Received: 26 March 2021 | Revised: 3 June 2021 | Accepted: 13 June 2021

DOI: 10.1002/npr2.12191

ORIGINAL ARTICLE

NEUROPSYCHOPHARMACOLOGY REPORTS

WILEY

Medications for attention-deficit/hyperactivity disorder in Japan: A retrospective cohort study of label compliance

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Funding information
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Abstract

Aim: To assess label compliance in prescription of medications approved for treatment of attention-deficit/hyperactivity disorder (ADHD) in Japan at the time of this study: methylphenidate (MPH), atomoxetine, and guanfacine.

Methods: Retrospective descriptive study was conducted in prevalent-user cohorts from the Japan Medical Data Center database. Patients who were prescribed a study drug between January 1, 2013 and September 30, 2018 and were in the database for ≥30 days were included. A prescription was considered compliant if all 4 criteria were satisfied: appropriate age, daily dose not exceeding the approved maximum, no contraindicated concurrent medications, and no contraindicated conditions.

Results: Among 17 418 patients who were prescribed a study drug during 2013-2018, 73% were male and 53% were children (aged <18 years). Fewer than 2% of prescriptions were for patients outside the approved age, 10%-13% of patients in the atomoxetine and MPH cohorts received ≥1 prescription exceeding maximum approved dose, no patients were co-prescribed a contraindicated medication, and 16%–18% of patients in the MPH cohorts had ≥1 contraindicated condition. During their first 500 days of use, for approximately 73%-86% of patients, all prescriptions were compliant with all label requirements.

Conclusions: Among patients exposed to ADHD medications in Japan during 2013-2018, nearly all prescriptions for these medications were label-compliant for age. For >85% of patients, all prescriptions were label-compliant for dose, and for approximately 80%, all prescriptions were label-compliant for contraindicated conditions. We did not find evidence of widespread abuse or noncompliant use of prescribed ADHD medications.

KEYWORDS

atomoxetine, guanfacine, JMDC, label compliance, methylphenidate

ClinicalTrials.gov Identifier: NCT04113551

1 | INTRODUCTION

During 2013 through 2018, the time period of the present study, only 3 drug substances were approved for the treatment of attention-deficit/hyperactivity disorder (ADHD) in Japan—extended-release methylphenidate (MPH) marketed as Concerta® (MPH-C; Janssen Pharmaceutical KK, Tokyo), atomoxetine, and guanfacine.[1,2] Methylphenidate, a central nervous system (CNS) stimulant, is widely used to treat ADHD and is a controlled substance. Atomoxetine and guanfacine are not stimulants and are not controlled substances in Japan. Another extended-release form of MPH, Ritalin® (MPH-R; Novartis Pharma KK, Tokyo), which differs from MPH-C in its release characteristics,[3,4] is also marketed in Japan and is only approved for the treatment of narcolepsy. Another stimulant, lisdexamfetamine dimesylate, was approved recently in Japan for the treatment of ADHD in children.[5]

The prescribing patterns of ADHD medications have evolved considerably in Japan in the past 15 years. An extended-release formulation of MPH (MPH-C) was approved in 2007 and replaced the short-acting formulation; atomoxetine was approved in 2009, and guanfacine was approved in 2017.[2] Use of ADHD medications in pediatric patients with ADHD increased substantially following approval of MPH-C and atomoxetine.[2,6] There are concerns about the safety and appropriate use of ADHD medications, and because MPH is a CNS stimulant with a potential for abuse, it is particularly important to understand the extent of its misuse, abuse, or off-label prescription.[7] Although physicians may have sound reasons to prescribe a medication "off-label," having a relatively high proportion of label-compliant prescriptions would suggest appropriate clinical use that is safe and effective, and information on the extent of off-label prescribing can help regulators and practitioners assess whether interventions are needed to improve prescribing.

Neither MPH-R nor any of the 3 drugs approved for ADHD in Japan at the time of this study have been assessed for safety and efficacy in patients aged below 6 years or over 65 years.[3,4,8,9] In addition, safety and efficacy of de novo use of guanfacine have not been assessed in patients aged 18 years or older, and those who are continuing from age <18 years are advised to use caution;[9] a similar limitation applied to MPH-C prior to December 20, 2013. The present study was conducted to understand the patterns of on-label and off-label prescription of MPH-C, MPH-R, atomoxetine, and guanfacine in Japan.

2 | METHODS

2.1 | Study design

This was a retrospective descriptive cohort study of prevalent-user cohorts derived from anonymized administrative claims data from the Japan Medical Data Center (JMDC) database[10] (Clinical trial registry identifier, NCT04113551). The JMDC has certified that the data are anonymously processed, so ethics approval is not necessary when using the data for publications. The copy of the database used for the present study included data from January 1, 2005 to September 30, 2018 from 60 society-managed health insurance plans covering workers aged 18 to 65 years and their dependents. All diagnoses in the database are coded using International Statistical Classification of Diseases and Related Health Problems, 10th revision; all prescriptions refer to national Japanese drug codes that have been linked to the Anatomical Therapeutic Chemical Classification System. Only prescriptions that were dispensed were recorded in the database. For this study, the database was converted to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) version 5.3.1.[11,12] Conversion to the OMOP CDM is a transformation of the source structure and content to a standardized structure and vocabulary for encoding healthcare information, allowing consistent application of standardized analytics for research.

We included MPH-R in the present study because it has the same active drug substance as MPH-C and thus can potentially lead to excessive dosing if both are prescribed. Although atomoxetine and guanfacine were not limited to any specific brands, MPH-C and MPH-R designated those respective brands because the two have different release characteristics, indications, and maximum approved doses.

2.2 | Participants and data extraction

Patients entered the study when, between January 1, 2013 and September 30, 2018, they first (1) had been in the database for ≥30 days and (2) received a prescription for a study drug, that is, an active drug substance approved in Japan for the treatment of ADHD at the time of this study. Other medications that are sometimes used to treat ADHD (eg, pemoline and modafinil)[13,14] were out of scope for the present study. The date of that prescription was the patient's index date. Exposures to MPH not identified as MPH-C or MPH-R were excluded because it was unclear which label requirements for dosing and indication would apply. Patients left the study with the first of (1) leaving the database or (2) reaching the study end date. Because the database provides the month and year of birth but not the day of the month, the 15th of the month was assigned as each patient's birth date. Duration of prescription was based on days' supply, if available; otherwise, it was based on dose per day and total amount prescribed. A prescription was considered noncompliant if any of 4 compliance criteria for the respective drugs was not satisfied at the time of the prescription: appropriate age, daily dose not exceeding the approved maximum, absence of contraindicated concurrent medications, and absence of contraindicated conditions (Table S1). To maximize inclusion of patients who were prescribed one or more of the study drugs, we required patients to be in the database for only 30 days before the first prescription. A diagnosis of ADHD or narcolepsy, as appropriate, recorded in the 30 days prior to the prescription for each study drug was not included as a

compliance criterion because the absence of a diagnosis in the past 30 days could reflect either the absence of the diagnosis or the absence of its recording in the past 30 days.

The age limitations in the drug labels were listed as precautions or warnings; however, for the purpose of this study, they were treated as contraindications. Study drugs prescribed ≤8 days before the last day of a previous prescription for the same medication were considered refills and not counted toward the maximum daily dose. Because the dosing of atomoxetine and guanfacine for pediatric patients (aged <18 years) is based on body weight, and children's body weights were not recorded in the database, the estimated 95th percentile body weights for age and sex based on published data were used for calculating the maximum approved daily dose.[15,16] To avoid false-positive cases, (eg, "rule-out" diagnoses), patients were considered to have a contraindicated condition only if they had ≥2 diagnoses of the contraindicated condition before or on the day of a prescription.

Patients were grouped in 14 cohorts (Table S2) that were constructed using ATLAS, a web-based open-source application.[17] The MPH-C, MPH-R, and MPH-C + R cohorts, respectively, represented patients who during the study, received MPH-C but never received MPH-R, received MPH-R but never received MPH-C, received MPH-C at some time and MPH-R at some (possibly different) time. The MPH-C/R cohort represented patients who received any MPH (ie, the preceding 3 cohorts combined). Inclusion in the atomoxetine and guanfacine cohorts depended only on whether a patient received atomoxetine or guanfacine, respectively, during the study (Table 1).

2.3 | Statistical analyses

Since this was an observational and descriptive study, no power or sample size calculations were necessary. Descriptive summary data are presented as two-way tables of counts and proportions. For MPH-C, MPH-R, MPH-C + R, atomoxetine, and guanfacine, the proportion of patients complying with all label requirements is shown as survival curves.

3 | RESULTS

3.1 | Patient disposition

Among approximately 5.7 million patients in the JMDC database, 18 504 (0.3%) were prescribed MPH, atomoxetine, or guanfacine between January 1, 2005 and September 30, 2018. Of these, 18 402 were prescribed ≥1 study drug (branded MPH [C/R], atomoxetine, or guanfacine) (Figure 1). Among these, 17 546 patients (95.3%) were prescribed ≥1 study drug between January 1, 2013 and September 30, 2018; 17 418 (99.3%) of these had an exposure after being in the database for ≥30 days and were included in the study.

3.2 | Demographic characteristics and treatments received

Most patients were male (73.0%). At study entry, 98.8% of patients were aged 6 to 65 years, 1.2% aged <6 years, and 0.1% aged 66 years or older; 52.7% of the patients were children (Table 1, last column). Among the 17 418 patients in the study, 10 084 (57.9%) received MPH (MPH-C, 9759 [56.0%]; MPH-R, 298 [1.7%]; MPH-C + R, 27 [0.2%]), 10 706 (61.5%) received atomoxetine, and 1623 (9.3%) received guanfacine. The majority of patients who received MPH-C (64.5%) or guanfacine (98.3%) were children. In contrast, the majority of patients who received atomoxetine (55.6%) or MPH-R (93.6%) were adults.

TABLE 1 Demographic characteristics

Characteristic	MPH-C N = 9759	MPH-R N = 298	MPH-C + R N = 27	MPH-C/R N = 10 084	Atomoxetine N = 10 706	Guanfacine N = 1623	Any Drug[a] N = 17 418
Age, years, n (%)[b]							
<6	61 (0.6)	0	1 (3.7)	62 (0.6)	151 (1.4)	22 (1.4)	205 (1.2)
6-17	6234 (63.9)	19 (6.4)	10 (37.0)	6263 (62.1)	4603 (43.0)	1573 (96.9)	8982 (51.6)
18-65	3460 (35.5)	277 (93.0)	16 (59.3)	3753 (37.2)	5948 (55.6)	28 (1.7)	8221 (47.2)
≥66	4 (< 0.1)	2 (0.7)	0	6 (0.1)	4 (< 0.1)	0	10 (0.1)
Sex, n (%)							
Male	7500 (76.9)	193 (64.8)	20 (74.1)	7713 (76.5)	7500 (70.1)	1338 (82.4)	12 707 (73.0)
Female	2259 (23.1)	105 (35.2)	7 (25.9)	2371 (23.5)	3206 (29.9)	285 (17.6)	4711 (27.0)

Abbreviations: MPH-C, methylphenidate (Concerta®); MPH-R, methylphenidate (Ritalin®); MPH-C + R, MPH-C and MPH-R; MPH-C/R, MPH-C, or MPH-R.

[a]MPH-C, MPH-R, atomoxetine, or guanfacine. Number of patients in this cohort is lower than the total number of patients in the MPH-C/R, atomoxetine, and guanfacine cohorts because some patients received more than 1 study drug.

[b]Age on November 15, 2015, the approximate midpoint of the study.

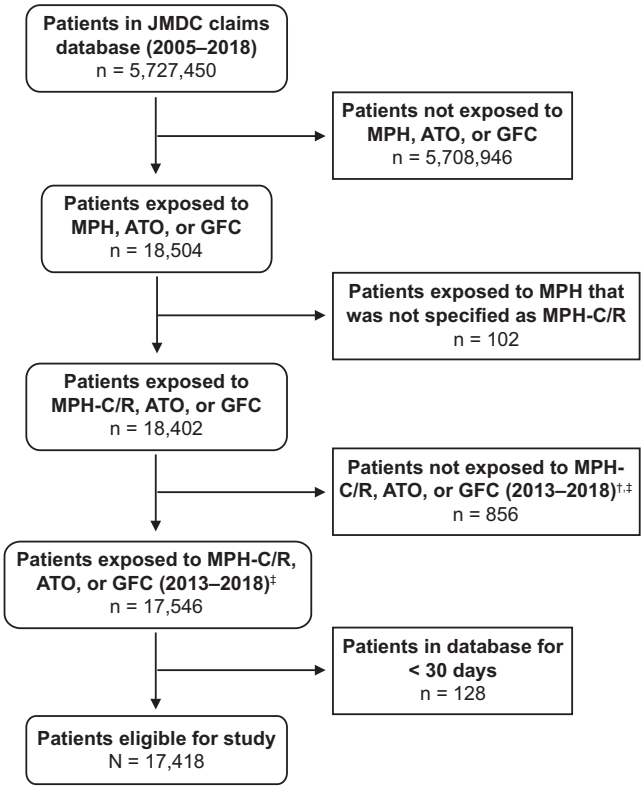

FIGURE 1 Patient disposition. †Not excluded were 3 patients who received MPH that was not specified as MPH-C or MPH-R; these patients also received atomoxetine. They were included in the ATO cohort but excluded from the MPH cohorts. ‡From January 1, 2013 to September 30, 2018. ATO, atomoxetine; GFC, guanfacine; JMDC, Japanese Medical Data Center; MPH, methylphenidate; MPH-C/R, methylphenidate that is MPH-C (Concerta®) or MPH-R (Ritalin®)

3.3 | First prescribers and year of entry

Approximately 90% of first prescribers of study drugs were from the psychiatry, pediatric medicine, internal medicine, or neurology departments (Table S3). The most frequent first prescribers for MPH-C (37.6%), MPH-R (38.3%), and atomoxetine (42.4%) were psychiatrists; for guanfacine, it was pediatricians (29.2%), followed by psychiatrists (28.1%) and internists (24.3%). The years in which patients entered the study and started each medication are described in Table S4.

3.4 | Approved indications

For each study drug, ≥96.0% of patients had the approved indication recorded in the 30 days prior to and including the first dispensing day (Table 2).

3.5 | Contraindicated concurrent medications

The only medications contraindicated for concurrent use with MPH or atomoxetine were monoamine oxidase inhibitors; no medications were contraindicated for concurrent use with guanfacine (Table S1). No patients in the MPH or atomoxetine cohorts received a monoamine oxidase inhibitor; therefore, all study prescriptions met the label requirements for contraindicated concurrent medications.

3.6 | Prescriptions to patients outside of approved age

This analysis focused on the number of prescriptions rather than the number of patients because patients could remain in the study cohort for several years, whereas each prescription is associated with a specific date and patient age. With the exception of guanfacine, fewer than 1% of prescriptions were written to patients outside the approved age range; for guanfacine, this proportion was 1.7% (Table S5).

3.7 | Maximum approved daily dose

The proportion of patients who ever received a prescription that exceeded the maximum approved dose of a study drug was 25.9% (7 of 27) in the MPH-C + R cohort, 13.3% (1427 of 10 706) in the atomoxetine cohort, 11.6% (1130 of 9759) in the MPH-C cohort, 9.7% (29 of 298) in the MPH-R cohort, and 3.9% (64 of 1623) in the guanfacine cohort (Table 3). The amount of the overage relative to the maximum approved dose was estimated only for the first dose that exceeded the approved maximum, and it was rarely above 100% (ie, double the maximum approved dose; Table 3). On the first dose that exceeded the approved maximum, 20 patients (0.2%) in the MPH-C cohort and 22 (0.2%) in the atomoxetine cohort received more than double the maximum approved dose. Of the former, 13 (65.0%) were children (5 [25.0%] aged 6-12 years and 8 [40.0%] aged 13-17 years). Of the latter, 21 (95.5%) were children (18 [81.8%] aged 6-12 years and 3 [13.6%] aged 13-17 years).

For pediatric patients (aged <18 years) prescribed atomoxetine or guanfacine, the maximum approved dose was estimated for the 95th percentile of body weight for age and sex based on the 95th percentile for weight in published population data.[15,16] Among the pediatric patients, 4226 and 1595 patients, respectively, were prescribed atomoxetine and guanfacine; of these, 933 (22.1%) and 64 (4.0%), respectively, were prescribed ≥1 dose of atomoxetine or guanfacine above the maximum approved dose. The total numbers of pediatric patients prescribed atomoxetine or guanfacine described above do not match those in Table 1, because age for this analysis was the age when the patient was first prescribed more than the maximum approved dose (for those who received a prescription above the maximum approved dose) or the age at index date (for those who did not), whereas age in Table 1 was the age at the midpoint of the study.

3.8 | Contraindicated conditions

A contraindicated condition (Table S1) was present at the time of a prescription for 16.1% of patients (1574 of 9759) in the MPH-C

TABLE 2 Patients by presence or absence of a diagnosis for the approved indication during 30 days prior to and including the first dispensing day

Parameter	MPH-C	MPH-R	MPH-C + R	Atomoxetine	Guanfacine
Approved indication	ADHD	Narcolepsy	ADHD or narcolepsy	ADHD	ADHD
First-time users, N[a]	8055	173	20	9259	1604
With approved indication, n (%)	7932 (98.5)	166 (96.0)	20 (100.0)	9065 (97.9)	1582 (98.6)
Prevalent users, N[b]	1704	125	7	1447	19
With approved indication, n (%)	1681 (98.7)	120 (96.0)	7 (100.0)	1426 (98.5)	19 (100.0)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MPH-C, methylphenidate (Concerta®); MPH-C + R, MPH-C, and MPH-R; MPH-R, methylphenidate (Ritalin®).

[a]First-time users (incident users) of a medication are those who did not receive the medication before their index date.

[b]Prevalent users of a medication are those who did receive the medication before their index date.

TABLE 3 Patients by daily dose relative to maximum approved daily dose

Parameter	MPH-C N = 9759	MPH-R N = 298	MPH-C + R N = 27	Atomoxetine N = 10 706	Guanfacine N = 1623
Never exceeded maximum approved daily dose, n (%)	8629 (88.4)	269 (90.3)	20 (74.2)	9279 (86.7)	1559 (96.1)
Received ≥1 dose above maximum approved dose, n (%)	1130 (11.6)	29 (9.7)	7 (25.9)	1427 (13.3)	64 (3.9)
Extent of dose overage, n (%)[a]					
≤50%	837 (8.6)	15 (5.0)	5 (18.5)	1072 (10.0)	54 (3.3)
>50%-100%	273 (2.8)	14 (4.7)	2 (7.4)	333 (3.1)	10 (0.6)
>100%-150%	12 (0.1)[b]	0	0	17 (0.2)[c]	0
>150%	8 (0.1)[b]	0	0	5 (<0.1)[c]	0

Abbreviations: MPH-C, methylphenidate (Concerta®); MPH-C + R, MPH-C, and MPH-R; MPH-R, methylphenidate (Ritalin®).

[a]Evaluated at the time the patient first exceeded the maximum approved daily dose.

[b]Of the 20 patients who received an overage of >100% of MPH-C, 13 (65.0%) were children (5 [25.0%] aged 6-12 years and 8 [40.0%] aged 13-17 years).

[c]Of the 22 patients who received an overage of >100% of atomoxetine, 21 (95.5%) were children (18 [81.8%] aged 6-12 years and 3 [13.6%] aged 13-17 years).

cohort, 18.1% (54 of 298) in the MPH-R cohort, 22.2% (6 of 27) in the MPH-C + R cohort, 2.1% (227 of 10 706) in the atomoxetine cohort, and 0% (0 of 1623) in the guanfacine cohort. Within the age groups for which the study medications were indicated, the prevalence of contraindicated conditions increased with age.

3.9 | Compliance with all label requirements

Kaplan-Meier curves in Figure 2 show by cohort the proportion of patients whose prescriptions were compliant with all label requirements (age, dose, and contraindications) since starting the medication. By 3 years of use, approximately 35% of patients receiving MPH-C and approximately 30% each of those receiving MPH-R or atomoxetine had at least one prescription that failed to comply with ≥1 label requirement for those medications. During the first 500 days since the index date (ie, the follow-up period available for guanfacine, the most recently approved medication), all prescriptions of approximately 73% of patients in the MPH-C cohort, 77% in the MPH-R cohort, 80% in the atomoxetine cohort, 86% in the guanfacine cohort, and 64% in the MPH-C + R cohort were compliant with all label requirements.

4 | DISCUSSION

This study was conducted in a prevalent-user cohort of patients in the JMDC database who received MPH (branded), atomoxetine, or guanfacine between January 1, 2013 and September 30, 2018. Although the database includes data since 2005, the study included approximately 95% of patients in the database who received a prescription for any study drug. By focusing on the period from 2013 through September 2018 (the most recent data available when the study was conducted), we were able to capture information on nearly all patients exposed to the medications of interest and still allow the study to focus on relatively recent

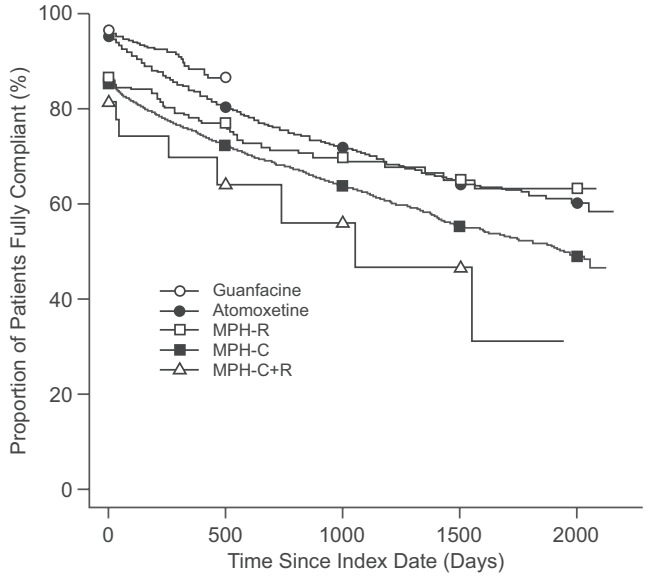

FIGURE 2 Label compliance over time. Note: A patient was considered noncompliant when 1 or more of the 4 compliance criteria for the respective drugs (age, maximum daily dose, contraindicated medications, and contraindicated conditions [see Table S1]) were not satisfied. MPH-C, methylphenidate (Concerta®); MPH-R, methylphenidate (Ritalin®); MPH-C + R, MPH-C, and MPH-R

exposures that reflect current practice. The Ministry of Health, Labour and Welfare of Japan issued an order in October 2019 to revise the MPH-C label, requiring that MPH-C be prescribed only to patients who are registered in management system, at hospitals with registered physicians and pharmacies with registered pharmacists.[18] Since this order came out after the present study had ended in September 2018, it did not affect the results reported here.

A recent study assessing usage of ADHD drugs in Japan reported that among child and adolescent prevalent users of ADHD medications, approximately 64% were prescribed MPH and 41% were prescribed atomoxetine during 2014.[19] These proportions are different from those reported here, likely because guanfacine was approved in Japan after the study by Okumura et al was done, and because the present study included adult patients. Because most patients in the present study who were prescribed MPH-C (64.5%) were children and most patients who were prescribed atomoxetine (55.6%) were adults, it is not surprising that inclusion of adults would lead to the present study having a smaller proportion of patients in the MPH cohorts and a greater proportion in the atomoxetine cohort. In addition, data from the present study indicate that the proportion of patients receiving atomoxetine has been increasing since 2014.

The most common label requirement that prescriptions to patients in the MPH-C and MPH-R cohorts failed to meet was related to contraindicated conditions. In contrast, the most common label requirement that prescriptions to patients in the atomoxetine and guanfacine cohorts failed to meet was exceeding the maximum approved daily dose. This difference may reflect the fact that the list of contraindicated conditions for MPH was substantially longer than for atomoxetine and guanfacine.

The MPH-C and atomoxetine cohorts were the two largest cohorts in the study. The proportion of patients who had a prescription that exceeded the maximum approved dose was slightly higher for atomoxetine (13.3%) than for MPH-C (11.6%). Only 0.2% of patients in the MPH-C and atomoxetine cohorts and none in the MPH-R and guanfacine cohorts received a prescription for more than double the maximum approved dose (ie, an overage of >100%, see Table 3) when they first received a prescription that exceeded the approved dose. For both MPH-C and atomoxetine, the majority (65.0% and 95.5%, respectively) of such patients were children, many of them young children. To the extent that drug abuse or misuse might be expected to be associated with very high dosages and to occur primarily during late adolescence or adulthood, these observations do not suggest abuse or misuse of either medication. In addition, MPH-C and atomoxetine (a nonscheduled nonstimulant medication) were similar in terms of maintenance of prescriptions with respect to dosing and over time. These too are not the findings one would expect if MPH-C was widely misused or abused. Although few patients were prescribed both MPH-C and MPH-R, it is unclear why patients were prescribed both formulations. One possibility is that, because the symptoms of ADHD and narcolepsy are associated,[20,21] these patients were treated for both conditions. Another possibility is that they had only one of those conditions but were prescribed both medications to make use of their differences in doses or release characteristics.

A recent study that assessed adherence to atomoxetine in adult patients with ADHD in Japan reported the mean adherence rate of 57%.[22] In addition, a 12-month prospective, observational, open-label study reported that the adherence rates in children and adolescents with ADHD in Germany were similar between psychostimulants (74.2%) and atomoxetine (67.5%).[23] However, to our knowledge, our current study is the first to comprehensively assess label compliance of prescriptions for ADHD medications in Japan.

This study's strengths include a prevalent-user design, which allowed characterization of all users of the study drugs rather than only the new users. Furthermore, unlike voluntary registries, the claims data are not subject to volunteer bias. The study limitations are as follows. The JMDC database describes employed patients and their dependents, a population that may differ from differently insured, underinsured, or uninsured populations. The database does not capture other potential sources of the medications, such as those obtained without insurance or illegally. For patients who were prescribed more than the approved dose, the extent of the overage was calculated only for the first prescription that exceeded the approved dose. Subsequent high doses may have been higher and thus more typical of doses seen in abuse or misuse. Since the date of patient's birth was arbitrarily assigned to be 15th of the month, the ages of some patients could have been misclassified (eg, patients aged 6 years could have been classified as aged 5 years and vice versa). The available data also did not allow clearly distinguishing between an early refill and a second dispensing of

the same medication intended to be taken concurrently; we addressed this by excluding the first 8 days of overlap. The dose compliance for prescriptions to pediatric patients who received atomoxetine or guanfacine was based on their estimated rather than measured weights. Although we adjusted for label changes we became aware of, we did not systematically track and adjust for all label changes. Finally, 3 patients who received MPH that was not identified as MPH-C or MPH-R were included in the study (see footnote to Figure 1). This deviated from the study protocol's exclusion of patients who received MPH that was not identified as MPH-C or MPH-R, but it is unlikely to have had any substantial effect on the study results.

5 | CONCLUSIONS

Subject to the limitations noted above, this study found that for >85% of patients, all prescriptions for ADHD medications were label-compliant for dose, and for approximately 80% of patients, all prescriptions for ADHD medications were label-compliant for contraindicated conditions. Nearly all prescriptions complied with the label requirements related to indication and age. The study did not find evidence of widespread abuse or noncompliant use of prescribed MPH-C or the other study medications. Additional sources of evidence (eg, published literature, registry data, and other databases, if available) should be applied to develop an overall understanding of label compliance of the ADHD medications in Japan.

ACKNOWLEDGMENT

The research was supported by Janssen Research & Development, LLC. Writing assistance was provided by Narender Dhingra, MBBS, PhD, CMPP, of System One, and funded by Janssen Global Services, LLC.

CONFLICT OF INTEREST

All authors are employees of Janssen Research & Development, LLC, and may own stock and/or stock options. The work on this study was part of their employment. The company manufactures Concerta®.

AUTHOR CONTRIBUTIONS

All authors contributed to all aspects (study design and execution, data analysis and interpretation, and writing of the manuscript) of the study.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY

NCT04113551 (ClinicalTrials.gov).

DATA AVAILABILITY STATEMENT

The data for these analyses were made available to the authors by JMDC, Inc The authors have a license for analysis of the JMDC data. Under the licensing agreement, the authors cannot provide the raw data themselves. Other researchers could access the data by purchase from JMDC, Inc; and the inclusion criteria specified in the Methods section would allow them to identify a similar cut of data.

REFERENCES

1. Ichikawa H, Miyajima T, Yamashita Y, Fujiwara M, Fukushi A, Saito K. Long-term study of lisdexamfetamine dimesylate in Japanese children and adolescents with attention-deficit/hyperactivity disorder. Neuropsychopharmacol Rep. 2020;40:52–62.
2. Yoshida M, Obara T, Kikuchi S, Satoh M, Morikawa Y, Ooba N, et al. Drug prescriptions for children with ADHD in Japan: a study based on health insurance claims data between 2005 and 2015. J Atten Disord. 2020;24:175–91.
3. CONCERTA® Prolonged-release tablets of methylphenidata hydrochloride [Prescribing Information]. Janssen Pharmaceutical K.K., Chioda-ku, Tokyo, Japan. 2016.
4. RITALIN® Methylphenidate hydrochloride tablets [Prescribing Information]. Novartis Pharma K.K., Minato-ku, Tokyo, Japan. 2018.
5. Shionogi & Co. Acquisition of marketing approval for VYVANSE® capsule 20mg/30mg for treatment of attention deficit hyperactivity disorder [Press Release]. April 12, 2019. [press release]. https://www.shionogi.com/content/dam/shionogi/global/news/pdf/2019/e_190412.pdf. Accessed March 15, 2021
6. Obara T, Satoh M, Ooba N, Morikawa Y, Nishigori H, Mano N. Prescription of drugs for children with attention-deficit/hyperactivity disorder (ADHD) in Japan: a study based on health insurance claims data. J Drug Interact Res. 2015;39:9–17.
7. Tagaya H, Murayama N, Fukase Y. [Methylphenidate]. Nihon Rinsho. 2015;73:1511–5.
8. STRATTERA® Atomoxetine hydrochloride capsules [Prescribing Information]. Eli Lilly Japan K.K., Chuo-ku, Kobe-shi. 2018.
9. INTUNIV® Guanfacine hydrochloride extended-release tablets [Prescribing Information]. Shire PLC-Shinogi & Co., Ltd, Chou-ku, Osaka, Japan. 2017.
10. JMDC claims database. (2018). https://www.jmdc.co.jp/en/jmdc-claims-database. Accessed March 15 2021.
11. Voss EA, Makadia R, Matcho A, Ma Q, Knoll C, Schuemie M, et al. Feasibility and utility of applications of the common data model to multiple, disparate observational health databases. J Am Med Inform Assoc. 2015;22:553–64.
12. Japan Medical Data Center (JMDC) ETL documentation. https://ohdsi.github.io/ETL-LambdaBuilder/docs/JMDC. Accessed March 22 2021.
13. Johansson V, Sandin S, Chang Z, Taylor MJ, Lichtenstein P, D'Onofrio BM, et al. Medications for attention-deficit/hyperactivity disorder in individuals with or without coexisting autism spectrum disorder: analysis of data from the Swedish prescribed drug register. J Neurodev Disord. 2020;12:44.
14. Pelham WE, Smith BH, Evans SW, Bukstein O, Gnagy EM, Greiner AR, et al. The effectiveness of short- and long-acting stimulant medications for adolescents with ADHD in a naturalistic secondary school setting. J Atten Disord. 2017;21:40–5.
15. Isojima T, Kato N, Ito Y, Kanzaki S, Murata M. Growth standard charts for Japanese children with mean and standard deviation (SD) values based on the year 2000 national survey. Clin Pediatr Endocrinol. 2016;25:71–6.
16. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. Stat Med. 1992;11:1305–19.
17. ATLAS: an open-source software tool for researchers to conduct scientific analyses on standardized observational data. https://github.com/OHDSI/Atlas. Accessed March 15 2021.
18. MHLW orders label revision for ADHD treatment Concerta based on new distribution control policy. PHARMA JAPAN. October 31, 2019. https://pj.jiho.jp/article/240900. Accessed May 18 2021.

19. Okumura Y, Usami M, Okada T, Saito T, Negoro H, Tsujii N, et al. Prevalence, incidence and persistence of ADHD drug use in Japan. Epidemiol Psychiatr Sci. 2019;28:692–6.
20. Lecendreux M, Lavault S, Lopez R, Inocente CO, Konofal E, Cortese S, et al. Attention-deficit/hyperactivity disorder (ADHD) symptoms in pediatric narcolepsy: a cross-sectional study. Sleep. 2015;38:1285–95.
21. Modestino EJ, Winchester J. A retrospective survey of childhood ADHD symptomatology among adult narcoleptics. J Atten Disord. 2013;17:574–82.
22. Imagawa H, Nagar SP, Montgomery W, Nakamura T, Sato M, Davis KL. Treatment patterns, health care resource utilization, and costs in Japanese adults with attention-deficit hyperactivity disorder treated with atomoxetine. Neuropsychiatr Dis Treat. 2018;14:611–21.
23. Wehmeier PM, Dittmann RW, Banaschewski T. Treatment compliance or medication adherence in children and adolescents on ADHD medication in clinical practice: results from the COMPLY observational study. Atten Defic Hyperact Disord. 2015;7:165–74.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Fife D, Voss EA, Hardin J, et al. Medications for attention-deficit/hyperactivity disorder in Japan: A retrospective cohort study of label compliance. *Neuropsychopharmacol Rep*. 2021;41:385–392. https://doi.org/10.1002/npr2.12191