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Systematic Review of Suicidal Behaviors Related to Methylphenidate and Atomoxetine in Patients With Attention Deficit Hyperactivity Disorder

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Objectives: This study investigated the relationship between suicidal behavior and the use of methylphenidate (MPH) or atomoxetine (ATX) in patients with attention deficit hyperactivity disorder (ADHD).
Methods: The Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines were used to conduct a meta-analysis. The Physiotherapy Evidence Database scale was used to score the quality of the studies.
Results: Nine studies were included in this quantitative analysis. The analysis included 602864 patients with ADHD (521125 and 81739 patients were taking methylphenidate [MPH group] and atomoxetine [ATX group], respectively) and 19230 healthy controls. The overall estimates were in the order of the control, MPH, and ATX groups; however, no statistically significant between-group difference was observed in the incidence of events (p=0.553 for control vs. MPH; p=1.000 for control vs. ATX; p=1.000 for MPH vs. ATX).
Conclusion: The rate of suicidal behavior was higher in the ADHD groups treated with MPH and ATX than in the control group. However, no statistically significant difference was observed between the ADHD groups treated with MPH and ATX, and the control group. Therefore, MPH and ATX did not increase suicidal behavior.

Keywords: Atomoxetine; Methylphenidate; Suicide; Attention deficit hyperactivity disorder.

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder associated with childhood onset [1]. Inattention, hyperactivity, and impulsivity experienced by children with ADHD cause significant functional impairment [1]. The symptoms of approximately 30%–50% of children with ADHD persist into adulthood [1,2]. The prevalence and treatment rates of ADHD have continued to increase over the years [3-7]. In the US, the diagnostic rate and medication use in children with ADHD increased steadily from 2007 to 2011 [3-5]. The diagnostic rate increased by 22% from 7.2% in 2007 to 8.8% in 2011, whereas the medication use rate increased by 27% from 4.8% in 2007 to 6.1% in 2011 [3,4]. In Taiwan, the prevalence rates of children diagnosed with ADHD and medication use increased from 2000 to 2011 [6]. A study using the Korea National Health Insurance claims database of South Korea found that the ADHD diagnostic rate increased by 31% from 0.71% in 2007 to 0.93% in 2011. In contrast, the medication use rate increased by 25% for methylphenidate (MPH) from 0.52% in 2007 to 0.65% in 2011 and by 200% in 2011 from 0.04% in 2009 to 0.12% [7].

Previous studies have reported the risk of suicidal behavior among patients with ADHD related to the use of atomoxetine (ATX) and MPH for treatment [8-11]. A meta-analysis [8] and clinical practice guidelines for ADHD published by the American Academy of Pediatrics [9] reported that ATX increased suicidal ideation among patients with ADHD. Additionally, the US Food and Drug Administration and Health Canada found suicidal ideation to be higher among children taking ATX than among those taking placebo [10]. The European Union Supplementary Protection certificates have reported that MPH is contraindicated in the presence of suicidal tendencies among patients with ADHD [11]. Other case reports have described the relationship between medication use and

suicidal behavior [12-17]. A cohort study found that the risk of suicide attempts and completed suicides increased even after adjusting for comorbidities in the ADHD group [18].

However, other studies [19-24] have suggested a relationship between suicidal behavior and ADHD symptoms or comorbidities, rather than medication use. In treatment-naive cohort studies [19,20], the ADHD cohort showed suicidal behaviors more frequently than the non-ADHD cohort. Adolescents displaying suicidal behavior after ATX administration had engaged in suicidal behavior before receiving ATX, i.e., they showed suicidal behavior regardless of the ATX administration [19]. Other studies [21,22] have reported that comorbidities such as depression, anxiety, and antisocial behavior cause suicidal behaviors among patients with ADHD. Some studies [23,24] have suggested that comorbidities accompanying ADHD may be confounding factors in the increased risk of suicidal behavior.

The relationship between ADHD and suicidal behaviors has been consistently reported in several studies; however, they have not reported consistent results regarding the leading causes of these behaviors [22-26]. The diagnostic rate of ADHD in the population that committed suicide ranged from 4% to 25.9%. Even after considering the prevalence of ADHD, the suicide rate was higher among them than among the general population [24]. It is crucial to accurately determine the risk of suicidal behavior due to medication, because an intervention is recommended in such cases along with parent training programs and behavioral interventions if ADHD symptoms are severe [27]. The incidence of suicidal behavior in ADHD is rare, and the study design is challenging because of difficulties in objective evaluation and data collection [28]. Moreover, it is difficult to examine suicidal behaviors associated with MPH and ATX in patients with ADHD. Therefore, a meta-analysis would be beneficial for verifying the clinically useful results in the existing literature.

The present study examined whether the side effects associated with MPH and ATX caused suicidal behavior among patients with ADHD through a meta-analysis of the results of previous studies.

METHODS

Search strategy

A systematic review was conducted according to the predefined guidelines of the Cochrane Collaboration [29]. The scientific search was based on population (patients with ADHD), intervention (daily or regular maintenance treatment with MPH or ATX), control (compared group), and outcome criteria (suicide, suicide attempt, self-mutilation, and self-injurious behavior).

Multiple comprehensive databases, including PubMed, EMBASE, and the Cochrane Library, were searched for articles published between January 1, 1989 and April 18, 2019, using MeSH terms including ["Attention Deficit Disorder with Hyperactivity" (MeSH)] OR ["Attention Deficit and Disruptive Behavior Disorders" (MeSH)], AND ["Amphetamine" (MeSH)] OR ["Atomoxetine Hydrochloride" (MeSH)] OR ["Dextroamphetamine" (MeSH)] OR ["Dexmethylphenidate Hydrochloride" (MeSH)] OR ["Methylphenidate" (MeSH)], AND ["Suicide"] OR ["Self Mutilation"] OR ["Self-Injurious Behavior"] OR ["Suicide, Attempted"]. There were no restrictions on language or publication year; however, reviews, conference abstracts, and editorial letters were excluded. Following the initial electronic search, a manual search was performed to identify articles potentially missed in the electronic search.

Selection criteria

In the initial screening of the electronic databases, articles were selected based on their title and abstract content. Two authors (JHK and YJL) independently performed the screening, and disagreements regarding the inclusion of studies were discussed by all the authors (JHK, SYP, and YJL). The authors extracted data from eligible studies, including medications other than MPH and ATX, disorders other than ADHD, study types, and inclusion criteria.

Assessment of the risk of bias in the included studies and reporting bias

The Cochrane Collaboration tool was used to evaluate the risk of bias. Six parameters were evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. The meta-analysis of study effects was performed using Begg's test to identify publication bias.

Data extraction

The same format was used to independently extract data from the articles, compare the data, and repeat the extraction and comparison of inconsistent items. Specifically, the following information was extracted from each study: study design, first author, country in which the study was performed, year of publication, number of events (the group of participants with an event) and total (participant groups), event term, follow-up period (year), and drug duration (month) (Table 1) [30-39].

The Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines [40] were used to conduct the meta-analysis. The Physiotherapy Evidence Database scale was used to score the quality of the studies [41].

Table 1. Characteristics of the included studies

Study	Study design	Nation	Year	Control		ATX		MPH		Event term	ATX/MPH maximum dosage	Age (yr)	F/U period (yr)	Drug duration (mo)
				Total	Event	Total	Event	Total	Event					
Kratochvil et al. [30]	Double blinded, placebo-controlled RCT	USA	2011	49	1	44	1			Self-harm	1.8 mg/kg	5–6	0.17	2
Chen et al. [31]	Register-based longitudinal study using within-patient	Sweden	2014			21174	4615	37936	7019	Self-harm, suicidal attempt, suicide	-	10–50	4	6
Cheng et al. [32]	Population-based cohort	USA	2015					12120	58	Suicidal attempt	-	2–21	13	-
Linden et al. [33]	Retrospective study	USA	2016			56012	60	223303	203	Suicidal ideation or suicidal attempt	-	5–18	3	6
Warrer et al. [34]	Retrospective study	Denmark	2016					55	4	Suicidal ideation or suicidal attempt	-	0–18	0.9	11.2
Davies et al. [35]	Observational cohort	UK	2017			4509	115			Suicidal ideation or suicidal attempt	-	2–18	1	-
Man et al. [36]	Population-based cohort	Hong Kong	2017					25629	154	Suicidal attempt		6–25	15	
Huang et al. [37]*	Population-based cohort	Taiwan	2018	61722	333					Suicidal attempt	-	12–29	9	-
Liang et al. [38]	Population-based cohort	Taiwan	2018	19181	37			65717	63	Suicidal attempt	-	0–18	7	-
King et al. [39]	Retrospective study	USA	2018					156365	9907	Suicidal attempt	-	0–19	15	-

*The study by Huang et al.'s study was excluded from the meta-analysis because it did not include the number of suicidal behaviors according to ATX and MPH. ATX, atomoxetine; MPH, methylphenidate; F/U, follow-up; RCT, randomized controlled trial

Statistical methods

Excel statistical analysis software (Rex Version 3.5.0.2; RexSoft Inc., Seoul, Korea, http://rexsoft.org/) with "meta" R packages version 3.6.3 (The R Foundation, Vienna, Austria, http://www.R-project.org/) was used to perform the meta-analysis. Since a randomized controlled trial (RCT) design cannot be used to conduct research on suicide, heterogeneity in study design is inevitable. The results were summarized using the following two measures: First, event rates were calculated for each of the three groups (control, ATX, and MPH). Second, relative risk (RR) was calculated by comparing each drug (control vs. ATX, Control vs. MPH, and ATX vs. MPH) using a random-effects model. Between-study variance was estimated using the DerSimonian-Laird method. The summary statistics of the proportion were estimated using the arcsine transform, which was used to reduce the bias of the estimate when the number of events was small. Proportions (%) and 95% confidence intervals (CIs) were presented. Additionally, summary statistics were calculated using the inverse variance method for RR values, and the results were displayed as RR and 95% CI.

The heterogeneity index (I^2) was calculated to test the heterogeneity of the included studies, with the significance level set at α=0.10. A value of $I^2 \leq 60\%$ indicated low statistical heterogeneity between the studies. Heterogeneity was observed in the MPH group (I^2=99.92%, p<0.001 for MPH; I^2= 0%, p=0.999 for ATX vs. MPH). The Begg's rank test was used to demonstrate publication bias; however, it could not be calculated in the ATX vs. MPH comparison with fewer than three studies (MPH, p=1.000).

RESULTS

Search results and study characteristics

Approximately 331 potentially relevant studies were identified through literature search. After removing duplicate articles (64), 270 studies were identified by screening titles and abstracts. One RCT, five observation/retrospective studies, and four population-based cohort studies were included in the qualitative analysis. Among population-based cohort studies, Huang et al. [37] did not include the number of suicidal behaviors according to ATX and MPH; therefore, they were excluded from the meta-analysis. Finally, the quantitative synthesis included 10 studies (one RCT, five observation/retrospective studies, and four population-based cohorts). Fig. 1 shows a summary of the review process.

Control vs. MPH vs. ATX groups

Analysis was performed according to drug type (control, MPH, and ATX groups). Table 2 displays the magnitudes of the effects and their statistical significance. One population-based cohort study with 61722 participants included a control group in their design (proportion=0.073, 95% CI [0.020−0.176], p<0.001). For the ATX group, event rates were calculated from an observational study that analyzed 4509 patients (proportion=0.026, 95% CI [0.021−0.030], p<0.001). For the MPH group, event rates were calculated from two retrospective studies and two population-based cohort studies that analyzed a total of 194169 patients. The random-effects model used to calculate the summary statistics revealed significant differences (proportion=0.026, 95% CI [0.001−0.080], p=0.011).

Group comparisons

Table 3 displays the summary statistics for each group comparison. The control vs. ATX comparison was not statistically significant (RR=1.114; 95% CI [0.072−17.277]; p=0.939), whereas the control vs. MPH comparison was statistically significant (RR=0.849; 95% CI [0.821−0.878], p=0.0007). Finally, the ATX and MPH groups were compared in one longitudinal study and one retrospective study. The overall estimate showed a statistically significant difference wherein MPH reduced suicidal behavior (RR=0.849, 95% CI [0.821−0.877], p<0.001).

DISCUSSION

This meta-analytic study examined the relationship between suicidal behavior and the use of MPH and ATX in patients with ADHD. The rate of suicidal behavior was higher in the ADHD groups treated with MPH and ATX than in the control group. However, no statistically significant difference was observed between the ADHD groups treated with MPH and ATX, and the control group. Therefore, the incidence of suicidal behaviors did not increase because of MPH or ATX.

Our finding that MPH and ATX do not increase suicidal behavior is supported by many previous studies [30-33,36-38]. Therefore, it is necessary to monitor changes in suicidal behaviors before and after taking medication to identify their effects. Previous studies [36-38] have examined suicidal behaviors over a period of time after taking medication. A study [37] examining the risk of suicide attempts in adolescents and young adults with ADHD found that suicide attempts did not increase after taking MPH and ATX and that long-term use of MPH for more than one year was associated with a significantly decreased risk of repeated suicide attempts in males. Another study [38] examining Taiwanese children and adolescents without a history of suicide attempts before being diagnosed with ADHD found that the risk of suicide attempts decreased by 59% at 90−180 days after taking MPH and by 72% after more than 180 days of taking MPH after adjusting for confounding factors. A previous study [36] examined the

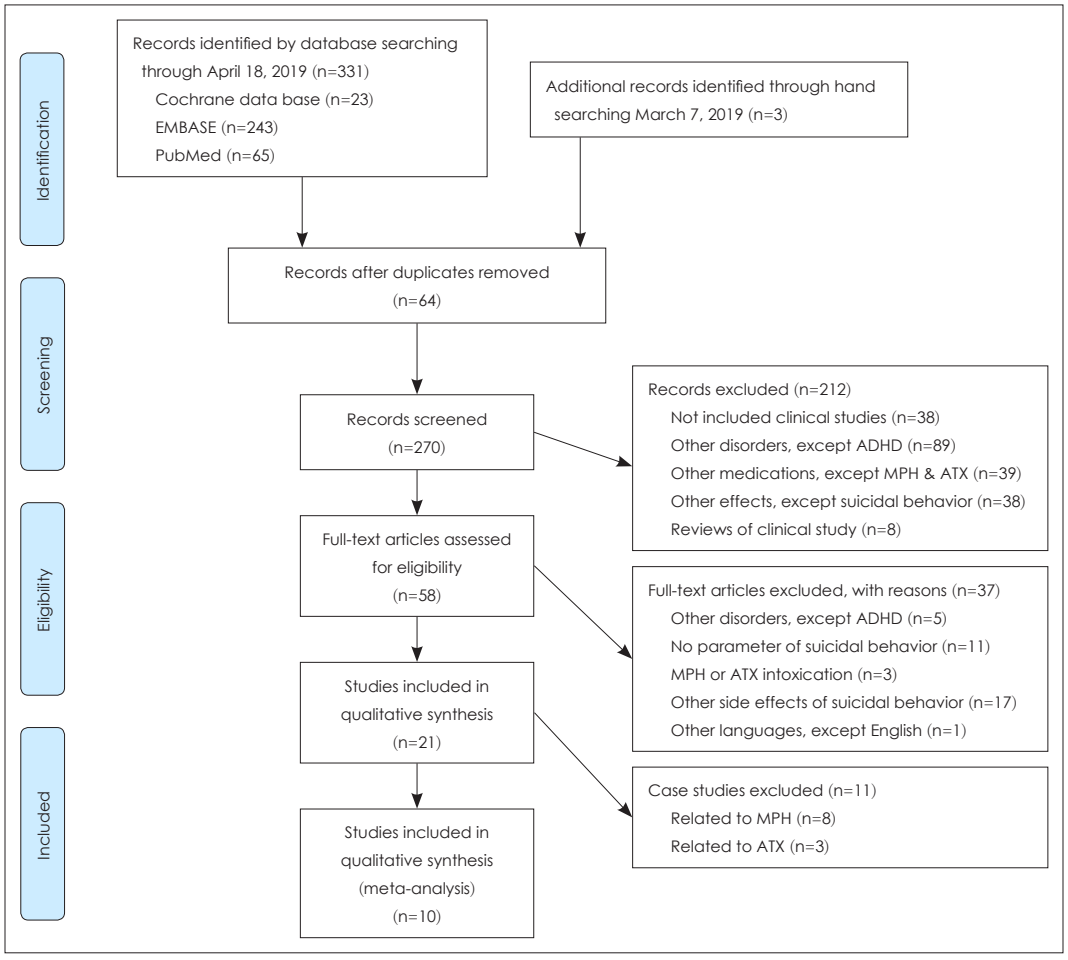

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the identification and selection of the studies included in this meta-analysis. ADHD, attention deficit hyperactivity disorder; ATX, atomoxetine; MPH, methylphenidate.

Table 2. Summary results of meta-analysis by control, MPH, and ATX

Group	Study	Total	Event	Proportion (%)	95% CI		p
					lower	upper	
Control	Huang et al. [37] (Taiwan, 2018)	61722	333	0.073	0.020	0.176	<0.001
ATX	Davies et al. [35] (UK, 2017)	4509	115	0.026	0.021	0.030	<0.001
MPH	Cheng et al. [32] (USA, 2015)	12120	58	0.006	0.005	0.007	<0.001
	Warrer et al. [34] (Denmark, 2016)	55	4	0.005	0.005	0.006	<0.001
	Man et al. [36] (Hong Kong, 2017)	25629	154	0.497	0.331	0.746	<0.001
	King et al. [39] (USA, 2018)	156365	9907	0.063	0.062	0.065	<0.001
	Overall			0.026	0.001	0.080	0.011

ATX, atomoxetine; CI, confidence interval; MPH, methylphenidate

risk of suicide attempts in patients with ADHD 90 days before MPH was initiated, 90 days after MPH initiation, and long-term use of MPH, and found that the risk decreased as MPH continued. Existing studies [8-11] that contradict our results are either cross-sectional or case studies. They have not directly compared suicidal behavior according to temporal changes before and after taking MPH and ATX. Although a direct comparison is difficult because the study method and evaluation time points after taking MPH and ATX vary between studies, studies [36-38] that examined the risk of suicidal behavior after taking medication have consistently reported a decreased risk.

Comorbidities related to ADHD are risk factors for suicide, which has been consistently reported in several studies [22, 42,43]. Previous psychological autopsy studies [22,42,44,45] have revealed critical predisposing factors for adolescent sui-

Table 3. Summary results of meta-analysis through group comparisons

Study	Control		ATX		MPH		RR	95% CI		p
	Total	Event	Total	Event	Total	Event		Lower	Upper	
Control vs. ATX										
Kratochvil et al. [30] (USA, 2011)	49	1	44	1			1.114	0.072	17.277	0.9387
Control vs. MPH										
Liang et al. [38] (Taiwan, 2018)	19181	37			65717	63	0.849	0.821	0.878	0.0007
ATX vs. MPH										
Chen et al. [31] (Sweden, 2014)			21174	4615	37936	7019	0.005	0.004	0.006	<0.001
Linden et al. [33] (USA, 2016)			56012	60	223303	203	0.849	0.636	1.132	0.2638
Overall							0.849	0.821	0.877	<0.001

ATX, atomoxetine; CI, confidence interval; MPH, methylphenidate; RR, relative risk

cide, including depressive disorders, previous suicide attempts, antisocial behaviors, substance abuse, and personality traits such as impulsivity and aggression. Compared to those with ADHD, children and adolescents with ADHD have higher incidences of depressive disorders, antisocial behaviors, substance abuse, and impulsivity, which are considered predisposing factors for suicide [22,46]. Comorbid psychiatric disorders, particularly common among adolescents with ADHD, have been strongly related to adolescents' suicide [43,47,48].

Theoretically, it has been concluded that taking MPH and ATX is not associated with increased suicidal behavior in patients with ADHD but could decrease them with long-term use. Impaired attention and impulse control regulation, which are the main symptoms of ADHD, appear to be caused by dopamine (DA) and norepinephrine (NE) deficits in the prefrontal cortex [49]. MPH increases DA release in the nucleus accumbens and NE and DA in the prefrontal cortex by blocking the reuptake pumps of the DA transporter and NE transporter (NET) [50]. ATX is a selective NE reuptake inhibitor or selective NE inhibitor that inhibits NET and increases DA and NE levels in the prefrontal cortex [50]. Therefore, MPH and ATX can reduce the symptoms of ADHD and prevent the comorbid symptoms related to ADHD. Therefore, suicidal behavior among patients with ADHD can be caused by comorbidities related to ADHD symptoms rather than the side effects of medication.

Our study had certain limitations. First, since RCTs cannot be used to examine suicidal behavior, heterogeneity in the study design cannot be avoided. Second, the present meta-analysis included a previous study with patients of all ages, as few studies have used suicidal behavior as a keyword. This meta-analysis also included the results of Kratochvil et al. [30] for children aged 5–6 years. As responses to medication may differ due to age, additional studies should be conducted in the future. Third, it is necessary to evaluate the differences in medication responses based on the duration of medication use to directly compare the effects of MPH and ATX. Considering the difficulties in conducting a prospective study on suicidal behavior, most previous studies have utilized a cross-sectional design. Moreover, comparison was difficult because the timing of evaluation after the administration of MPH and ATX was too diverse in each study.

CONCLUSION

Nevertheless, this study confirmed through meta-analysis that suicidal behaviors did not increase because of MPH and ATX in patients with ADHD. Therefore, when treating patients with ADHD, MPH or ATX should be actively considered, if necessary, for symptom control and comorbidity prevention. Long-term follow-up is needed in future studies to identify the factors related to suicidal behaviors.

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: all authors. Formal analysis: all authors. Funding acquisition: all authors. Investigation: all authors. Methodology: all authors. Project administration: all authors. Resources: all authors. Software: Suyeon Park. Supervision: all authors. Validation: all authors. Visualization: all authors. Writing—original draft: all authors. Writing—review & editing: all authors.

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