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Original article

Expert consensus on pharmacotherapy for tic disorders in Japan

Yu Hamamoto [a], Miyuki Fujio [b], Maiko Nonaka [b], Natsumi Matsuda [c], Toshiaki Kono [c,d,e], Yukiko Kano [c,f,*]

[a] Department of Child and Adolescent Psychiatry, Tokyo Metropolitan Children's Medical Center, Japan
[b] Graduate School of Education, The University of Tokyo, Japan
[c] Department of Child Psychiatry, The University of Tokyo Hospital, Japan
[d] Department of Neuropsychiatry, The University of Tokyo Hospital, Japan
[e] Department of Forensic Psychiatry, National Institute of Mental Health, National Center of Neurology and Psychiatry, Japan
[f] Department of Child Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, Japan

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Abstract

Objective: We aimed to clarify the current status of pharmacotherapy for tic disorders and comorbidities in Japan. We used a systematic survey to collate the consensus of Japanese experts and compare it with the recent international evidence.

Methods: We devised a questionnaire on pharmacotherapy for tics and comorbidities and sent it to Japanese experts on tic disorders. Based on the response to the first survey, we revised the questionnaire and conducted a second survey to determine the consensus among the experts on a 4-point Likert scale by the Delphi method.

Results: The first survey revealed variability in preferred medications and dosages among the experts in Japan. However, we were able to build a general consensus on pharmacotherapy for tic disorders and comorbidities based on the second survey. Aripiprazole and risperidone were the first- and second-line medication for tic disorders, respectively. Agonists of α-$_2$ adrenergic receptors were seldom prescribed. Fluvoxamine was the first-line medication for comorbid obsessive-compulsive disorder, and atomoxetine for comorbid attention deficit/hyperactivity disorder.

Conclusions: This study will help Japanese physicians choose medications for tic disorders more judiciously and will improve the quality of tic pharmacotherapy in Japan.

Keywords: Tic disorder; Tourette syndrome; Pharmacotherapy; Expert consensus; Comorbidity

1. Introduction

Tic disorders are neurodevelopmental disorders characterized by repetitive spasmodic muscle contractions [1]. Tourette syndrome (TS) is a tic disorder with multiple motor tics and at least 1 phonic tic over the course of more than a year. Although over two-thirds of individuals with TS experience improvement of tics in late adolescence, a minority continue to have severe tics and need intensive treatment in adulthood [2]. Tic disorders are frequently comorbid with other psychiatric conditions, including attention deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety disorder, depression, and "rage attacks" (sudden, explosive episodes of rage) [3–5]. The choice of treatment for individuals with tic disorders should consider these comorbidities.

* Corresponding author at: 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
E-mail address: kano-tky@umin.ac.jp (Y. Kano).

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Clinical guidelines for tic disorder treatment based on expert consensus and randomized controlled study evidence have been proposed in the USA, Europe, and Canada [6–8]. These guidelines propose that treatment for tic disorders address impairment and distress caused not only by the tics but also by any comorbid conditions. Psycho-education on tic disorders and their accommodation is recommended as the foundation of treatment. The guidelines propose that behavioral interventions should be considered before pharmacotherapy in cases of moderate tic severity, and that medication should be reserved for moderate to severe tics causing marked impairment in the quality of life.

Recent systematic reviews and meta-analyses of tic disorder treatments have recommended α-$_2$ adrenergic receptor agonists and aripiprazole while stating that the effectiveness of pharmacotherapy in general is limited [9–11]. A report based on clinical experience in Europe showed variability in medication selection and dosage for tic disorders and their comorbidities [12]. Evidence on the pharmacotherapy of tic-related OCD and ADHD has been accumulating, yet further research is needed [6,8]. Evidence on other comorbidities is very poor.

In Japan, all medications for tic disorders are off-label use. We can use methylphenidate, atomoxetine and guanfacine for comorbid ADHD in Japan. Methylphenidate was first approved for patients between 6 and 18 years old in 2007, and then for patients of 18 and over in 2013. However, methylphenidate is stipulated as contraindication for chronic tic disorders including TS and only qualified doctors are allowed to prescribe it. Atomoxetine was approved for patients between 6 and 18 years old in 2009, and for patients of 18 and over in 2012. In May 2017, guanfacine was approved for patients between 6 and 18 years old. For comorbid OCD, we can use fluvoxamine, paroxetine and clomipramine for adults, but only fluvoxamine we can use for children over the age of 8 years old.

In Japan, a handbook of clinical practice for tic disorders mainly based on previous Western studies as applied to the Japanese situation was released in 2011 [13]. Although the usefulness of the handbook has been confirmed by a survey of clinicians, it does not reflect the above-mentioned recent findings. Moreover, clinicians of various specialties, including pediatrics, psychiatry, child psychiatry, and neurology, are involved in the treatment of tic disorders in Japan, and specialty-related differences in pharmacotherapy remain to be examined. In order to improve the quality of pharmacotherapy for tic disorders and comorbidities in Japan, a consensus of experts with various specialties is needed.

Therefore, in this study, we aimed to clarify the pharmacotherapy approaches for tic disorders and comorbidities currently used by experts in Japan, and obtain their consensus through a systematic survey. We compared the consensus of the Japanese experts with the recent international evidence to identify the commonalities of the pharmacotherapy of tics as well as their comorbidities.

2. Methods

2.1. Questionnaire development and survey design

We conducted a 2-step survey. At the first step, we developed a questionnaire and sent it to the experts. At the second step, we revised the questionnaire based on the coincidence rate of each question and sent the modified questionnaire back with feedback of the findings from the first survey. As the initial survey, we devised a questionnaire referring to the recent clinical guidelines for tic disorders and the survey on pharmacotherapy for TS by Rickards et al. [12] (Suppl. 1). The questionnaire asked for the most important factor in deciding to start pharmacotherapy for tics, dosage increase timing and standards, representative medications for tic disorders and comorbidities with their starting and maximum doses both in childhood (<18 years) and late adolescence/adulthood (≥18 years). In childhood, age at first prescription for tic disorders was queried. We also collected the participants' medical specialties, years of experience as a medical doctor, and clinical experience in tic disorders.

We sent this questionnaire to medical doctors who were members of the Japanese Society of Tourette Syndrome Research or had published papers on tic disorders or childhood OCD during the 5-year period preceding the survey. If an expert did not answer some questions, we eliminated only these unanswered questions and validated the answered ones. The first survey was performed during the period of September 1 to November 30, 2015.

After the first survey, we reviewed the questionnaire to determine the extent of agreement among the experts by the Delphi technique. The revised questionnaire used a 4-point Likert scale (1: agree, 2: somewhat agree, 3: somewhat disagree, 4: disagree) asking mostly the same questions as in the original questionnaire. We asked about the 2 most preferred medications for the representative medications, and the most selected item for the other questions. We sent the revised survey back with feedback of the findings from the first step. When >75% of the participants answered "agree" or "somewhat agree" to a question, we considered the participants to have reached "sufficient agreement". The participants did not reach sufficient agreement on several questions in the second survey, which was repeated. When <50% of the participants answered "agree" or "somewhat agree" in the second survey repeat, we considered reaching sufficient agreement on that question not feasible. The second survey was performed during the period of September 1 to October 31, 2016.

Before the start of the survey, the Institutional Ethical Committee of the University of Tokyo Hospital approved this study (10905-(1)).

2.2. Statistics

In the second step, agreement across specialties was assessed using the chi-square test, Fisher's exact test for categorical variables, and the Mann-Whitney *U* test for continuous variables. When differences among the specialties were examined, a "psychiatrist group", consisting of psychiatrists and child psychiatrists, and a "pediatrician group" consisting of pediatricians and child neurologists, were compared.

Analyses were performed using the EZR software on R commander version 1.27 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). We defined statistically significant differences as having *p*-values of <0.05.

3. Results

3.1. Survey execution

The first step of the survey was conducted from September 1 to November 30, 2015. We sent the questionnaire to 71 medical doctors – members of the Japanese Society of Tourette Syndrome Research, and 52 medical doctors who had published papers; a total of 8 doctors did not receive the questionnaire (Fig. 1). Out of the 115 clinicians who received the questionnaire, 54 (46.9%) responded, and out of the 54, 38 (72.2%) agreed to participate in the second step of the survey. We sent the revised questionnaire to the 38 clinicians in September 1-October 31, 2016, and 30 (78.9%) responded. In the repeat survey of the second step, we sent the same questionnaire to the 30 clinicians, with 1 medical doctor not receiving it. Out of the 29 clinicians who received the questionnaire, 24 (82.8%) answered it. Some clinicians did not answer some of the questions; those were excluded from statistical analysis.

3.2. Participant characteristics

Of the 54 medical doctors in the first step of the survey, 10 (18.5%) were psychiatrists, 17 (31.5%) child psychiatrists, 23 (42.6%) pediatricians, and 3 (5.6%) child neurologists, 1 (1.9%) other. Of the 24 responders to the repeat survey of the second step, 4 (16.7%) were psychiatrists, 6 (25.0%) child psychiatrists, 12 (50.0%) pediatricians, and 1 (4.2%) child neurologists, 1 (4.2%) other. The average number of years of experience was 26.3 (SD: 11.8; range: 5–50) in the first step.

3.3. Childhood

The most important factors considered in deciding to start pharmacotherapy in children with tic disorders were functional impairment caused by tic symptoms (100% in the repeat survey of the second step. The age at first prescription for tics $\leq$6 years (68.2%). The clinicians increased dosage at 2 or 4 weeks of staying on the same dose (76.2% and 86.4%, respectively); the principal reason for dosage increase was the lack of effect on the

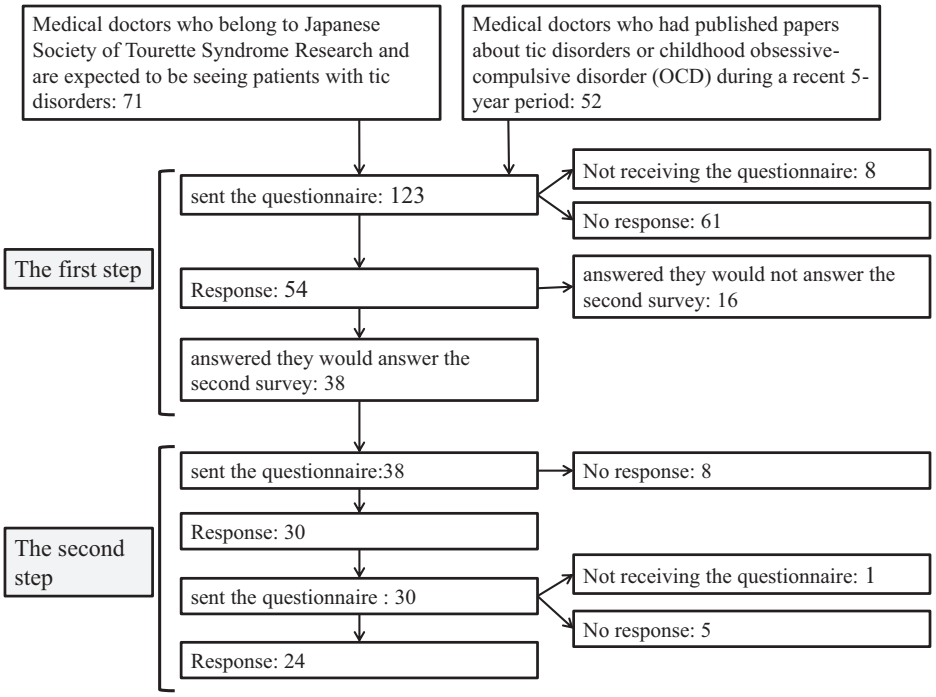

Fig. 1. Procedure of the survey.

tics (86.4%). The most important factor in prescribing medication for tics was quality of life (100%).

Aripiprazole and risperidone, prescribed equally frequently, were the most prescribed medications for tic disorders, followed by haloperidol, in the first step of the survey. Three or more experts chose blonanserin, pimozid, diazepam, clonidine, L-Dopa, Yokukansan (herbal medicine; Kanpo). In the repeat survey of the second step, aripiprazole was found to be the first-line medication (90.9%) (Table 1). The preferred starting dose of aripiprazole was 1.5 mg or 3.0 mg (66.7% and 71.4% of respondents, respectively). Although the preferred maximum doses were 6 mg and 12 mg in the first step, the rates of agreement were <50% in the repeat survey of the second step (42.9% and 47.6%, respectively).

As the first-line medication for comorbid OCD, fluvoxamine (26.6%) was the most favored, followed by aripiprazole (12.6%), in the first step. In the repeat survey of the second step, aripiprazole and fluvoxamine were favored (72.7% and 59.1%, respectively) (Table 2). The preferred starting dose of fluvoxamine was 25 mg (77.3%). Although its preferred maximum dose was 100 mg or 150 mg, the rates of agreement were <50% in the repeat survey of the second step (27.3% and 31.8%, respectively). Most clinicians indicated atomoxetine as the first-line medication for comorbid ADHD (90.9% of the repeat survey respondents). The most favored starting dose of atomoxetine was 0.5 mg/kg (95.2%), and the favored maximum dose was 1.6 mg/kg (65.0%). Fluvoxamine was the most preferred for comorbid depression (61.9%). Both aripiprazole and fluvoxamine were favored as the first-line medication for comorbid anxiety, albeit both rates of agreement were <50% in the repeat survey of the second step (42.9% and 33.3%, respectively). Risperidone was listed the most frequently as the first-line medication for comorbid anger/aggressive behaviors (85.7%), followed by aripiprazole (71.4%).

3.4. Late adolescence/adulthood

The most important factor considered when deciding to start pharmacotherapy in older adolescents and adults with tic disorders was functional impairment owing to tic symptoms (100% of respondents). The clinicians increased dosage at 2 or 4 weeks of staying on the same dose (68.2% and 86.4%, respectively), and the main reason for the dosage increase was tics continuing without change (90.9% of respondents). The most important factor considered in prescribing medication for tics was a side effect (90.9%).

Aripiprazole was considered the first-line medication for tic disorders by most doctors (90.9%), with risperidone being the most common second-line medication (90.9%). The preferred starting dose of aripiprazole was 3.0 mg (85.7%), and the preferred maximum dose 12 mg or 24 mg (42.9% and 47.6% of respondents to the repeat survey, respectively). The preferred starting dose of risperidone was 1 mg (77.3%), and the preferred maximum dose 3 mg or 6 mg (36.4% and 20.9%, respectively).

Fluvoxamine was the most favored first-line medication for comorbid OCD (63.6% of respondents). Its preferred starting dose was 25 mg (77.3%), and preferred maximum dose 150 mg or 200 mg (54.5% and 45.5%, respectively).

3.5. Differences by specialty

We examined the differences in the answers to the repeat survey of the second step by specialty, focusing on the starting and maximum doses of each medication. We found no significant differences between the psychiatrist and pediatrician groups in the selection of medications or their starting and maximum doses.

Table 1
Medications for tics, and their starting dose and maximum dose in Japan; the repeated survey of the second step.

	Childhood (n = 22, *n = 21)	Late Adolescence/Adulthood (n = 22, *n = 21)
The first choice is aripiprazole	20 (90.9%)	20 (90.9%)
The first choice is risperidone	15 (68.2%)	15 (68.2%)
The second choice is risperidone	19 (86.4%)	20 (90.9%)
The second choice is haloperidol	8 (36.4%)	6 (27.3%)*
ARP's starting dose is 3 mg/day	15 (71.4%)*	18 (85.7%)*
ARP's starting dose is 1.5 mg/day	14 (66.7%)*	–†
ARP's maximum dose is 12 mg/day	10 (47.6%)*	9 (42.9%)*
ARP's maximum dose is 6 mg/day	9 (42.9%)*	–†
ARP's maximum dose is 24 mg/day	–†	10 (47.6%)*
RIS's starting dose is 0.5 mg/day	20 (95.2%)*	–†
RIS's starting dose is 1 mg/day	10 (45.5%)	17 (77.3%)
RIS's maximum dose is 3 mg/day	10 (45.5%)	8 (20.9%)
RIS's maximum dose is 6 mg/day	–†	9 (40.9%)

ARP; aripiprazole, RIS; risperidone.
† We asked some question items only for childhood or late adolescence/adulthood.

Table 2
Medications for comorbidities of tics, and their starting dose and maximum dose in Japan; the repeated survey of the second step.

Symptoms	Medication	Childhood (n = 22, *n = 21, **n = 20)	Late Adolescence/Adulthood (n = 22, *n = 21)
OCD	Fluvoxamine	13 (59.1%)	14 (63.6%)
	starting dose is 25 mg/day	17 (77.3%)	17 (77.3%)
	maximum dose is 100 mg/day	6 (27.3%)	–†
	maximum dose is 150 mg/day	7 (31.8%)	12 (54.5%)
	maximum dose is 200 mg/day	–†	10 (45.5%)
	Aripiprazole	16 (72.7%)	–†
ADHD	Atomoxetine	20 (90.9%)	–†
	starting dose is 0.5 mg/kg/day	20 (95.2%)*	–†
	starting dose is 10 mg/day	12 (57.1%)*	–†
	maximum dose is 1.6 mg/kg/day	13 (65%)**	–†
	maximum dose is 80 mg/day	10 (50%)**	–†
	Methylphenidate	8 (36.4%)	–†
Depression	Fluvoxamine	13 (61.9%) *	–†
	Aripiprazole	10 (47.6%) *	–†
Anxiety	Fluvoxamine	7 (33.3%) *	–†
	Diazepam	9 (42.9%) *	–†
	Aripiprazole	5 (23.8%) *	–†
Anger	Risperidone	18 (85.7%) *	–†
	Aripiprazole	15 (71.4%) *	–†

† We asked some question items only for childhood or late adolescence/adulthood.

4. Discussion

We conducted a 2-step survey of prevailing practices in the treatment of tic disorders in Japan. The first step revealed variability in medication choices and dosages for tic disorders and their comorbidities. However, in the second step, many answers reached "fully agreed" status, enabling us to build a general consensus on tic pharmacotherapy.

Aripiprazole was the first-line medication for tic disorders, and risperidone was the most common second-line drug among the Japanese experts. These results are consistent with recent guidelines on pharmacotherapy [6–8]. However, the Japanese experts showed a higher preference for aripiprazole than risperidone, whereas the guidelines recommend both equally. This preference may be caused by the approval of aripiprazole for TS by the FDA in December 2014, and is consistent with recent systematic reviews indicating the efficacy of aripiprazole for tic treatment [9,10]. In contrast, the total aripiprazole dose tended to be lower in Japan compared to those in other countries (2–15 mg). This difference in dosage may be caused by confounding factors such as ethnic differences.

Although α-$_2$ adrenergic receptor agonists are commonly used for tic disorders and have been internationally reported to be effective, Japanese experts seldom chose them. This difference in clinical practice may be caused by the fast-acting receptor agonist clonidine being the only α-$_2$ adrenergic receptor agonist officially accepted for hypertension in Japan. In May 2017, extended-release guanfacine has been approved for ADHD in Japan, allowing physicians to consider it for tics in children with ADHD. One recent report suggested that guanfacine can be effective in such cases [14], but another report suggested that guanfacine does not show a large effect on tic disorders [17], then we should follow the future trends.

Fluvoxamine was the first-line medication for comorbid OCD. This finding is consistent with the American guidelines recommending selective serotonin reuptake inhibitors (SSRIs) [6]. We suspect that fluvoxamine is preferred over other SSRIs because it was the first SSRI to become available in Japan in 1999. Knowledge and experience of fluvoxamine use have been accumulating among Japanese physicians, culminating in fluvoxamine approval for children's OCD in Japan in July 2017. Aripiprazole was favored for comorbid OCD as well, especially in childhood. This finding is consistent with the recent report that augmentation of aripiprazole or risperidone with SSRIs in tic-related OCD was effective in about half of the patients failing to respond to an SSRI [15], and the report that aripiprazole monotherapy was effective for resistant OCD [16].

Atomoxetine was especially favored for comorbid ADHD, consistent with international trends. In contrast, methylphenidate was much less used than atomoxetine in spite of recent meta-analysis suggesting that methylphenidate does not worsen tics [18]. The difference of attitudes towards methylphenidate between international trends and Japanese practice is likely caused by methylphenidate being contraindicated in patients with chronic tic disorders in Japan and only qualified doctors being allowed to prescribe it.

This study has several limitations. A major limitation of this survey is its cross-sectional design, which is unable to differentiate between the cause and effect of variability in prescribing practices [12]. Next limitation

is a small sample size problem. This may reflect the small number of experts of tic disorders in Japan. In addition, there may be selection bias since final respondents were only 24 (21%) although 115 doctors received the first questionnaire. Nevertheless, we think this study reflects the trends of whole Japanese experts because there was no difference of the group composition of experts' specialty through the first and the second step. Another limitation is that for medication dosage, especially the maximum dose, a consensus was not always reached in the second step of the survey. The dosage may vary because of the wide ranges of age and severity of the Japanese experts' patients.

In spite of these limitations, this exploratory study reports the certain expert opinion of Japanese pharmacotherapy for tic disorders and comorbidities based on the rigorous method. This study will help Japanese physicians choose medication more judiciously and based on the evidence.

5. Clinical significance

In the absence of universally accepted up-to-date guidelines on tic treatment in Japan, medications and dosages prescribed for tic disorders by Japanese experts vary. In a survey aimed to identify the current consensus, aripiprazole and risperidone were found to be prescribed for tics the most frequently, whereas fluvoxamine and atomoxetine were preferred for comorbid psychiatric disorders. This study will improve the quality of tic pharmacotherapy in Japan.

6. Disclosure statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2019.02.003.

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