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Prescription of drugs for children with attention-deficit/hyperactivity disorder (ADHD) in Japan: a study based on health insurance claims data

Taku Obara[1,2,3], Michihiro Satoh[3], Nobuhiro Ooba[4,5], Yoshihiko Morikawa[6], Hidekazu Nishigori[7], Nariyasu Mano[3]

[1]Division of Preventive Medicine and Epidemiology, Tohoku University Tohoku Medical Megabank Organization
[2]Division of Molecular Epidemiology, Tohoku University Graduate School of Medicine
[3]Department of Pharmaceutical Sciences, Tohoku University Hospital
[4]Department of Pharmacoepidemiology, Graduate School of Medicine, University of Tokyo
[5]Department of Clinical Pharmacy, Nihon University School of Pharmacy
[6]Clinical Research Support Center, Tokyo Metropolitan Children's Medical Center
[7]Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine

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In Japan, methylphenidate osmotic controlled release oral delivery system (OROS) tablets and atomoxetine were approved for children with attention deficit hyperactivity disorder (ADHD) in 2007 and 2009, respectively. However, the annual change of medications for ADHD children has not been evaluated in Japan. Only two drugs are now available for children with ADHD in Japan. It was previously reported that many medications prescribed to children were classed as off-label utilization in Japan. The aim of the present study was to provide information on the use of drugs prescribed to children with ADHD in Japan before and after the approval of methylphenidate OROS tablets and atomoxetine. A retrospective study was conducted with Japanese medical claims data from January 2005 to December 2010 to examine the use of drugs in children with ADHD in Japan. The prescription rate of methylphenidate tablet/powder decreased from 13.4% in 2005 to 0.5% in 2008 (trend P<0.0001). This fall was accompanied by a rapid rise in the prescription rate of methylphenidate OROS tablets from 19.5% in 2008 to 31.2% in 2010 (trend P<0.0001). The prescription rate of atomoxetine also increased, reaching 3.8% in 2009 and 13.0% in 2010 (trend P<0.0001). The prescription rate for risperidone, aripiprazole, valproate, and fluvoxamine increased (all trend P<0.05), but none of the other drugs showed any change in the profile of annual changes in prescription rates. It was found that prescription patterns of drugs for children with ADHD changed before and after the approval of methylphenidate OROS tablets and atomoxetine in Japan. We need to establish the drug safety monitoring system for children with ADHD.

Key Words: : attention deficit hyperactivity disorder, children, methylphenidate, atomoxetine

Background

Methylphenidate osmotic controlled release oral delivery system (OROS) tablets and atomoxetine were approved for children with attention deficit hyperactivity disorder (ADHD) in 2007 and 2009, respectively, in Japan. However, pharmaceutical treatment options for pediatric ADHD patients are limited, with only methylphenidate OROS tablets and atomoxetine indicated for ADHD in children. In contrast, the US has approved a range of central nervous stimulants such as amphetamines (which are not sold in Japan), and it is possible

[1] Division of Preventive Medicine and Epidemiology, Tohoku University Tohoku Medical Megabank Organization, 2-1 Seiryo-cho, Aoba-ku, Sendai, Miyagi 980-8573, Japan
[2] Division of Molecular Epidemiology, Tohoku University Graduate School of Medicine, 2-1 Seiryo-cho, Aoba-ku, Sendai, Miyagi 980-8573, Japan
[3] Department of Pharmaceutical Sciences, Tohoku University Hospital, 1-1 Seiryo-cho, Aoba-ku, Sendai 980-8574, Japan
[4] Department of Pharmacoepidemiology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[5] Department of Clinical Pharmacy, Nihon University School of Pharmacy, 7-7-1 Narashinodai, Funabashi, Chiba 274-8555, Japan
[6] Clinical Research Support Center, Tokyo Metropolitan Children's Medical Center, 2-8-29, Musashicai, Fuchu, Tokyo 183-8561, Japan
[7] Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-cho, Aoba-ku, Sendai, Miyagi 980-8574, Japan
連絡著者： Taku Obara (E-mail: obara-t@hosp.tohoku.ac.jp)

that some of these medications available overseas have been used off-label for pediatric ADHD patients in Japan. In fact, a report by a research group of the Ministry of Welfare over 10 years ago stated that 76.6% of medications prescribed to children were classed as off-label utilization (http://mhlw-grants.niph.go.jp/niph/search/NIDD00.do?resrchNum=199900758A). Also, in foreign countries, off-label drugs are often used for children with ADHD[1]. However, the annual change of usage of medications for ADHD children before and after the approval of methylphenidate OROS tablets and atomoxetine for children with ADHD has not been evaluated in Japan. The aim of the present study was to clarify the annual change of usage of medications among children with ADHD in Japan before and after the approval of methylphenidate OROS tablets and atomoxetine.

Methods

1. Subjects

Health insurance claims data held by the Japan Medical Data Center (JMDC)[2] were used. Of the 3,667,503 National Health Insurance beneficiaries between January 1, 2005 and June 30, 2011, the JMDC held in its database the claims data for 2,844,948 people (77.6%) for whom claims had been issued. In conducting this study, the claims data of patients aged 2 to 17 years with an International Classification of Diseases (ICD)-10 diagnosis of F80-F89 (disorders of psychological development) and/or F90-F98 (behavioral and emotional disorders with onset usually occurring in childhood and adolescence), were received from a total of 823,354 patients aged under 20 years for whom a health insurance claim had been processed. The target of the analysis was pediatric patients newly diagnosed with ADHD (F90.0 in ICD-10) within the period from January 1, 2005 to December 31, 2010. Patients reaching 18 years of age during the target analysis period were excluded from the prescription data for that year and subsequent years.

2. Comorbidities

According to the Japanese guidelines on the diagnosis and treatment of ADHD[3], comorbidities fall into the categories of behavioral disorders, emotional disorders, nervous habits, and developmental disorders. Under the ICD-10 classification, 'behavioral disorders' corresponds to conduct disorders (F91) including oppositional defiant disorder (F91.3) and unsocialized conduct disorder (F91.1); 'emotional disorders' corresponds to phobic anxiety disorders (F40), other anxiety disorders (F41), adjustment disorders (F43.2), mood disorders (F30-39), and obsessive-compulsive disorder (F42); 'nervous habits' corresponds to nonorganic enuresis (F98.0), nonorganic encopresis (F98.1), tic disorders (F95), nonorganic sleep disorders (F51), sleep disorders (G47), and stuttering [stammering] (F98.5); and 'developmental disorders' corresponds to specific developmental disorders of scholastic skills (F81), specific developmental disorder of motor function (F82), and pervasive developmental disorders (F84), and patients not falling under any of the above were defined as having 'no developmental disorders'.

3. Data collection method

Hospital admission/non-admission claims data submitted when a patient attended a hospital or clinic, and pharmacists' fee claims data submitted when a drug was dispensed by a pharmacy based on a prescription were used. The name of the disorder, ICD-10 code, and date of diagnosis were extracted from the hospital admission/non-admission claims data. The brand name, generic name, and dosage of the prescribed medication were extracted from the hospital admission/non-admission claims data and pharmacists' fee claims data. The year, month, and day of prescription could be extracted from the pharmacists' fee claims data, but since the exact prescription date does not appear in hospital admission/non-admission claims data, the prescription date was defined as the first day of the month of medical examination. Where there was overlap of pharmacists' fee claims data and hospital admission/non-admission claims data, the pharmacists' fee claims data took precedence because of the greater precision of the prescription date. The World Health Organization - Anatomical Therapeutic Chemical (WHO-ATC) codes using the

ATC classification system, first published in 1976 by the WHO Collaborating Centre for Drug Statistics Methodology, were assigned to each medication[4].

4. Extraction and tabulation of drug data

The claims data used in this research contained 339 drug types as classified by ATC class name and 2,585 drug types by generic name. For this research, drugs excluding 'other general anesthetics', 'inhalational anesthetics', 'other local anesthetics', 'topical local anesthetics', 'injected local anesthetics', 'non-narcotic and antipyretic analgesics', 'drugs used in opioid dependence', and 'narcotic analgesics' were extracted from the class of nervous system drugs, as identified by the initial WHO-ATC code 'N'. Prescribed drugs were tabulated for each year from 2005 to 2010 to exclude the effect of variations in prescription over the course of a year. A drug was deemed to have been prescribed in a given year even if only prescribed once in that year. In order to calculate prescription rates, the number of patients prescribed a particular drug was taken as the numerator, and the cumulative number of ADHD patients under 18 years of age up to the end of each prescription year was taken as the denominator. Tabulation was done for each ATC class name and generic name, and as a rule, dosage form was ignored. However, because of differences in the approval conditions of methylphenidate OROS tablets and other dosage forms, and differences of the prescription rates between diazepam suppositories and other dosage forms, prescription rates for these two forms were tabulated separately. Prescription rates for each comorbidity in 2010 were calculated to ascertain annual changes in all extracted ATC class names and the generic names of the 30 most frequently prescribed drugs in 2010, and to investigate differences according to comorbidity.

5. Statistical analysis

To analyze the relationship between years and age or sex, we compared means and proportions using analysis of variance (ANOVA) and the chui-square 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 +/- standard deviation 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 prevalence of pediatric ADHD patients slightly increased (Table 1), with boys accounting for over 85% in each year. In each ATC class name, there was a consistent increase from 2005 to 2010 in prescriptions of psychostimulants, all other agents affecting the central nervous system, and atypical antipsychotics (trend $P<0.0001$). Psychostimulants had the highest prescription rate of all these drug classes in 2010. Other ATC class names other than selective serotonin reuptake inhibitors (SSRIs) showed no consistent annual changes in prescription rates (Table 2).

Table 1. Characteristics of patients with ADHD by year

Year of diagnosis	2005	2006	2007	2008	2009	2010	P
Number of all patients aged 0–20 years in the database	42,071	45,125	47,442	112,695	163,496	258,431	
Cumulative number of ADHD patients, n (% of the all patients aged 0-20 years in the database)	67 (0.16)	144 (0.32)	245 (0.52)	430 (0.38)	665 (0.41)	1,021 (0.40)	<0.0001
Age, years	8.3±3.2	8.7±3.1	9.5±3.1	9.9±3.2	10.1±3.2	10.6±3.3	<0.0001
Boys, n (%)	66 (98.5%)	125 (86.8%)	215 (87.8%)	380 (88.4%)	577 (86.8%)	874 (85.6%)	0.06

Data are expressed as mean ± standard deviation or percentage. ADHD, attention deficit hyperactivity disorder.

Figure 1 shows annual changes in prescription rates for methylphenidate tablet/powder, methylphenidate OROS tablets, and atomoxetine. The prescription rate of methylphenidate tablet/powder decreased from 13.4% in 2005 to 0.5% in 2008 (trend P<0.0001). This fall was accompanied by a rapid rise in the prescription rate of methylphenidate OROS tablets from 19.5% in 2008 to 31.2% in 2010 (trend P<0.0001). The prescription rate of atomoxetine also increased, reaching 3.8% in 2009 and 13.0% in 2010 (trend P<0.0001). The prescription rate for risperidone, aripiprazole, valproate, and fluvoxamine increased (all trend P<0.05), but none of the other drugs showed any change in the profile of annual changes in prescription rates (Figure 2, Table 3).

Table 4 shows drug prescription rates for each comorbidity in 2010. Prescriptions were given for developmental disorders in 406 patients, anxiety and other emotional disorders in 123 patients, epilepsy in 112 patients, tic disorders and other nervous habits in 88 patients, and behavioral disorders in 12 patients. Prescription rates for patients with emotional disorders and epilepsy were relatively higher than for other comorbidities. For emotional disorders, the rates were 52.0% for methylphenidate OROS tablets, 12.2% for fluvoxamine, and 10.6% for aripiprazole, and for epilepsy, the rates were 37.5% for valproic acid, 19.6% for carbamazepine, and 17.0% for triclofos. In patients with no developmental disorders, not only methylphenidate OROS tablets (18.7%) and atomoxetine (6.8%) but also risperidone (2.3%), valproate (0.4%), triclofos (1.9%), and aripiprazole (1.0%) were prescribed.

Table 2. Annual changes of drug prescriptions among children with ADHD

Prescription year	2005	2006	2007	2008	2009	2010	
Cumulative number of ADHD patients, n	67	144	245	430	665	1021	Sex- and age-adjusted trend P
Prescription rate, %							
Psychostimulants, etc.							
Psychostimulants	13.4	11.1	9.0	20.0	22.7	31.5	<0.0001
All other central nervous system drugs	0.0	0.7	0.0	0.0	4.4	13.5	<0.0001
Antipsychotics							
Atypical antipsychotics	1.5	0.0	0.8	5.6	6.6	11.6	<0.0001
Other antipsychotics	1.5	2.1	0.8	0.7	0.5	2.0	0.7
Antidepressants							
SSRI antidepressants	0.0	0.0	0.4	1.2	1.1	2.5	0.007
SNRI antidepressants	0.0	0.0	0.0	0.0	0.0	0.2	NA
Other antidepressants	3.0	2.1	1.6	1.6	1.4	1.9	0.3
Antianxiety / mood stabilizer drugs							
Antianxiety drugs (tranquilizers)	3.0	3.5	1.2	2.1	2.0	3.0	0.7
Mood stabilizers (antimanic drugs)	0.0	0.0	0.0	0.2	0.2	0.1	1.0
Psychotropic drugs (either of above)	17.9	15.3	12.2	24.2	29.0	45.5	<0.0001
Others							
Antiepileptic drugs	6.0	5.6	5.3	5.8	6.0	8.5	0.1
Barbiturates, single drug	1.5	1.4	0.4	0.5	0.9	0.6	0.6
Non-barbiturates, single drug	4.5	6.3	2.9	3.3	3.8	4.9	0.3
Parkinson's disease / syndrome drugs	0.0	0.7	0.0	0.7	0.9	1.2	0.2
Triptans for migraine	0.0	0.0	0.0	0.0	0.0	0.1	NA
Other drugs for migraine	0.0	0.0	0.0	0.0	0.0	0.1	NA
Anti-vertigo drugs	0.0	0.0	0.0	0.0	0.2	0.0	0.9
Nootropic drugs (cognitive enhancers)	0.0	0.0	0.0	0.0	0.0	0.1	NA

Prescription rates for each generic name were calculated as percentage values using the number of patients prescribed each drug as the numerator and the cumulative number of ADHD patients age <18 years up to each prescription year as the denominator. ADHD, attention deficit hyperactivity disorder; SNRI, serotonin and norepinephrine reuptake inhibitor selective; SSRI, selective serotonin reuptake inhibitor. NA, not applicable (because of the limited number of drug prescription)

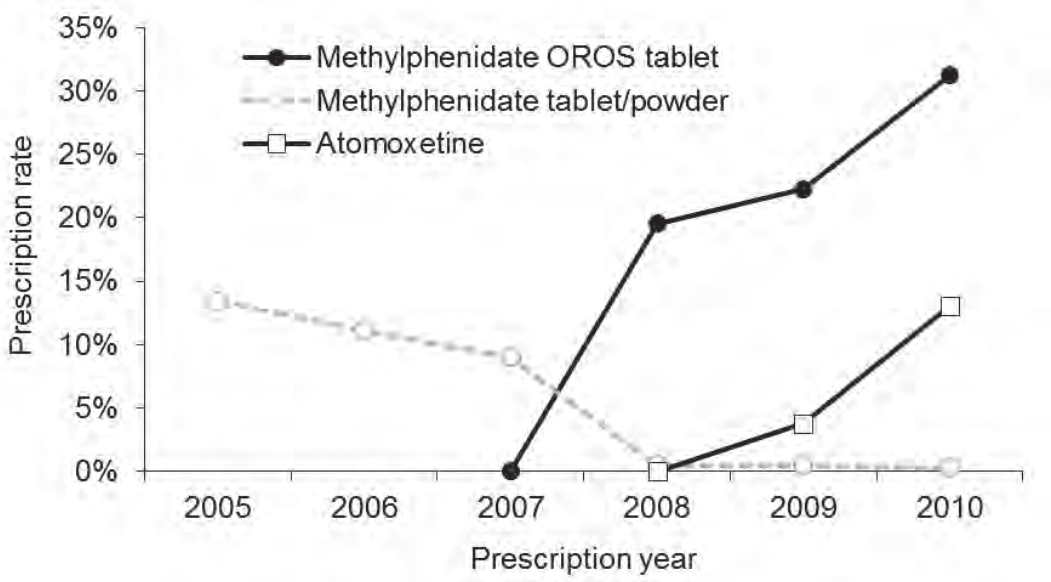

Figure 1. Annual changes of prescription rates of methylphenidate tablet/powder, methylphenidate OROS tablets, and atomoxetine for children with ADHD in Japan

Prescription rates of methylphenidate tablet/powder, methylphenidate OROS tablets, and atomoxetine were calculated as percentage values using the number of patients prescribed each drug as the numerator and the cumulative number of ADHD patients age <18 years up to each prescription year as the denominator. ADHD, attention deficit hyperactivity disorder; OROS, osmotic controlled release oral delivery system. All trend P values were <0.0001 after adjustment for sex and age.

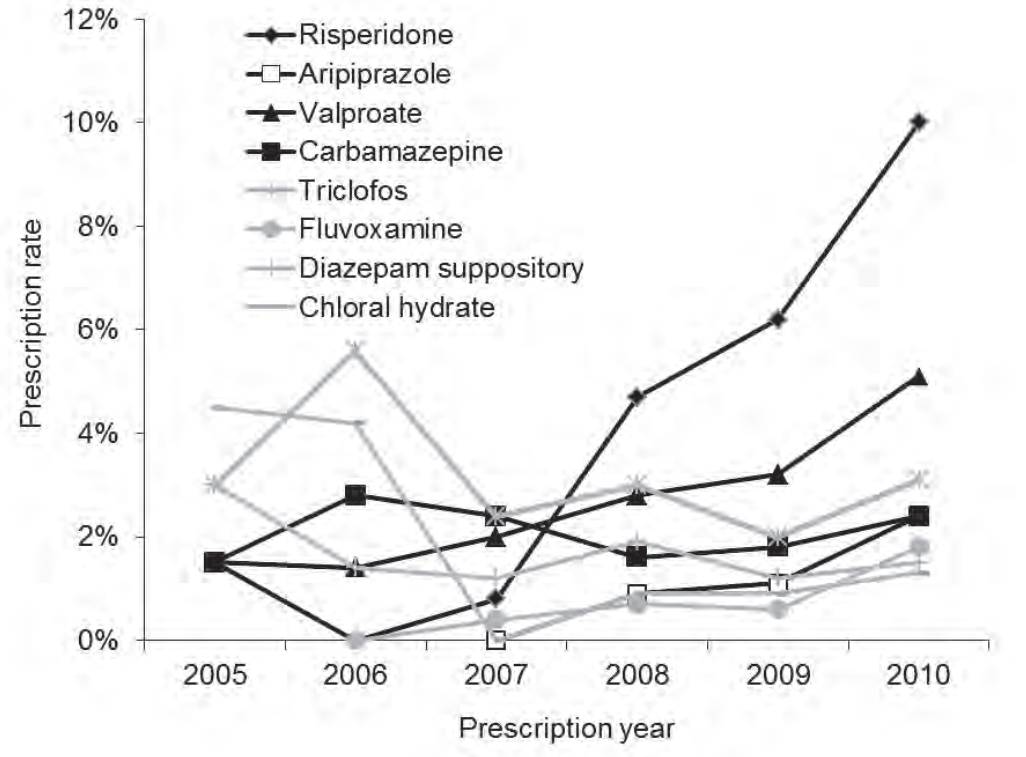

Figure 2. Drugs whose prescription rates were in the top 3-10 for year 2010 and their annual changes

Prescription rates for each generic name were calculated as percentage values using the number of patients prescribed each drug as the numerator and the cumulative number of ADHD patients age <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. ADHD, attention deficit hyperactivity disorder. Trend P values were <0.0001 for risperdone, 0.002 for aripiprazole, 0.01 for valproate, 0.9 for carbamazepine, 0.7 for triclofos, 0.02 for fluvoxamine, 0.9 for diazepam suppository, and 0.7 for chloral hydrate after adjustment for sex and age.

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

Year of diagnosis	2005	2006	2007	2008	2009	2010	
Cumulative number of ADHD patients, n	67	144	245	430	665	1021	Sex- and age-adjusted trend P
Prescription rate, %							
Hydroxyzine	1.5	2.8	0.8	0.9	1.2	1.3	0.7
Clomipramine	0.0	0.7	1.2	1.2	0.9	1.0	0.7
Imipramine	3.0	1.4	0.4	0.5	0.3	0.8	0.1
Diazepam other than suppository	0.0	0.7	0.0	0.0	0.3	0.8	0.1
Sertraline	0.0	0.0	0.0	0.5	0.5	0.8	0.2
Propericiazine	1.5	0.7	0.4	0.2	0.3	0.7	0.8
Biperiden	0.0	0.7	0.0	0.2	0.3	0.7	0.4
Clobazam	1.5	0.7	0.8	0.7	0.8	0.6	0.2
Haloperidol	0.0	0.7	0.0	0.2	0.2	0.5	0.6
Phenobarbital	0.0	0.7	0.0	0.2	0.6	0.5	0.3
Clonazepam	0.0	0.7	0.8	0.7	0.5	0.4	0.5
Brotizolam	0.0	0.0	0.0	0.0	0.6	0.4	0.2
Lamotrigine	0.0	0.0	0.0	0.0	0.3	0.4	0.1
Levomepromazine	1.5	0.7	0.0	0.0	0.0	0.3	0.2
Pimozide	0.0	0.7	0.4	0.2	0.0	0.3	0.6
Neostigmine	0.0	0.7	0.0	0.0	0.5	0.3	0.7
Ethyl loflazepate	0.0	0.0	0.4	0.0	0.0	0.3	0.6
Olanzapine	0.0	0.0	0.0	0.0	0.2	0.3	0.3
Levodopa	0.0	0.0	0.0	0.0	0.2	0.3	0.3

Prescription rates for each generic name were calculated as percentage values using the number of patients prescribed each drug as the numerator and the cumulative number of ADHD patients age <18 years up to each prescription year as the denominator. ADHD, attention deficit hyperactivity disorder.

Table 4. Prescription rates of major drugs by comorbidities in 2010

	Developmental disorders	Emotional disorders	Nervous habits	Epilepsy	No develop -mental disorder
Number of patients, n	406	123	88	112	486
Prescription rate, %					
Methylphenidate OROS tablets	41.1	52.0	36.4	39.3	18.7
Atomoxetine	17.2	24.4	25.0	21.4	6.8
Risperidone	17.5	26.8	19.3	25.9	2.3
Valproate	7.1	11.4	11.4	37.5	0.4
Triclofos	3.2	0.8	3.4	17.0	1.9
Carbamazepine	3.9	5.7	9.1	19.6	0.0
Aripiprazole	4.2	10.6	6.8	5.4	1.0
Fluvoxamine	2.7	12.2	4.5	1.8	0.0

Prescription rates for each generic name of major drugs by comobidities were calculated as percentage values using the number of patients prescribed each drug as the numerator and the number of ADHD patients age <18 years for year 2010 as the denominator. Because behavioral disorders were observed only in 12 children, the results were not shown. OROS, osmotic controlled release oral delivery system. ADHD, attention deficit hyperactivity disorder.

Discussion

The present study found that methylphenidate tablet/powder might have been mainly used for children with ADHD before the approval of methylphenidate OROS tablets and atomoxetine, and the prescription rates of methylphenidate OROS tablets and atomoxetine increased in recent years. Many medications not indicated for ADHD in children have also been used in these patients, suggesting the possibility that these medications have been used off-label to treat ADHD.

According to several reports on drug utilization in children (0 to 17 years) in the US, methylphenidate and amphetamine salts are widely used as ADHD medications, whereas atomoxetine, which is on the increase in Japan, is seeing a downward trend in the US, while utilization of dexmethylphenidate, lisdexamfetamine, and guanfacine has increased[5]. There is also a slight upward trend in the utilization of central nervous system agents, which include ADHD medications, in the US[5,6]. These studies illustrate the difference in utilization of ADHD medications between Japan and other countries, and this highlights the need for a Japan-specific understanding of drug utilization.

Differences in utilization of ADHD medications are presumably greatly influenced by the content of different ADHD treatment guidelines, irrespective of differences in indications and off-label use. The guidelines for the diagnosis and treatment of ADHD in Japan recommend methylphenidate OROS tablets and atomoxetine as first-line drugs[3]. In the US, the Texas Children's Medication Algorithm Project recommends central nervous stimulants, such as methylphenidate, as first-line drugs, and combined use of atomoxetine and central nervous stimulants, as well as antidepressants (serotonin and norepinephrine reuptake inhibitors; SNRIs) and alpha-2 agonists, as second-line drugs and beyond[7]. European clinical guidelines for hyperkinetic disorder recommend central nervous stimulants, such as methylphenidate, as first-line drugs, and noradrenergic agents, such as atomoxetine, if there is no improvement[8]. One of the reasons for the wide use of methylphenidate and atomoxetine seen in this study might be that, in addition to being approved for ADHD in Japan, these drugs are recommended as first- or second-line treatment in all guidelines. It is unclear from the present study whether the prescribed medications were used as first-line therapy. However, a questionnaire survey of Japanese physicians on prescribing practices for drug treatment of pediatric ADHD patients found that methylphenidate OROS tablets and atomoxetine were prescribed as first- and second-line drugs by 92.5% and 89.4% of respondents, respectively[9].

Apart from methylphenidate OROS tablets and atomoxetine, pediatric ADHD patients in Japan have often been prescribed antipsychotics, antidepressants, antiepileptic drugs, and nonbarbiturate agents. It is possible that prescribing trends among physicians differ according to type of comorbidity and guidelines consulted, and this may be a factor in the off-label use of drugs to treat pediatric ADHD in Japan. The present study suggested that risperidone, valproate, triclofos, and aripiprazole might be prescribed as off-label use in pediatric ADHD patients. In the questionnaire survey of Japanese physicians mentioned above, many respondents cited risperidone, aripiprazole, antiepileptic drugs, and SSRIs as drugs they would like to see approved for clinical use in children with developmental disorders[9]. It is therefore likely that some drugs are knowingly used off-label because physicians are forced by necessity to do so. Given the possibility that patients suffering adverse reactions following off-label use might not receive the appropriate remedial care, there is an urgent need to gather data to evaluate efficacy and safety based on actual utilization, to decide whether or not to expand the indications, and to eliminate discrepancies between package inserts and guidelines, using health insurance claims data and other information sources.

Recently, cases of sudden death, myocardial infarction, and stroke among children who were treated with drugs for ADHD were reported as adverse events in Canada and the United States[10,11]. In response, the United States Food and Drug Administration (FDA) and the Agency for Healthcare Research and Quality (AHRQ) embarked on a large-scale, joint study of ADHD medications and cardiovascular risk using health insurance

data[12]. The study concluded that even if there is an increased risk, the absolute risk is low, and there is no evidence of a link between current use of ADHD medication and serious cardiovascular risk[12]. Subsequently, however, effects of ADHD medications on cardiovascular risk factors have been reported[13,14]. The prevalence of pediatric ADHD patients slightly increased in this study. This phenomenon might be partly caused by increasing mean age of father due to trend of late marriage[15] and increasing the opportunity of exposure to environmental chemicals[16]. Additionally, because prescription rate of psychotropic drugs for children with ADHD were gradually increased in this study, combination therapies might be increased. Okumura Y et al. also reported that ADHD medications were used as combination therapy with other psychotropic agents in 17% of outpatients aged 18 years or younger in Japan[17]. Therefore, we also need to establish the baseline for regular monitoring of adverse drug reactions by these drugs and combination therapies for children with ADHD.

There are some limitations to the present study. Because prescription dates could only be determined to the month and year of diagnosis listed on the hospital admission/non-admission claims data, the dates of all prescriptions and diagnoses within the same month were identical. It is therefore possible that some drug prescriptions in the tabulated data were made in the same month as a new diagnosis of ADHD but before the actual diagnosis. In addition, all ADHD diagnoses and comorbidity terms were based on the health insurance claims and, therefore, need to be validated.

Conclusion

Prescription patterns of drugs for children with ADHD changed before and after the approval of methylphenidate OROS tablets and atomoxetine in Japan. We need to establish the baseline for regular monitoring of adverse drug reactions by drugs for children with ADHD.

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References

1) Carton L, Cottencin O, Lapeyre-Mestre M, Geoffroy PA, Favre J, Simon N. Off-label prescribing of antipsychotics in adults, children and elderly individuals: a systematic review of recent prescription trends. Curr Pharm Des. 21, 3280-97, 2015.

2) Kimura S, Sato T, Ikeda S, Noda M, Nakayama T. Development of a database of health insurance claims: standardization of disease classifications and anonymous record linkage. J Epidemiol. 20, 413-9, 2010.

3) Saito K, Watanabe K. The guidelines for the diagnosis and treatment of ADHD. Jiho, Inc. Tokyo. 2008. (in Japanese)

4) World Health Organization Collaborating Centre for Drug Statistics Methodology. http://www.whocc.no/news/ (Accessed 8 Sep 2015)

5) Chai G, Governale L, McMahon AW, Trinidad JP, Staffa J, Murphy D. Trends of outpatient prescription drug utilization in US children, 2002-2010. Pediatrics. 130, 23-31, 2012.

6) Zuvekas SH, Vitiello B. Stimulant medication use in children: a 12-year perspective. Am J Psychiatry. 169, 160-6, 2012.

7) Pliszka SR, Crismon ML, Hughes CW, Corners CK, Emslie GJ, Jensen PS, McCracken JT, Swanson JM, Lopez M; Texas Consensus Conference Panel on Pharmacotherapy of Childhood Attention Deficit Hyperactivity Disorder. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 45, 642-57, 2006.

8) Taylor E, Döpfner M, Sergeant J, Asherson P, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Rothenberger A, Sonuga-Barke E, Steinhausen HC, Zuddas A. European clinical guidelines for hyperkinetic disorder -- first upgrade. Eur Child Adolesc Psychiatry. 13

Suppl 1, I7-30, 2004.
9）Miyachi T, Miyazima T, Ishizuka Y, Fukai Y, Nagai A, Otsuka S, Hayashi K, Ishizaki A, Tanaka H. Investigation of drug therapy for children with ADHD in Japan. The 107th Meeting of Japanease Society of Pediatric Psychiatry and Neurology. Tokyo. June 16-17, 2012.
10）Tannenbaum H, Bombardier C, Davis P, Russell AS; Third Canadian Consensus Conference Group. An evidence-based approach to prescribing nonsteroidal antiinflammatory drugs. Third Canadian Consensus Conference. J Rheumatol. 33, 140-57, 2006.
11）Nissen SE. ADHD drugs and cardiovascular risk. N Engl J Med. 354, 1445-8, 2006.
12）Cooper WO, Habel LA, Sox CM, Chan KA, Arbogast PG, Cheetham TC, Murray KT, Quinn VP, Stein CM, Callahan ST, Fireman BH, Fish FA, Kirshner HS, O'Duffy A, Connell FA, Ray WA. ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med. 365, 1896-904, 2011.
13）Avery AJ, Anderson C, Bond CM, Fortnum H, Gifford A, Hannaford PC, Hazell L, Krska J, Lee AJ, McLernon DJ, Murphy E, Shakir S, Watson MC. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. Health Technol Assess. 15, 1-234, 2011.
14）Sert A, Gokcen C, Aypar E, Odabas D. Effects of atomoxetine on cardiovascular functions and on QT dispersion in children with attention deficit hyperactivity disorder. Cardiol Young. 22, 158-61, 2012.
15）Kong A, Frigge ML, Masson G, Besenbacher S, Sulem P, Magnusson G, Gudjonsson SA, Sigurdsson A, Jonasdottir A, Jonasdottir A, Wong WS, Sigurdsson G, Walters GB, Steinberg S, Helgason H, Thorleifsson G, Gudbjartsson DF, Helgason A, Magnusson OT, Thorsteinsdottir U, Stefansson K. Rate of de novo mutations and the importance of father's age to disease risk. Nature. 488, 471-5, 2012.
16）Council on Environmental Health. Pesticide exposure in children. Pediatrics 130: e1757-63, 2012.
17）Okumura Y, Fujita J, Matsumoto T. Trends of psychotropic medication use among children and adolescents in Japan data from the national insurance claims database between 2002 and 2010. Seishin Shinkeigaku Zasshi. 116, 921-35, 2014. (in Japanese)