retrospective pharmacovigilance study using the Japanese Adverse Drug Event Report (JADER) database provided by the Pharmaceuticals and Medical Devices Agency (PMDA). Data were downloaded with permission from the PMDA website (*https://www.pmda.go.jp*) on December 2021, and they included more than 600,000 case reports with potential drug AEs recorded in Japan between April 2004 and September 2021. The JADER database consists of 4 component data tables (*6,7*): [1] "demo", which provides each unique case IDs, sex, age group (*e.g.*, 40s or 60s), year of the report, route of the report (*e.g.*, from a clinical trial or spontaneous reporting), and reporters' demographics (*e.g.*, medical doctor, pharmacist, lawyer, consumer); [2] "reac", which includes all adverse reactions potentially due to drug use for each patient; [3] "drug", which includes all possibly associated drugs, their dose, indications for their usage, and the date of administration and discontinuation; and [4] "hist", which includes each patient's primary illness or medical history. In the "drug" table, the extent to which a drug is suspected of causing an AE is classified as "suspected", "concomitant", or "interacting". The current analysis included only the "suspected" drug category to reduce the number of false-positive cases in order to obtain sufficient specificity of the reported DIP with respect to true DIP. The types of reporters to the database were limited to doctors, pharmacists, or any other medical staff but excluded lawyers or consumers to increase the diagnostic certainty of the reported DIP. The report's quality, evaluated in accordance with the World Health Organization criteria (*8*), was also examined, and reports of poor quality (*i.e.*, grade = 0) were excluded from the analysis. Duplicate AEs in the "reac" table reported for the same case ID or duplicate drug names in the "drug" table reported for the same case ID were subsequently deleted.

Since the JADER database infrequently contains potentially duplicate records for the same patient but reported by different reporters (*e.g.*, by the hospital doctor and the pharmaceutical company) with different case IDs, reported AEs in the "reac" table were excluded when all of the following data matched completely: the AE, outcome, date of AE onset, age group, sex, weight, height, year of the report, and quarter of the report (Q1-Q4). Moreover, reported drug information records in the "drug" table were excluded when all of the following data matched completely: drug name, date of drug administration and discontinuation, age group, sex, weight, height, year of the report, and quarter of the report (Q1-Q4).

2.2. Database search

In the JADER database, AEs and disease indications are given by the Preferred Terms determined by the Medical Dictionary for Regulatory Activities/Japanese version (version 22; *https://www.pmrj.jp/jmo/php/indexe.php*). Here, the term "Parkinsonism" (level, PT) alone was used for the search, and patients presenting with this AE were deemed to have DIP. Other terms related to PD symptoms (*e.g.*, "Resting tremor", "Rigidity", "Akinesia", or "Postural instability") were not included as criteria for DIP in order to obtain greater specificity for a parkinsonian diagnosis.

Suspected drugs in these cases of DIP were identified. Fourteen drug categories were arbitrarily defined in accordance with the literature (*1,2,4*), as listed in Table 1. Table 1 also provides the corresponding drug names actually identified in the database, including the following: antipsychotic types (including categories of phenothiazine, butyrophenone, benzamide, and atypical antipsychotics); peripheral dopamine antagonists; antidepressants (including categories of tricyclic/tetracyclic antidepressants, SSRI, serotonin and noradrenaline reuptake inhibitors [SNRIs], noradrenergic and specific serotonergic antidepressants [NaSSAs], and other antidepressants); hypnotic drugs, including benzodiazepine or non-benzodiazepine categories; and other types of drugs, including categories of antiepileptic drugs, anti-dementia drugs, anti-PD drugs, CCBs, and histamine blockers. Any miscellaneous drugs not included in these categories are not shown in the table.

Cases in which parkinsonism was present before the use of the drug were excluded, and then each reported case was classified (*9,10*) depending on binomial factors:

Table 1. List of the 14 drug categories and the corresponding drug names identified from the database

Drug category	*n*	Included drugs
Phenothiazine	13	Chlorpromazine (*n* = 6), prochlorperazine (*n* = 3), levomepromazine (*n* = 1), perphenazine (*n* = 1), fluphenazine decanoate (*n* = 2)
Butyrophenone	10	Haloperidol (*n* = 10)
Benzamide	22	Sulpiride (*n* = 18)
Atypical antipsychotics	85	Risperidone (*n* = 17), aripiprazole (*n* = 22), olanzapine (*n* = 4), quetiapine (*n* = 8), paliperidone (*n* = 11), perospirone (*n* = 5), blonanserin (*n* = 5), clozapine (*n* = 8), asenapine (*n* = 5)
Peripheral dopamine antagonist	9	Metoclopramide (*n* = 8), domperidone (*n* = 1)
Tricyclic antidepressants	4	Amoxapine (*n* = 2), mianserin (*n* = 1), amitriptyline (*n* = 1)
Novel antidepressants (SSRI, SNRI, NaSSA)	24	Paroxetine (*n* = 8), mirtazapine (*n* = 4), sertraline (*n* = 1), duloxetine (*n* = 3), escitalopram (*n* = 3), fluvoxamine (*n* = 2), milnacipran (*n* = 2), venlafaxine (*n* = 1)
Other antidepressants	5	Lithium carbonate (*n* = 1), trazodone (*n* = 4)
Benzodiazepines	14	Etizolam (*n* = 4), clonazepam (*n* = 4), flunitrazepam (*n* = 3), lorazepam (*n* = 1), bromazepam (*n* = 2)
Antiepileptic drugs	5	Valproate (*n* = 3), carbamazepine (*n* = 1), levetiracetam (*n* = 1)
Anti-dementia drugs	19	Donepezil (*n* = 7), galantamine (*n* = 5), memantine (*n* = 4), rivastigmine (*n* = 3)
Anti-Parkinson drugs	9	Levodopa (*n* = 2), pramipexole (*n* = 2), biperiden (*n* = 3), amantadine (*n* = 2)
Calcium channel blockers	2	Amlodipine (*n* = 1), nicardipine (*n* = 1)
H_2 antagonists	2	Famotidine (*n* = 1), lafutidine (*n* = 1)

Parentheses indicate the number of patients with drug-induced parkinsonism and the exposure to each drug (or drug category). Other miscellaneous drugs not included in the above categories are not considered. *Abbreviations*: SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant.

with/without exposure to the drug category of interest as listed above and with/without the occurrence of an AE involving parkinsonism, regardless of the timing of drug administration or occurrence of an AE.

2.3. Statistical analyses

All statistical analyses were performed using the software R (version 3.6.3). For each included drug, the reporting odds ratio (ROR) was calculated to identify drugs potentially associated with the development of DIP. The (crude) ROR was calculated using a two-by-two contingency table (*9,10*), where all reports were classified using two factors: with/without DIP and with/without exposure to each drug category. When the lower 95% confidence interval (CI) of the ROR was greater than 1, the DIP was significantly reported more often following the use of the drug category of interest than after the use of all other drugs/drug categories.

Next, a time-to-onset analysis was performed. The period (in weeks) after administration of the drug to the onset of DIP was considered to be the disease-free survival, and the Kaplan-Meier method was used to calculate an estimated survival curve. The drug categories with sufficient cases were selected for further statistical analysis. The 50% survival and its 95% CI were calculated using the R package *survival*. In addition, survival was compared between two drug categories using the Gehan-Wilcoxon test. *P*-values from multiple Gehan-Wilcoxon tests were adjusted using the Benjamini-Hochberg (BH) method for multiple comparisons.

2.4. Ethics

This study was approved by the Institutional Ethics Committee of the University of Tokyo Graduate School of Medicine (ID: 11628-[3]). Informed consent was not required for this type of study because this study only used publicly distributed data. This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki.

3. Results and Discussion

In total, 392,835 AEs were reported within the period studied. There were 311 reported cases (0.08%) of DIP. More than half of the patients with DIP were women (172/311, 55.3%), and their median age group was 60-69 years (interquartile range: 50-70 years). Atypical antipsychotics were the most frequent drug category taken by patients with DIP (85/311, 27.3%), followed

Table 2. Detailed summary of the 14 drug categories

Drug category	*n*	Crude ROR (95% CI)		Medication to onset (weeks)		
				Median (95% CI)	Minimum	Maximum
Phenothiazine	13	23.98 (14.55 - 37.5)	*	5.70 (2.1 - NA)	0.1	232.1
Butyrophenone	10	33.08 (19.23 - 53.72)	*	0.70 (0.3 - NA)	0.1	56
Benzamide	22	100.25 (72.01 - 137.55)	*	4.05 (1.4 - 12.1)	0.1	846
Atypical antipsychotics	85	23.29 (18.21 - 29.64)	*	3.30 (2 - 5.7)	0	166.9
Peripheral dopamine antagonists	9	25.57 (14.04 - 43.1)	*	0.10 (0.1 - NA)	0	95.9
Tricyclic antidepressants	4	14.12 (6.01 - 28.33)	*	17.15 (2.7 - NA)	2.7	19.3
Novel antidepressants (SSRIs, SNRIs, NaSSAs)	24	11.15 (7.84 - 15.5)	*	2.45 (1.3 - 5.6)	0.1	115
Other antidepressants	5	17.68 (9 - 31.55)	*	3.70 (0.9 - NA)	0.9	6.6
Benzodiazepines	14	7.23 (4.22 - 11.66)	*	0.50 (0 - 43.1)	0	120.3
Antiepileptic drugs	5	1.21 (0.48 - 2.52)		28.40 (11.4 - NA)	5	258.1
Anti-dementia drugs	19	15.54 (10.12 - 23.01)	*	9.90 (6.4 - 40.1)	0.3	160.6
Anti-Parkinson drugs	9	11.30 (6.36 - 18.71)	*	9.10 (4 - NA)	1.4	382
Calcium channel blockers	2	6.96 (3.43 - 12.67)	*	0.75 (0.4 - NA)	0.4	1.1
H_2 antagonists	2	1.98 (0.54 - 5.14)		18.4 0(0.9 - NA)	0.9	35.9

*, Significantly elevated ROR (lower 95% CI > 1). The median and 95% confidence interval (CI) of the time to onset were obtained *via* a survival analysis. When the number of reported cases was insufficient, the 95% CI could not be adequately determined. In such instances, the upper limit of the 95% CI is marked N/A. Abbreviations: DIP, drug-induced parkinsonism; ROR, reporting odds ratio; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressants; N/A, not available.

by novel antidepressants (24/311, 7.7%) and benzamide (22/311, 7.1%).

A detailed summary of the results for the 14 drug categories is shown in Table 2. Most of the drug categories were significantly reported more often for DIP (as shown with an asterisk (*), meaning that the lower limit of the 95% CI was > 1). This was especially true of benzamide (*e.g.*, sulpiride). Figure 1A shows the median time to onset of DIP for each of the 14 drug categories (excluding those with significantly few cases [$n < 3$]) arranged in order of their medians. The boxes for the drug categories with a sample size large enough to determine the 50% survival and 95% CI are colored in gray (Figure 1A). The number of eligible patients in each drug category and the disease-free survival varied substantially depending on the drug category.

The median disease-free survival was shorter than 1 month in more than half of patients with DIP (50% of the disease-free survival for all patients with DIP was 28.0 days). This was shortest in patients administered peripheral dopamine antagonists (median: 0.1 weeks), followed by benzodiazepine (median: 0.5 weeks), butyrophenone (median: 0.7 weeks), novel antidepressants (median: 2.5 weeks), atypical antipsychotics (median: 3.3 weeks), other antidepressants (*e.g.*, lithium, median: 3.7 weeks), and benzamide (median: 4.5 weeks). In contrast, anti-dementia drugs resulted in a relatively long disease-free survival (median: 9.9 weeks). Patients administered TCAs or antiepileptic drugs had a significantly longer disease-free survival (median: 17.2 and 28.4 weeks, respectively), but their limited sample size decreased the reliability of those numbers.

Considering the maximum disease-free survival, the maximum delay of more than 2 years was reported for benzamide (846 weeks), anti-PD drugs (382 weeks), phenothiazine (232 weeks), atypical antipsychotics (167 weeks), anti-dementia drugs (161 weeks), and benzodiazepines (120 weeks). Moreover, the minimum disease-free survival was < 1 week in many drug categories, although antiepileptic drugs resulted in a minimum disease-free survival of > 1 month.

Five drug categories had a sufficient number of reported cases to determine the 50% survival and its 95% CI (boxplots in gray in Figure 1A): benzodiazepine novel antidepressants (*i.e.*, SSRI, SNRI, and NaSSA), atypical antipsychotics, benzamide, and anti-dementia drugs. The disease-free survival was compared among these five drug categories. Among the 10 pairs in the Gehan-Wilcoxon test, anti-dementia drugs versus novel antidepressants (corrected $p = 0.044$), anti-dementia drugs versus atypical antipsychotics (corrected $p = 0.044$), and anti-dementia drugs versus benzamide (corrected $p = 0.023$) resulted in significant differences in disease-free survival. Survival curves in Figure 1B reveal a longer disease-free survival distribution for anti-dementia drugs.

This study investigated reports of parkinsonism as a potential drug-induced AE along with the administration of several causative drug categories. Results indicated that most of the defined drug categories resulted in DIP significantly more often. Moreover, they resulted in varied median disease-free survival and maximum disease-free survival of varying lengths, which were as long as 2-16 years. The minimum disease-free survival was less than 1 week. These results suggest that the disease-free survival may substantially differ depending on the type of drugs causing DIP. This finding may help to inform clinical practice when diagnosing patients with parkinsonism.

The clinical utility of the current study is particularly

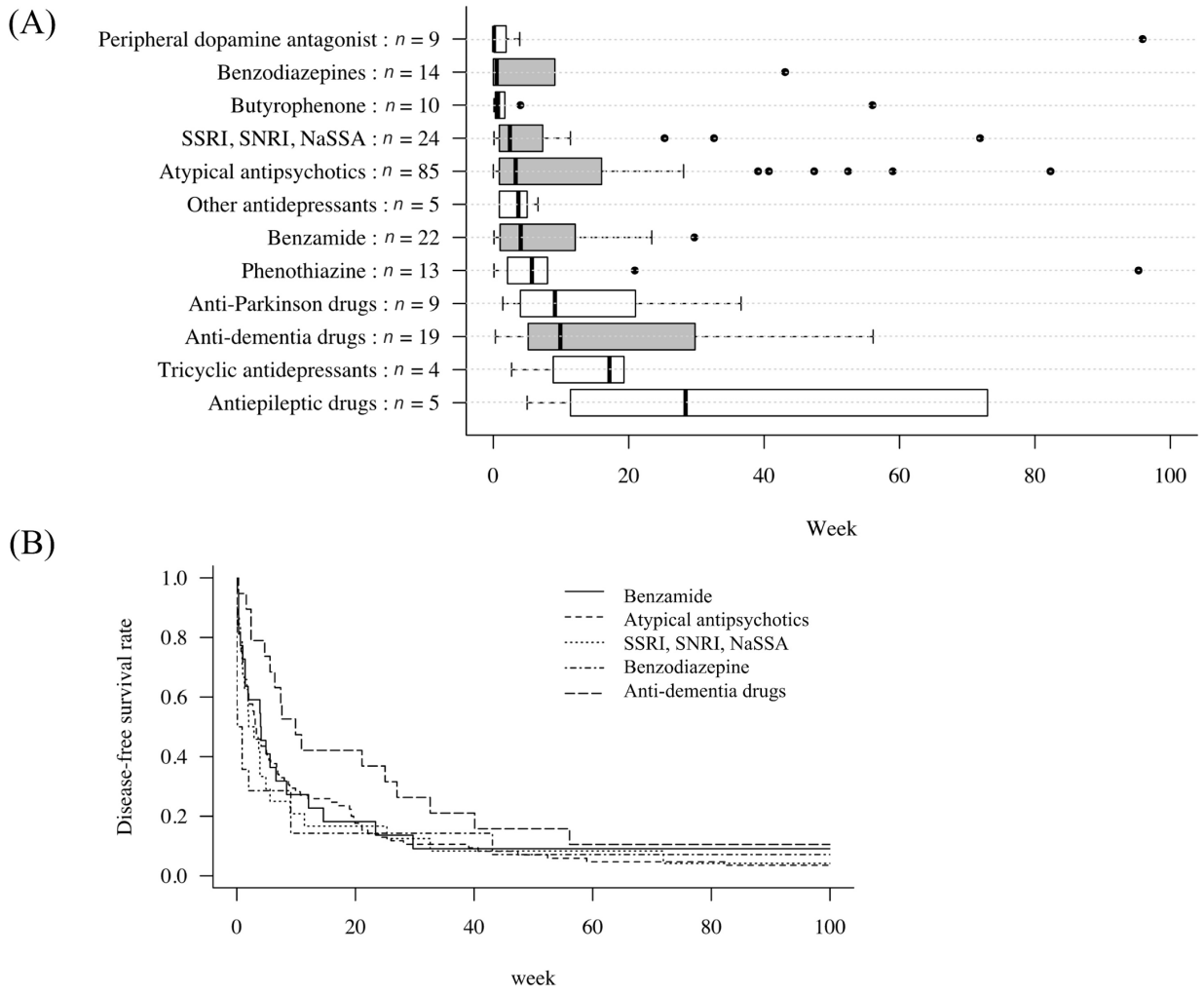

Figure 1. Summary of the disease-free survival in each drug category. The period of onset for the 16 drug categories is summarized as boxplots **(A)**, in order of median time. Cells in a category with a sample size large enough to determine the 50% survival and its 95% confidence interval are colored gray. **(B)** Survival curves from the administration of benzodiazepines or anti-dementia drugs to the onset of drug-induced parkinsonism (DIP). Anti-dementia drugs resulted in a significantly longer disease-free survival than atypical antipsychotics ($p = 0.040$, corrected using the Benjamini-Hochberg [BH] method), selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, and noradrenergic and specific serotonergic antidepressants ($p = 0.040$, corrected using the BH method), but no other drug pairs resulted in significant differences in survival.

evident in several specific clinical scenarios as follows (here, etizolam is used as an example of a drug with a short delay and donepezil as a drug with a long delay):

i) When one patient with acute-onset parkinsonism was administered etizolam 1 week before onset and donepezil 1 year before onset, both should be considered potential causes of parkinsonism.

ii) When one patient exhibited parkinsonism soon after donepezil was administered for dementia, donepezil should not be ruled out as the potential cause of parkinsonism, regardless of its long disease-free survival.

iii) In one patient with acute-onset parkinsonism and a long (2 years) concurrent history of taking etizolam, the possibility that DIP was due to etizolam cannot be immediately discounted.

iv) When one patient with acute-onset parkinsonism was administered both etizolam and donepezil 1 week before onset, etizolam would more likely be the cause of parkinsonism based on its disease-free survival.

The major strength of the current study is its use of the JADER database. DIP is not a frequent disease, with an annual incidence of 3.3 per 100,000 person-years in 1976-2005 in the United States (*11*) and an estimated incidence of 7.1 per 100,000 person-years in 2012 in South Korea (*12*). Thus, collecting a sufficient number of cases of DIP to conduct an observational study of a large enough scale is not always easy. The self-reporting pharmacovigilance database features reports from a large number of Japanese patients in the real world, allowing a review of a sufficient number of reports that would be difficult in earlier observational studies.

The basic characteristics of the cases of DIP identified in the current study were generally consistent with an earlier pharmacovigilance study from France summarizing reports from 1993 to 2009 (*4*), where approximately half of the patients with DIP were in

their 60s and 70s, and 60% of all patients with DIP were women. The frequency of DIP in that study was 0.7%, which was higher than that in the current study (0.080%), and whether the frequency of DIP differed among all of the self-reported cases examined is uncertain. DIP is defined as the presentation of at least one PD symptom (*i.e.*, resting tremor, rigidity, and akinesia), whereas the current study defined DIP as having "parkinsonism" alone. However, this difference in the definition of DIP alone cannot explain the difference in frequency because the frequency of DIP in the JADER database increased to 0.12% when a definition like that used in the earlier study was used. In addition, the higher frequency of atypical antipsychotics reported in the current study (27.3%, 85/311) also differed from the lower frequency reported in the earlier study (13.5%, 21/155). The increased use of atypical antipsychotics and the decreased use of conventional antipsychotics over time since the 1990s (*13*) may partly explain the fewer reports of DIP since the data analyzed here included cases reported from 2004-2021, about a decade more recent than the earlier study (*4*).

Varied median time to onset may reflect the different underlying mechanisms of the parkinsonism observed. Dopamine antagonists, antidepressants, or benzodiazepines directly inhibit the dopaminergic pathway. Thus, they can induce parkinsonism with a relatively short delay. The reason DIP was reported as an AE after using anti-PD drugs, which should relieve parkinsonism symptoms by themselves, is still unclear. Presumably, these reports represented a spurious correlation confounded by the underlying Lewy body pathology: these "reported" cases may have actually been the prodromal phase (*14*) or paradoxical worsening (*15*) of the underlying PD or patients with dementia with Lewy bodies.

Antiepileptic drugs also resulted in a longer disease-free survival, and the mechanism for this remains unclear. Although infrequent, valproate causes parkinsonism (*5,17*). An earlier review discussed several possible mechanisms of valproate-induced parkinsonism (*18*), such as altered neurotransmitter signaling *via* its GABAergic effect, altered gene expression by activating extracellular-regulated kinase activity, or the unmasking of subclinical dopaminergic deficits by these mechanisms (*5*). In the case of levetiracetam, an earlier study reported a patient with DIP due to levetiracetam administered for Huntington's disease (*18*); however, this patient had taken olanzapine and paroxetine, so the true contribution of levetiracetam to the development of parkinsonism in the current data remains unclear.

The maximum length of the disease-free survival of patients with DIP on dopamine antagonists of more than 2-10 years suggests that it may be longer in range. In other words, when a patient who has used sulpiride for more than 10 years exhibits acute-onset parkinsonism, the possibility of sulpiride-induced parkinsonism cannot be ruled out until confirmation by discontinuing sulpiride. Long-term use of dopamine antagonists will eventually lead to slowly progressing dopaminergic degeneration in patients with prodromal PD (*5,14*).

The current study has several limitations due to the nature of its use of a self-reporting database (*6*); it includes several types of bias that cannot be eliminated in this type of study. First, there may be reporting bias: dopamine-antagonist drugs are known to cause DIP, whereas other drugs, such as antiepileptic drugs or CCBs, may not always cause DIP. Such a discrepancy may prejudice a clinician to believe that non-dopamine antagonists are less likely to be the cause of parkinsonism, so those reactions may be less likely to be reported to JADER. In addition, due to the lack of denominators, the incidence of DIP for each drug cannot be discussed and potentially causative drugs cannot be differentiated from other types of drugs. Moreover, other types of medications or concurrent/past medical history that are potentially related to the development/worsening of DIP were not considered, nor was the concurrent use of potentially causative drugs. Disease-free survival is sometimes not accurate, and the total dose of drugs was not considered in this analysis.

In conclusion, the current results demonstrated that disease-free survival might substantially differ depending on the types of drugs causing DIP. This is informative for clinicians when diagnosing patients with parkinsonism.

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