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Stimulant Induced Movement Disorders in Attention Deficit Hyperactivity Disorder

Seok-Hyun Nam[1], Myung Ho Lim[2], and Tae Won Park[1,3]

[1]Department of Psychiatry, Jeonbuk National University Hospital, Jeonju, Korea
[2]Department of Psychology, College of Public Human Resources, Dankook University, Cheonan, Korea
[3]Department of Psychiatry, Jeonbuk National University College of Medicine, Jeonju, Korea

Stimulants, such as amphetamine and methylphenidate, are one of the most effective treatment modalities for attention deficit hyperactivity disorder (ADHD) and may cause various movement disorders. This review discusses various movement disorders related to stimulant use in the treatment of ADHD. We reviewed the current knowledge on various movement disorders that may be related to the therapeutic use of stimulants in patients with ADHD. Recent findings suggest that the use of stimulants and the onset/aggravation of tics are more likely to be coincidental. In rare cases, stimulants may cause stereotypies, chorea, and dyskinesia, in addition to tics. Some epidemiological studies have suggested that stimulants used for the treatment of ADHD may cause Parkinson's disease (PD) after adulthood. However, there is still a lack of evidence that the use of stimulants in patients with ADHD may cause PD, and related studies are only in the early stages. As stimulants are one of the most commonly used medications in children and adolescents, close observations and studies are necessary to assess the effects of stimulants on various movement disorders, including tic disorders and Parkinson's disease.

Keywords: Stimulant; Movement disorders; Attention deficit hyperactivity disorder; Tics; Parkinson's disease.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children and adolescents, with a prevalence of 4%−12% [1]. Approximately 35%−65% of children diagnosed with ADHD show the main symptoms of ADHD and have comorbid disorders as adults [2,3]. There is a 70% chance that a child with ADHD has one or more comorbidities [4]. Psychoeducation, cognitive behavioral therapy, and drug therapy may be used to treat ADHD. Among the different treatment options, drug treatment using stimulants is the most effective method. A multimodal treatment study of children with ADHD (Multimodal Treatment Study of Children With ADHD study) conducted on 579 children over 14 weeks reported that drug treatment should be prioritized even when behavioral treatment is simultaneously provided [5]. Moreover, considering its efficacy and safety, stimulants such as amphetamine or methylphenidate are more effective than non-stimulants and α2-

agonists [6,7].

Amphetamine was first used in the US in the 1930s [8], followed by the use of methylphenidate for the treatment of ADHD. Methylphenidate accounted for approximately 80% of stimulants used for the treatment of ADHD in the U.S from the late 1980s to the mid-1990s [9]. Dextro- and levo-amphetamine mixtures (product name: Adderall) were also introduced at the same time and are currently used more frequently in the US than methylphenidate. However, in many other countries, methylphenidate remains the main stimulant used for the treatment of ADHD. In the early days, the stimulants used for the treatment of ADHD were short-acting medications. In contrast, recently, long-term drug formulations drugs are used mainly [10]. Stimulants are among the most commonly used drugs for the treatment of pediatric psychiatric disorders. The use of stimulants for ADHD has increased rapidly worldwide. In the US, the amount of stimulants used in 2016 increased by more than two-fold compared to that in 2006 [11].

ADHD requires lifelong disease management. Thus, the long-term use of drugs may lead to side effects. Movement disorders are among the many side effects of stimulants. Move-

ment disorders associated with stimulants include tics that are commonly associated with ADHD, tremors, stereotypies, gait disturbances, chorea, dystonia, akathisia, and Parkinson's disease (PD). Abnormal movement signs/symptoms in patients with ADHD undergoing stimulant treatment are mostly caused by overuse, abuse, and withdrawal of drugs; however, the symptoms may also develop with drug use in the clinical therapeutic dosage range and may be aggravated by abnormal movement symptoms that the patient previously had [12].

Herein, we review movement disorders caused by stimulant use in ADHD with a focus on studies involving human subjects. We have divided movement disorders into three categories: tic disorders, stereotypies and other movement disorders, and PD.

TIC DISORDERS

Tics are sudden, rapid, and repetitive arrhythmic movements or sounds that can develop in any part of the body. Tourette's disorder is diagnosed when multiple motor and vocal tics last for more than one year, and typically develops at the age of three−eight years. Symptoms peak between the ages of 10 and 12 years and are gradually alleviated throughout puberty. In adulthood, 60%−80% of tic symptoms disappear or decrease significantly [13,14]. ADHD is the most common disease associated with Tourette's disorder. Approximately 50% of patients with Tourette's disorder also have ADHD [15], and 8%−10% of children with ADHD develop Tourette's disorder [16,17]. In certain cases, ADHD and tic disorders develop simultaneously; however, in general, ADHD symptoms appear 2−3 years before tic symptoms develop [18]. Although the causal relationship between ADHD and tic disorders has not been clearly established, the two are neurobiologically related, and there is controversy over the most effective drug for treatment when ADHD and tic disorders co-exist.

In the 1970s and 1980s, several case reports showed that stimulants used for the treatment of ADHD in children led to the development or aggravation of tic disorders [19,20]. Accordingly, the US Food and Drug Administration (FDA) banned the use of stimulants in patients with tic disorders or a family history of tic disorders [21]. In fact, many clinicians have observed that tic disorders develop or worsen after the use of stimulants and patients experience difficulties in responding to treatment outcomes. On the other hand, many important pieces of evidence suggest that stimulants do not affect tic disorders, as shown in Table 1 [22-25]. In a placebo-controlled, double-blind, crossover study, Castellanos et al. [22] administered methylphenidate, d-amphetamine, and placebo to ADHD patients with Tourette's disorder for nine weeks. In that study, the two stimulants reduced the symptoms of ADHD at all doses. Methylphenidate and d-amphetamine increased the severity of tics, as evaluated using the Yale Global Tic Severity Scale (YGTSS), at medium and high doses in the first cohort. However, in the second and third cohorts tested by the same group, there was no difference in the severity of tics between those who received either of the two stimulants and placebo. Altogether, tic disorder was transiently aggravated in a small number of participants and resolved over time, whereas ADHD symptoms were consistently controlled. Gadow et al. [23] administered three different doses of immediate-release methylphenidate (MPH-IR) for a short period to 71 children with ADHD and Tourette's disorder (or chronic motor tic disorder), and followed up with the participants from 1989 to 2004. All doses of MPH-IR effectively reduced the severity of ADHD, oppositional defiant disorder, and peer aggression behaviors, and did not aggravate tics compared to placebo. Contrastingly, the teacher ratings showed that MPH-IR improved the frequency and severity of tics. In another multicenter, randomized, double-blind clinical trial published by the Tourette's Syndrome Study Group in 2002 [24], patients with ADHD and Tourette's disorder were divided into clonidine only, methylphenidate only, clonidine+methylphenidate,

Table 1. Effects of stimulants on ADHD and tic symptoms compared with placebo

Authors	Years	No. of participants	Age range (yr)	Study duration	Drug	Control	Results
Castellanos et al. [22]	1997	20	9.4 (mean age)	9 weeks	MPH 15, 25, 45 mg bid AMP 7.5, 15, 22.5 mg bid	Placebo	ADHD symptoms improved without aggravation of tics
Nolan et al. [25]	1999	19	12.3 (mean age)	6 weeks	MPH 0.57 mg/kg (mean total daily dose) AMP 5, 10 mg bid	Placebo	ADHD symptoms improved without aggravation of tics
Tourette's Syndrome Study Group [24]	2002	136	7−14	16 weeks	MPH+Clonidine MPH only Clonidine only	Placebo	ADHD symptoms improved without aggravation of tics
Gadow et al. [23]	2007	71	6−12	15 years	MPH 0.1, 0.3, 0.5 mg/kg	Placebo	ADHD symptoms improved without aggravation of tics

ADHD, attention deficit hyperactivity disorder; AMP, amphetamine; MPH, methylphenidate

and placebo groups. The clonidine only, methylphenidate only, and clonidine+methylphenidate groups showed decreased Conners Abbreviated Symptom Questionnaire scores compared to the placebo group. In particular, clonidine was effective in improving hyperactivity and impulsivity, while methylphenidate was effective in improving inattention. In contrast, 20%, 26%, and 22% of the methylphenidate, clonidine, and placebo groups, respectively, showed worsening of tics with no differences between the groups. In addition, in objective evaluation using a measurement tool, the YGTSS score decreased in the order of clonidine+methylphenidate, clonidine only, and methylphenidate only groups compared to the placebo group.

Therefore, if tics develop or worsen after the administration of stimulants in patients with ADHD, the following confounding variables can be considered. First, tics have a natural course of wax and wane in terms of frequency and severity [18]. In most patients, tics develop or worsen a few days to one year after the administration of stimulants [26,27]. Clinicians must follow-up with the patients for more than three months to ensure that such a phenomenon is not a natural course of tic [28]. In other words, clinicians must check whether such temporal relationships of tics develop and worsen immediately after administration of stimulants or if disappearing and relieving immediately upon discontinuation of the drug is repeated. Second, the onset of tics often overlaps with the time when ADHD symptoms are discovered and medication is initiated. As previously described, motor tics are commonly observed between the age of three and eight, and ADHD develops a few years earlier. Among them, the prevalence of provisional tics is up to 20% [29]. Many patients often neglect or are unaware of provisional tics and may misunderstand that tics have developed due to medication for ADHD treatment. Most patients who developed tics after a certain amount of time from the first use of stimulations to treat ADHD were younger than those who did not [30,31]. This supports the hypothesis that stimulants may play a role in the early triggers of tic development rather than in causing tics [26]. Third, the initial symptoms of tics are similar to those of hyperactivity observed in ADHD. As tics are naturally aggravated following the administration of stimulants, it may be misunderstood that stimulants may have caused tics [19]. Lastly, fatigue and stress worsen tics, and most children with ADHD are treated for the first time using stimulants as they enter elementary school, which may be stressful. Unlike before, children are exposed to serious stress as they study and build new relationships with peers in a structured school environment [32].

ADHD with tic disorder shows poor cognitive performance, such as reduced executive functions, learning ability, and sustained attention, and difficulties in getting along with their peers [33-36]. These cognitive and behavioral problems are related more to ADHD than tic symptoms. Moreover, externalizing problems such as aggressive behaviors, tantrums, oppositional behaviors, and conduct behaviors are closely related to ADHD [37-39]. To recover from such extensive functional impairment observed in children with ADHD accompanied by tic disorders, symptoms of ADHD must be treated first. Stimulants are effective in improving the symptoms of ADHD regardless of the tic disorder and are an important treatment method [40]. Therefore, although tics may develop or worsen after the use of stimulants, clinicians must observe patients without discontinuing or reducing the stimulant dose. However, if tics do not improve over time or cause severe functional impairment, stimulants may be reduced or discontinued and re-administered once they are relieved [41]. In this case, clonidine can be added to or replace the stimulants, and these options are effective for both ADHD and tics [24,42]. Non-stimulants such as atomoxetine and D2-blockers such as aripiprazole may also be alternatives [40].

Stimulants induce dopamine (DA) secretion. In contrast, anti-tic medications act as antagonists of dopaminergic function. Therefore, it is logical to suspect that stimulants may cause tics. In addition, individual cases in which the onset or aggravation of tics is induced by medication may be observed. In fact, in 5%−7% of patients, tics develop or worsen after the use of stimulants [41]. However, this rate is similar to that induced by placebo administration, and a greater number of patients did not develop or show worsening of tics after the use of medication. In other words, various confounding variables, as well as neural circuits related to the onset of tics, complex relationships between neurotransmitters, and individual factors such as genetic vulnerability must be comprehensively considered. In conclusion, as the development or worsening of tics after the use of stimulants is likely to be coincidental and the wide range of functional impairment caused by ADHD and comorbidities is greater than that caused by tic symptoms, clinicians must prioritize using stimulants to treat ADHD.

STEREOTYPIES AND OTHER MOVEMENT DISORDERS

Stimulants induce stereotypies, chorea, and dyskinesia, in addition to tics [43]. Stereotypies are rhythmic and involuntary movements that are repeated without purpose. Although there are many animal studies on amphetamine-induced grooming, facial grimacing, gnawing, and lip licking [44], there are only a few studies on humans, most of which are mainly related to addiction rather than treatment [45].

Chorea is an irregular and involuntary movement character-

ized by unpredictable 'dancing' of muscle contractions. The first case of chorea caused by the use of stimulants was reported in an 8-year-old boy whose upper extremity chorea worsened after the administration of 5 mg amphetamine for hyperactivity [46]. Symptoms improved immediately after discontinuing the medications and rechallenges using the same dose of amphetamine-aggravated chorea. Melvin and Heiraty [47] reported a case of a 10-year-old girl who developed writhing, irregular hand movement, and twisting 'dance-like' gait after increasing methylphenidate OROS dose from 36 mg to 54 mg for treatment of ADHD. Abnormal movements were relieved within 24 h of discontinuation of medication and administration of lorazepam. The movements were no longer observed after three weeks. Recently, a case of a 6-year-old boy with Sydenham chorea as an sequela of acute rheumatic fever was reported [48]. The child was administered 18 mg of methylphenidate OROS for the treatment of ADHD, and in three days, the choreiform movement was aggravated in the extremities. Abnormal movement severity, evaluated using the Chorea intensity scale, increased from 12 to 27 points, and then decreased to 11 points after 2 weeks of discontinuing methylphenidate OROS. Subsequently, 10 mg of atomoxetine was administered, the dose was increased to 25 mg, and chorea did not aggravate. As such, stimulants at clinical therapeutic doses may cause the worsening of chorea. In these cases, medications may be discontinued or changed, and D2-blocker, benzodiazepine, and diphenhydramine may be used instead [49]. However, there is no clear consensus on the treatment of stimulant-induced chorea.

Although there are many case reports of dyskinesia after the administration of stimulants in therapeutic settings, only a few studies have compared stimulants to controls. In one case-control study, the ADHD group treated with methylphenidate had a higher abnormal involuntary movement scale (AIMS) score at baseline than the control group [50]. However, a single dose of methylphenidate did not alter the AIMS score. Keresztény et al. [51] compared three groups: drug-naïve ADHD, stimulant treatment, and healthy controls. The ADHD group treated with methylphenidate had a higher AIMS score than the other two groups, and dyskinesia was mainly observed in the orofacial area and upper extremities. In contrast, the AIMS scores were not significantly different between the drug-naïve ADHD and healthy control groups. This finding suggests that dyskinesia is not an inherent characteristic of ADHD. Recently, dyskinesia has been added to the drug labels and instructions as a side effect of methylphenidate. Clinicians must carefully examine dyskinesia when treating patients with ADHD with stimulants.

PARKINSON'S DISEASE

PD is the second most common neurodegenerative disorder in the elderly, after Alzheimer's dementia. The incidence of PD increases rapidly every year after the age of 60 years, and its prevalence is slightly higher in men than in women [52]. Various studies have sought to determine the cause of PD, and various genetic and environmental factors are involved in its pathogenesis. PD is diagnosed based on a combination of abnormal motor symptoms, including resting tremor, rigidity, bradykinesia, impaired posture, and balance. Although motor symptoms are the main symptoms of PD, other non-motor signs and symptoms are observed before the onset or symptoms of PD [53]. These include sleep problems, such as rapid eye movement sleep behavior disorder, olfactory dysfunction, such as hyposmia, and other symptoms of constipation, cognitive impairment, and depression.

PD is caused by the degeneration of DA neurons in the substantia nigra (SN) and the abnormal misfolding and aggregation of mutant α-synuclein [54,55]. DA neurons in the SN are more sensitive to mutant α-synuclein than those in other parts of the brain [54].

PD and ADHD are closely related. Both diseases are related to functional changes in DA neurons in the midbrain [56]. In transcranial cranial sonography (TCS), SN hyperechogenicity is observed in both patients with PD and children with ADHD [57,58]. In addition, both PD and ADHD are associated with pathological abnormalities in the brain regions (for example, dorsal striatum and nucleus accumbens) projected by DA neurons in the midbrain. In PD, abnormal biomarker findings that indicate DA function in the dorsal striatum are often observed. Among these biomarkers, abnormal findings in dopamine transporter (DAT) proteins are frequently observed in patients with ADHD [56]. Stimulants used for the treatment of ADHD block the binding of DAT and DA in neuron synapses, thereby increasing the concentration of DA in the synapses for therapeutic effects. The use of stimulants changes DAT expression levels in synapses. In a study using single photon emission tomography and positron emission tomography (PET), DAT level in the striatum was higher in patients with ADHD who underwent stimulant treatment for a longer period than in drug-naïve patients with ADHD [59]. Moreover, neuropsychological tests have shown similar cognitive deficits between patients with ADHD and those with PD [56]. Both ADHD and PD are often accompanied by psychiatric disorders such as depression and anxiety disorder, and stimulants help to improve cognitive deficits in PD. These findings indirectly suggest an association between ADHD and PD [56]. Cognitive disturbances and psychiatric disorders are common comorbidities in PD. This suggests that DA nerve

system disorder in PD is not limited to the nigrostriatal DA system and is related to dopaminergic pathways and other neurotransmitter systems [60]. In fact, methamphetamine (METH) causes sustained damage to the DA nerve terminal as well as the serotonin nerve terminal [61].

Animal studies on amphetamines and neurotoxicity studies on abusers of illegal stimulants suggest that stimulants are one of the many neurotoxins that cause PD [56]. However, in most animal studies, stimulants were used at significantly higher doses than those used for the clinical treatment of patients with ADHD. There are only a few studies on the neurotoxicity of stimulants in humans, and most of these limited number of studies have been conducted on METH abusers. In post-mortem studies, METH abusers had reduced striatal DA, TH, and DAT levels; however, the findings were different from those observed in patients with PD [62,63]. Possible explanations for such differences include the mean age of METH abusers to be 30 years in the post-mortem studies, which is an early age for symptoms of PD [62,64]. In a PET study of chronic METH abusers, DAT was reduced. Although participants discontinued METH (abstinent state), decreased striatal DA and memory deficits persisted [65,66]. In another study, TCS was used to determine differences in SN echogenic signals between chronic amphetamine abusers and controls. In that study, the amphetamine abuser group had higher echogenicity than the control group [67,68]. In another study using TCS to evaluate differences in echogenic signals and PD symptoms between amphetamine abusers and controls (ecstasy, cannabis, and non-drug users), the amphetamine group showed hyperechogenicity in the SN [69]. Patient group that used amphetamines (amphetamine, METH, d-amphetamine) more than twice a week for more than three months or weekly for more than a year had more occurrences of PD than the control group (patient spouses or caregivers). PD develops after an average of 27 years of exposure to amphetamines [70]. Additionally, in another survey conducted by the same group of investigators using the same method, patients with PD with a history of long-term exposure to amphetamines developed the disease approximately three years earlier on average than those without such history. However, there were no differences in the characteristics of the symptoms and MRI findings [71].

Methylphenidates have relatively low neurotoxicity compared with amphetamines [72,73]. Some animal studies have reported that methylphenidate can induce neurotoxicity and continuous exposure to methylphenidate in early life can lead to persistent problems in the development of the DA nervous system [74,75]. However, in a study using brain MRI to examine the differences between methylphenidate and placebo groups of adult ADHD patients, there was no detectable cerebral volume loss in the methylphenidate group at three and 12 months

of administration. Instead, there was an increasing trend toward bilateral cerebellar gray matter [76].

There is insufficient evidence to explain why methylphenidate is relatively safe compared to amphetamines. As previously described, aggregation and misfolding of intracellular α-synuclein in neurons often leads to neurodegenerative diseases, such as dementia with Lewy bodies and PD. Amphetamines have a higher affinity for the N-terminus than for the C-terminus of α-synuclein, which induces misfolding of α-synuclein. In contrast, methylphenidate binds to both N- and C-termini to form a loop conformation, which does not cause α-synuclein misfolding [54,77].

In addition, methylphenidate has been used to decrease cognitive, affective, and motor deficits in PD, even in advanced cases [78-86]. Methylphenidate is known to improve motor function in PD [78,79]. Chronic administration of high doses of methylphenidate improved gait and reduced excessive daytime sleepiness in patients with advanced PD [80]. Methylphenidate has also shown positive effects on anhedonia and vigor in patients with PD [82]. After more than a year of levodopa treatment, acute methylphenidate increased positive affect (reward responsiveness) [83] and improved apathy in patients with advanced PD [84]. Auriel et al. [85] reported improved attention in patients with PD after the administration of a single dose of methylphenidate. Fatigue is also a common non-motor symptom in PD; methylphenidate improved fatigue in a randomized, double-blind, placebo-controlled trial [86]. Although these results are promising, further research is required.

Some findings have indicated that stimulants may induce PD [64,87]. Baumeister [64] summarized previous epidemiological study findings on the trend of PD and suggested that stimulants might cause PD. In a recent retrospective cohort study, the association between ADHD and PD was investigated in people born between 1950 and 1992 in Utah, USA [87]. The prevalence of basal ganglia and cerebellum (BG&C)-related diseases (such as PD, secondary PD, essential tremor, and other degenerative diseases of the basal ganglia) was 2.4 times higher in those diagnosed with ADHD than in the control group. Additionally, the prevalence of BG&C-related diseases was six times higher in those who received stimulants and eight times higher in those who received only methylphenidate than in those in the control group. The researchers argued that the use of stimulants in ADHD patients could increase the incidence of PD, while suggesting that caution is needed in interpreting the results. In other words, the use of stimulants such as methylphenidate in patients with ADHD does not directly increase the incidence of PD; however, patients with ADHD who use stimulants may have more severe ADHD symptoms than drug-naïve patients, which may be re-

lated to PD. Furthermore, researchers pointed out that factors that may increase the incidence of PD may not have been controlled. As the study not only investigated the incidence of PD but also included BG&C related diseases (for example, essential tremor), stimulants may not directly increase the incidence of PD [56,87]. In a genetic linkage study on a possible genetic link between ADHD and PD, none of the nine candidate genes showed any association between ADHD and PD, suggesting that the genetic link between the two diseases is low [88].

CONCLUSION

Many studies have investigated whether the use of stimulants in patients with ADHD causes or worsens abnormal movements. Tic disorders are the most commonly studied type of disease. Contrary to the initial belief, recent studies have reported that stimulants may be a factor that influences emotion rather than causing tic symptoms. Studies on abnormal motor symptoms other than tics are mostly case reports, and further evidence is required. Stimulants have been used to treat ADHD for the last several decades, and it is controversial whether these medications act as neurotoxins which cause PD. As the life expectancy of the human race has increased, the incidence of degenerative diseases, such as PD, has rapidly increased. Studies on whether stimulants can affect the onset of PD have mainly been conducted on animals or on illegal drug abusers using METH. Although many studies have reported that among the stimulants used to treat ADHD, methylphenidate is relatively safe compared to amphetamines, recent epidemiological studies have shown that methylphenidate may also increase the incidence of BG&C-related diseases such as PD. However, there is still a lack of evidence to support that the use of stimulants in patients with ADHD may be a direct cause of PD, and related studies are in the early stages. As stimulants are one of the most commonly used medications in children and adolescents, close observations and studies are necessary in the future to assess their effects on the development of movement disorders.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: all authors. Data curation: Seok-Hyun Nam, Tae Won Park. Formal analysis: Seok-Hyun Nam, Tae Won Park. Investigation: Seok-Hyun Nam, Tae Won Park. Methodology: Myung Ho Lim, Tae Won Park. Project administration: all authors. Resources: Seok-Hyun Nam, Tae Won Park. Software: Seok-Hyun Nam, Myung Ho Lim. Supervision: Myung Ho Lim, Tae Won Park. Validation: all authors. Writing—

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ORCID iDs

Seok-Hyun Nam   https://orcid.org/0000-0003-3972-1553
Myung Ho Lim   https://orcid.org/0000-0001-5370-4376
Tae Won Park   https://orcid.org/0000-0001-5980-0756

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