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Circumstances of prescriptions for ADHD treatment and concurrent medication in juveniles and adults at a psychiatric institution in Japan

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ABSTRACT

Purpose: Relatively few ADHD drugs are available in Japan, but psychotropics are often used for the comorbidity of ADHD. We aimed to compare juvenile and adult patients in terms of drugs used for ADHD. Methods: We retrospectively surveyed the circumstances of prescriptions for atomoxetine and concurrent medications for ADHD patients (36 men, 39 women) using electronic medical records from a single-department psychiatric hospital in rural Japan. Mean dosage, period and rate of administration continuation, side effects, reasons for cessation, comorbid diagnoses, and use of concurrent medication were statistically compared between juvenile (<18 years old) and adult (≥18 years old) groups using the t-test and χ^2 test. Results: Continuation rate was significantly higher in the adult group (43.5%) than in the juvenile group (20.7%; p= 0.043). In the juvenile group, 65.5% received monotherapy and 34.5% received combination therapy, compared to monotherapy for 37.0% and combination therapy for 63.0% in the adult group. Combination therapy was significantly more frequent in the adult group (p=0.015). Discussion: These findings were attributed to differences in motivations for medical treatment and care-receiving patterns between groups. Since juvenile people often start treatment for ADHD as a primary condition, rather than as a comorbidity, concomitant medications are less frequent. Juvenile patients tend to drop out because of poor subjective symptoms. Among adults, treatment for ADHD often begins as treatment of comorbidity, so concomitant medications and maintenance therapy are more frequent than among juvenile patients.

Keywords: ADHD, Atomoxetine, combination therapy, juvenile, adult

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INTRODUCTION

Atomoxetine has been marketed in Japan as a medication for treating attention deficit hyperactivity disorder (ADHD) in patients <18 years old since June 2009, and a 2012 expansion of indications expanded the indications for this drug to include adults. Atomoxetine is now used in a broad range of age groups alongside methylphenidate, which has a different mechanism of action. In addition, guanfacine, as another non-central nervous system stimulant, finally gained approval for use in Japan in May 2017. Nonetheless, although Japan may indeed use relatively simple guidelines [1] reflective of findings from research by the Ministry of Health, Labour and Welfare, fewer medications and treatment strategies are indicated for ADHD than is the case in Western countries [2, 3]. Clinicians in Japan are therefore currently forced to be inventive while working with the limited drugs available for treating ADHD.

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Table 1. Comparison of juveniles and adults patients

	juveniles (n=29)		Adults (n=46)		p*
Sex, n (%)	Male, 19 (65.6%)	Female, 10 (34.5%)	Male, 17 (37.0%)	Female, 29 (63.0%)	0.016
Age, years	15.0±5.5		32.8±11.2		
Atomoxetine administration, months	7.8±7.9		8.0±9.4		n.s
Treatment continuation rate, %	20.7		43.5		0.043
Dosage, mg/day	66.2±18.5		69.1±24.5		n.s
Side effects (%)	6.9		21.7		n.s
Comorbid diagnosis (%)	Yes 58.6	None 41.4	Yes 78.3	None 21.7	n.s
Monotherapy or combination therapy (%)	Mono 65.5	Combination 34.5	Mono 37.0	Combination 63.0	0.015

In addition, ADHD frequently involves comorbid disorders such as mood disorders, substance abuse disorders, and anxiety disorders [4, 5]. Medications are therefore commonly used not only for core symptoms of inattention, hyperactivity, and impulsivity, but also for comorbid symptoms. In daily clinical practice, we get the impression that the needs of ADHD patients often differ widely between adult and juvenile patients. In fact, adult ADHD is often comorbid with psychiatric disorders. These adult patients present with secondary mental disorders caused by masking primary ADHD, or that the ADHD is condition discovered after/while treating the primary condition. Psychiatrists are able to reach a diagnosis of ADHD after providing treatment for secondary mental disorder and focusing on the growth history and difficulties in daily life [6].

However, few reports have investigated the circumstances of prescriptions that include atomoxetine along with concurrent medications in Japan. We considered that dividing ADHD patients who have been prescribed atomoxetine at our hospital into a juvenile group (age <18 years) and an adult group (≥18 years old) and surveying the circumstances of prescription, characteristics, and differences might reveal meaningful and actionable differences between these groups.

SUBJECTS AND METHODS

This survey was conducted at Yatsushiro Kosei Hospital, a single-department psychiatric hospital with 260 beds located in a provincial city with a population of 130,000 in the central southern part of Kumamoto Prefecture, Japan. The area serviced spans from the south of the prefecture to northern Kagoshima Prefecture, and the hospital accepts about 140 outpatients a day and 30-40 inpatients a month. The hospital offers psychiatric day care, in-hospital sobriety meetings, in- and outpatient occupational therapy, home-visit nursing, peer groups for developmental disabilities, and more, and is involved in medical care for various psychiatric disorders in a broad range of age groups.

We used electronic medical records to retrospectively investigate 75 patients (36 males, 39 females) who received a prescription for atomoxetine under in- or outpatient care during the period from October 1, 2011, when our hospital introduced electronic medical records, to June 2015. The Diagnostic and Statistical Manual of Mental Disorders (4th ed. text rev.; DSM-IV-TR) criteria for all clinical diagnoses [7]. Under the medical insurance system in Japan, clinical diagnosis and insurance disease names do not always match. Medical diagnoses therefore need to be translated to insurance disease names. Subjects were divided into juvenile and adult groups, and the t-test or χ^2 test was used to test the items of mean dosage, period and Persistence rate of atomoxetine, side effects, reasons for cessation, comorbid diagnosis, and concurrent medication between groups. The magnitude of an association was estimated using a statistical significance level of 0.05. SPSS for Windows version PASW statistics 18 software (SPSS, Japan) was used for all analyses. This survey was approved by the ethics committee at Yatsushiro Kosei Hospital, oral informed consent was obtained from all adult patients and all parents of juvenile patients.

RESULTS

Table 1 shows the results. Mean patient age was 25.9 ± 12.8 years (range, 7-59 years). Overall mean dosage was 68.0 ± 22.3 mg and overall mean period of continuous atomoxetine administration was 7.9 ± 1.0 months. No significant differences in either

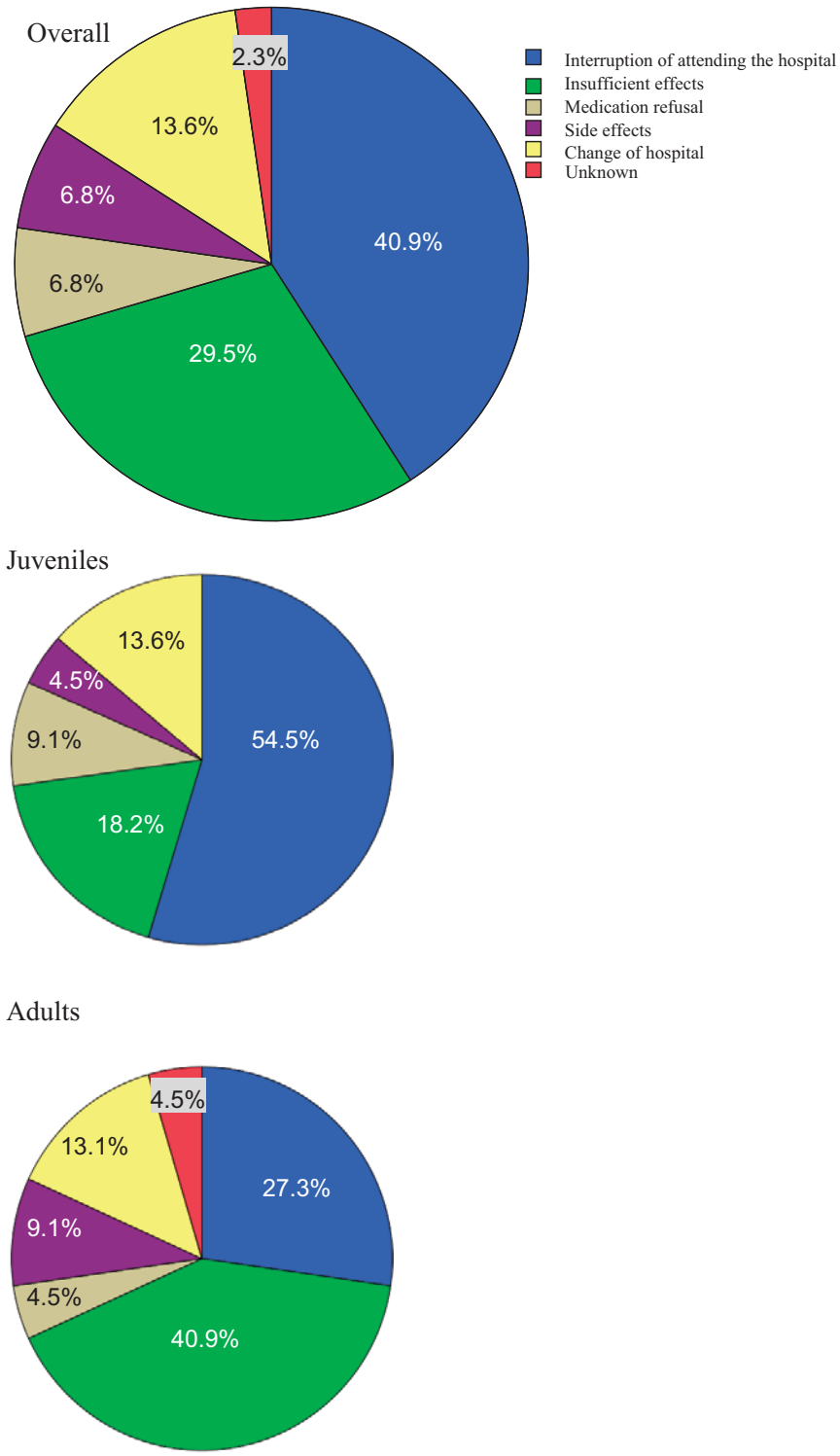

Figure 1. Reasons for cessation of ADHD treatment

mean dosage or continuous administration period were evident between groups. In terms of differences between sexes, results for the juvenile group conformed with the larger proportion of males, whereas the reverse was true for the adult group, in which women were significantly more frequent. A significantly higher rate of continuous administration was identified among adults. Figure 1 shows the recorded reasons for cessation in cessation cases. Interruption of attending the hospital accounted for the majority (54.5%) of cessations in the juvenile group, while insufficient effect (40.9%) was the most common reason among adults, representing a significant difference between groups. Side effects, representing one reason for cessation, were observed in 6.8% of patients, most commonly

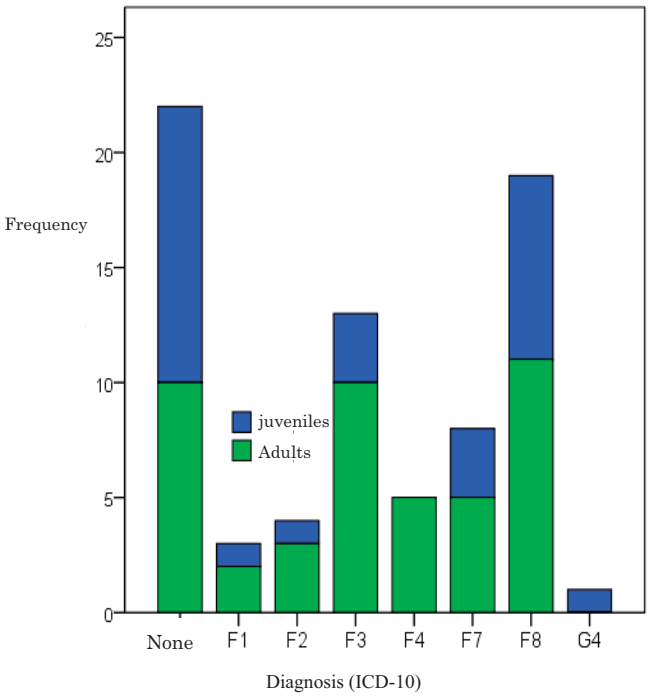

Figure 2. Comorbid diagnosis

involving gastrointestinal tract symptoms (7 cases) such as loss of appetite, followed by nightmares, drowsiness, anxiety and irritability, and liver dysfunction. Overall, psychotropics other than atomoxetine were prescribed to a majority of subjects, but only around one-third of juvenile patients were receiving concurrent medication, compared to >60% of adults, again representing a significant difference.

Figure 2 shows comorbid diagnoses. Clinical diagnoses were based on DSM-IV-TR, as previously described, but in patient statistics from our hospital the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) are used [8]. Therefore, diagnoses are denoted on the basis of ICD-10 corresponding to DSM-IV-TR. In the juvenile group, patients most commonly did not show any diagnosis other than ADHD, and the most common comorbidities were in the F8 category, such as autism-spectrum disorders. Adults included comparable numbers of patients with autism-spectrum or mood disorders and patients without comorbid diagnoses, and also tended to show more comorbidities than juveniles. Table 2 shows concurrent medications. Antipsychotics were the most common concurrent medication overall, followed by antidepressants and mood-stabilizers. In terms of individual medications, quetiapine was most common, and along with valproic acid and olanzapine, accounted for more than

Table 2. Concurrent medications

		juveniles (n=29)	Adults (n=46)
Antipsychotic	Quetiapine	2	11
	Olanzapine	2	6
	Risperidone	1	1
	Aripiprazole	0	1
	Other antipsychotics	0	5
Antidepressant	Mirtazapine	1	3
	Fluvoxamine	0	6
	Escitalopram	0	5
	Other antidepressants	1	8
Mood-stabilizer	Valproic acid	5	6
	Lamotrigine	2	2
	Other mood-stabilizers	0	4
Methylphenidate		1	0

40% of all concomitant medications. Frequently used antidepressants were fluvoxamine, escitalopram, and mirtazapine. Only one case with concurrent use of methylphenidate was identified.

DISCUSSION

In our hospital, different age groups showed different care-receiving patterns, with juvenile patients appearing more passive in seeking consultation, probably because of difficulties faced in the environment based on developmental characteristics, whereas treatment for different disorders in adults provide a gateway to treatment for ADHD. Reflective of this difference, the results demonstrated that adults made greater use of concurrent medications, and that ADHD adults with comorbidity were more likely to maintain treatment motivation and thus showed higher treatment continuation rates.

We have described recorded reasons why adult patients more frequently received concomitant medication. Adult patients tended to show comorbid conditions more frequently than juvenile patients. Adult patients were typically first treated for conditions such as mood and anxiety disorders. This means that in adults, ADHD characteristics were revealed during treatment for comorbid disorders, with a subsequent transition to treatment for ADHD. In terms of specific concurrent medication, the results showed that quetiapine, valproic acid, and olanzapine were common, but antipsychotics, mood-stabilizers, and antidepressants are also often used outside Japan [9, 10], where results have been broadly equivalent. According to a large cohort

study conducted in Germany, diagnosis of ADHD at an older age and the presence of other psychiatric comorbidities represent significant predictors of starting pharmacotherapy [11]. The fact that another psychiatric comorbidity prompts adults to begin drug treatment could be considered a widespread pattern not limited to our hospital.

Treatment for a comorbidity is also reportedly a factor predictive of favorable adherence to treatment [12]. Our hospital sees many cases of juvenile patients with no comorbidity, who exhibit a primary ADHD characteristic such as hyperactivity that is viewed as problematic and seek consultation due to requests from the family, school, or child consultation center. Adults, on the other hand, seek consultation because of their own difficulties, and in some cases may even seek consultation because they have already considered the possibility of ADHD. This difference in consultation patterns between patients may indicate differences in underlying motivations for treatment between groups. A juvenile may not have as strong a conviction as an adult regarding the difficulties they are experiencing, and may thus be correspondingly less likely to comply with medication regimes or continuation of treatment. Adults, meanwhile, tend to be more able to sustain motivation based in their own perception that inattention or other symptoms have improved, or with feedback from their environment, such as the family or workplace. This is regarded as one potential reason for the significant difference in continuation rates observed between groups.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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