Received: 29 December 2021 | Revised: 9 March 2022 | Accepted: 30 March 2022

DOI: 10.1002/npr2.12253

NEUROPSYCHOPHARMACOLOGY REPORTS

WILEY

ORIGINAL ARTICLE

Identification of factors associated with the efficacy of atomoxetine in adult attention-deficit/hyperactivity disorder

Tsutomu Nagai[1,2] | Tatsuya Kurihara[3] | Hiroaki Koya[1] | Yukako Nakano[1] | Satoru Sugisawa[1] | Takehiko Sambe[2] | Keiko Kishimoto[4] | Mari Kogo[5] | Haruhisa Ota[6] | Akira Iwanami[7] | Naoki Uchida[2]

[1]Department of Hospital Pharmaceutics, School of Pharmacy, Showa University, Tokyo, Japan

[2]Division of Clinical Pharmacology, Department of Pharmacology, School of Medicine, Showa University, Tokyo, Japan

[3]Division of Natural Medicine and Therapeutics, Department of Clinical Pharmacy, School of Pharmacy, Showa University, Tokyo, Japan

[4]Division of Social Pharmacy, Department of Healthcare and Regulatory Sciences, School of Pharmacy, Showa University, Tokyo, Japan

[5]Division of Pharmacotherapeutics, Department of Clinical Pharmacy, School of Pharmacy, Showa University, Tokyo, Japan

[6]Medical Institute of Developmental Disabilities Research, Showa University, Tokyo, Japan

[7]Department of Psychiatry, School of Medicine, Showa University, Tokyo, Japan

Correspondence
Tatsuya Kurihara, Division of Natural Medicine and Therapeutics, Department of Clinical Pharmacy, School of Pharmacy, Showa University, 1-5-8 Hatanodai Shinagawa-ku, Tokyo 142-8555, Japan.
Email: kurihara@pharm.showa-u.ac.jp

Funding information
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Abstract

Aim: Atomoxetine (ATX) is a non-central stimulant and a standard treatment for adult attention-deficit/hyperactivity disorder (ADHD). The long-term efficacy of Atomoxetine is about 40% at 6 months. The variability in efficacy between individuals is thought to be related to patient-specific factors, but no detailed research has been conducted. In this retrospective cohort study, we aimed to identify the factors associated with Atomoxetine efficacy.

Methods: A total of 147 patients with attention-deficit/hyperactivity disorder aged ≥18 years who were using Atomoxetine for the first time were included in this study. The outcome was treatment success (treatment maintained for at least 6 months and improvement in symptoms). Symptom assessment was based on the overall improvement in symptoms judged by an expert physician.

Results: Of the patient sample, 103 (70.1%) achieved the outcome. Logistic regression analysis identified "the maximum dose of ATX" and "gambling habit" as factors associated with efficacy ($P < 0.05$). In the process of Atomoxetine titration, the larger the maximum dose, the higher the efficacy was shown to be. Gambling habits may be indicative of impulsivity, which is among the core symptoms of attention-deficit/hyperactivity disorder. Thus, a gambling habit may be considered a surrogate marker for impulsivity.

Conclusions: Knowledge of these factors will help healthcare professionals to predict the likely efficacy of Atomoxetine in a given patient before subscribing it, facilitating individualized pharmacotherapy for adult attention-deficit/hyperactivity disorder.

KEYWORDS
adrenergic uptake inhibitors, atomoxetine hydrochloride, attention-deficit disorder with hyperactivity, cohort studies, multivariate analysis

1 | INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a developmental mental condition characterized by inattention, hyperactivity, and impulsivity. Its onset is usually in childhood or adolescence, and symptoms may persist into adulthood.[1,2] The symptoms of hyperactivity and impulsivity often go into remission in teenage years, but inattention persists in many cases into the twenties and beyond.[3] Thus, in adult ADHD, inattention is often the primary symptom. In contrast, when hyperactivity/impulsivity symptoms are present, the impact on social life is greater and symptom control is considered more important. Recently, there has been an increase in the number of adult ADHD diagnoses. This may be because of the increased public recognition of ADHD. The prevalence of ADHD in adults, including those diagnosed in childhood, is estimated to be about 3.4% worldwide.[1]

The etiology of ADHD has not been fully determined, but genetic factors are thought to play a significant role. The risk of ADHD is two to eight times greater in a child whose parents or siblings have ADHD, and twin studies have estimated heritability at 76%.[4,5] The pathogenesis of ADHD appears to involve structural abnormalities in the brain[6] and decreased dopaminergic and noradrenergic activity in the frontal subcortical circuits, resulting in functional impairment.[7] Therefore, pharmacotherapy for ADHD comprises drugs that inhibit the synaptic reuptake of dopamine and noradrenaline or stimulate their release.[8] The standard treatment for ADHD is psychosocial and pharmacological treatment, with psychosocial treatment as the base treatment and additional pharmacological treatment as appropriate. In Japan, different drugs are approved for pediatric and adult ADHD. In adults, the central stimulant, methylphenidate, or the non-central stimulants, atomoxetine (ATX) or guanfacine, are prescribed. ATX is a selective noradrenaline reuptake inhibitor. The desired outcome of pharmacotherapy for adult ADHD is the continuation of treatment, the absence of major symptoms, and the maintenance of a stable social life. Long-term use of ATX in adults with ADHD has been shown to improve outcomes.[9] However, the efficacy of ATX varies widely between individuals, and the overall efficacy rate after 6 months of use in those with adult ADHD is about 40%.[10]

There have been several studies on the factors associated with the efficacy of ATX in children and adolescents. It has been reported that a lower initial dose of ATX reduces the duration of medication adherence[11] and that patients receiving concomitant central stimulants had a higher response rate.[12] However, there has been no research into factors that affect the efficacy of ATX in adult ADHD. Such factors might be used by clinicians as indicators of potential efficacy. There are significant differences in treatment strategies, therapeutic environments, and social support between adult and childhood ADHD. Therefore, it is necessary to separately investigate factors affecting the treatment efficacy of ATX on adult ADHD. ATX efficacy with adult ADHD at 4 weeks was found to correlate with a 6-month treatment efficacy index.[13] The presence of depression was also shown to be associated with treatment success.[14] However, as mentioned, no studies have focused specifically on factors that might predict the efficacy of ATX at the initiation of treatment. Therefore, we performed a retrospective cohort study to identify factors associated with ATX efficacy in adult ADHD.

2 | METHODS

2.1 | Subjects

A total of 147 adults (aged ≥18 years) diagnosed with ADHD at Showa University Karasuyama Hospital between 2008 and 2018, who had been started on ATX as the first-line treatment for ADHD, were identified. The diagnosis of ADHD was made by a psychiatrist using DSM-IV-TR or DSM-5 criteria.[15,16] Patients who had used other ADHD medications prior to ATX and patients who had used central stimulants (methylphenidate, amphetamine, or methamphetamine) for purposes other than ADHD treatment were excluded from the study. Patients who were treated concurrently with other ADHD medications and patients with no follow-up information on record were excluded from the study. The dosages of ATX were determined according to the dosage regimen approved in Japan. The titration schedule was based on the individual patient's symptoms with a maximum dose of 120 mg/day.

2.2 | Variables and outcomes

The outcome measure in this study was treatment success. This was defined as adherence to medication for at least 6 months after the initiation of ATX and improvement in symptoms at 6 months. The follow-up period was 6 months from the initiation of ATX. Symptom improvement was assessed through a comprehensive evaluation of symptoms as reported by Scott et al.[12]

Table 1 shows the demographic and clinical characteristics of the patients in our sample. These were obtained from medical records. Education was categorized as anything up to, and including, high school graduation, or college, junior college, or vocational school degrees.

This is because, in Japan, over 95% of young people graduate from high school, so these two educational categories are frequently used. The initial dose, maintenance dose, and maximum dose for each patient during the observation period were also investigated. The maintenance dose was defined as the dose taken after the effects had stabilized and was calculated only for those patients who achieved a successful outcome. The maximum dose was defined as the highest dose administered to each patient during the follow-up period, regardless of the maintenance dose.

2.3 | Statistical analyses

Subjects were divided into a success group and a failure group, according to whether a successful outcome was achieved.

TABLE 1 Patient characteristics (n = 147)

	n (%) mean ± SD
Age (y)	33.3 ± 11.0
Sex	
Male / female	**80 (54.4) / 67 (45.6)**
Age (y) at ADHD diagnosis	33.0 ± 11.1
Trouble at birth	19 (12.9)
Family history of ADHD	34 (23.1)
Living alone	38 (25.9)
Experience of school refusal	39 (26.5)
Experience of repeating the same class	16 (10.9)
Education level	
High school/university[a]	43 (29.3) / 102 (69.4)
Career change history	95 (64.6)
Unmarried	114 (77.6)
Divorce history	8 (5.4)
Gambling habit	8 (5.4)
Initial dose of atomoxetine (mg/day)	22.4 ± 9.6
Maintenance dose of atomoxetine (mg/day)[b]	88.7 ± 29.5
Maximum dose of atomoxetine (mg/day)	87.2 ± 32.9
Comorbidities	
Schizophrenia	6 (4.1)
Depression	31 (21.1)
Bipolar disorder	6 (4.1)
Pervasive developmental disorder	6 (4.1)
Autism spectrum disorder	19 (12.9)
Asperger's syndrome	5 (3.4)
Panic disorder	4 (2.7)
Social anxiety disorder	4 (2.7)
Obsessive–compulsive disorder	2 (1.4)
Phobia	1 (0.7)
Generalized anxiety disorder	2 (1.4)
Adjustment disorder	7 (4.8)
Symptoms of ADHD	
Inattention	141 (95.9)
Hyperactivity/impulsivity	81 (55.1)
Both symptoms	75 (51.0)
Poor adherence	29 (19.7)
Concomitant medication	
Antipsychotic	20 (13.6)
Antidepressant	30 (20.4)
Mood stabilizer	9 (6.1)
Anticonvulsant	5 (3.4)
Anxiolytic, hypnotic	46 (31.3)

Abbreviations: SD, standard deviation.

[a]University, junior college, or vocational school.

[b]The maintenance dose is the mean value for subjects in the successful group only.

Differences between the two groups were compared using univariate analyses. For the univariate analyses, we used the Student's *t* test or Welch's *t* test with continuous variables and the chi-squared test and Fisher's direct probability test for nominal variables. A univariate analysis was conducted to exclude factors that were not clearly relevant to maintain the detection sensitivity of a multivariate analysis. In the univariate analysis, $P < 0.1$ was set to ensure that related factors were not missed. Subsequently, logistic regression analysis (stepwise) was performed with those variables that showed significant differences in the univariate analyses ($P < 0.05$). The statistical software, SPSS, was used to perform the analyses.

3 | RESULTS

During the follow-up period, 103 patients (70.1%) achieved a successful outcome. Thus, the success group consisted of 103 (70.1%) patients and the failure group consisted of 44 (29.9%) patients. The median age of our patients was 31.0 (18-68) years, and 80 (54.4%) were male. The mean initial and maximum doses were 22.2 and 87.2 mg/day, respectively. A gambling habit was observed in eight patients (5.4%). The most common comorbidity was depression, present in 31 patients (21.1%). Of the clinical symptoms distinguishing the types of ADHD, 141 (95.9%) patients had inattentive symptoms, 81 (55.1%) had hyperactivity/impulsivity, and 75 (51.0%) had both. The most common concomitant medications were anxiolytics and sleep medication, used by 46 patients (31.3%).

The results of our univariate analyses are shown in Table 2. Significant differences were observed between the success and failure groups for a history of career change ($P = 0.036$) and in the maximum dose of ATX ($P < 0.001$). There were also significant differences in the history of truancy ($P = 0.074$), gambling habit ($P = 0.052$), obsessive-compulsive disorder ($P = 0.088$), and generalized anxiety disorder ($P = 0.088$) between the groups, with all these being more prevalent in the failure group. No significant differences were found for any of the other variables, including comorbidities, poor adherence, and concomitant medications (univariate analyses).

Table 3 shows the results of a logistic regression analysis (stepwise) of the six variables identified as significant in the univariate analysis. The maximum dose of ATX ($P < 0.001$) and gambling habit ($P = 0.030$) was identified as significant factors that independently contribute to the efficacy of ATX. The odds ratios (95% confidence interval) of the maximum dose of ATX and gambling habits were 0.14 (0.03-0.83) and 1.41 (1.23-1.62), respectively.

4 | DISCUSSION

We found that a higher maximum dose of ATX may contribute to the efficacy of ATX treatment in adult ADHD. The study also revealed that having a gambling habit may contribute to the lack of efficacy. Our identification of factors affecting the inter-individual efficacy of

TABLE 2 Univariate analyses of potential predictive factors for associations with atomoxetine efficacy in adult ADHD (n = 147)

	Success group (*n* = 103) *n* (%), mean ± SD	Failure group (*n* = 44) *n* (%), mean ± SD	*P*-Value
Age (y)	33.7 ± 11.3	32.5 ± 10.3	.535
Sex			
Male / female	55 (53.4) / 48 (46.6)	25 (56.8) / 19 (43.2)	.703
Age (y) at ADHD diagnosis	33.4 ± 11.5	32.2 ± 10.1	.533
Trouble at birth	14 (13.6)	5 (11.4)	.712
Family history of ADHD	24 (23.5)	10 (23.3)	.972
Living alone	26 (25.2)	12 (28.6)	.679
Experience of school refusal	23 (22.8)	16 (37.2)	.074*
Experience of repeating the same class	13 (12.9)	3 (7.1)	.396
Education level			
High school/university[a]	29 (28.4) / 73 (71.6)	14 (32.6) / 29 (67.4)	
Career change history	61 (59.2)	34 (77.3)	.036*
Married	22 (21.4)	11 (25.0)	.628
Divorce history	4 (3.9)	4 (9.1)	.240
Gambling habit	3 (2.9)	5 (11.4)	.052*
Initial dose of atomoxetine (mg/day)	22.5 ± 9.4	22.2 ± 10.0	.855
Maintenance dose of atomoxetine (mg/day)	88.7 ± 29.5	-	-
Maximum dose of atomoxetine (mg/day)	96.8 ± 26.3	64.8 ± 35.9	<.001*
Comorbidities			
Schizophrenia	3 (2.9)	3 (6.8)	.364
Depression	20 (19.4)	11 (25.0)	.447
Bipolar disorder	4 (3.9)	2 (4.5)	1.000
Pervasive developmental disorder	4 (3.9)	2 (4.5)	1.000
Autism spectrum disorder	14 (13.6)	5 (11.4)	.712
Asperger's syndrome	3 (2.9)	2 (4.5)	.636
Panic disorder	3 (2.9)	1 (2.3)	1.000
Social anxiety disorder	3 (2.9)	1 (2.3)	1.000
Obsessive–compulsive disorder	0 (0.0)	2 (4.5)	.088*
Phobia	1 (1.0)	0 (0.0)	1.000
Generalized anxiety disorder	0 (0.0)	2 (4.5)	.088*
Adjustment disorder	4 (3.9)	3 (6.8)	.428
Symptoms of ADHD			
Inattention	100 (97.1)	41 (93.2)	.364
Hyperactivity/impulsivity	57 (55.3)	24 (54.5)	.929
Both symptoms	54 (52.4)	21 (47.7)	.602
Poor adherence	17 (16.5)	12 (27.3)	.133
Concomitant medication			
Antipsychotic	12 (11.7)	8 (18.2)	.290
Antidepressant	20 (19.4)	10 (22.7)	.648
Mood stabilizer	4 (3.9)	5 (11.4)	.128
Anticonvulsant	3 (2.9)	2 (4.5)	.636
Anxiolytic, hypnotic	28 (27.2)	18 (40.9)	.100

Abbreviation: SD, standard deviation.

*$P < .1$.

[a]University, junior college, or vocational school.

TABLE 3 Multivariate analyses of factors associated with the efficacy of atomoxetine in adult ADHD

Variable	β	OR	95% Confidence interval	*P*-Value
Gambling habit	−1.935	0.144	0.025–0.831	.030
Maximum dose of atomoxetine[a]	0.345	1.412	1.234–1.616	<.001

Abbreviation: β, regression coefficient; OR, odds ratio.
[a]Odds ratio per 10-mg increase.

ATX in adult ADHD under clinical practice conditions provides new and useful data previously absent from the literature.

The maximum dose of the ATX variable identified in this study indicates a higher probability of efficacy when patients receive higher doses of ATX, up to the maximum of 120 mg/day in the process of titration. ATX can take over a month to achieve stable efficacy and patients often stop taking the drug before it begins to take full effect. When patients experience unsatisfactory results from the drug during titration, they must be encouraged to persevere. Increasing the dose to the maximum may enhance efficacy. In fact, the mean maximum dose of ATX in the failure group was 64.8 mg/day, suggesting that many patients may have discontinued ATX when titration was still possible. In other words, it is possible that patients in the success group were aware of the effects of ATX earlier in the course of treatment. At the same dose, the determination of whether the failure group is less likely to show effects than the success group, or whether the failure group has some characteristics that make them more prone to discontinuation, requires further study in the future.

In this study, we defined the maintenance dose as the dose administered regularly over a period of time once the effects have stabilized. As the maintenance dose of ATX could not be determined and measured in the failure group, the maximum dose was used as the dose-related variable for comparison in our data analysis. Some of the patients in the success group had a maintenance dose lower than their maximum dose. In such cases, the dose increase was tried once to the maximum dose as the patient realized a certain effect, but the dose was reduced because further improvements in the effect were not obtained. In other cases, the dose was reduced to the maintenance dose because of side effects. However, in the success group, the mean values of the maximum and maintenance doses were equivalent. Therefore, the maximum dose was similar to the maintenance dose, which may indicate the need to maintain the maintenance dose at a high level. Previous research found that in patients who responded well to 80 mg/day of ATX, the greatest benefit was achieved at week 26,[13] but doses of 80-100 mg are important for ATX to achieve adequate efficacy.[17] The maximum dose of ATX in our success averaged 96.8 mg, supporting these findings.

In this study, it was suggested that patients with a gambling habit may be less likely to experience the efficacy of ATX. In this context, a gambling habit is a novel factor that has not been detected in previous studies. Although the *act of gambling* itself may affect the efficacy of ATX, the *preference for gambling* itself may be a marker that reflects some patient characteristics. The rate of gambling addiction is higher in adults with ADHD than in the general population, and the severity of the addiction is often greater in those with ADHD.[18–22] Furthermore, impulsivity has been reported to be strongly correlated with gambling habits.[23–27] Thus, gambling habits may have been identified as a surrogate indicator of impulsivity. In accordance with previous reports, hyperactivity and impulsivity, which are core symptoms of ADHD, were categorized together in this study. Therefore, the details of the composition of these two symptoms in the patients are unknown, and we were unable to evaluate whether the impulsivity symptom had an independent influence on the effect of ATX. In adults with ADHD, symptoms of hyperactivity and impulsivity often go into remission or become latent when the individual is sufficiently socially engaged. When latent, these symptoms are difficult to assess. Habitual gambling is an alternative indicator of latent impulsivity, which may have been identified as a factor influencing the effects of ATX. Further studies are needed on the association between gambling and impulsivity in adults with ADHD, and the effect of impulsivity on the efficacy of ATX. Addiction tendencies other than gambling were not examined in this study. Previous research has shown that ATX significantly improves alcohol cravings in adult ADHD with comorbid alcohol use disorder.[28] Further investigations of the relationship with other addictions are needed.

Based on a study by Scott et al,[12] the outcome measures of this study were treatment adherence for 6 months and symptom improvement at 6 months. In randomized controlled trials, Conners' Adult ADHD Rating Scale (CAARS) has been used as a measure of the effectiveness of ADHD treatments. However, CAARS is not suitable for frequent assessments over time and is not widely used in clinical practice because of the large number and complexity of items. In addition, patients with ADHD often become aware of improvements in their daily lives only when those around them point them out, so practitioners need to interview members of their patient's support network. In clinical practice, treatment outcomes are evaluated comprehensively based on assessments by medical staff, the subjective experiences of patients, and improvements in daily life ascertained from detailed interviews by physicians. Our study outcomes were, therefore, determined in the same manner as that used in the clinical setting. Any correlations between the outcomes of this study and the assessment scores used in clinical trials need to be investigated separately.

The efficacy of this study at 6 months was 70.1%, which was high in comparison with previous research using randomized controlled trials. As mentioned above, the difference in our outcome measure is probably the most important factor in this difference, but another factor might be the wide range of symptom severity among the patient sample as the sample was drawn from clinical practice. Although there has been no research on the relationship

between ATX efficacy and ADHD severity, it is possible that efficacy was higher in patients with more severe symptoms. It may also be more difficult to recognize the effects of ATX in mild cases. All patients in this study were prescribed ATX by specialists in ADHD treatment, and although the severity of the disease was within a certain range, further studies are needed to determine differences in the effect of ATX with differing symptom severity. In addition, it is thought that the influence of the different contents of the psychosocial treatment of the study participants must be additionally examined. The participants in this study attempted psychosocial treatment at the discretion of the attending physician as a prerequisite for the introduction of drug treatment, but the content of the treatment and its effects were not standardized. This lack of standardization is because no protocol is available with established evidence in psychosocial treatment for adult patients with ADHD. In the future, it will be necessary to conduct a detailed investigation of the content of psychosocial treatment and establish clear evidence.

Our results may also have been affected by the low starting dose. In clinical practice, the initial dose is often low and it is then titrated closely to minimize side effects. The initial dose in this study was lower than the approved starting dose in Japan. This may have led to more frequent medical visits during the titration process, with fewer patients discontinuing treatment because of greater attention to side effects. Although the initial dose was not identified as a variable in this study, further investigation of the effects of different titration processes is necessary.

The study sample was limited to a single university hospital, and bias in the patient characteristics may need to be considered. In fact, 54.4% of the study participants were male, and the mean age at diagnosis was 33.0 + 11.1 years. Although the symptom types of ADHD were not classified, 95.9% had inattentive symptoms, 55.1% had hyperactivity/impulsivity symptoms, and 51.0% had both symptoms. The comorbidity of depression was 21.1%. Previous large-scale epidemiological studies on adult ADHD included a national survey in Taiwan (n = 5397),[29] and the participants in the current study are similar to the population in the national survey. Therefore, we consider the results of this study to be broadly applicable to general adult patients with ADHD.

For the results of this study to be more reliable and generalizable, validation studies are needed with other populations using the factors identified in this study. The identification of factors associated with the efficacy of other adult ADHD medications, such as central stimulants, could promote greater individualization of treatment choices.

This study identified the maximum dose and gambling habits as factors that contribute to the efficacy of ATX in adult ADHD. Considering these factors during treatment decisions could contribute to the individualization of pharmacotherapy for adult ADHD.

ACKNOWLEDGMENT

We would like to thank Y. Ugajin and C. Okajima for their technical assistance. We would also like to thank the staff of Karasuyama Hospital. This work was supported by the School of Pharmacy, Showa University. Further, the authors would like to thank Enago (www.enago.jp) for the English language review.

ETHICAL APPROVAL

This study was conducted in accordance with the tenets of the Declaration of Helsinki, 1964. The study was approved by the Clinical Trial Review Committee of Showa University Karasuyama Hospital (B-2018-038).

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

TN and TK were involved in the conceptualization of this study, the acquisition and analysis of data, and the writing of the first draft of the manuscript. TN, TK, TS, KK, MK, AI, and NU were involved in data interpretation. TN, TK, HK, YN, SS, KK, MK, HO, and AI contributed to the design of this study. All authors collaborated in writing and editing the manuscript and approved the final draft.

PATIENT CONSENT STATEMENT

This study is posted on the institution website as a clinical study using opt-out consent.

DATA AVAILABILITY STATEMENT

The raw data of the present study cannot be made publicly available because the disclosure of personal data was not included in the research protocol of the present study.

ORCID

Tsutomu Nagai https://orcid.org/0000-0002-6501-2702
Tatsuya Kurihara https://orcid.org/0000-0002-6145-452X
Satoru Sugisawa https://orcid.org/0000-0002-4066-8545
Keiko Kishimoto https://orcid.org/0000-0001-6341-8138
Mari Kogo https://orcid.org/0000-0001-7553-0872

REFERENCES

1. Fayyad J, De Graaf R, Kessler R, Alonso J, Angermeyer M, Demyttenaere K, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry. 2007;190:402–9.
2. Lara C, Fayyad J, deGraaf R, Kessler RC, Aguilar-Gaxiola S, Angermeyer M, et al. Childhood predictors of adult attention-deficit/hyperactivity disorder: results from the World Health Organization World Mental Health Survey Initiative. Biol Psychiatry. 2009;65:46–54.
3. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry. 2000;157:816–8.
4. Smith AK, Mick E, Faraone SV. Advances in genetic studies of attention-deficit/hyperactivity disorder. Curr Psychiatry Rep. 2009;11:143–8.
5. Franke B, Faraone SV, Asherson P, Buitelaar J, Bau CH, Ramos-Quiroga JA, et al. The genetics of attention-deficit/hyperactivity disorder in adults, a review. Mol Psychiatry. 2012;17:960–87.

6. Cortese S, Kelly C, Chabernaud C, Proal E, diMartino A, Milham MP, et al. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am J Psychiatry. 2012;169:1038–55.
7. Arnsten AF. Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. J Clin Psychiatry. 2006;67(Suppl 8):7–12.
8. Wilens TE. Mechanism of action of agents used in attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2006;67(Suppl 8):32–8.
9. Durell TM, Adler LA, Williams DW, Deldar A, McGough JJ, Glaser PE, et al. Atomoxetine treatment of attention-deficit/hyperactivity disorder in young adults with assessment of functional outcomes: a randomized, double-blind, placebo-controlled clinical trial. J Clin Psychopharmacol. 2013;33:45–54.
10. Asherson P, Bushe C, Saylor K, Tanaka Y, Deberdt W, Upadhyaya H. Efficacy of atomoxetine in adults with attention deficit hyperactivity disorder: an integrated analysis of the complete database of multicenter placebo-controlled trials. J Psychopharmacol. 2014;28:837–46.
11. Treuer T, Feng Q, Desaiah D, Altin M, Wu S, el-Shafei A, et al. Predictors of pharmacological treatment outcomes with atomoxetine or methylphenidate in patients with attention-deficit/hyperactivity disorder from China, Egypt, Lebanon, Russian Federation, Taiwan, and United Arab Emirates. Int J Clin Pract. 2014;68:1152–60.
12. Scott NG, Ripperger-Suhler J, Rajab MH, Kjar D. Factors associated with atomoxetine efficacy for treatment of attention-deficit/hyperactivity disorder in children and adolescents. J Child Adolesc Psychopharmacol. 2010;20:197–203.
13. Wietecha LA, Clemow DB, Buchanan AS, Young JL, Sarkis EH, Findling RL. Atomoxetine increased effect over time in adults with attention-deficit/hyperactivity disorder treated for up to 6 months: pooled analysis of two double-blind, placebo-controlled, randomized trials. CNS Neurosci Ther. 2016;22:546–57.
14. Spencer TJ, Faraone SV, Michelson D, Adler LA, Reimherr FW, Glatt SJ, et al. Atomoxetine and adult attention-deficit/hyperactivity disorder: the effects of comorbidity. J Clin Psychiatry. 2006;67:415–20.
15. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR Fourth edition, text revision. Washington, DC: American Psychiatric Publishing; 2000.
16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed.Washington, DC: American Psychiatric Publishing; 2013.
17. Clemow DB. Suboptimal dosing of Strattera (atomoxetine) for ADHD patients. Postgrad Med. 2014;126:196–8.
18. Theule J, Hurl KE, Cheung K, Ward M, Henrikson B. Exploring the relationships between problem gambling and ADHD: a meta-analysis. J Atten Disord. 2019;23:1427–37.
19. Brandt L, Fischer G. Adult ADHD is associated with gambling severity and psychiatric comorbidity among treatment-seeking problem gamblers. J Atten Disord. 2019;23:1383–95.
20. Fatseas M, Alexandre JM, Vénisse JL, Romo L, Valleur M, Magalon D, et al. Gambling behaviors and psychopathology related to Attention-Deficit/Hyperactivity Disorder (ADHD) in problem and non-problem adult gamblers. Psychiatry Res. 2016;239:232–8.
21. Waluk OR, Youssef GJ, Dowling NA. The relationship between problem gambling and attention deficit hyperactivity disorder. J Gambl Stud. 2016;32:591–604.
22. Aymamí N, Jiménez-Murcia S, Granero R, Ramos-Quiroga JA, Fernández-Aranda F, Claes L, et al. Clinical, psychopathological, and personality characteristics associated with ADHD among individuals seeking treatment for gambling disorder. Biomed Res Int. 2015;2015:965303.
23. Mestre-Bach G, Steward T, Potenza MN, Granero R, Fernández-Aranda F, Mena-Moreno T, et al. The role of ADHD symptomatology and emotion dysregulation in gambling disorder. J Atten Disord. 2021;25:1230–9.
24. Jacob L, Haro JM, Koyanagi A. Relationship between attention-deficit hyperactivity disorder symptoms and problem gambling: a mediation analysis of influential factors among 7,403 individuals from the UK. J Behav Addict. 2018;7:781–91.
25. Mak C, Tan KK, Guo S. ADHD symptoms in pathological and problem gamblers in Singapore. Int J Environ Res Public Health. 2018;15:1307.
26. Romo L, Rémond JJ, Coeffec A, Kotbagi G, Plantey S, Boz F, et al. Gambling and attention deficit hyperactivity disorders (ADHD) in a population of French students. J Gambl Stud. 2015;31:1261–72.
27. Specker SM, Carlson GA, Christenson GA, Marcotte M. Impulse control disorders and attention deficit disorder in pathological gamblers. Ann Clin Psychiatry. 1995;7:175–9.
28. Wilens TE, Adler LA, Tanaka Y, Xiao F, D'Souza DN, Gutkin SW, et al. Correlates of alcohol use in adults with ADHD and comorbid alcohol use disorders: exploratory analysis of a placebo-controlled trial of atomoxetine. Curr Med Res Opin. 2011;27:2309–20.
29. Cheng YS, Shyu YC, Lee SY, Yuan SS, Yang CJ, Yang KC, et al. Trend, characteristics, and pharmacotherapy of adults diagnosed with attention-deficit/hyperactivity disorder: a nationwide survey in Taiwan. Neuropsychiatr Dis Treat. 2017;13:643–51.

How to cite this article: Nagai T, Kurihara T, Koya H, Nakano Y, Sugisawa S, Sambe T, Identification of factors associated with the efficacy of atomoxetine in adult attention-deficit/hyperactivity disorder. Neuropsychopharmacol Rep. 2022;42:249–255. https://doi.org/10.1002/npr2.12253