Prescription trends in children with pervasive developmental disorders: a claims data-based study in Japan

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Background: **The only drug approved for pervasive developmental disorders (PDD) in Japan is pimozide. Several psychotropic drugs are also prescribed for off-label use in Japan, but details regarding their prescription and use are largely unknown. The purpose of this study was to clarify the use of drug treatment in Japanese children with PDD.**

Methods: **Data were extracted from claims data from the Japan Medical Data Center for children younger than 18 years of age who were newly diagnosed with PDD (International Classification of Diseases version 10 codes: F84) from 2005 to 2010 (total of 3276 patients as of 2010). The prescription rates were presented as the percentage of PDD patients who were prescribed each drug.**

Results: **Prior to 2010, the prescription rates for atypical antipsychotics, other antipsychotics, psychostimulants, all other central nervous system drugs, anticovnvulsants, non-barbiturates, and Parkinson's disease/syndrome drugs significantly increased among the Anatomical Therapeutic Chemical classifications defined as the "nervous system" (trend $P \leq 0.02$). The prescription rate for risperidone consistently increased, reaching 6.9% in 2010 (trend $P<0.0001$), the highest rate of the surveyed drugs among the antipsychotics. The prescription rate for aripiprazole also increased (trend $P<0.0001$), reaching 1.9% in 2010. The prescription rate for pimozide showed no annual changes, with a low rate of 0.4% in 2010.**

Conclusions: **Compared with pimozide, the prescription rates for risperidone, aripiprazole and other psychotropic drugs have increased. Because safety data for these drugs in Japanese children are sparse, there is a need for future safety evaluations of these drugs in Japanese children.**

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Introduction

Pervasive developmental disorders (PDD) are characterized by marked impairments in reciprocal social interaction, language, and communication and by the presence of repetitive/stereotypic patterns of behavior and interests.[1] Subclassifications include autism, Rett syndrome, childhood disintegrative disorder, and Asperger's syndrome.[1-6] Autism is characterized by repetitive behaviors and impaired socialization.[1-6] Rett syndrome is characterized by normal development followed by severe regression of language, motor, and social skills.[1-4,6] Childhood disintegrative disorder is characterized by late onset of developmental delays in language, social, and motor skills.[1-4,6] Asperger's syndrome is characterized by impaired social skills and rigid focused interests without a delay in language development and cognitive function.[1-4,6] Studies have reported that the prevalence of PDD ranges between 1% to 2% in children[2,5] and that there are approximately 1.2 to 2.5 million individuals with PDD in Japan, including adults.[5] However, the pathophysiology of PDD has not yet been well clarified. Therefore, drug

therapies that reliably aim to improve core symptoms, which are referred to as the Wing's triad of impaired social, communicative, and imaginative development, have not yet been established. In contrast, drug therapy has been effective for secondary symptoms derived from the following core symptoms, including repetitive behavior, compulsive symptoms, hyperactivity, impulsive behavior, irritability, aggression, insomnia/night-time awakening, anxiety, self-injurious behavior, and depression.[7] Children with PDD frequently display these behaviors, which often interfere with adaptive functioning and cause distress for affected individuals and caregivers alike.

Among drugs covered by the Japanese health insurance system, pimozide is the only drug that has been approved for PDD as a treatment for "autism in children". Meanwhile, atypical antipsychotics other than pimozide or other psychotropic drugs have been prescribed for off-label use in Japan.[8] However, details including trends in the prescription rate of these drugs in Japan have not yet been determined. Overseas, atypical antipsychotics are commonly used for treating several of the behavioral symptoms associated with PDD.[7,9-13] Other drug classes such as anticonvulsants, antidepressants, or psychostimulants have also been used for reducing aggression and irritability in PDD.[7,9-13] The U.S. Food and Drug Administration (FDA) approved risperidone in 2006 and aripiprazole in 2009 for treating irritability in children with autism. As noted by Kiriono, risperidone demonstrated the greatest evidence among atypical antipsychotics in treating irritability.[8] Therefore, from the perspective of efficacy and tolerability, it might be better to prescribe risperidone for the treatment of irritability in children with PDD.

The purpose of the present study was to clarify the use of drug treatment in Japanese children with PDD.

Methods

Patients

The present study used claims data from the Japan Medical Data Center (JMDC).[14] Of the 3 667 503 persons covered by health insurance between January 1, 2005 and June 30, 2011, we obtained data from patients aged 2 to 18 years, diagnosed with codes F80-F89 or with F90-F98 based on the 10th revision of the International Classification of Diseases (ICD-10). Codes F80-F89 and codes F90-F98 represent "*Disorders of psychological development*" and "*Behavioral and emotional disorders with onset usually occurring in childhood and adolescence*", respectively. For the present analyses, data from children who were newly diagnosed with PDD (ICD-10: F84) between January 1, 2005 and December 31, 2010 were included in the study. Among the F84 codes, we defined F84.0 as autism disorder. Data from patients who turned 18 years of age after diagnosis during the data analysis period were excluded from prescription totals for that specific year. Patient consent was not needed because the collected data were anonymized in JMDC[14] from which we obtained the de-identified dataset. Each patient was assigned a new and unique number, only for the purposes of merging datasets.

Data collection

The data used in this study included hospitalization/outpatient claims data for prescriptions issued during a visit to a medical facility. Additionally, we collected data from pharmacist's fee claims for prescriptions dispensed by a pharmacy based on written prescriptions. The name of the disorder, ICD-10 code, and date of examination were obtained from hospitalization/outpatient claims data. The nonproprietary names of drugs, anatomical therapeutic chemical (ATC) classification, and ATC code were obtained from hospitalization/outpatient claims data and pharmacist's fee claims data. The prescription date was obtained from pharmacist's fee claims data. Because the prescription date was not available from the hospitalization/outpatient claims data, the prescription date was defined as the first day of the month of the medical examination. For any redundant information between the pharmacist's fee claims and hospitalization/outpatient claims data, the pharmacist's fee claims data containing an exact prescription date was given priority. Antipsychotics, antidepressants, anti-anxiety/mood stabilizer drugs, psychostimulants, and all other central nervous system drugs were classified as psychotropic drugs.

Extraction and collection of drug data

The claims data used in the present study included 339 types of drugs based on the ATC classification and 2585 types of drugs based on nonproprietary names. Drug data were extracted among the drugs related to the "nervous system" designated as the initial "N" in the ATC code, but with exclusion of "other general anesthetics", "inhalation anesthetics", "other local anesthetics", "local anesthetics for topical use", "local anesthetics for injection", "non-narcotic and antipyretic analgesics", "treatment for narcotic dependence", and "narcotic analgesics".

Data were compiled for each ATC classification and nonproprietary name, but dosage form was not considered. However, because there were differences in the prescription rates for methylphenidate-sustained

release and its other dosage forms, as well as for diazepam suppository and its other dosage forms, the prescription rates were calculated separately for the sustained-release and suppository formulations in relation to these two drugs.

To eliminate the effects of seasonal variation in prescription status, prescribed drugs were compiled for each year from 2005 to 2010. Annual changes were examined for all extracted ATC classifications as well as for the nonproprietary names of drugs whose prescription rates were in the top 30 for the year 2010. When a drug was prescribed even once, it was presumed that the drug was prescribed in that particular year. The prescription rates were calculated by each prescription year and were presented as the percentage of PDD patients who were prescribed each drug.

Statistical analysis

To analyze the relationship between years and age or sex, we compared means and proportions using analysis of variance (ANOVA) and the χ^2 test for univariate analysis. We examined trends in prescription medications using multiple logistic analyses with adjustments for sex and age. The values are expressed as means±SD unless otherwise noted. All data were statistically analyzed using SAS version 9.3 software (SAS Institute, Cary, NC, USA). The level of significance was $P<0.05$.

Results

The patients' characteristics are shown in Table 1. We observed an increase in the number of all patients aged 0-20 years who were included in the database. The cumulative number of PDD patients increased from 342 in 2005 to 3276 in 2010. Although there were a significant difference in the percentage of the PDD patients between years ($P<0.0001$), the trend was inconsistent. The percentage of boys was higher in each year. Among patients with PDD, the proportion of patients with autism disorder decreased over time (Table 1).

Among the ATC classifications collected in the present study, the rates for atypical antipsychotics, other antipsychotics, psychostimulants, all other central nervous system drugs, anticovnvulsants, non-barbiturates, and Parkinson's disease/syndrome drugs significantly increased from 2006 to 2010 (Table 2). Of these, the highest prescription rate in 2010 was for atypical antipsychotics. There were no significant changes in annual trends for other ATC classifications after adjustments for age and sex ($P\geq0.09$). The number of drugs prescribed to a patient also increased. The proportion of patients who were prescribed two or more drugs significantly increased over time (trend $P<0.0001$) (Table 2). For the combinations of two drugs shown in Table 2, atypical antipsychotics with anticonvulsants (2.0%), non-barbiturates with anticonvulsants (1.8%), atypical antipsychotics with selective serotonin reuptake inhibitors (1.4%), atypical antipsychotics with psychostimulants (1.4%), and atypical antipsychotics with non-barbiturates (1.3%) were the top five prescribed drug combinations in 2010. The prescription rate for psychotropic drugs increased consistently from 6.4% in 2005 to 17.9% in 2010 (trend $P<0.0001$) when we classified antipsychotics, antidepressants, antianxiety/mood stabilizer drugs, and psychostimulants as psychotropic drugs (Table 2).

In the 3276 patients evaluated in 2010, we conducted logistic regression analyses including age and sex as independent variables, and each type of drug classified by ATC as a dependent variable. Serotonin and norepinephrine reuptake inhibitors, triptan and other drugs for migraine, anti-vertigo drugs, and nootropic drugs were excluded from the present analyses due to a limited number in prescriptions ($n\leq1$). Higher age was significantly associated with higher prescription rates for all drug types shown in Table 2 ($P\leq0.03$), except for barbiturates ($P=1.0$). The minimum age of patients who were prescribed drugs was 3.0 years. Moreover, being female was associated

Table 1. Total cumulative number of PDD patients and patients' characteristics

Variables	Year of diagnosis						*P*
	2005	2006	2007	2008	2009	2010	
Number of all patients aged 0-20 y in the database	42 071	45 125	47 442	112 695	163 496	258 431	NA
Number of PDD patients, *n* (%*)	342 (0.8)	742 (1.6)	1260 (2.7)	1881 (1.7)	2501 (1.5)	3276 (1.3)	<0.0001
Characteristics of patients with PDD							
Age (mean±standard deviation, y)	7.2±3.7	7.6±3.6	8.1±3.5	8.4±3.6	8.9±3.6	9.3±3.7	<0.0001
Males, *n* (%)	283 (82.7)	595 (80.2)	983 (78.0)	1445 (76.8)	1926 (77.0)	2509 (76.6)	0.052
Autism disorder,† *n* (%)	192 (56.1)	422 (56.9)	715 (56.8)	1020 (54.2)	1254 (50.1)	1510 (46.1)	<0.0001

Data from patients who turned 18 years of age after diagnosis during the data analysis period were excluded from prescription totals for that specific year. NA: not applicable; PDD: pervasive developmental disorders. *: The percentages were calculated when compared with the number of the patients in the database; †: Data are indicated as the number of patients who have been diagnosed as having autism disorder (ICD-10 codes: F84.0).

Table 2. Annual changes in drug prescription rates (%) by ATC classification in children with PDD

Items	Prescription year						Sex- and Age-adjusted trend *P*
	2005	2006	2007	2008	2009	2010	
Cumulative number of PDD patients, *n*	342	742	1260	1881	2501	3276	
Prescription rate, %							
Antipsychotics							
Atypical antipsychotics	2.0	1.6	2.5	4.5	5.4	8.3	<0.0001
Other antipsychotics	0.9	0.9	1.2	1.3	1.4	2.3	0.02
Antidepressants							
SSRI antidepressants	1.5	0.9	1.0	1.6	1.6	2.4	0.2
SNRI antidepressants	0.0	0.0	0.0	0.1	0.0	0.0	1.0
Other antidepressants	0.6	0.4	0.5	1.1	1.1	1.2	0.2
Antianxiety/mood stabilizer drugs							
Antianxiety drugs (tranquilizers)	2.9	4.3	2.3	3.6	4.2	4.0	0.5
Mood stabilizers (antimanic drugs)	0.0	0.0	0.0	0.0	0.0	0.2	0.1
Psychostimulants, etc.							
Psychostimulants	1.8	0.8	1.3	2.8	3.6	4.9	<0.0001
All other central nervous system drugs	0.0	0.0	0.2	0.2	1.2	2.7	<0.0001
Psychotropic drugs (either of above)	6.4	7.7	7.1	11.2	13.4	17.9	<0.0001
Antiepileptic drugs							
Anticonvulsants	5.3	4.0	3.8	4.4	5.7	7.2	<0.0001
Others							
Barbiturates, single drug	1.2	1.1	0.8	0.8	0.8	0.8	0.2
Non-barbiturates, single drug	4.1	6.6	3.9	5.8	5.4	6.0	0.02
Parkinson's disease/syndrome drugs	0.0	0.1	0.2	0.8	0.8	1.0	0.005
Triptans for migraine	0.0	0.0	0.0	0.1	0.0	0.0	0.8
Other drugs for migraine	0.0	0.1	0.0	0.1	0.0	0.0	0.09
Anti-vertigo drugs	0.0	0.1	0.1	0.0	0.1	0.0	0.3
Nootropic drugs (cognitive enhancers)	0.0	0.0	0.0	0.0	0.0	0.0	NA
The number of drugs							
Two or more	4.4	3.8	4.1	6.0	7.7	10.1	<0.0001
One	9.4	11.6	8.3	11.7	12.4	14.8	NA
Two	2.6	2.4	3.0	3.7	5.2	6.1	
Three	1.5	0.8	0.8	1.8	1.8	2.6	
Four or more	0.3	0.5	0.2	0.5	0.7	1.4	

Drug prescription rates for each anatomical therapeutic chemical (ATC) classification are calculated using the number of patients prescribed each drug as the numerator and the cumulative number of PDD patients aged <18 years up to each prescription year as the denominator. NA: not applicable; PDD: pervasive developmental disorders; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

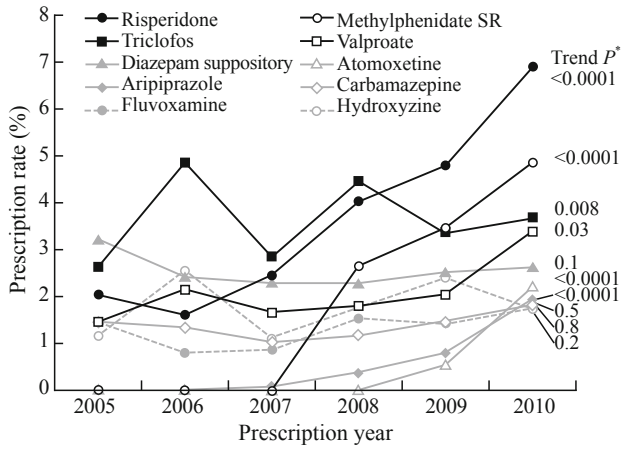

Fig. Drugs whose prescription rates were in the top ten for year 2010 and their annual changes (%) in children with PDD. Drug prescription rates for each nonproprietary (generic) name were calculated as percentage (%) values using the number of patients prescribed each drug as the numerator and the cumulative number of PDD patients age <18 years up to each prescription year as the denominator. Because differences were seen in prescription rates for methylphenidate sustained-release and its other dosage forms, as well as for diazepam suppository and its other dosage forms, the prescription rates were calculated separately for the sustained-release and suppository formulations regarding these two drugs. PDD: pervasive developmental disorders; SR, sustained-release. *: *P* values were adjusted for sex and age.

with higher prescription rates of anti-anxiety drugs, anticonvulsants, and non-barbiturates, and a lower rate of psychostimulant prescriptions ($P \leq 0.02$).

Fig. and Table 3 present the annual changes in prescription rates by nonproprietary name. The prescription rate for risperidone has consistently increased since 2006 (trend $P<0.0001$), reaching 4.8% in 2009 and 6.9% in 2010, which was the highest rate of all drugs surveyed in the current study. The prescription rate for aripiprazole has also consistently increased (trend $P<0.0001$), reaching 0.8% in 2009 and 1.9% in 2010 (Fig.). In contrast, the rate for pimozide showed no consistent changes (trend $P=0.6$), with a low prescription rate of 0.4% in 2010 (Table 3). The prescription rates for the psychostimulant methylphenidate (slow-release) and for atomoxetine increased markedly (trend $P<0.0001$), reaching 4.9% and 2.2% in 2010, respectively. A further adjustment for autism disorder did not change the significance of prescription trends of all drugs.

Discussion

While a consistently low prescription rate for pimozide

Table 3. Drugs whose prescription rates were in the top 11-30 for year 2010 and their annual changes (%)

Items	Prescription year						Sex- and Age-adjusted trend *P*
	2005	2006	2007	2008	2009	2010	
Cumulative number of PDD patients, *n*	342	742	1260	1881	2501	3276	
Prescription rate, %							
Chloral hydrate	1.8	3.0	1.5	2.1	1.8	1.7	0.2
Haloperidol	0.0	0.1	0.2	0.3	0.5	0.7	0.006
Biperiden	0.0	0.0	0.0	0.3	0.4	0.7	0.002
Diazepam other than suppository	0.9	0.7	0.5	0.8	1.0	0.6	0.7
Brotizolam	0.6	0.7	0.2	0.2	0.4	0.6	0.4
Etizolam	0.3	0.5	0.4	0.4	0.5	0.5	0.4
Clomipramine	0.6	0.3	0.3	0.5	0.6	0.5	1.0
Propericiazine	0.3	0.4	0.3	0.3	0.4	0.5	0.6
Imipramine	0.0	0.1	0.2	0.4	0.4	0.5	0.1
Levomepromazine	0.3	0.1	0.2	0.2	0.2	0.5	0.3
Phenobarbital	1.2	0.8	0.6	0.6	0.5	0.5	0.1
Clonazepam	0.0	0.1	0.2	0.3	0.4	0.5	0.1
Nitrazepam	0.0	0.1	0.3	0.4	0.3	0.4	0.5
Pimozide	0.3	0.3	0.5	0.5	0.3	0.4	0.6
Olanzapine	0.0	0.0	0.0	0.1	0.2	0.4	0.009
Sertraline	0.0	0.0	0.0	0.1	0.1	0.4	0.01
Zonisamide	0.0	0.1	0.0	0.3	0.3	0.3	0.03
Flunitrazepam	0.0	0.0	0.0	0.2	0.1	0.3	0.04
Clobazam	0.3	0.3	0.2	0.2	0.4	0.3	0.7
Lamotrigine	0.0	0.0	0.0	0.0	0.1	0.3	0.02

Prescription rates for each nonproprietary (generic) name are calculated as percentage (%) values using the number of patients prescribed each drug as the numerator and the cumulative number of PDD patients aged <18 years up to each prescription year as the denominator. Because differences were seen in prescription rates for diazepam suppository and its other dosage forms, the prescription rates were calculated separately for the suppository. PDD: pervasive developmental disorders.

was observed, the prescription rates for risperidone and aripiprazole continued to increase toward 2010. To the best of our knowledge, the present study was the first survey of prescription drug use in Japanese children with PDD.

Pimozide is the only drug specified and approved in Japan for the treatment of autism in children. However, the prescription rate for pimozide was only 0.4% in 2010 and there were no consistent annual changes. Meanwhile, the prescription rates for risperidone and aripiprazole for off-label use in PDD increased, with prescription rates of 6.9% and 1.9%, respectively in 2010. To date, there have been only a few clinical studies that have investigated the use of pimozide in childhood autism both in Japan and overseas, thus, its efficacy and safety have not yet been properly established.[15] On the other hand, more than 20 clinical trials have been conducted on risperidone for use in childhood autism,[15] and risperidone has been approved by the FDA for self-injurious or aggressive behavior in children with autism. Aripiprazole is a relatively new drug, which was first marketed in Japan in 2006. In a meta-analysis based on two clinical trials, aripiprazole was shown to be effective for irritability in children with PDD.[16] The results from the meta-analysis also demonstrated that aripiprazole was specified and approved by the FDA for irritability in PDD.[16] This evidence regarding efficacy and adverse reactions might encourage physicians to prescribe off-label antipsychotic drugs in Japan.

The prescription rates for sustained-release methylphenidate and atomoxetine tended to increase. In Japan, sustained-release methylphenidate and atomoxetine acquired an approval for use in attention deficit-hyperactivity disorder (ADHD) in 2007 and 2009, respectively. ADHD symptoms have been reported in 25% to 80% of children with PDD.[17-20] The results of the present study suggest that the comorbidity between PDD and ADHD may be increasing in Japan. However, hyperactivity and impulsiveness, which are closely associated with PDD, can be frequently misdiagnosed as ADHD.[1] Therefore, in the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Text Revision (DSM-IV TR) classification, a diagnosis of both PDD and ADHD is not recognized, and when both coexist, only a diagnosis of PDD should be given.[1] The results from the present study may suggest that the use of sustained-release methylphenidate or atomoxetine in childhood PDD is becoming more common without careful consideration.

Aside from risperidone and aripiprazole, safety evaluations for sustained-release methylphenidate and atomoxetine have also relied on clinical results from overseas studies.[15,16] There is a possibility that a sudden increase in the use of these drugs may also increase adverse reactions in Japanese children with PDD. In fact, we observed a significant increase in the prescription rate of Parkinson's disease/syndrome

drugs, which is partly used for extrapyramidal disorder caused by antipsychotics (Table 2). Previous overseas studies have reported that 30% to 60% of children diagnosed with autism spectrum disorders are taking at least one psychotropic drug.[9-13] The present study found that the prescription rate for psychotropic drugs in Japan in 2010 was 17.9%. This indicated that the rate of use of psychotropic drugs in children with PDD was lower in Japan than overseas. However, compared to the 6.4% prescription rate for psychotropic drugs in 2005, there was approximately a threefold increase in prescriptions for psychotropic drugs in Japan in 2010. Furthermore, the prescription rates of related drugs such as anticonvulsants or non-barbiturates also significantly increased (Table 2). In the present study, psychotropic drugs were more frequently used by older patients than by younger ones. Meanwhile, some drugs have been prescribed in children as young as 3.0 years of age. Safety evaluations of the psychotropic drugs and related medications prescribed to children are an urgent issue in Japan. Since several studies have suggested an association between gene polymorphisms and risperidone responses,[21,22] it would be preferable to take genetic polymorphisms into consideration in future clinical trials. Although sex differences were observed in the prescription rates of several drugs in the present study, these might be caused by the fact that anxiety disorders are more common in girls[23] and that ADHD is more common in boys.[24]

The present study had several limitations. First, for the hospitalization/outpatient claims data in Japan, because the prescription date could only be extracted as the month of medical evaluation, prescriptions within the same month and dates of diagnosis were all the same. Therefore, some drugs prescribed before a diagnosis that were prescribed in the same month may be included in the present survey. Second, although we collected the PDD patients from claims data, the validity of disease names in health insurance have not been confirmed. Therefore, we cannot exclude the possibility that data in the current study might include some patients without PDD. The disease names recorded on claims data might include "suspected disease name" or "disease name for health insurance", which were recorded to include fees for reimbursed tests and medications. This can lead to an overestimation of patient numbers, and therefore, little effect on the overall conclusion of this study would be expected. The male-female ratio in the present study was consistent with that in previous reports.[4] Finally, diagnostic criteria change regularly. The DSM-IV TR was used during the present study period, while it was being updated from the 2013 criteria to the DSM-V. Thus, the change in diagnostic criteria might partly affect the present findings.

In conclusion, the prescription rate for pimozide, which is indicated only in childhood autism, is low among Japanese children with PDD. However, the increased use of antipsychotics such as risperidone and other drugs such as sustained-release methylphenidate were observed. The safety of these drugs for off-label use in Japanese children has not been adequately assessed. Therefore, safety evaluations of these drugs, based on after-use surveys using claims data, are urgently needed.

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