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Submission

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- **Running Title:** ADHD treatment with stimulants and non-stimulants
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Combined medication with stimulants and non-stimulants for attention-deficit/hyperactivity disorder

Running title: ADHD treatment with stimulants and non-stimulants

Abstract [249 words]

Objective

To study the efficiency and indication of combined medication with a stimulant and non-stimulant for attention-deficiency/hyperactivity disorder (ADHD). Herein, the authors examined children and adult patients with ADHD.

Methods

Subjects included patients diagnosed with ADHD who paid two or more visits to the outpatient clinic of the Kyung Hee University hospital from January 2009 to December 2019. The authors examined the age, sex, drugs, treatment adherence, and reason for combined medication. The subjects were classified into four groups: treatment with a non-stimulant (atomoxetine) only (Group ATX), treatment with a stimulant (methylphenidate immediate-release [IR], extended-release [ER], or osmotic-release oral system [OROS]) only (Group MPH), exposed to both but separately used (Group SEP), and exposed to both with combined use (Group COM). The patient was considered adherent to treatment (1) on visiting the hospital ten or more times or consecutively for six months, and (2) medication possession ratio ≥ 0.8 .

Results

Of 929 patients, 229 (24.7%) were female. Group ATX comprised 146 (15.7%) patients,

Group MPH comprised 627 (67.5%) patients, Group SEP comprised 106 (11.4%) patients, and Group COM comprised 50 (5.4%) patients. Longer-term adherence was seen with combined medication and in females than with [monopharmacy therapy](#) and in males. The main indication for combination was dose-limiting untoward effects.

Conclusion

These results suggest that combined medication would facilitate treatment adherence for ADHD. Further research is essential for the replication of these results in a large sample and the investigation of the indications for administering combined medication in children and adults with ADHD.

Keywords : combination, ADHD, atomoxetine, stimulants, pharmacotherapy, adult

Introduction

Drugs approved by the U.S. Food and Drug Administration (FDA) for attention-deficit/hyperactivity disorder (ADHD) are amphetamine and methylphenidate (MPH) as [CNS stimulants](#) and atomoxetine (ATX) as a non-stimulant [1]. [Methylphenidate is a predominantly dopaminergic drug and acts as a norepinephrine-dopamine reuptake inhibitor.](#) [Atomoxetine is a selective norepinephrine reuptake inhibitor \[2\].](#) The response rate of [monopharmacy therapy](#) with these drugs reaches 70%; however, there are cases with a partial response, less effect than expected, and good effect but with serious side effects [1, [32](#)]. Some parents refuse pharmacotherapy because they are afraid of uncertain complications of the drugs that could affect their children [[43](#)]. Unlike children, adult patients can decide by themselves whether to use medication or not because they are more likely to refuse medications owing to side effects such as sleep disturbance and sexual dysfunction [[54](#)]. Therefore, a treatment strategy is required for these treatment resistant and reluctant patients.

There is a growing interest and need for combined medication because of non-responders to monopharmacy or reluctance towards medication due to drug side effects; however, there is not enough research or data about drug combination [65]. One of the reasons for the lack of data on drug combination is that the ~~practice guideline of the U.S. FDA~~ has not approved the combination of more than one anti-ADHD medication for the treatment of ADHD, so it has not been insured and has been prescribed at the patient's own expense [76]. Although the Health Insurance Review and Assessment Service (HIRA) in the Republic of Korea did not provide insurance coverage for combined medication for ADHD, it began to serve insurance benefits to prescribe two anti-ADHD medications, each with a different mechanism of action, on December 1, 2019 [87]. Another reason for the lack of research data on combined medication may be that children were the main subjects for the treatment of ADHD treatment, and prescribing drugs combined without sufficient evidence was cautiously done [98].

Brown et al. [109] reported four cases in which the combination therapy of ATX and stimulants was effective for ADHD to extend the symptom relief period without side effects or to alleviate a wider range of impairment than monopharmacy. In a comparative study between monopharmacy and combined medication with MPH and ATX, although more side effects occurred with the use of combined medication, most of them were generally tolerable [98]. In a study investigating the efficacy, safety, and tolerability of the combined therapy of MPH and ATX, symptoms were improved significantly in nine out of twelve patients, and the combined therapy enhanced the effectiveness of monotherapy [110].

Previous studies were conducted with a small number of subjects, mostly children and adolescents, and the duration of drug maintenance was short. Therefore, this study investigated the clinical characteristics of long-term combined medication for patients with ADHD, including children and adults.

서식 지정함: 취소선

Subjects and Methods

Subjects

A total of 1,189 outpatients, aged 2-74 years who visited the Kyung Hee University Hospital between January 2009 and December 2019 were included in this study. To be eligible for this study, patients had to meet the following criteria: diagnosis of ADHD, any type, by psychiatrists in accordance with the DSM-IV [124] and DSM-5 [132] diagnostic criteria, and visit to the outpatient clinic at least twice. Those in whom ADHD was not the primary diagnosis were excluded from this study.

Methods

The authors collected data on the sex, age, drug, and treatment adherence of each patient by reviewing their medical records. The age was evaluated based on the date when ADHD was first diagnosed. The subjects were classified into two groups: over and below 18 years of age. The reason for choosing 18 years as the standard age is that [the standards of the HIRA for the ADHD drug treatment standards](#) changed over the study period, ~~as the standards of the National Health Insurance in Korea health insurance standards changed continuously~~ [87]. Until December 2012, patients over 18 years of age could not receive medications under insurance even if they were diagnosed with ADHD [143]. From January 2013, patients younger than 18 years of age diagnosed with ADHD could receive insurance benefits after the age of 18 years, and from September 2016, the age for receiving insurance benefits for the use of non-stimulants and stimulants was changed to 6-65 years [87]. Owing to these variables, age-specific comparisons were made with 18 years set as the standard age, taking into account the instability of the data. While most patients included were aged 6 years and older as in the insurance policy, children who had severe behavioral problems, including extreme

hyperactivity, violence against peers, and highly shortened sleep duration, were allowed ~~forced~~ to take medications even under the age of 5 years under the supervision of HIRA.

Therefore, the youngest patient included in the study was aged 2 years.

This study focused on non-stimulants such as ATX and stimulants such as the MPH immediate-release formulation (MPH IR), MPH extended-release formulation (MPH ER), and MPH osmotic-release oral system (MPH OROS). The subjects were divided into four groups: Group ATX, monotherapy with ATX only; Group MPH, monotherapy with MPH IR, ER, or OROS; Group SEP, alternative prescription of MPH and ATX; and Group COM, the combined use of non-stimulants and stimulants.

Treatment duration was calculated as the time and frequency of visiting the hospital from the day of diagnosis of ADHD to the day of treatment cessation. A patient was considered adherent to treatment on visiting the outpatient clinic more than six months or on paying ten or more visits to the outpatient clinic after the first prescription. Those with a medication possession ratio (MPR) less than 0.8 were considered drop-outs. These inclusion and exclusion criteria were based on the authors' previous study [154] in which the treatment cessation rate exceeded 40% on a six-month visit or the tenth visit after initial exposure to the medication.

In this study, ~~the authors focused on 21 patients [12 males, 9 females] of the 929 subjects, who were adherent to treatment in the Group COM, to examine the reason for combination.~~

~~By~~ reviewing and analyzing the contents of the medical records, the authors examined ~~found~~ the cause of drug combination and one or more reasons per person were admitted.

All patients were started on medications after laboratory tests including electrocardiography, liver function test (aspartate aminotransferase [~~AST~~] and alanine aminotransferase [~~ALT~~] level evaluation), thyroid hormone test (T3, free T4, TSH), and complete blood count (CBC),

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to confirm the absence of physical disabilities. This study was approved by the Institutional Review Board of the Kyung Hee University Hospital (KHUH 2020-03-055). Written informed consent from the subjects was exempted because this study was a retrospective chart review of the patients.

Statistical analysis

Chi-square tests were conducted to determine the differences in categorical variables, sexgender, age, and maintenance of treatment, among the four groups (MPH, ATX, COM, and SEP). The Kruskal-Wallis test was performed to examine the group difference according to the continuous variables, frequency and duration of the treatment, and multiple comparisons were performed through the Bonferroni post hoc analysis. Interaction effect among the types of medication used, sexgender, and age was examined by interaction analysis, and subgroup analysis was additionally confirmed according to sexgender and age. The Kaplan-Meier analysis was performed to analyze the influence on treatment maintenance, and multiple Cox regression that adjusted for age and sexgender was also performed. Statistical analysis was performed using SAS 9.4 (Statistical Analysis System version 9.4, SAS Institute Inc., Cary, NC, USA), and a value of 0.05 was considered statistically significant.

Results

Of the 1,189 patients, 260 were excluded because they were not exposed to any anti-ADHD medication. Then, 929 patients (age range, 2-74 years) were included as subjects in the final analysis, of which 229 (24.7%) were female. There were no significant differences in sex and age between the patients excluded and those included in the analysis (sex, p-value=0.2378; age, p-value=0.6588).

Among the 929 patients, Group MPH comprised 627 (67.5%), Group ATX comprised 146 (15.7%), Group SEP comprised 106 (11.4%), and Group COM comprised 50 (5.4%) patients (Table 1). There were no significant differences in sex and age among the four groups. Treatment frequency and duration, and outcome were significantly higher in Group COM and Group SEP than in the monopharmacy groups (Table 1). ~~In the analysis of the effect for medication adherence, Group COM and Group SEP and patients over 18 years of age showed a significantly positive correlation (Table 2). In the analysis of the effect for medication adherence, monopharmacy groups showed significantly higher hazard ratio of discontinuation of medication than Group COM and Group SEP (Table 2). The risk of discontinuance of medication is 1.21 times higher significantly in the subjects over 18 years of age than those less than 18 years old.~~ In terms of interaction, adherence to treatment in Group COM was significantly better in females than in males (Table 3).

~~For the analysis of the reason for combination, the authors focused on 21 patients (12 males, 9 females) who were adherent to treatment in the Group COM (Table 1). Among the 21 patients showing adherence to treatment in Group COM, There were the 32 reasons for combination therapy were as follows:~~ 16 patients with untoward effects, seven with a partial response (less effectiveness with enough dosage for bodyweight and age), six with associated disorders (i.e., sleep disorders and tic), and three for controlling non-ADHD symptoms (i.e., behaviors in ~~patients with low intelligence or autistic characteristics—autism spectrum disorder or intellectual disability~~) (Table 4).

Discussion

Combined medication with anti-ADHD drugs was significantly effective for the long-term compliance with treatment for ADHD than monopharmacy, in terms of the frequency and duration of the treatment in this study. This result cannot be generalized to the treatment for

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ADHD; however, it can be interpreted that combined medication is effective in some patients who did not sufficiently improve with monotherapy. This is because the monotherapy response rate of MPH drugs is around 70% and increases to 90% when dextroamphetamines are included [54]. It is also necessary to consider that combination therapy is being applied to very few cases compared with monotherapy. In this study, 5.4% of patients were using MPH and ATX at the same time. In a Turkish university hospital. Among 824 patients with ADHD, 12 patients (1.45%) among 824 patients with ADHD were treated with combinations of MPH and ATX in a Turkish university hospital [110]. Based on big data from the Danish Registry, treatment with 2% of MPH overlapped treatment with ATX [165]. After the introduction of MPH ER in the Netherlands, the switch from MPH IR to MPH ER and the addition of MPH ER to MPH IR have lowered the rate of discontinuation of medications, which indirectly proves the effectiveness of the combined medication therapy [16]. When MPH IR reacted partially in patients with ADHD, MPH IR and MPH ER were used together to increase the duration and extent of therapeutic effect for partial responders to monotherapy [1].

In terms of prevalence, the male to female ratio is 2:1 in childhood and 1.6:1 in adulthood [132]. In a Swedish study, the overall dispensing prevalence increased with an average of 53% yearly among women aged 22-45 years, and this result is probably an indication of increased awareness among affected individuals and clinicians about the symptoms and impairments of ADHD in female adults [187]. Girls who are undertreated or undiagnosed in childhood live with their complaints longer, which increase the chance of both a lower educational level and lower productivity at work than in the case of boys who are administered treatment [54]. Because of several failures in both work and relationships, women with ADHD have low self-esteem. As females are usually diagnosed later than males, the results of the treatment are expected to be worse. However, the difference in therapy effects by gender is uncertain. In the

authors' previous study, the IQ of the children and mothers' education levels of the group with a long-term treatment of more than three years were significantly lower than those of the early discontinuation group; however, there was no gender difference between the two groups [198]. Additionally, in a total population study in Sweden, there were no significant differences in treatment discontinuation between males and females [187]. In this study, while the treatment adherence was significantly better among females in the combined medication group, there is a limit to generalizing this as a characteristic of ADHD, since the study comprises fewer subjects and is a retrospective chart review. Nevertheless, since female patients are less likely prone to antisocial personality disorder and substance abuse than males [54], it can be assumed that treatment compliance can be better in female patients than in male patients.

In Korea, the combination pharmacotherapy policy in national insurance was changed recently. Since December 2019, despite monopharmacytherapy for ADHD for at least a month, another type of medication for ADHD (MPH, ATX, or clonidine) can be added when physicians decide that the clinical response from the primary drug is insufficient [87]. As other countries have similar situations, there are no proper practice guidelines for combined medication. Adler *et al.* [1] cited partial response, dose-limiting side effects, associated disorders (sleep disturbance and tic disorders), and comorbid disorders as the four main areas in which combinations of medication are used for ADHD. In this study, the most common reason for combined medication among the patients with adherence to treatment was untoward or unexpected effects (dose-limiting side effects) followed by associated disorders such as tic disorder. Although it is known that drugs used for the treatment of ADHD can cause sleep problems or worsen tics, it is possible that physicians did not accurately assess whether these disorders were present before the medication for ADHD was started. From an update review based on standard methodological procedure of Cochrane, although few

individuals may exacerbate tics, stimulants for ADHD have not been shown worsening tics in most patients with tic [2019]. The reason for the high rate of discontinuation of medication within six months after the commencement of medication for ADHD in a university hospital (42.4%) [198] and the National Health Insurance Claims Data (41.0%) [154] may be the resistance to untoward effects in the early stages of treatment or deterioration of associated disorders, despite the improvement of ADHD-related symptoms with medication.

Among the subjects of this study, some cases were treated with combined medication because of less effectiveness with enough dosage for bodyweight, or less effectiveness by the limitation of dosage in the insurance policy. Especially for children, MPH dosage may be insufficient if the age and weight standards are met. Therefore, the application of combined medication may be necessary for overweight children to comply with the health insurance regulations on drug treatment [210].

Under the insurance policy, the criteria for determining drug dosage depend on weight and age; however, there are no requirements for appropriate standards for the period of drug titration. Mui et al [224] reported a 120-day period until the establishment of the optimal pharmacological treatment for adults with ADHD. The retrospective study of one university hospital showed a significant difference in the time from the first visit to the clinic to the start of medication between the early drop-out group and the treatment continuation group, 36.8 ± 26.8 days and 57.4 ± 46.0 days, respectively [232]. The slower the onset of the medication, the higher the treatment continuation rate is. If the duration to titrate the dose of a drug can be set correctly, we can consider a combined medication when the first drug is ineffective within the appropriate period of titration.

As more than half of the children and adults with ADHD have psychiatric comorbidities [87], physicians have to consider psychiatric symptoms beyond ADHD while setting up the

combined medication regimen. In this study, [few](#) patients with neurodevelopmental disorders such as intellectual disability were treated with combined drugs to treat behavioral problems. Based on the clinical guidelines for the treatment of ADHD for people with intellectual disability, MPH, and ATX at higher doses have shown clear benefits in behavioral and/or cognitive domains [\[243\]](#).

Results in this study should be interpreted in the context of limitations. First, as this was a retrospective study of the medical records, there were no randomly matched control groups, and the authors did not use any objective measurement tools to evaluate symptom changes or response rates for the medication. Second, there was no comparison depending on the types of MPH formulations, i.e., IR, ER, and OROS. Third, in patients over 18 years of age, there may be a problem with the stability of the data due to changes in the [HIRA insurance](#) standards during the study period. [Given these limitation, although the results of this study suggested that the combined medication for ADHD may be beneficial, a large-scale study of the mechanism, effectiveness and safety of the combination with stimulant and non-stimulant is urgently needed to ensure the generalization of the findings is possible.](#)

To the best of the authors' knowledge, this is the first study to conduct a factor analysis and indication analysis that affects the long-term follow-up of combined medication with MPH and ATX in children and adults with ADHD.

Conclusion

Combined pharmacotherapy with MPH and ATX, especially in females, would be beneficial for adherence to treatment for ADHD. Indications for combined medication are dose-limiting untoward effects, a partial response including less effectiveness with enough dosage for the bodyweight or by the limitation of dosage in the insurance policy, associated disorders, and control of non-ADHD symptoms. Further research is essential for the practice guidelines of

the combined medication for ADHD.

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Author contributions

Conceived and designed the study: Bahn GH. Performed the study: Bahn GH, Seo KH. Analyzed the data: Seo KH. Wrote the first draft of the manuscript: Bahn GH. Revision of manuscript: Bahn GH. Agree with results and conclusions and accept final manuscript: all authors.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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Table 1. Demographic and clinical characteristics according to the type of pharmacotherapy (%)

		ATX	MPH	SEP	COM	Total	p-value
Subjects and sex	Total	146 (15.7)	627 (67.5)	106 (11.4)	50 (5.4)	929 (100.0)	
	male	120(82.2)	460(74)	82(77.4)	38(76)	700	0.1543
	female	26(17.8)	167(26)	24(22.6)	12(24)	229	
Age (years)	18 <	109(74.7)	464(74)	77(72.6)	42(84)	692	0.4487
	18 ≥	37(25.3)	163(26)	29(27.4)	8(16)	237	
Outcome	Discontinuation (or dropout)	116(79.4)	509(81.2)	75(70.8)	29(58.0)	722	0.0003
	maintenance	30(20.6)	118(18.8)	31(29.2)	21(42.0)	207	
Number of OPD visit (SD)		22.7(25.5)	20.1(21.6)	39.5(36.6)	45.1(38.2)	24.1(26.6)	<0.0001
Treatment duration, year (SD)		1.87(2.28)	2.38(2.78)	3.85(2.98)	4.56(3.72)	2.58(2.88)	<0.0001

ATX: group treated with atomoxetine only, MPH: group treated with methylphenidate only, SEP: group exposed to ATX and MPH but separately used
 COM: group exposed to ATX and MPH with combined use, SD: standard deviation, OPD: outpatient department

Table 2. Statistical analysis to determine the significant way of pharmacotherapy for ADHD

variable	survival duration (year)				simple cox regression (ref. maintenance)			multiple cox regression (ref. maintenance)						
	median	CI		mean	SE	HR	CI		P-value	HR	CI		P-value	
group_	ATX and MPH	1.44	1.24	1.68	2.86	0.13	1.00	.	.	.	1.00	.	.	
	COM	5.84	2.65	10.41	6.00	0.65	0.39	0.27	0.57	<.0001	0.40	0.27	0.58	<.0001
	SEP	3.78	2.76	4.95	4.72	0.37	0.57	0.45	0.73	<.0001	0.57	0.45	0.73	<.0001
sex	Male	1.76	1.53	2.16	3.37	0.14	1.00	.	.	.	1.00	.	.	
	Female	1.61	1.24	2.15	2.88	0.23	1.15	0.97	1.37	0.0986	1.16	0.98	1.37	0.0930
age	<18	1.90	1.64	2.28	3.40	0.14	1.00	.	.	.	1.00	.	.	
	≥18	1.25	0.91	1.53	2.84	0.25	1.24	1.05	1.47	0.0137	1.21	1.02	1.44	0.0270

ATX: group treated with atomoxetine only, MPH: group treated with methylphenidate only, SEP: group exposed to ATX and MPH but separately used
 COM: group exposed to ATX and MPH with combined use, CI: confidence interval, HR: hazard ratio, SE: standard error

Table 3. Interaction analysis according to sex and age among groups

sub-group	variable	survival duration (year)				multiple cox regression (ref. maintenance)					interaction analysis*				
		median	CI		mean	SE	HR	CI		P-value	HR	CI		P-value	
ATX and MPH	Male	1.47	1.23	1.74	2.99	0.15	1.00	.	.	.	1.00	.	.	.	
	Female	1.41	0.85	1.85	2.46	0.22	1.18	0.98	1.41	0.0772		.	.	.	
COM	Sex	Male	5.36	1.76	8.75	5.51	0.70	1.00	.	.	.	0.34	0.12	0.99	0.0481
	Female	10.67	0.43	ND	7.92	1.56	0.19	0.05	0.70	0.0131					
SEP	Male	3.78	3.00	6.70	4.95	0.42	1.00	.	.	.	1.16	0.65	2.04	0.6190	
	Female	2.94	0.73	5.30	3.77	0.70	1.53	0.88	2.66	0.1302					
ATX and MPH	Age (years)	<18	1.62	1.38	1.87	2.98	0.15	1.00	.	.	.	1.00	.	.	.
		≥18	1.10	0.72	1.36	2.50	0.25	1.21	1.01	1.46	0.0410				
COM	<18	7.53	2.87	10.41	6.40	0.68	1.00	.	.	.	1.60	0.60	4.30	0.3505	
	≥18	0.91	0.10	ND	1.14	0.35	6.85	1.94	24.25	0.0029					
SEP	<18	3.67	2.68	5.30	4.79	0.43	1.00	.	.	.	0.87	0.50	1.51	0.6222	
	≥18	3.78	2.15	7.05	4.18	0.57	1.17	0.69	1.99	0.5653					

*wilcoxon rank sum test, adjusted by age, sex

ATX: group treated with atomoxetine only, MPH: group treated with methylphenidate only, SEP: group exposed to ATX and MPH but separately used

COM: group exposed to ATX and MPH with combined use, CI: confidence interval, HR: hazard ratio, SE: standard error

N.D.: not detected

Table 4. Reasons for drug combination among 21 long-term follow-up patients in group COM*

Reason for combination	Number of comments†
Untoward effects	
Depressive mood	4
Irritability	4
Appetite loss	3
Psychotic change	2
Somatic symptoms	2
[blunting of effect] Zombie like changes	1
Less effective with enough dosage for body weight	7
Associated disorders	6
Non-ADHD symptom control	3

*COM: combined use of methylphenidate and atomoxetine

†Comments about the reason for combination can be duplicated per person