INTRODUCTION

Drug-induced parkinsonism (DIP) presents with symptoms, such as rigidity, postural instability, and gait disturbance, which also occur in idiopathic Parkinson disease (IPD). Most cases of DIP can be cured by discontinuing the offending drugs, whereas IPD becomes exacerbated over time. However, some DIP patients do not recover completely after discontinuation of the offending drugs.1,2 Approximately 20–22% of IPD patients are ultimately diagnosed with DIP.3,4 Furthermore, patients taking offending drugs have a 1.9–3.2 times higher possibility of developing Parkinson disease than those who do not.5,6 Therefore, to cure DIP and to decrease the risk of IPD, it is very important for doctors to differentiate whether a patient

Trends in the Prevalence of Drug-Induced Parkinsonism in Korea

Ji-Hye Byun1, Hyemin Cho2, Yun Joong Kim3, Joong-Seok Kim4, Jong Sam Baik3, Sunmee Jang2, and Hyeo-Il Ma3

1Pharmaceutical Policy Research Team, Health Insurance Review and Assessment Service, Wonju; 2College of Pharmacy and Gachon Institute of Pharmaceutical Sciences, Gachon University, Incheon; 3Department of Neurology, Hallym University Sacred Heart Hospital, College of Medicine, Hallym University, Anyang; 4Department of Neurology, College of Medicine, The Catholic University of Korea, Seoul; 5Department of Neurology, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea.

Purpose: Discontinuation of offending drugs can prevent drug-induced parkinsonism (DIP) before it occurs and reverse or cure it afterwards. The aim of this study was to investigate the prevalence of DIP and the utilization of offending drugs through an analysis of representative nationwide claims data.

Materials and Methods: We selected DIP patients of ages ranging from 40 to 100 years old with the G21.1 code from the Korean National Service Health Insurance Claims database from 2009 to 2015. The annual standardized prevalence of DIP was explored from 2009 to 2015. Trends were estimated using the compound annual growth rate (CAGR) and the Cochran-Armitage test for DIP over the course of 6 years. Additionally, the utilization of offending drugs was analyzed.

Results: The annual prevalence of DIP was 4.09 per 100000 people in 2009 and 7.02 in 2015 (CAGR: 9.42%, p<0.001). Levosulpiride use before and after DIP diagnosis showed a clear trend for decreasing utilization (CAGR: -5.4%, -4.3% respectively), whereas the CAGR for itopride and metoclopramide increased by 12.7% and 6.4%, respectively. In 2015, approximately 46.6% (858/1840 persons) of DIP patients were prescribed offending drugs after DIP diagnosis. The most commonly prescribed causative drug after DIP diagnosis was levosulpiride.

Conclusion: The prevalence of DIP has increased. To prevent or decrease DIP, we suggest that physicians reduce prescriptions of benzamide derivatives that have been most commonly used, and that attempts be made to find other alternative drugs. Additionally, the need for continuing education about offending drugs should be emphasized.

Key Words: Drug-induced parkinsonism, Parkinson disease, offending drugs, antiemetic and gastric mobility agents, levosulpiride
presenting with Parkinsonism is a case of DIP. In patients with DIP, it is necessary to identify which offending drugs the patient uses and to reduce the usage of those drugs to the greatest extent possible.

The most commonly used offending drugs have changed over time. In the past, DIP was commonly reported to be caused by antipsychotics, while today, the common offending drugs are atypical neuroleptics, benzamide derivatives (metoclopramide, levosulpiride, and clebopride), and calcium channel-blocking agents (flunarizine and cinnarizine).

There are some differences among countries in the utilization of offending drugs. Some benzamide derivatives, such as levosulpiride, clebopride, and itopride, are not approved for use in the United States or United Kingdom, although they are prescribed to many people in Korea.

To reduce the occurrence of DIP, the epidemiological characteristics of DIP should be clearly understood. However, little research has investigated the current status of DIP and the use of offending drugs. The aim of this study was to estimate the prevalence of DIP through an analysis of the Korean National Health Insurance Claims (KNHIC) database. Trends in the utilization of offending drugs were investigated in this study as well.

MATERIALS AND METHODS

Data source
This study used the KNHIC database, which contains data from all hospitals and clinics concerning the health care services that they provide to their patients. This cumulative database includes individual data from the entire Korean population, with information on age, sex, diagnosis according to International Classification of Disease and Related Health Problems 10th revision (ICD-10) codes, date of diagnosis, medication adherence, insurance type, institutional characteristics of the healthcare provider, and the requested medical care costs. We obtained the data related to DIP patients in the KNHIC database from the National Health Insurance Service (NHIS).

Study population and offending drugs
We defined DIP patients as people who were aged 40–100 years old and had a diagnosis code for DIP (ICD-10: G21.1) as a principal diagnosis in 2009–2015. Those who were registered as having IPD (extra benefit code: V124) and who died in the year of diagnosis were excluded. Patients were classified according to whether they had used offending drugs before or after DIP diagnosis. The former group comprised DIP patients who were prescribed an offending drug for at least 28 days over the course of 1 year before the DIP diagnosis, and the latter group comprised DIP patients who were prescribed an offending drug for at least 28 days over the course of 6 months after the DIP diagnosis.

This study used the list of offending drugs reported in a previous study that have been approved by the Korean Ministry of Food and Drug Safety. The previous study classified the offending drugs depending on the potential risk levels of DIP. The list of drugs that may cause DIP is provided in Supplementary Table 1 (only online). The high-risk group contains dopamine D2 receptor antagonists (haloperidol, pimozide, amisulpride, levomepromazine, promazine, sulpiride, risperidon, olanzapine, aripiprazole, and ziprasidone), dopamine depleters (tetrabenazine), and calcium channel antagonists (P-channel: flunarizine). The intermediate-risk group includes atypical antipsychotics (ziprasidone), antiemetic and gastrointestinal motility agents (metoclopramide, levosulpiride, clebopride, and itopride), calcium channel antagonists (L-channel: verapamil and diltiazem), and others (lithium and valproate). The low-risk group includes selective serotonin reuptake inhibitors (fluoxetine and sertraline), monoamine oxidase inhibitors (moclobemide), and others (amiodarone, procaine, and cyclosporin).

We analyzed the proportion of offending drugs used before and after the DIP diagnosis in 2015 and the frequency of utilization of the offending drugs, focusing on the top five most frequently prescribed drugs by age.

Statistical analysis
The annual prevalence of DIP from 2009 to 2015 was calculated using age- and sex-standardized methods based on data regarding the population distribution issued by the Korea National Statistical Office in 2015. Trends in prevalence were estimated using the compound annual growth rate (CAGR) and Cochran-Armitage test (CAT) for DIP over 6 years. The CAGR was used to explore growth in a more precise, annualized manner. The CAGR was estimated with the formula \([\text{ending value/starting value}]^{1/\text{no. of years}} - 1\). A null hypothesis in the CAT is the hypothesis of no trend, which would indicate an equal binomial proportion for all levels of the explanatory variable. Statistical significance was evaluated by applying two-tailed tests, and \(p\) values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using version 9.4 (SAS institute, Cary, NC, USA).

Ethics statement
It was impossible to identify the patients because individual data were anonymized in the KNHIC database. Therefore, the Institutional Review Board (IRB) of Hallym University Medical Center exempted this study from the IRB process according to IRB regulations (IRB No: 2016-1081).

RESULTS

Prevalence of DIP in 2009–2015
The total number of DIP cases was 859 in 2009, and it increased
to 1840 in 2015. Of the DIP patients recorded in 2015, offending drugs had been used by 1285 (69.83%). The remaining DIP patients may have taken an offending drug for fewer than 28 days over the course of 1 year before DIP diagnosis. Genetic differences may also have been a relevant factor, as a previous study reported that not all patients using dopamine receptor blocking agents experience Parkinsonism, suggesting that genetic factors may affect the occurrence of DIP. The annual prevalences of DIP, standardizing the population by age and sex to 2015 values, were 4.09 per 100000 in 2009 and 7.02 in 2015. The prevalence of DIP was highest in 2015. The CAGR increased by 9.42%, and this increasing trend was statistically significant. Table 1 shows the annual prevalence rates of DIP per 100000 people according to sex. The annual prevalence of DIP among females was 1.98 times higher than that among males. The CAGR increased more in men (8.68%) than in women (9.82%). Between 2009 and 2015, the prevalence was highest in individuals aged 70–79 years and was lowest in those aged 40–59 years. In the former group, CAGRs were 14.6 per 100000 people in 2009 and 24.0 in 2015. However, for the latter group, they were 0.6 in 2009 and 1.5 in 2015. The CAGR increased in every age group (Fig. 1).

**Utilization of offending drugs**

*Offending drugs used before DIP diagnosis*

Offending drugs were identified by classifying DIP patients who were prescribed an offending drug for at least 28 days

| Age group (n) | Patients with DIP (n) | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | Growth rate (CAGR) (%) | Cochran-Armitage |
|--------------|----------------------|------|------|------|------|------|------|------|------------------------|-----------------|
| 40–49        | 859                  | 1132 | 1166 | 1430 | 1616 | 1633 | 1840 | 13.54 | <0.001                |
| 50–59        | 109                  | 110  | 138  | 179  | 202  | 194  | 228  | 13.09 | <0.001                |
| 60–69        | 257                  | 332  | 322  | 354  | 381  | 360  | 422  | 8.62  | 0.001                 |
| 70–79        | 357                  | 517  | 514  | 640  | 704  | 716  | 750  | 13.17 | <0.001                |
| ≥80          | 81                   | 131  | 146  | 191  | 246  | 271  | 312  | 25.20 | 0.001                 |

The percentage of having a prescription for an offending drug before DIP diagnosis

- Crude prevalence (per 100000): 75.32, 76.50, 74.87, 70.84, 71.41, 70.61, 69.84
- Annual age- and sex-standardized prevalence* (per 100000): 4.09, 5.21, 5.15, 6.04, 6.54, 6.36, 7.02
- Age-standardized prevalence by sex* (per 100000): Male 2.84, 3.36, 3.58, 4.25, 4.52, 3.99, 4.68; Female 5.25, 6.93, 6.61, 7.70, 8.42, 8.57

DIP, drug-induced parkinsonism; CAGR, compound annual growth rate.

*Standardized using the 2015 population.

**Fig. 1.** Age-specific prevalence of DIP in Korea from 2009 to 2015. DIP, drug-induced parkinsonism.
over the course of 1 year prior to the index date (1285 people). The index date was defined as the date of the first diagnosis of DIP. The offending drugs that DIP patients were most commonly prescribed were antiemetic and gastrointestinal motility agents (68.40%), followed by atypical antipsychotics (38.21%) and typical antipsychotics (23.66%) (Table 2). We then investigated the utilization of causative drugs among those who had been prescribed an offending drug for at least 28 days.

We identified the five most frequently used offending drugs. In 2009, the most common offending drug was levosulpiride (68.62%), followed by itopride (30.76%), risperidone (15.30%), metoclopramide (43.43%), and valproate (12.98%). In 2015, levosulpiride (49.26%) was still the most frequently prescribed offending drug, followed by itopride (31.36%), risperidone (23.97%), metoclopramide (19.92%), and valproate (17.82%). The offending drugs most commonly used by individuals ≤59 years of age and those ≥60 years of age were risperidone and levosulpiride, respectively. Notable differences were found by age group. Individuals 59 years of age or younger used antipsychotic drugs more frequently, whereas those aged 60 years or over were more likely to be prescribed antiemetic and gastrointestinal motility agents.

Among the antiemetic and gastrointestinal motility agents, levosulpiride showed a clear trend for decreasing utilization in all age groups. The CAGR of levosulpiride utilization decreased by 5.38% (p<0.001). Metoclopramide utilization decreased by a mean annual average of over 10% (p<0.001). Meanwhile, the CAGRs for risperidone and valproate utilization increased by 7.77% (p=0.019) and 5.42% (p=0.208), respectively (Table 3).

### Offending drugs used after DIP diagnosis

The use of offending drugs after the DIP diagnosis was defined by identifying patients who were prescribed an offending drug for at least 28 days over the course of 6 months after being diagnosed with DIP. In 2009, the rate was 41.61%, and it increased by an average of 0.69% each year. The over-70 group diagnosed with DIP. In 2009, the most common offending drug was levosulpiride (24.71%), metoclopramide (22.03%), and valproate (15.38%). In 2015, the most commonly prescribed offending drug was levosulpiride (25.64%), followed by itopride (25.17%), risperidone (24.71%), metoclopramide (22.03%), and valproate (15.38%). Levosulpiride was the most widely used drug in all age groups, although its mean annual growth rate decreased by 4.28% (p=0.009). In contrast, the rate of itopride utilization consistently increased. The CAGR of itopride, which is also an

![Table 2. Utilization of Offending Drugs before and after DIP Diagnosis in 2015](https://doi.org/10.3349/ymj.2019.60.8.760)
antiemetic and gastrointestinal motility agent, plunged by 12.65% \((p=0.004)\). Physicians might consider itopride to be a less-risky alternative to levosulpiride (Table 5).

Additionally, the rate of risperidone utilization consistently decreased by an average of 8.82\% \((p<0.05)\) each year. The rate of valproate utilization consistently increased, and its mean annual growth rate showed an increase of 3.44\% \((p=0.400)\). Physicians might have switched to prescribing other drugs as less-risky alternatives to risperidone, with the exception of cases in which risperidone is essential for the treatment plan and it is impossible to change the prescription.

**DISCUSSION**

This study analyzed the prevalence of DIP from 2009 to 2015 using the NHIS database. DIP is generally characterized by the absence of symptoms of Parkinsonism before the use of an offending drug and by resolution of the symptoms within 6 months of the withdrawal of that drug.\(^7\) To calculate DIP prevalence using a nationwide large-scale database, which is distinct from using patients’ medical records, an operational definition of DIP is needed. In this study, when a doctor used a DIP diagnostic code as the principal diagnosis, that patient was defined as having DIP. The problem with this definition is that many patients with DIP may be misdiagnosed with IPD because the clinical features of these two conditions are indistinguishable.\(^7\) In addition, because the NHIS database is a medical utilization record, this does not include people who did not visit medical institutions. As a result, the actual number of DIP patients could have been underestimated.

According to the results of this study, there were 7.02 DIP patients per 100000 people aged 40–100 years in 2015. Among those aged 70–79, there were 24.0 patients per 100000 in 2015. Few previous studies have investigated the prevalence of DIP using nationwide administrative data. In one study in Brazil, a

| Table 3. The Five Offending Drugs Most Commonly Used before DIP Diagnosis (%) |
| --- |
| **Age (yr)** | Drug | **2009** | **2010** | **2011** | **2012** | **2013** | **2014** | **2015** | **Growth rate (CAGR)** | **Cochran-Armitage** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Total | Levosulpiride | 68.62 | 72.40 | 65.52 | 58.34 | 56.85 | 54.29 | 49.26 | -5.38 | <0.001 |
| | Itopride | 30.76 | 36.49 | 43.99 | 38.10 | 35.53 | 32.26 | 31.36 | 0.32 | 0.527 |
| | Risperidone | 15.30 | 12.47 | 14.43 | 17.77 | 18.46 | 20.29 | 23.97 | 7.77 | 0.019 |
| | Metoclopramide | 43.43 | 38.80 | 36.88 | 40.08 | 36.05 | 27.67 | 19.92 | -12.18 | 0.001 |
| | Valproate | 12.98 | 11.32 | 14.20 | 12.24 | 13.95 | 15.44 | 17.82 | 5.42 | 0.208 |
| 40–49 | Risperidone | 38.24 | 40.63 | 39.47 | 44.90 | 48.33 | 37.50 | 46.36 | 3.26 | 0.317 |
| | Haloperidol | 35.29 | 40.63 | 28.95 | 44.90 | 51.67 | 42.50 | 38.18 | 1.32 | 0.176 |
| | Valproate | 32.35 | 40.63 | 34.21 | 30.61 | 38.33 | 30.00 | 34.55 | 1.10 | 0.720 |
| | Aripiprazole | 11.76 | 3.13 | 15.79 | 6.12 | 11.67 | 17.50 | 27.27 | 15.04 | <0.001 |
| | Olanzapine | 17.65 | 15.63 | 7.89 | 16.33 | 15.00 | 16.25 | 24.55 | 5.65 | 0.152 |
| 50–59 | Risperidone | 28.92 | 24.10 | 33.33 | 29.63 | 40.88 | 40.27 | 45.51 | 7.85 | 0.010 |
| | Haloperidol | 32.53 | 25.30 | 32.43 | 33.33 | 31.45 | 26.85 | 34.83 | 1.15 | 0.714 |
| | Valproate | 24.10 | 26.51 | 31.53 | 21.48 | 28.93 | 30.20 | 34.27 | 6.05 | 0.166 |
| | Levosulpiride | 44.58 | 55.42 | 40.54 | 36.30 | 35.22 | 36.91 | 27.53 | -7.72 | 0.001 |
| | Itopride | 20.48 | 22.89 | 35.14 | 25.19 | 26.42 | 22.82 | 26.40 | 4.32 | 0.696 |
| 60–69 | Levosulpiride | 61.31 | 70.31 | 68.62 | 58.47 | 50.75 | 47.92 | 44.37 | -5.25 | <0.001 |
| | Risperidone | 16.08 | 16.80 | 15.90 | 18.94 | 18.28 | 25.28 | 29.90 | 10.89 | 0.005 |
| | Haloperidol | 36.66 | 36.33 | 43.51 | 40.32 | 36.19 | 27.92 | 27.97 | -2.04 | 0.153 |
| | Valproate | 15.08 | 11.33 | 14.64 | 14.92 | 13.43 | 21.13 | 22.51 | 6.91 | 0.037 |
| | Haloperidol | 9.55 | 11.33 | 12.55 | 11.69 | 11.19 | 16.23 | 19.94 | 13.05 | 0.034 |
| 70–79 | Levosulpiride | 79.10 | 78.97 | 73.72 | 66.59 | 66.53 | 64.07 | 62.33 | -3.89 | 0.001 |
| | Itopride | 34.33 | 39.85 | 45.41 | 41.76 | 36.63 | 38.81 | 36.09 | 0.24 | 0.877 |
| | Metoclopramide | 47.39 | 38.88 | 40.05 | 45.93 | 39.60 | 29.77 | 21.89 | -12.08 | 0.001 |
| | Risperidone | 8.96 | 6.85 | 7.14 | 12.97 | 10.89 | 11.29 | 13.41 | 6.96 | 0.133 |
| | Flunarizine | 11.57 | 9.78 | 11.73 | 10.33 | 9.70 | 9.03 | 10.45 | -1.67 | 0.536 |
| ≥80 | Levosulpiride | 87.30 | 70.93 | 64.52 | 66.67 | 71.60 | 66.86 | 59.22 | -6.26 | 0.001 |
| | Itopride | 34.92 | 37.21 | 52.69 | 39.68 | 48.77 | 36.63 | 36.31 | 0.65 | 0.969 |
| | Metoclopramide | 44.44 | 44.19 | 38.71 | 45.24 | 43.21 | 31.40 | 22.91 | -10.46 | 0.001 |
| | Risperidone | 9.52 | 4.65 | 8.60 | 13.49 | 9.26 | 12.79 | 8.38 | -2.11 | 0.521 |
| | Haloperidol | 4.76 | 8.14 | 6.45 | 11.90 | 8.02 | 8.72 | 7.82 | 8.62 | 0.365 |

DIP, drug-induced parkinsonism; CAGR, compound annual growth rate.
prevalence of DIP of 2.7% was estimated using a community-based survey. In three regions of Spain, a prevalence of 0.49% was calculated using the door-to-door method among older adults. However, it is difficult to compare these results, since the definition of patients and research methods used were different in each study.

Our study found that DIP was more common in women than in men in all age groups. Female has consistently been reported as a risk factor for DIP. The underlying mechanisms are unknown, and genetic, endocrine, social, and cultural differences may contribute to the higher prevalence of DIP in women. In general, old age is known to be a risk factor for DIP, which this study confirmed using large-scale nationwide data. The increasing risk of DIP with age reflects the frequent use of dopamine-blocking agents in recent years for the control of mental disorders with agitation, confusion, delirium, and anxiety.

There are no clinical criteria for how long offending drugs must be used to cause DIP symptoms. However, since the length of treatment is a risk factor for DIP, we investigated the types of offending drugs used by DIP patients who had been prescribed them for at least 28 days over the course of 6 months after DIP diagnosis.

Antiemetic and gastric mobility agents, particularly levosulpiride, were the offending drugs most commonly used by DIP patients. Atypical antipsychotics were the next most frequently used type. Antiemetic and gastric mobility agents, such as levosulpiride, clebopride, and itopride, are not approved in the United States or United Kingdom.

Remarkably, between 2009 and 2015, the usage of levosulpiride drastically decreased while the usage of itopride increased slightly. This downward trend in levosulpiride utilization may have been due to studies reporting the occurrence of DIP caused by levosulpiride, which may reflect differences in the ability of levosulpiride and itopride to penetrate the central nervous system.

With respect to therapeutic class, both levosulpiride and itopride are benzamide derivatives, although they have slightly different mechanisms. According to a previous study, levosulpiride has a high affinity (Ki: 27–134 nM) for dopamine 2 receptor antagonism and targets selective dopamine presynaptic auto-receptors in the central nervous system. In contrast, itopride has the same effect in terms of dopamine 2 receptor antagonism, but little effect on the central nervous system. Similarly to other reported results, the time trend of DIP prevalence in all age groups decreased over this recent 7-year period, which may have been related to changes in the usage of prokinetics, including levosulpiride and itopride. Although their CAGRs clearly decreased, these drugs are still frequently and readily prescribed in Korea. Although prokinetics have a low potency for dopamine receptor blocking, they can cause DIP and have also been shown to be associated with cognitive dysfunction.

Over 40% of patients continued to use offending drugs after being diagnosed with DIP. In particular, the age group of 40–49 received the most atypical antipsychotic prescriptions for treatment, whereas the age group of 70–79 took the most anti-
emetic and gastric mobility agents. We believe that physicians regularly prescribe these drugs to treat patients younger than 60 years old. Doctors commonly prescribed benzamide derivatives, such as levosulpiride, itopride, and metoclopramide, in the over-60 group after DIP diagnosis. It is need that physicians pay more attention to prescription patterns in patients who are older than 60.

To prevent and cure DIP, doctors need to reduce the utilization of offending drugs and to find less-risky substitutes. Checking a patient’s medication history after the onset of Parkinsonism is also important. In particular, in older adult patients who are at high risk for both DIP and IPD, the long-term use of offending drugs should be considered more carefully and, if necessary, be limited. Additionally, it is necessary to emphasize the need for continuous education on offending drugs.

This is the first representative study to estimate the prevalence of DIP and to identify the usage patterns of offending drugs among the Korean population. Despite these contributions, our study has several limitations. First, we used prescription claims data, so we could not identify whether patients actually took the prescribed medicines. Second, the diagnosis of DIP was determined in this study using an operational definition. Since some doctors may not have recognized DIP in their patients, some patients might have not been included in this study.

**ACKNOWLEDGEMENTS**

This study used NHIS-NHID data (NHIS-2017-1-242) made available by the National Health Insurance Service (NHIS). The author(s) declare no conflicts of interest with the NHIS. We would like to thank the NHIS for its cooperation. This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health In-

### Table 5. The Five Offending Drugs Most Commonly Used after DIP Diagnosis (%)

| Age (yr) | Drug      | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | Growth rate (CAGR) | Cochran-Armitage |
|----------|-----------|------|------|------|------|------|------|------|-------------------|------------------|
|          | Total     | 33.33| 41.84| 36.69| 33.07| 25.92| 26.41| 25.64| -4.28             | 0.009            |
|          | Levosulpiride | 12.32| 15.20| 15.32| 16.14| 20.05| 22.46| 25.17| 12.65              | 0.004            |
|          | Itopride  | 43.00| 44.28| 35.89| 35.11| 31.79| 25.85| 24.71| -8.82              | 0.001            |
|          | Risperidone | 15.22| 12.95| 14.72| 14.11| 16.92| 20.76| 22.03| 6.36               | 0.048            |
|          | Metoclopramide | 12.56| 11.26| 11.49| 13.32| 13.64| 13.70| 15.38| 3.44               | 0.399            |
| 40–49    | Levosulpiride | 19.35| 53.85| 40.00| 48.84| 46.03| 35.71| 42.86| 14.17              | 0.107            |
|          | Itopride  | 29.03| 26.92| 30.00| 18.60| 34.92| 25.71| 36.19| 3.74               | 0.317            |
|          | Risperidone | 25.81| 34.62| 30.00| 34.88| 31.75| 31.43| 27.62| 1.14               | 1.000            |
|          | Valproate | 6.45 | 7.69 | 6.67 | 2.33 | 6.35 | 18.57 | 24.76 | 25.13              | <0.001           |
|          | Olanzapine | 0.00 | 3.85 | 10.00| 9.30 | 9.52 | 14.29 | 18.10 | -                 | -                |
| 50–59    | Levosulpiride | 18.84| 25.37| 28.21| 23.08| 33.60| 33.04| 41.96| 14.28              | 0.001            |
|          | Itopride  | 28.09| 23.88| 33.33| 25.00| 30.40| 35.71| 31.47| 3.18               | 0.135            |
|          | Risperidone | 18.84| 17.91| 26.92| 25.96| 20.80| 20.54| 27.27| 6.36               | 0.279            |
|          | Valproate | 20.29| 29.85| 16.67| 22.12| 15.20| 16.96| 18.88| -1.19              | 0.143            |
|          | Itopride  | 10.14| 4.48 | 14.10| 15.38| 13.60| 16.07| 16.78| 8.75               | 0.011            |
| 60–69    | Levosulpiride | 17.07| 15.19| 15.86| 14.20| 17.65| 24.58| 28.44| 8.87               | 0.008            |
|          | Itopride  | 15.45| 15.82| 15.86| 12.96| 18.82| 27.37| 27.01| 9.76               | 0.003            |
|          | Risperidone | 40.65| 39.87| 35.17| 37.65| 30.00| 20.67| 24.17| -8.30              | 0.001            |
|          | Valproate | 31.71| 39.87| 40.00| 33.33| 25.29| 24.02| 21.33| -6.40              | 0.001            |
|          | Itopride  | 10.57| 9.49 | 7.59 | 11.11| 11.76| 12.29| 16.11| 7.28               | 0.135            |
| 70–79    | Levosulpiride | 52.76| 48.51| 47.12| 42.80| 40.21| 34.85| 32.12| -7.94              | 0.001            |
|          | Itopride  | 42.94| 50.64| 41.83| 36.36| 30.58| 31.06| 31.79| -4.89              | 0.001            |
|          | Metoclopramide | 5.52 | 8.51 | 7.21 | 12.12| 12.37| 14.77| 14.57| 17.55              | 0.008            |
|          | Risperidone | 33.13| 32.77| 31.25| 28.41| 31.96| 17.80| 13.91| -13.47             | 0.001            |
|          | Flunarizine | 7.98 | 7.66 | 4.33 | 9.47 | 10.31| 14.02| 12.25| 7.42               | 0.051            |
| ≥80      | Levosulpiride | 42.86| 34.04| 60.00| 50.77| 42.86| 43.37| 36.08| -2.83              | 0.447            |
|          | Itopride  | 46.43| 55.32| 37.14| 38.46| 38.10| 31.33| 35.05| -4.58              | 0.002            |
|          | Metoclopramide | 0.00 | 6.38 | 5.71 | 3.08 | 1.19 | 7.23 | 11.34 | -                 | 0.008            |
|          | Risperidone | 32.14| 36.17| 45.71| 32.31| 21.43| 18.07| 10.31| -17.26             | <0.001           |
|          | Haloperidol | 14.29| 10.64| 11.43| 7.69 | 9.52 | 10.84| 10.31| -5.29              | 0.427            |

DIP, drug-induced parkinsonism; CAGR, compound annual growth rate.
Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI15 C1240).

AUTHOR CONTRIBUTIONS

Conceptualization: Hyeo-Il Ma and Sunmee Jang. Funding acquisition: Hyeo-Il Ma and Sunmee Jang. Data curation and Formal analysis: Sunmee Jang, Hyeo-Il Ma, Hyemin Cho, and Ji-Hye Byun. Methodology: Sunmee Jang, Hyeo-Il Ma, Yun Joong Kim, Joong-Seok Kim, and Jong Sam Baik. Interpreting the results and the discussions: Hyeo-Il Ma, Sunmee Jang, Ji-Hye Byun, Yun Joong Kim, Joong-Seok Kim, and Jong Sam Baik. Writing—original draft: Ji-Hye Byun, Hyemin Cho, Sunmee Jang, and Hyeo-Il Ma. Writing—review & editing: Ji-Hye Byun, Hyemin Cho, Sunmee Jang, Hyeo-Il Ma, Yun Joong Kim, Joong-Seok Kim, and Jong Sam Baik.

ORCID iDs

Ji-Hye Byun https://orcid.org/0000-0002-2211-5349
Hyemin Cho https://orcid.org/0000-0002-3686-3401
Yun Joong Kim https://orcid.org/0000-0002-2956-1552
Joong-Seok Kim https://orcid.org/0000-0001-8087-7977
Jong Sam Baik https://orcid.org/0000-0002-8771-8693
Sunmee Jang https://orcid.org/0000-0001-6733-9779
Hyeo-Il Ma https://orcid.org/0000-0002-2211-5349

REFERENCES

1. Brigo F, Erro R, Marangi A, Bhatia K, Tinazzi M. Differentiating drug-induced parkinsonism from Parkinson’s disease: an update on non-motor symptoms and investigations. Parkinsonism Relat Disord 2014;20:808-14.
2. Klavans HJ, Jr, Bergen D, Bruyn GW. Prolonged drug-induced Parkinsonism. Confin Neurol 1973;35:368-77.
3. Wenning GK, Kiechl S, Seppi K, Müller J, Högl B, Saletu M, et al. Prevalence of movement disorders in men and women aged 50-89 years (Bruneck Study cohort): a population-based study. Lancet Neurol 2005;4:815-20.
4. Benito-León J, Bermejo-Pareja F, Rodríguez J, Molina JA, Gabriel R, Morales JM, et al. Prevalence of PD and other types of parkinsonism in three elderly populations of central Spain. Mov Disord 2003;18:267-74.
5. Foubert-Samier A, Helmer C, Perez F, Le Goff M, Auriacombe S, Elbaz A, et al. Past exposure to neuroleptic drugs and risk of Parkinson disease in an elderly cohort. Neurology 2012;79:1615-21.
6. Noyes K, Liu H, Holloway RG. What is the risk of developing Parkinsonism following neuroleptic use? Neurology 2006;66:941-3.
7. Shin HW, Chung SJ. Drug-induced Parkinsonism. J Clin Neurol 2012;8:15-21.
8. Ma HJ, Kim JH, Chu MK, Oh MS, Yu KH, Kim J, et al. Diabetes mellitus and drug-induced Parkinsonism: a case-control study. J Neurol Sci 2009;284:140-3.
9. López-Sendón JL, Mena MA, de Yébenes JG. Drug-induced parkinsonism in the elderly: incidence, management and prevention. Drugs Aging 2012;29:105-18.
10. US Food and Drug Administration (FDA). Drugs@FDA 2017: FDA approved drug products [Internet]. Silver Spring (MD): FDA; c2017 [accessed on 2018 December 20]. Available at: http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.
11. GOV.UK. Agency (MHRA) MaHpR [Internet]. United Kingdom: GOV.UK; c2017 [accessed on 2018 December 20]. Available at: https://www.gov.uk/search?q=levosulpiride&show_organisations=filter=true.
12. Health Insurance Review and Assessment Service (HIRA). Korea Health Insurance Review and Assessment Service Database 2014 [Internet]. Wonju: HIRA; c2015 [accessed on 2018 December 18]. Available at: http://www.hira.or.kr/bbsDummy.do?pgmId=HIRA A020045010000&brdScnBltNo=4&brdBltNo=2281&pageIndex=1.
13. Bondon-Guitton E, Perez-Lloret S, Bagheri H, Brefel C, Rascol O, Monastruc JL. Drug-induced parkinsonism: a review of 17 years’ experience in a regional pharmacovigilance center in France. Mov Disord 2011;26:2226-31.
14. Erro R, Bhatia KP, Tinazzi M. Parkinsonism following neuroleptic exposure: a double-hit hypothesis? Mov Disord 2015;30:788-95.
15. Belatti DA, Phistikpal P. Declines in lower extremity amputation in the US Medicare population, 2000-2010. Foot Ankle Int 2013:34; 923-31.
16. Armitage P. Tests for linear trends in proportions and frequencies. Biometrics 1955;11:375-86.
17. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Time trends in the incidence of Parkinson disease. JAMA Neurol 2016; 73:981-9.
18. Barbosa MT, Caramelli P, Maia DP, Cunningham MC, Guerra HL, Lima-Costa MF, et al. Parkinsonism and Parkinson’s disease in the elderly: a community-based survey in Brazil (the Bambui study). Mov Disord 2006;21:800-8.
19. Kim JS, Oh YS, Kim YI, Yang DW, Chung YA, You IB, et al. Combined use of (1)(2)(3)I-metaiodobenzylguanidine (MIBG) scintigraphy and dopamine transporter (DAT) positron emission tomography (PET) predicts prognosis in drug-induced Parkinsonism (DIP): a 2-year follow-up study. Arch Gerontol Geriatr 2013;56: 124-8.
20. Kim JS, Ko SB, Han SR, Kim YI, Lee KS. Levosulpiride-induced Parkinsonism. J Korean Neurol Assoc 2003;21:418-21.
21. Shin HW, Kim MJ, Kim JS, Lee MC, Chung SJ. Levosulpiride-induced movement disorders. Mov Disord 2009;24:2249-53.
22. Ahn HJ, Yoo WK, Park J, Ma HI, Kim YJ. Cognitive dysfunction in drug-induced Parkinsonism caused by parkin and antiemetics. J Korean Med Sci 2015;30:1328-33.
23. Kim YD, Kim JS, Chung SW, Song IU, Yang DW, Hong YJ, et al. Cognitive dysfunction in drug induced parkinsonism (DIP). Arch Gerontol Geriatr 2011;53:222-6.
24. Tonini M, De Giorgi R, Spelta V, Bassotti G, Di Nucci A, Anselmi L, et al. 5-HT4 receptors contribute to the motor stimulating effect of levosulpiride in the guinea-pig gastrointestinal tract. Dig Liver Dis 2003;35:244-50.
25. Quigley EM. Prokinetics in the management of functional gastrointestinal disorders. J Gastroenterol Motil 2003;18:267-74.