Psychopharmacology for Attention-Deficit/Hyperactivity Disorder in Japan

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In Japan, treatment with medication for attention-deficit/hyperactivity disorder (ADHD) is less favorable than psychosocial treatment, as in Europe. Overall, Japanese guidelines offer few descriptions of stimulant-refractory or complicated ADHD treatments. However, carbamazepine has been preferably prescribed for ADHD with electroencephalogram abnormality or aggression. Only one stimulant (long-acting methylphenidate) is now available in Japan. Under the current circumstances, Japanese psychiatrists and pediatricians are trying to make the most of available psychosocial treatment and medication, including formulation of the guidelines. Epidemiologic studies on the prevalence, comorbidity, and course of ADHD should also be administered in Japan. This article describes the history of psychopharmacology for minimal brain dysfunction or ADHD and introduces recently established guidelines for ADHD treatment in Japan compared with those in other countries.

Introduction

The prevalence of attention-deficit/hyperactivity disorder (ADHD) when using *DSM-IV* diagnoses is estimated at 11.4% to 16.1% in four studies in the US population, 16% to 19.8% in five high-prevalence studies, and 2.4% to 7.5% in four low-prevalence studies in the non-US population [1]. These results indicate that ADHD is not purely an American disorder. Unfortunately, few studies are available on the prevalence of ADHD in Japan. Kanbayashi et al. [2] administered a rating scale, according to *DSM-III-R* criteria of ADHD, to 1022 parents of 4- to 12-year-old children living in the greater Tokyo area, estimating the prevalence of ADHD at 7.7%. Because this study had certain methodologic problems, a full-fledged prevalence study is urgently needed. However, it is clear from these figures that children with ADHD represent a substantial group whose treatment needs are as important in Japan as in other countries.

This review focuses on psychopharmacology for ADHD in Japan, describes the history of psychopharmacology for ADHD in Japan, and discusses recently established guidelines for the treatment of ADHD in Japan and other countries.

Psychostimulants

In many countries, the current mainstay of ADHD-related psychopharmacotherapy involves psychostimulants, despite recent abuse issues with Ritalin (Novartis, Basel, Switzerland). In Japan, amphetamine-type stimulants that are available in other countries are treated as narcotics; their manufacture, storage, and use are strictly prohibited by the Stimulant Drugs Control Law enacted in 1951. Pemoline is available but rarely used by Japanese doctors due to fears of possible liver injuries.

Methylphenidate

In 1954, methylphenidate (MPH) was first marketed in Germany as a mood enhancer. In 1961, MPH was approved to treat depression and depressive neurosis; in Japan, its appropriate dose for adults was set at 20 to 30 mg. In those days, regulation by the Japanese government was not as strict as it has been lately. Therefore, the government approved earlier psychotropics such as chlorpromazine, imipramine, and meprobamate, based on results from uncontrolled trials. MPH was not an exception.

After MPH became available in Japan, it was not long before cases of abuse were reported. In 1973, a warning that "MPH should be given cautiously because of a possible risk for dependency" appeared in the drug information. In 1978, narcolepsy was added to its indication, and the next year its indication for the treatment of depression was changed to mild depression. In the 1960s, the first double-blind, placebo-controlled clinical trials of MPH, as well as dextroamphetamine, were completed in

the United States, confirming efficacy for hyperactivity, impulsivity, and moodiness. Following these US trials, to reconfirm its efficacy for the Japanese population, uncontrolled trials of MPH for ADHD symptoms were performed by Japanese child psychiatrists who claimed that ADHD should be added to MPH indication. This claim was rejected, however, mainly because the trial was not double-blind. Since then in Japan, Ritalin has been prescribed for ADHD as an off-label use until quite recently. MPH's efficacy in depression was reevaluated by the Ministry of Health, Labor, and Welfare (MHLW) in 1995. Based on overseas studies and clinical consensus among Japanese psychiatrists, MPH's indication for mild depression and depressive neurosis was modified to augmentation treatment with antidepressants refractory to depression or chronic depression. However, in the United States, the indication for mild depression was removed in 1983 because well-controlled clinical trials did not demonstrate efficacy. Since then, the indication of MPH has been limited to narcolepsy and ADHD in the United States. The situation has been similar in European countries. In Japan only, however, the indication of MPH for depression has been approved. Further, a well-controlled study of MPH, which should be required for a depression indication, has not yet been administered [3].

Methylphenidate abuse in Japan

Cases with MPH addiction or dependency have been detected in Japan since the 1980s, although they are not as prominent or numerous as cases involving methamphetamine dependency. However, largely thanks to the Internet, an increasing number of MPH addiction cases have become apparent. For example, in 2003, a newspaper reported increasing cases of MPH addiction and warned that easily obtained MPH prescriptions were a possible cause of MPH addiction. Sato et al. [4] concurrently doubted MPH's antidepressant efficacy and augmentative, pharmacotherapeutic use in refractory depression. The authors reviewed the literature and concluded that little evidence warranted the use of MPH for antidepressant augmentation in chronic depression treatment. They then set a strictly limited guideline for MPH use for depression. Kazamatsuri [3] maintained that the indication of MPH for depression should be removed in favor of approval for ADHD.

Based on The National Survey on Drug-Related Mental Disorder at Psychiatric Facilities conducted in 2004, Ozaki et al. [5] reported that, of all 453 cases, 93 (20.5%) involved prescription or other medical drug abuse, 19 (4.2%) had a history of MPH use, and eight (1.8%) mainly indicated MPH abuse. Almost all reported cases of MPH abuse were triggered by prescriptions from medical facilities intending to improve depressive states, further revealing how psychological dependence on MPH was rapidly created and easily became severe. Thereafter, sporadic warnings against MPH abuse/dependence were published; some reported that MPH abusers/dependents in search of large quantities of Ritalin visited multiple psychiatric clinics, feigned narcolepsy or hypersomnia, and even falsified prescriptions using color copiers.

In my experience, after patients receive Ritalin for a depressive state, they firmly refuse to replace Ritalin with antidepressants. They favor its rapid and solid subjective sense of effect. My impression is that the more Ritalin is prescribed, the more desperately patients cling to it.

In 2007, prescribed Ritalin for inappropriate cases became a public concern when it was uncovered that, without proper medical examination, a clinic in Tokyo prescribed massive doses of Ritalin to probable Ritalin abusers/dependents. In October 2007, the Ritalin indication was limited to narcolepsy only, after the removal of depression. Subsequently, the Ritalin Distribution Control Panel, a third-party organization, was established at the end of 2007. The panel consisted of key figures in narcolepsy-related academic societies, a pharmacist, a bioethicist, and an attorney. The panel decided that Ritalin must be prescribed by registered physicians from registered pharmacies. To become a registered physician, physicians must take an online lecture on Ritalin dependence, submit a pledge of appropriate use, demonstrate familiarity with narcolepsy, and obtain certification by a narcolepsy-related academic society. Ritalin sales have drastically plunged since distribution control began in early January 2008.

Osmotic, controlled-release, oral stimulant methylphenidate

After Ritalin regulation limited prescriptions, Concerta (Janssen Pharma, Tokyo, Japan), an osmotic controlled-release oral stimulant methylphenidate (OROS MPH), appeared in October 2007 as the first MHLW-approved ADHD drug in Japan. In 2000, the US Food and Drug Administration (FDA) approved Concerta for ADHD. At the end of 2007, a Concerta distribution control panel was established, functioning similarly to the Ritalin distribution control panel.

Psychopharmacology for Minimal Brain Dysfunction in Japan

Dellis [6] critically described minimal brain dysfunction (MBD) as "a huge wastebasket term into which physicians dump a large number of children who have intelligence within the normal range but who have difficulty in the classroom because of hyperactivity, aggressive behavior, clumsiness, or inability to read or spell or do sums" [6]. In other words, MBD is a heterogeneous mix of current ADHD, learning disabilities, developmental coordination disorder, pervasive developmental disorders, and so on. Thus, it can be safely said that MBD always contains ADHD.

To survey the notion, etiology, prevalence, and treatment of MBD/ADHD in Japan, Sakuta [7] administered a questionnaire by Bloomingdale and Bloomingdale [8] to Japanese psychiatrists and pediatricians twice: in 1978

Table 1. Results of the survey on MBD/ADHD from Japanese psychiatrists and pediatricians using Bloomingdale's questionnaire

		MBD		ADHD
Is MBD/ADHD a recognizable entity?		Yes, 81.0%; no, 18.9% (*n* = 37)		Yes, 93.2%; no, 0.0%; NR, 6.8% (*n* = 45)
Prevalence of MBD/ADHD in the general population		0% to ~5%, 59.5%; 5% to ~10%, 18.92%; NR, 21.7% (*n* = 37)		0% to ~1%, 51%; 1% to ~5%, 11.36%; 5% to ~10%, 2.3%; 10 to ~15%, 2.3%; NR, 18.2% (*n* = 45)
Concept of etiology		A, 46.0%; B, 0.0%; C, 0.0%; D, 0.0%; E, 48.7%; F, 0.0%; G, 10.8%; NR, 5.4% (*n* = 37)		A, 15.9%; B, 9.1%; C, 2.3%, D, 9.1%; E, 57.8%; F, 0.0%; G, 20.45%; NR, 9.1% (*n* = 45)
Treatment	Hyperkinetic symptoms	Drugs, 70.3%; psychological, 56.8%; other, 2.7%; NR, 21.6% (*n* = 37)	Hyperactivity disorder symptoms	Drugs, 62.2%; psychological, 45.5%; other, 6.8%; NR, 30.0% (*n* = 45)
	Learning dysfunction	Drugs, 32.4%; psychological, 56.8%; other, 2.7%; NR, 51.9% (*n* = 37)	Attention deficit	Drugs, 61.4%; psychological, 45.5%; other, 6.8%; NR, 25.0% (*n* = 45)
	Behavior symptoms	Drugs, 62.1%; psychological, 64.9%; other, 2.7%; NR, 24.3% (*n* = 37)	Conduct disorder with ADHD	Drugs, 50.0%; psychological, 40.9%; other, 2.3%; NR, 38.6% (*n* = 45)
Medication	Hyperkinetic symptoms	I, 88.5%; II, 69.2%; III, 26.9%; IV, 3.6%; V, 19.2% (*n* = 26)	Hyperactivity disorder symptoms	I, 72.7%; II, 42.4%; III, 18.2%; IV, 6.1%; V, 0.0%; VI, 33.3% (*n* = 33)
	Learning dysfunction	I, 26.9%; II, 34.6%; III, 19.2%; IV, 3.9%; V, 11.5%; NR, 53.9% (*n* = 26)	Attention deficit	I, 69.7%; II, 21.2%; III, 12.1%; IV, 3.0%; V, 0.0%; VI, 18.2% (*n* = 33)
	Behavior symptoms	I, 57.7%; II, 76.9%; III, 34.6%; IV, 7.7%; V, 11.5%; NR, 11.5% (*n* = 26)	Conduct disorder with ADHD	I, 39.4%; II, 42.4%; III, 15.2%; IV, 3.0%; V, 3.0%; VI, 36.4% (*n* = 33)

I—psychostimulants; II—tranquilizers; III—tricyclic antidepressants; IV—drugs enhancing brain oxygenation and/or glucose metabolism; V—others; VI—anticonvulsants; A—brain damage, prenatal, perinatal, or early postnatal; ADHD—attention-deficit/hyperactivity disorder; B—genetic; C—psychodynamic; D—maturational lag or "disharmony cognitive"; E—multi-determined (including A, B, C, D, F, other); G—unknown or idiopathic; MBD—minimal brain dysfunction; NR—no response.
(*Data from* Sakuta [7] and Sakuta and Sakuta [10].)

[7], 2 years before attention deficit disorders appeared in the *DSM-III* [9], and in 1997 [10], 3 years after ADHD appeared in *DSM-IV* [11]. Because MBD cannot be regarded as equal to ADHD, comparison between these two studies requires caution. These studies are helpful, however, in that they demonstrate the vicissitudes of MBD/ADHD treatment in Japanese children.

The rate of positive recognition of MBD/ADHD increased before and after the establishment of the concept of ADHD (Table 1). Estimated total prevalence in the general population decreased as a matter of course because MBD is a larger entity than ADHD, mostly estimated to be under 1%. The most noticeable feature of the MBD/ADHD etiology is that brain damage is less assumed to cause ADHD than MBD. In the ADHD survey, respondents were asked to name specific drugs. Psychiatrists prescribed MPH, haloperidol, carbamazepine (CBZ), and pimozide, and pediatricians prescribed MPH and CBZ in descending order of frequency. In total, CBZ was most frequently prescribed, second to MPH, which Sakuta and Sakuta [10] reported was characteristic of treatment in Japan.

Recent Surveys on ADHD in Japan

In 2004, a questionnaire on MPH (Ritalin) use was administered to 775 randomly sampled members of the Japanese Society of Psychiatry and Neurology (collect rate, 61.2%) and important figures in the departments of psychiatry at university hospitals or mental health and welfare centers throughout the country (704 respondents) [12]. About half of psychiatrists prescribed MPH for its target diseases, including depression, narcolepsy, and ADHD in descending order. About 45% of psychiatrists examined patients who voluntarily asked for MPH, 80% of whom did not neces-

sarily need MPH. Thirty percent of psychiatrists examined possible MPH abuse/dependent patients, 0.8% of whom had suspected ADHD. Saito [11] concluded that, although it may be rare, some ADHD patients became dependent or abused MPH; therefore, when prescribing MPH, possibility of abuse must always be considered.

In connection with this survey, a questionnaire on diagnoses and treatments of ADHD was administered to certified physicians by the Japanese Society of Child Neurology (356 respondents; collect rate, 37.9%) and members of the Japanese Society of Child and Adolescent Psychiatry (366 respondents; collect rate, 35.0%) at the same period (700 valid respondents) [12]. Diagnostic criteria included the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)* and *DSM-IV,* which were used by 244 and 541 respondents, respectively (including multiple answers). To diagnose ADHD, intellectual tests, Kaufman Assessment Battery for Children, electroencephalography (EEG), brain MRI, head CT, ADHD–Rating Scale, and Child Behavior Checklist were necessarily administered by 460, 25, 271, 110, 81, 181, and 93 respondents and was administered as needed by 125, 86, 242, 287, 188, 54, and 95 respondents, respectively.

As for ADHD treatment, in a similar survey conducted in 2001 [13], 16% of respondents "basically use no medication" and 47% of respondents start medication at Global Assessment of Functioning (GAF) score 31 to 40, which revealed the prudent Japanese attitude toward ADHD medication. Saito [12] concluded that medication or MPH prescription was more positively initiated in 2004 than in 2001.

Establishing Guidelines and Algorithms

The annual report of the International Narcotic Control Board for 1998 indicated a significant rise in stimulant use. The board called on countries to probe the possibility of ADHD overdiagnosis and restrain MPH overuse. Around the same time, the Drug Enforcement Administration reported that MPH production drastically increased from 1768 kg in 1990 to 14,957 kg in 1999 in the United States [14].

After this period, many countries, starting with the United States, developed guidelines for the diagnosis and treatment of ADHD. In 1997, the American Academy of Child and Adolescent Psychiatry (AACAP) developed Practice Parameters for the Assessment and Treatment of Children, Adolescents, and Adults with ADHD [15], revising its child-related aspects in 2007 [16•]. In 1998, the Texas Department of Mental Health and Mental Retardation developed Algorithms for Medication Treatment of ADHD [17], which was modified and updated in 2005 [18•]. In 2001, the American Academy of Pediatrics developed a Clinical Practice Guideline for School-Aged Children with ADHD [19]. In Europe, clinical guidelines for hyperkinetic disorder were developed in 1998 [20] and upgraded in 2004 [21]. In Asia–Pacific Rim countries, the New Zealand Guidelines for the Assessment and Treatment of ADHD were developed in 2001 [22].

In Japan, after the first guideline for the diagnosis and treatment of ADHD was published by Kanbayashi et al. [13], Saito and Watanabe [23••] developed a revised guideline in 2006 that defined the treatment of ADHD per four fundamental elements: psychoeducation, school liaison, child interview, and pharmacotherapy. The guideline suggested that social skills training, parent training, child consultation office liaison, inpatient treatment, and individual psychotherapy should be administered as needed, and every district must establish systems to offer these therapies. As for medication, the 2006 guideline recommended that children with a GAF score of 50 (serious symptoms or any serious impairment in social, occupational, or school functioning) or below be positively treated by medication, whereas in children with a GAF score of 51 to 60 (moderate symptoms or moderate difficulty in social, occupational, or school functioning), psychoeducation and school liaison should be administered first and, if unsuccessful, medication may be considered. This recommendation followed the 2003 guideline's suggestion that severe ADHD symptoms are a definite indication for medication. However, in cases with mild or moderate symptoms, environmental coordination at home and school should be administered first, and only if this is ineffective (after a few months) should medication be initiated. This was predicated on the idea that appropriate environmental coordination may improve problems in mild or moderate cases and, moreover, that the provided medication is more effective in a better environment. Essential target outcomes will not be accomplished only by medication unless children are in an appropriate environment.

The 2006 guideline clarified that the first-line drug for the treatment of ADHD is MPH, whereas second-line drugs are mood stabilizers (CBZ), antipsychotics (risperidone), and antidepressants (selective serotonin reuptake inhibitors). If MPH is ineffective or cannot be used due to side effects, second-line drugs are used alone or in conjunction with MPH. The 2006 guideline also elaborated the use of MPH as follows (note that the 2006 guideline was developed when Ritalin was the only stimulant available in Japan):

1. When prescribing Ritalin, obtain informed consent from parents about its off-label use.
2. In principle, prescribing Ritalin is contraindicated for children 6 years old or younger.
3. The initial dose of Ritalin is 5 to 10 mg/d.
4. The daily dose of Ritalin is 0.3 to 0.6 mg/kg.
5. The standard dose of Ritalin is up to 30 mg, and the maximum dose is 40 mg.
6. During the middle school years (12–15 years old), termination of Ritalin should be considered.

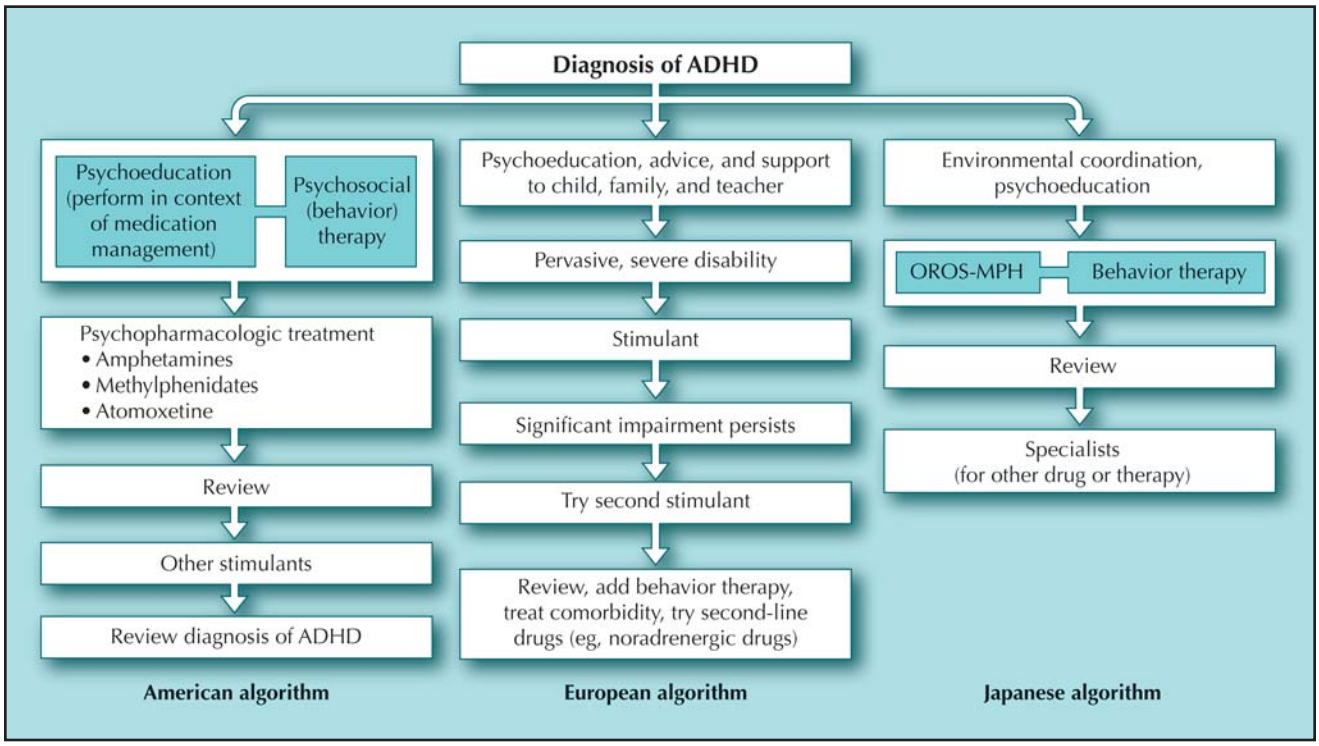

Figure 1. Algorithms for treatment of attention deficit/hyperactivity disorder (ADHD) in the United States, Europe, and Japan. The Japanese algorithm was developed for general pediatricians. In Europe, psychological therapy takes precedence over medication in cases falling short of the severe level. To facilitate comprehension of and comparison among the three algorithms, some simplifications were made (ie, in the cases of uncomplicated stimulant-refractory ADHD in school-age children). OROS-MPH—osmotic controlled-release oral stimulant methylphenidate. (*Data from* American Academy of Child and Adolescent Psychiatry [16•], Taylor et al. [20], and Miyajima et al. [24••].)

7. Always be aware of the possibility of MPH dependence/abuse when prescribing Ritalin; it should only be prescribed by a physician who can diagnose substance dependence and abuse.

In 2007, Miyajima et al. [24••] developed a guideline for pediatricians related to the diagnosis and treatment of ADHD in children. This guideline emerged from strong concerns that general pediatricians, who examine many patients in their daily practice, may diagnose ADHD simply according to *DSM-IV* criteria and prescribe MPH solely based on information about the efficacy of MPH, resulting in MPH overuse without comprehensive medical treatment, including psychosocial therapy. A revised treatment algorithm was issued in accordance with the emergence of Concerta, the first MHWL-approved stimulant for ADHD children (Fig. 1).

Characteristics and Future Challenges in Psychopharmacology for ADHD in Japan

In general, Japan prudently administers (stimulant) medication for ADHD, even though medication has been yielding more positive results than before. The 2006 guideline [23••] recommends that children with mild or moderate symptoms or difficulty in daily life should be treated by parent guidance and school liaison first. Similarly, the pediatrician guideline [24••] recommended that psychosocial treatment, such as environmental coordination and psychoeducation, be administered first, accompanied by required behavioral therapy, even after the initiation of treatment with medication. This is in strong contrast to the AACAP parameter in which psychosocial (behavioral) therapy may be selected as an initial treatment under specific situations, such as mild ADHD symptoms with minimal impairment or family preference; psychoeducation also assumes medication (Fig. 1). Moreover, the maximum dose of Ritalin differs greatly between Japan (40 mg per the 2006 guideline) and the United States (60 mg per the FDA; 100 mg [off-label use] per the AACAP parameter). Generally, however, medication doses are smaller in Japan than in the United States in all areas of medicine. Further, the 2006 guideline recommended termination of Ritalin during the middle school years. In the United States, there is consensus that individuals with continuing ADHD symptoms should be treated throughout the life span and stimulant treatment should not stop just because patient has achieved puberty and is less overly hyperactive [24••]. These descriptions from two countries are not necessarily mutually exclusive, but they do reveal somewhat differing attitudes toward stimulant use during and after adolescence.

This passive Japanese attitude toward medication for ADHD can be partly explained by poor expectations about medication among parents of children with ADHD. A medication-related survey of parents of children with

ADHD revealed that 58% to 70% of parents expected to receive a full explanation about therapeutic options and the nature or clinical course of ADHD, a definite announcement of diagnosis, and attentive listening to descriptions of their children's symptoms, whereas only 23% expected medication [12]. Another plausible reason for this attitude is that medication tends to be initiated only after the "caseness of ADHD" emerges. In response to the results of the 2003 survey that found that most Japanese doctors initiate medication for ADHD at GAF scores 31 to 40, Kanbayashi et al. [13] pointed out that medication is often used to quell nuisances caused by children with ADHD, such as disturbing classes, breaking rules, or fighting, instead of improving hardwired difficulties in children with ADHD, such as attention deficit or lower academic performance. Kanbayashi et al. [13] suggested that parents, doctors, and teachers should keep in mind that medication was administered on behalf of children with ADHD and not on behalf of those around them.

In developing Japanese guidelines, as a whole, there are few descriptions of the treatment of children with complicated ADHD or medications other than MPH, especially when compared with the medication-specific Revised Texas Algorithm. With the establishment of the guideline for general pediatricians, guidelines are anticipated for stimulant refractory or complicated ADHD.

Under the circumstances, it is noteworthy that, in Japan, CBZ has been a longstanding, common treatment for MBD/ADHD based on clinical consensus rather than evidence [25]. Effectiveness of anticonvulsants was mentioned in the 2006 guideline as follows: "For cases with epilepsy or epileptiform EEG abnormality, anticonvulsants are the first-line drugs. For cases with severe hyperactivity or impulsivity, CBZ or valproic acid (VPA), which is a mood stabilizer as well as an anticonvulsant, is commonly prescribed." In contrast, the New Zealand guidelines do not recommend CBZ for ADHD [22], because a meta-analysis of the effectiveness of CBZ in ADHD [26] produced statistically significant therapeutic effect, but its effect size was too small and CBZ involves side effects such as leukopenia, anemia, and hepatoxicity. The Revised Texas Algorithm ranked mood stabilizers (lithium, VPA) lower (fourth vs second) and behavioral therapy higher (second vs fourth) than the former Texas Algorithm did for the treatment of ADHD and comorbid aggression [18•].

In other countries, unless there is strong evidence of such factors in the medical history, neurologic studies (EEG, MRI, single-photon emission computed tomography, positron emission tomography) are not indicated for the evaluation of ADHD [16•,20,25]. However, EEG is routinely administered to children with ADHD. More emphasis is placed on EEG findings in ADHD treatment in Japan than in other countries. In two studies in the United States, 7% to 15% of children with uncomplicated ADHD demonstrated epileptiform EEG abnormalities [27]. Further research is needed on the effectiveness of anticonvulsants in hyperactivity or impulsivity in children with an epileptiform EEG abnormality [28•].

In general, symptoms improve in 73% to 77% of children with ADHD initially treated with a stimulant [25]. Some studies suggest that both an MPH and amphetamine preparation should be tried to increase the response rate before consideration of other classes of agents [29]. Similarly, the New Zealand guideline noted that MPH and dexamphetamine may require separate clinical trials to determine which medication is most suitable [22]. In this sense, an increase in stimulant options for ADHD is favorable, although an amphetamine preparation increases the risk of abuse more than MPH and medication does not cure ADHD completely. However, it is unlikely that amphetamine-type stimulants will be introduced in Japan as a treatment for ADHD. Japan had a bitter experience with methamphetamine synthesized by a Japanese chemist and distributed after World War II. Consequently, in 1954, methamphetamine users and abusers reportedly numbered 550,000 and 200,000, respectively [30].

A nonstimulant for ADHD, atomoxetine, is nearing MHLW approval for use in children and is under phase 2 clinical trials for use in adults. Currently, only one stimulant (Concerta) is available for children with ADHD and no stimulant is available for adults with ADHD in Japan, which compels reliance on psychosocial treatment for ADHD. As the 2006 guideline requested, systems providing psychosocial treatments for individuals with ADHD should be developed. Further, the minimum dose, 18 mg, of Concerta, which may not be divided in two, is excessive, especially for low-weight Japanese children in early grades. Some measures to tackle this problem, including approval of Ritalin, should be addressed.

As for the treatment of adult ADHD, now that even off-label Ritalin use is practically prohibited, there is no stimulant for adult ADHD. Further, it is doubtful whether there is clinical consensus about adult ADHD among psychiatrists. Therefore, clear consensus must be achieved for this complicated condition as well as sufficient support for undiagnosed adult ADHD and diagnosed adult ADHD in patients who have already used off-label Ritalin.

Essentially, the risk is different in stimulant-treated children with ADHD developing substance use disorders (SUD; denoting drug or alcohol abuse or dependence) later and individuals without ADHD abusing/depending on stimulants. In the former group, the long-acting agent, OROS MPH, has a lower potential risk of abuse and is the only stimulant available in Japan. Wilens et al. [31] presumed four working hypotheses about the mechanisms by which stimulant pharmacotherapy protects against SUD. First, stimulant pharmacotherapy reduces ADHD symptoms, demoralization, poor self-esteem, and academic or occupational failure, resulting in reduced SUD. Second, stimulants may indirectly reduce SUD risk by reducing the risk that conduct imparts on SUD. Third, families who seek medication treatment for their children may be more intact (eg, parents still married), of higher socioeconomic status, more invested in education success, or more involved in parenting. Fourth, close monitoring of

children who receive medications may directly influence SUD risk. Follow-up studies on SUD in stimulant-treated children should be performed to determine how strictly limited options on stimulants in Japan effect SUD. As for the latter risk, we need to wait to see how Japanese stimulant-control systems work.

Smalley et al. [32•] noted that Finland, which has relatively low stimulant use, and the United States share similarities in ADHD comorbidity and course. These results indicate that it is possible that effectiveness in early detection and psychosocial interventions via comprehensive public health may compensate for the sparseness of stimulant options in Japan. Establishing a comprehensive public health care system is an urgent need.

Conclusions

In response to counsel on stimulant use from the International Narcotics Control Board in 1998, several countries established guidelines for the diagnosis and treatment of ADHD. It is a welcome development that guidelines have been formulated and the first MHLW-approved stimulant for ADHD, OROS MPH, recently appeared in Japan, a country compelled to make the most of psychosocial treatment and medication other than stimulants. Under Japan's conservative, holistic approach to stimulant treatment of ADHD, systems that can offer psychosocial treatments as needed should be established and epidemiologic studies on ADHD's prevalence, comorbidity, and course administered.

Disclosure

No potential conflict of interest relevant to this article was reported.

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This working guideline, in succession with the 2003 guideline [13], has established a basic framework for ADHD treatment. The third edition of this book was published while this article was in preparation. The core strategy for treating ADHD essentially did not change from the former version, but an OROS MPH–centered guideline of pharmacotherapy for ADHD was finally provided.

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EEG findings and behavioral problems improved in some children with ADHD and epileptiform EEG discharges who were prescribed VPA. Frontal epileptiform discharges were strongly related to the clinical condition of ADHD, suggesting that anticonvulsants were considered effective for children with ADHD and frontal epileptiform discharges. Although the number of subjects was very limited, this study is considerably suggestive.
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This study conducted in the Northern Finland Birth Cohort carries considerable cross-cultural implications. Its interpretation may be controversial, but it revealed that early detection and psychosocial ADHD treatments are no less effective than stimulant treatments.