Original Article
https://doi.org/10.9758/cpn.2022.20.1.143 pISSN 1738-1088 / eISSN 2093-4327
Clinical Psychopharmacology and Neuroscience 2022;20(1):143-153

Comparison between Atomoxetine and OROS Methylphenidate as an Adjunctive to SSRIs in Attention-deficit/Hyperactivity Disorder Adults with Comorbid Partially Responsive Major Depressive Disorder: A Head-to-head, 12-week, Randomized, Rater-blinded Clinical Trial

Se-hoon Shim[1,*], Young Sup Woo[2,*], Ji Sun Kim[1], In Soo Heo[1], Hee-jung Yoon[3], Hyung Mo Sung[4], Jonghun Lee[5], Won-Myong Bahk[2]

[1]Department of Psychiatry, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan, [2]Department of Psychiatry, College of Medicine, The Catholic University of Korea, [3]Korean Society of Infectious Diseases, Seoul, [4]Department of Psychiatry, Soonchunhyang University Gumi Hospital, Soonchunhyang University College of Medicine, Gumi, [5]Department of Psychiatry, Daegu Catholic University School of Medicine, Daegu, Korea

Objective: This study aimed to compare the efficacy and safety of atomoxetine (ATX) and OROS methylphenidate (MPH) as adjunctive to selective serotonin reuptake inhibitors (SSRIs) in adults with attention-deficit hyperactivity disorder (ADHD) with comorbid partially responsive major depressive disorder (MDD).
Methods: Sixty Korean adults with ADHD and comorbid partially responsive MDD were recruited in a 12-week, randomized, rater-blinded, active-controlled trial and were evenly randomized to ATX or OROS MPH treatment.
Results: Depressive symptoms measured using the Hamilton Depression Rating Scale and Clinically Useful Depression Outcome Scale, and ADHD symptoms measured using the Adult ADHD Self-Report Scale, as well as the Clinical Global Impression-Severity, Clinical Global Impression-Improvement, and the Sheehan Disability Scale scores were significantly improved in both groups during the 12 weeks of treatment. The changes in all outcome measures during the 12-week treatment were not significantly different between the two groups (all $p > 0.05$). No serious adverse events were reported and there were no significant differences in systolic and diastolic blood pressure, pulse rate, weight, or body mass index between the ATX and MPH groups.
Conclusion: Our findings suggest that ATX and MPH can be used as adjunctive treatments in adults with ADHD and comorbid partially responsive MDD. The efficacy and tolerability of ATX and MPH in adults with ADHD did not differ significantly. Further studies should be conducted to draw a definitive conclusion.

KEY WORDS: Depression; Attention-deficit hyperactivity disorder; Atomoxetine; OROS methylphenidate; SSRIs.

INTRODUCTION

Major depressive disorder (MDD) is a common mental health disorder that leads to morbidity and severe functional and cognitive impairments [1-3]. Monotherapeutic antidepressants, including selective serotonin reuptake inhibitors (SSRIs), are effective treatment options for MDD. However, they often demonstrate insufficient therapeutic efficacy [4]. In Step 1 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 1,776 of 3,671 patients had a Quick Inventory of Depressive Symptomatology-defined response, and the STAR*D reported a 48.6% response rate [5]. Furthermore, the remission rate is quite low; only 25% to 35% of all patients treated for MDD have been in symptom remission with antidepressant monotherapy [6].

Received: February 1, 2021 / **Revised:** February 26, 2021
Accepted: February 27, 2021
Address for correspondence: Won-Myong Bahk
Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10 63-ro, Yeongdeungpo-gu, Seoul 07345, Korea
E-mail: wmbahk@catholic.ac.kr
ORCID: https://orcid.org/0000-0002-0156-2510
*These authors contributed equally to this study.

Poor treatment outcomes in depression are associated with various risk factors. One of the major risk factors is comorbid psychiatric illnesses. MDD is accompanied by cognitive dysfunction, anxiety, somatic symptoms, and other clinically relevant symptoms and illnesses, which reinforces the need for polypharmacy or personalization of treatment strategies in patients with MDD [7,8].

Approximately one-fourth of adolescents with MDD respond poorly to initial antidepressant treatment. Psychiatric comorbidities of attention-deficit hyperactivity disorder (ADHD) may increase the risk of treatment resistance in adolescents with MDD, which is considered treatment-resistant depression (TRD) [9,10]. Therefore, treatment strategies for augmentation or combination therapy with different pharmacological interventions are recommended.

ADHD is a pervasive, complex, and heterogeneous disorder. Population surveys have estimated the prevalence of ADHD in adults to be 4.4% [11-13]. Adults with ADHD have a greater risk of developing psychiatric disorders. Most adults with ADHD can exhibit one or more comorbid psychiatric disorders during their lifetime [14]. Approximately 65% to 89% of all patients with ADHD experience one or more psychiatric disorders [15]. Adult ADHD is significantly comorbid with a wide range of psychiatric disorders. ADHD and MDD co-occur frequently, with the prevalence rates of depression in individuals with ADHD ranging from 18.6% to 53.3% [13,16]. In addition, the prevalence rate of comorbid ADHD in individuals with depression ranges from 9% to 16% [11], with a mean rate of 7.8% [17]. A recent study reported that 28% of individuals referred to a tertiary clinic for mood and anxiety assessment could not detect ADHD [18]. In addition, 34% of patients referred for TRD met the criteria for ADHD with predictors of this comorbidity (e.g., SSRI failure and chronic anhedonia) [19]. Stress, depression, and anxiety can manifest due to undiagnosed and untreated ADHD [20]. Many patients with ADHD receive treatment for comorbid mood disorders, but not ADHD [21]. Overall, these challenges have contributed to the underdiagnosis and undertreatment of adult ADHD [22]. Therefore, when a clinician treats depression, if a patient does not respond adequately to an antidepressant medication, consideration should be given to re-evaluating both the depression and ADHD diagnoses and, if appropriate, initiating ADHD treatment [11].

An extended-release formulation of methylphenidate (OROS MPH; Concerta) has been approved for attention deficit disorder. Atomoxetine (ATX) is a selective noradrenaline reuptake inhibitor that has been studied for use in the treatment of ADHD. It is the first nonstimulant approved by the Food and Drug Administration for the treatment of ADHD. The existing medical treatment of ADHD in adults primarily involves psychostimulants and ATX, and prescriptions of ADHD medications are increasing [23].

The Canadian Network for Mood and Anxiety Treatments task force [17] recommends combining an SSRI and a long-acting stimulant for patients with MDD and comorbid ADHD. Furthermore, ATX can be used effectively and safely with SSRIs in the treatment of adult patients with ADHD and comorbid generalized anxiety disorder [24]. To the best of our knowledge, no head-to-head comparison study of OROS MPH and ATX in adult patients with ADHD and comorbid partially responsive MDD has been conducted.

This study aimed to directly compare the treatment response between ATX combination and OROS MPH combination in adult patients with ADHD and comorbid partially responsive MDD in a head-to-head, 12-week, randomized, rater-blinded clinical trial.

METHODS

Participants

Eligible patients diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria and those who did not respond or only partially responded to 8−12 weeks of treatment with an SSRI in recommended doses were considered for this study. Partial response was defined as a Hamilton Depression Rating Scale (HAMD) score of >16 at the beginning of the study (before adding ATX or OROS MPH as an adjunctive treatment) [25]. At baseline, the participants were ≥ 19 and ≤ 65 years of age and were on one of the following SSRIs: escitalopram, sertraline, or fluoxetine. Among them, only patients who met the DSM-5 criteria for adult ADHD were included in the present study. The diagnosis of adult ADHD was established based on the childhood history of symptoms and existing symptoms, disability, associated ratings, and self-reports of symptom severity. Further, the diagnosis was con-

firmed using the Mini-International Neuropsychiatric Interview. Patients with bipolar disorders, substance abuse disorders, eating disorders, or suicidal patients were excluded from this study.

Prior to the addition of ATX or OROS MPH, 51 of the recruited patients (85%) responded partially to the maximum recommended dose of SSRI escitalopram 10−20 mg/day, four patients (6.6%) responded partially to sertraline 150−200 mg/day, and two patients (3.3%) responded partially to fluoxetine 40 mg/day.

Study Design and Procedures

This study was a 12-week, prospective, randomized, rater-blinded, active-controlled trial conducted between January 2018 and December 2019 at three university hospitals in the Republic of Korea. Maintenance of the existing dose of the drug during the study period was recommended for patients who were on SSRIs; however, in case of tolerability and lack of effectiveness, the dose could be adjusted according to the judgment of the investigator within the dose range within the approved standard. Eligible patients were randomized in a 1:1 ratio to one of two treatment arms: OROS MPH (MPH group) or ATX (ATX group). Drug dosages and titration schedules were based on the recommendations of the prescribing information for each product and according to the judgment of the clinicians involved in the study (Table 1). No other psychotropic drugs were permitted during the study period, except for benzodiazepines (up to 2 mg/day of lorazepam or equivalent).

Assessments

Study patients were assessed at the following five time points: baseline, week 2, week 4, week 6, week 8, and week 12. The main outcome measure was the 17-item HAMD [26] and 18-item Korean version of the World Health Organization Adult ADHD Self-Report Scale (ASRS) [27]. Other instruments used were the Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I), Clinically Useful Depression Outcome Scale (CUDOS) [28], and the Sheehan Disability Scale (SDS) [29]. All assessors received the same investigator training module and were blinded to the patients' conditions and prescribed medications. Safety was assessed via adverse events (AEs), vital signs, weight, and physical examination findings at each visit. The AEs during the study period were recorded by clinical research coordinators using the Udvalg for Kliniske Undersogelser Side-Effect Rating Scale [30], and were further evaluated for severity and the causal relationship to the study drug.

Table 1. The average atomoxetine and osmotic release oral system methylphenidate dose

Visit	Atomoxetine (mg) (male/female)	Methylphenidate (mg) (male/female)
Baseline	32.8 ± 7.4 (33.3/31.4)	27.3 ± 1.6 (26.9/30.9)
12 weeks	65.1 ± 15.1 (59/80)	56.6 ± 16.5 (56.3/58.5)

Values are presented as mean ± standard deviation (mean only).

Statistical Analysis

The sociodemographic and baseline clinical characteristics were compared between the ATX and MPH groups using the chi-square test and independent t test. The changes in scores in efficacy and safety variables, including vital signs, weight, and body mass index (BMI) within groups were analyzed using one-way repeated measures analysis of variance (RM-ANOVA) with Bonferroni multiple comparison test. The RM-ANOVA with covariates (age, sex, and smoking) was performed to compare the differences in changes in all efficacy variables between the two groups. The chi-square test or Fisher's exact test was used to compare the HAMD and CGI-S response rates between the groups at each visit. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the SPSS 21.0 (IBM Co., Armonk, NY, USA).

Ethics

The study protocol complied with the current amendment of the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. All participants provided written informed consent before participating in the study. The study protocol was approved by the Institutional Review Board at all research sites (The Soonchunhyang University Cheonan Hospital (No. 2018-01-024)).

RESULTS

Demographic and Clinical Characteristics Data

Sixty participants were enrolled from three university hospitals. Among them, 28 and 32 participants were randomized to the ATX and MPH groups, respectively (Fig. 1). The demographic and clinical characteristics of the participants are shown in Table 2. There were no significant differences between the two groups in terms of demographic and clinical characteristics and baseline HAMD, ASRS, CUDOS, CGI-S, CGI-I, and SDS scores, except that the proportion of smokers was significantly higher in the MPH group (65.6%, n = 21) than in the ATX group (35.7%, n = 10; $p = 0.021$).

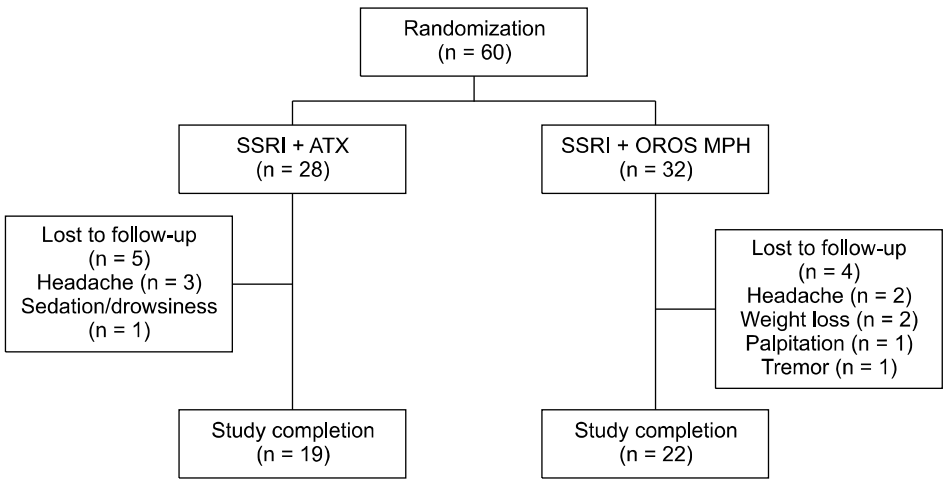

Fig. 1. Subject disposition.
SSRI, selective serotonin reuptake inhibitor; ATX, atomoxetine; OROS, osmotic release oral system; MPH, methylphenidate.

Table 2. Baseline demographic and clinical characteristics

Variable	SSRI + ATX (n = 28)	SSRI + OROS MPH (n = 32)	Significance
Age (yr)	23.1 ± 5.6	23.3 ± 5.9	0.924
Male	20 (71.4)	28 (87.5)	0.121
Drinkers	22 (78.6)	24 (75.0)	0.744
Smokers	10 (35.7)	21 (65.6)	0.021*
Education (yr)	12.3 ± 1.3	12.7 ± 1.6	0.277
Duration of current episode (mo)	6.6 ± 3.2	5.8 ± 5.8	0.525
Duration of illness (yr)	3.5 ± 3.2	3.5 ± 2.8	0.963
Mean dose of ATX/MPH (initial, mg/day)			
At baseline	32.8 ± 7.4	27.3 ± 1.6	NA
At week 12	65.1 ± 15.1	56.6 ± 16.5	NA
CGI-S	4.4 ± 0.7	4.4 ± 0.8	0.930
CGI-I	4.0 ± 0.2	4.0 ± 0.0	0.326
HAMD	22.5 ± 6.7	20.9 ± 3.4	0.250
ASRS	42.6 ± 12.6	42.0 ± 12.2	0.849
SDS	18.7 ± 6.0	20.4 ± 6.0	0.262
CUDOS	37.6 ± 14.0	36.8 ± 13.8	0.826
BMI (kg/m^2)	24.0 ± 5.0	24.3 ± 5.4	0.808
SBP (mmHg)	122.8 ± 9.8	126.2 ± 15.1	0.317
DBP (mmHg)	77.3 ± 6.6	79.6 ± 8.8	0.256

Values are presented as mean ± standard deviation or number (%).
SSRI, selective serotonin reuptake inhibitor; ATX, atomoxetine; OROS, osmotic release oral system; MPH, methylphenidate; CGI-S, Clinical Global Impression-Severity; CGI-I, Clinical Global Impression-Improvement; HAMD, Hamilton Depression Rating Scale (17-item); ASRS, Adult ADHD Self-Report Scale; SDS, Sheehan Disability Scale; CUDOS, Clinically Useful Depression Outcome Scale; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NA, not applicable.
*$p < 0.05$.

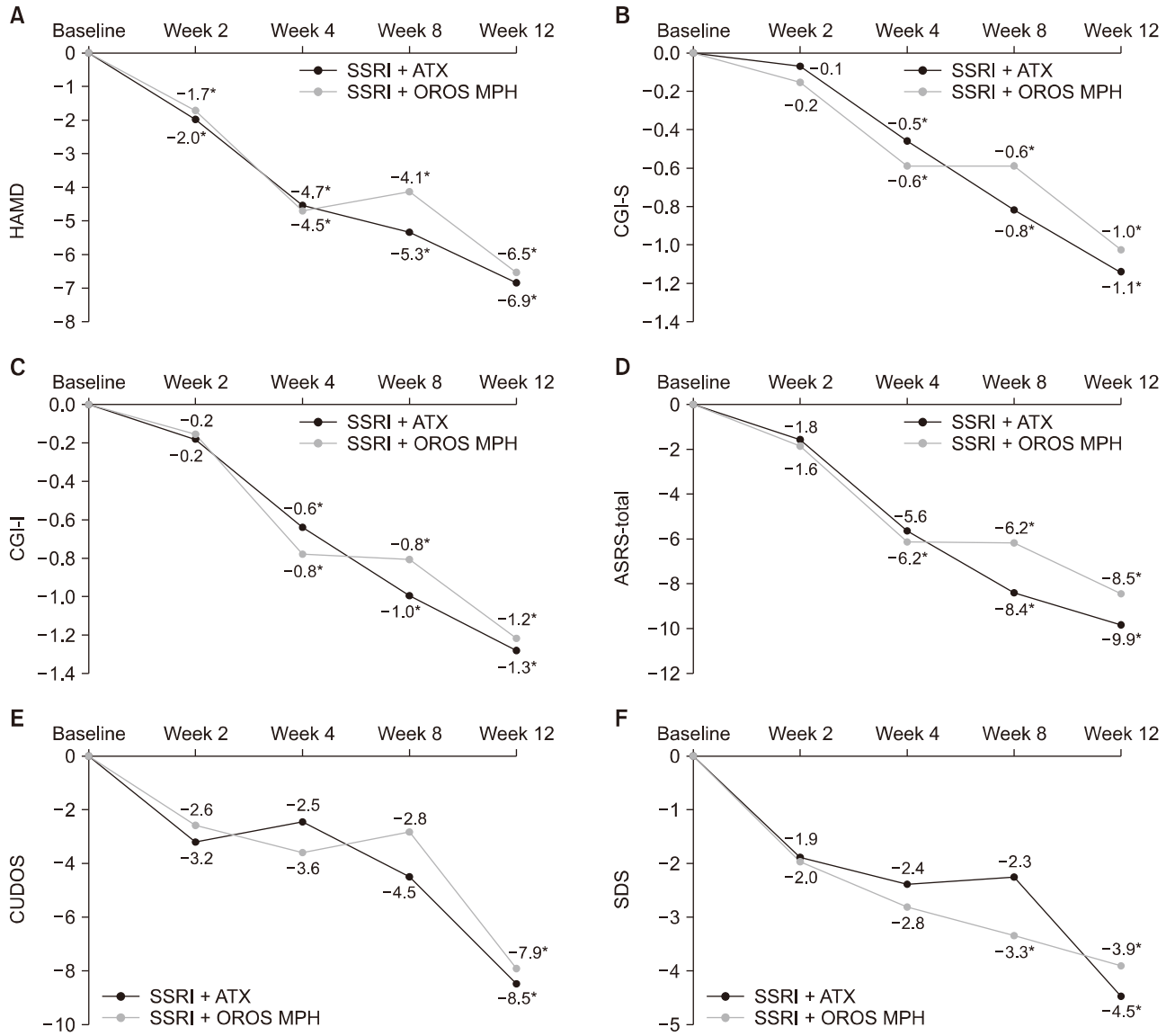

Fig. 2. Changes in mean differences from baseline scores for (A) HAMD, (B) CGI-S, (C) CGI-I, (D) ASRS, (E) CUDOS and (F) SDS during the study. HAMD, Hamilton Depression Rating Scale (17-item); CGI-S, Clinical Global Impression-Severity; CGI-I, Clinical Global Impression-Improvement; ASRS, Adult ADHD Self-Report Scale; CUDOS, Clinically Useful Depression Outcome Scale; SDS, Sheehan Disability Scale; SSRI, selective serotonin reuptake inhibitor; ATX, atomoxetine; OROS, osmotic release oral system; MPH, methylphenidate.
*Significant difference from baseline scores ($p < 0.05$, RM-ANOVA with Bonferroni post hoc test).

Efficacy

In both the ATX and MPH groups, the changes in the mean scores of all efficacy variables including HAMD, CGI-S, CGI-I, ASRS, CUDOS, and SDS from baseline to endpoint were significant (all $p < 0.05$, Fig. 2). The reduction in the HAMD score was significant at all visits when compared with baseline values, and the reductions in the CGI-S and CGI-I scores were significant from week 4 onwards in both groups. The change in the CUDOS score was significant only at week 12 in both groups. However, reductions in ASRS scores reached a significant difference at week 8 in the ATX group, unlike the MPH group, which attained significance at week 4. Moreover, reductions in SDS scores from baseline were not significant until week 8 in the ATX group, while those of the MPH group were significant from week 8 to week 12 (Fig. 2). However, there were no significant differences in the changes in all efficacy variables between the treatment

Table 3. The changes on the HAMD, CGI-S, CGI-I, ASRS, CUDOS and SDS total scores from baseline during the study

Visit		SSRI + ATX (n = 28)	SSRI + OROS MPH (n = 32)	Significance
HAMD	Week 2	−1.964 ± 2.646	−1.719 ± 2.976	0.956
	Week 4	−4.536 ± 4.384	−4.719 ± 4.726	
	Week 8	−5.321 ± 6.189	−4.125 ± 5.222	
	Week 12	−6.857 ± 5.183	−6.531 ± 4.958	
CGI-S	Week 2	−0.071 ± 0.378	−0.156 ± 0.448	0.691
	Week 4	−0.464 ± 0.693	−0.594 ± 0.712	
	Week 8	−0.821 ± 0.983	−0.594 ± 0.712	
	Week 12	−1.143 ± 1.044	−1.031 ± 0.933	
CGI-I	Week 2	−0.179 ± 0.612	−0.156 ± 0.515	0.934
	Week 4	−0.643 ± 0.826	−0.781 ± 0.906	
	Week 8	−1.000 ± 0.861	−0.813 ± 1.091	
	Week 12	−1.286 ± 0.937	−1.219 ± 1.099	
ASRS	Week 2	−1.571 ± 8.324	−1.844 ± 5.519	0.803
	Week 4	−5.643 ± 10.601	−6.156 ± 10.093	
	Week 8	−8.429 ± 11.445	−6.219 ± 11.675	
	Week 12	−9.857 ± 12.492	−8.469 ± 10.907	
CUDOS	Week 2	−3.214 ± 9.327	−2.594 ± 5.435	0.968
	Week 4	−2.464 ± 11.574	−3.625 ± 8.027	
	Week 8	−4.500 ± 11.702	−2.844 ± 10.623	
	Week 12	−8.464 ± 11.338	−7.906 ± 7.892	
SDS	Week 2	−1.893 ± 3.478	−1.969 ± 4.707	0.812
	Week 4	−2.393 ± 5.990	−2.813 ± 5.462	
	Week 8	−2.250 ± 6.513	−3.344 ± 6.003	
	Week 12	−4.464 ± 7.623	−3.906 ± 6.827	

Values are presented as mean ± standard deviation.
HAMD, Hamilton Depression Rating Scale (17-item); CGI-S, Clinical Global Impression-Severity; CGI-I, Clinical Global Impression-Improvement; ASRS, Adult ADHD Self-Report Scale; CUDOS, Clinically Useful Depression Outcome Scale; SDS, Sheehan Disability Scale; SSRI, selective serotonin reuptake inhibitor; ATX, atomoxetine; OROS, osmotic release oral system; MPH, methylphenidate.

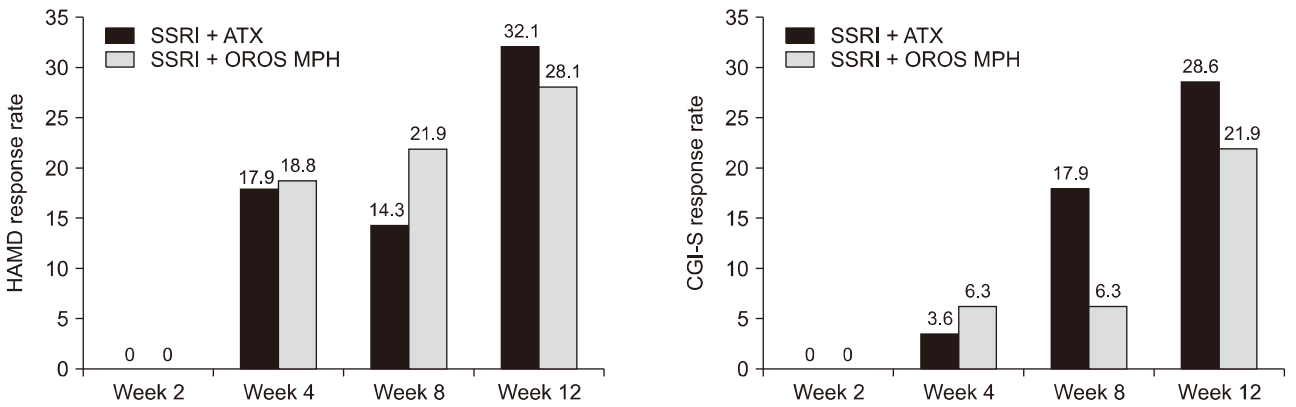

Fig. 3. The response rates by HAMD and CGI-S between the ATX and MPH groups during the study.
HAMD, Hamilton Depression Rating Scale (17-item); CGI-S, Clinical Global Impression-Severity; SSRI, selective serotonin reuptake inhibitor; ATX, atomoxetine; OROS, osmotic release oral system; MPH, methylphenidate.

groups during the 12-week study period by RM-ANOVA adjusted for age, sex, and smoking (Table 3, all $p > 0.05$). The HAMD and CGI-S response rates at each visit were not significantly different between the two groups (Fig. 3, all $p > 0.05$).

Safety and Tolerability

Nine participants in the ATX group (32.1%) and 10 in the MPH group (31.3%) did not complete the study. The main reason for incompletion was "lost to follow-up" (five patients in the ATX group and four patients in the MPH

group). Seventeen patients (28.3%) experienced AEs. Four and six patients in the ATX and MPH groups, respectively, discontinued the study owing to AEs. Furthermore, the AEs that caused discontinuation of the study were headache (n = 3) and sedation/drowsiness (n = 1) in the ATX group, and headache (n = 2), weight loss (n = 2), palpitation (n = 1), and tremor (n = 1) in the MPH group. The reported AEs are shown in Table 4. No serious AEs were reported, and all AEs were transient and mild or moderate in severity.

Table 4. Commonly reported adverse events during the study period

Adverse event	Total (n = 60)	SSRI + ATX (n = 28)	SSRI + OROS MPH (n = 32)
Nausea/vomiting	7 (11.7)	3 (10.7)	4 (12.5)
Orthostatic dizziness	5 (8.3)	2 (7.1)	3 (9.4)
Headache	5 (8.3)	3 (10.7)	2 (6.3)
Tremor	2 (3.3)	0 (0)	2 (6.3)
Reduced salivation	2 (3.3)	1 (3.6)	1 (3.1)
Sedation/drowsiness	2 (3.3)	1 (3.6)	1 (3.1)
Palpitation	2 (3.3)	0	2 (6.3)
Weight loss	2 (3.3)	0	2 (6.3)
Diarrhea	1 (1.7)	1 (3.6)	0
Constipation	1 (1.7)	1 (3.6)	0
Weight gain	1 (1.7)	0	1 (3.1)

Values are presented as number (%).
SSRI, selective serotonin reuptake inhibitor; ATX, atomoxetine; OROS, osmotic release oral system; MPH, methylphenidate.

Table 5. Changes in SBP, DBP, pulse, weight and BMI during the study

Visit		SSRI + ATX (n = 28)			SSRI + OROS MPH (n = 32)		
		Mean	SD	Significance	Mean	SD	Significance
SBP (mmHg)	Baseline	122.8	9.4	0.290	126.2	15.1	0.339
	Week 2	121.0	10.9		124.3	14.3	
	Week 4	119.7	10.7		123.0	15.8	
	Week 8	123.4	10.6		125.0	13.4	
	Week 12	121.6	8.9		124.4	14.4	
DBP (mmHg)	Baseline	77.3	6.7	0.758	79.6	8.8	0.763
	Week 2	76.8	6.0		78.5	6.5	
	Week 4	78.0	8.2		78.2	6.7	
	Week 8	77.4	7.0		79.0	6.3	
	Week 12	76.9	6.3		79.2	7.4	
Pulse (bpm)	Baseline	77.6	16.7	0.277	82.4	17.3	0.725
	Week 2	81.4	23.3		80.9	17.8	
	Week 4	83.0	24.9		82.7	18.5	
	Week 8	80.5	20.8		83.0	17.7	
	Week 12	80.6	22.0		82.4	18.7	
Weight (kg)	Baseline	69.3	14.7	0.441	72.3	18.8	0.304
	Week 2	69.2	14.7		71.3	17.7	
	Week 4	69.2	14.5		71.4	17.9	
	Week 8	68.3	16.2		71.4	18.1	
	Week 12	69.3	15.0		71.9	18.6	
BMI (kg/m^2)	Baseline	24.0	5.0	0.428	24.3	5.4	0.316
	Week 2	24.0	4.9		24.0	5.1	
	Week 4	24.0	4.9		24.1	5.2	
	Week 8	23.6	5.4		24.1	5.2	
	Week 12	24.0	5.0		24.2	5.4	

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; SSRI, selective serotonin reuptake inhibitor; ATX, atomoxetine; OROS, osmotic release oral system; MPH, methylphenidate; SD, standard deviation.

During the 12-week study, there were no significant changes in systolic and diastolic blood pressure, pulse rate, weight, or BMI in either group (Table 5).

DISCUSSION

In this study, the combination of ATX and OROS MPH with an SSRI significantly improved all efficacy variables at the end point of the study (week 12) compared to the baseline in adult patients with ADHD and comorbid partially responsive MDD who failed to respond sufficiently to treatment with an SSRI. Similar to the present study, in a large, population-based cohort study [31], ADHD medication including ATX and MPH was associated with a reduced long-term risk of depression and reduced rates of concurrent depression.

To the best of our knowledge, this study is the first to compare the treatment response between ATX combination and OROS MPH combination and to investigate the changes in the profile of depressive and ADHD symptoms and the tolerability to adjunctive treatments of OROS MPH or ATX to SSRIs in adult patients with ADHD and comorbid partially responsive MDD.

In this study, for both groups, the HAMD scores started to significantly decrease by week 2, and there were point reductions in the HAMD scores from 22.5 and 20.9 to 15.6 and 14.4 in the ATX and MPH groups, respectively. After the addition of ATX or MPH, the HAMD score was 16 or less, with a marked reduction in both groups. At the end point, the HAMD response rates were 32.1% and 28.1% in the ATX and MPH groups, respectively.

Two open-label trials have demonstrated improved outcomes with the use of an SSRI along with a psychostimulant in the treatment of ADHD and comorbid MDD [32,33]. In the former trial, comorbid patients who had mood symptoms that improved with an SSRI experienced improvement in ADHD symptoms only when a psychostimulant was added to the antidepressant. In the latter trial, comorbid patients who had inadequate therapeutic responses to MPH alone had positive therapeutic responses in ADHD and depressive symptoms with administration of concomitant fluoxetine.

In a randomized, flexible-dose, double-blinded, placebo-controlled study to evaluate the efficacy and safety of augmentation with extended-release MPH in patients with TRD, numerically more patients responded to MPH than to placebo [34]. Another open-level study of standard antidepressant augmentation with ATX indicated that ATX is beneficial in reducing depressive symptoms in some patients who had a partial response or no response to antidepressant trials [35]. However, these studies did not assess comorbid ADHD, and it is possible that patients with such comorbidities could have shown a more favorable response.

In a recent study on the safety and effectiveness of ATX monotherapy compared with combined ATX and fluoxetine therapy in children and adolescents with ADHD and concurrent symptoms of depression, reductions in depressive symptoms were greater in the combined group. The completion rates for the two groups were similar, as were the discontinuation rates for AEs. The data presented indicate that if a child is already being treated with fluoxetine, the addition of ATX is clinically warranted [36].

Therefore, the results of these previous studies indicate that ATX and OROS MPH combination may help to improve refractory comorbid depressive symptoms. These results are consistent with the results of this study, which reported a significant improvement in adjunctive treatments of OROS MPH or ATX to SSRIs in adult patients with ADHD and comorbid partially responsive MDD. However, more studies are warranted to evaluate the antidepressant adjunctive effect of ATX or OROS MPH by treating comorbid ADHD or by antidepressant augmentation action.

An SSRI alone is not expected to improve ADHD symptoms, which typically respond to catecholaminergic agents, such as ATX or MPH. In this study, the ASRS scores at baseline in both the ATX and MPH groups were maintained at 42.6 and 42, respectively, despite adequate treatment with an SSRI; both scores were higher than the optimal cutoff score of 32 [27]. After the combination of ATX and MPH with an SSRI, the ASRS scores in the ATX group and the MPH group started to significantly decrease by week 8 and week 4, respectively. However, the ASRS scores in both groups were near the cutoff point at the endpoint, with a significant reduction from baseline.

Despite the lack of head-to-head clinical studies powered to compare ATX and OROS MPH, consistent with this result, according to a network meta-analysis of ATX and OROS MPH in the treatment of attention-deficit/hyperactivity disorder in adult patients, there was no significant difference in discontinuation rates between

ATX and OROS MPH. Moreover, the efficacy of ATX and OROS MPH in adults did not differ significantly [37].

No major safety issues associated with combining ATX or OROS MPH with therapeutic doses of SSRIs were noted. The addition of ATX or OROS MPH with SSRIs did not increase the side-effect profile. Overall, the dropout rate was low, and dropouts due to AEs were comparable between the two groups. Clinicians should be careful when administering MPH or ATX with SSRIs because of the potential for pharmacokinetic interactions. However, in this study, both drugs were gradually titrated as tolerated. Consistent with this study, combining extended-release MPH with therapeutic doses of various antidepressants [34] and adjunctive treatment of ATX with an SSRI were safe and tolerable [24].

The CUDOS is a useful tool for screening depression because it fully covers the DSM-IV symptoms of MDD and dysthymic disorder [38]. The ability of the Korean version of CUDOS to discriminate among different levels of depression severity was significant, and the measure was sensitive to change after treatment [28]. In this study, there were point reductions in the CUDOS scores from 37.6 and 36.8 to 29.1 and 28.9 in the ATX and MPH groups, respectively. After adding ATX or OROS MPH, both groups were mitigated from moderate to mild depression in five categories in the empirically derived range of the depression severity of the CUDOS.

This study reported that there were significant differences in the HAMD, ASRS, CGI-S, and CGI-I scores from week 4, and there were significant differences at 12 weeks in the CUDOS and SDS scores. In line with this study, two rater-blinded, randomized comparative studies also reported delayed efficacy on the CUDOS compared to the HAMD (Lee et al., unpublished observations, Shin et al., unpublished observations). Furthermore, these previous studies assessed the functional aspects of depression and sensitively evaluated the remission of depression and its residual symptoms [39].

Limitations

There are a number of limitations that should be considered when interpreting the results of this study. First, this study had a small sample size. Another limitation of this study was the lack of a placebo arm. Hence, this study was unable to detect the placebo response rate and to exclude the possibility of an improvement in depressive symptoms as a part of the natural course of the disease. The absence of an inter-rater reliability assessment was another limitation of this study. Finally, because most of the patients included in this study were treated with escitalopram (85.0%), the results of this study did not infer the effectiveness and tolerability of ATX or OROS MPH combined with other SSRIs.

As a safe and effective adjunctive therapy to SSRIs in adults with ADHD and comorbid partially responsive MDD, ATX combination and OROS MPH combination would be the relevant treatment strategies. The results of this randomized, rater-blinded, 12-week, prospective, head-to-head comparison study demonstrated a significant improvement in ADHD and depressive symptoms in adult patients with ADHD and comorbid partially responsive MDD, which were well tolerated. There were no significant differences in the changes in all efficacy variables and in the HAMD and CGI-S response rates between the treatment groups. Further, controlled studies with double-blind designs are needed to better understand the relationship between ADHD and depressive disorders.

■ Funding

None.

■ Acknowledgments

This work was supported by a grant (2020R1I1A3A04036435) of the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education and a grant (2020R1I1A3068017) of the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education. This study was also supported by Soonchunhyang University.

■ Conflicts of Interest

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

■ Author Contributions

Se-hoon Shim and Young Sup Woo had full access to all study data, and take responsibility for the integrity of the data and accuracy of data analysis. Se-hoon Shim, Young Sup Woo, Ji Sun Kim, Hee-jung Yoon, In Soo Heo, Hyung Mo Sung, Jonghun Lee, and Won-Myong Bahk drafted the manuscript. All authors developed the study

concept and design, and aided in data interpretation, as well as critical revisions of the manuscript. Se-hoon Shim and Won-Myong Bahk reviewed the manuscript. All authors approved the final version of the paper for submission.

■ **ORCID**

Se-hoon Shim https://orcid.org/0000-0002-3137-6591
Young Sup Woo https://orcid.org/0000-0002-0961-838X
Ji Sun Kim https://orcid.org/0000-0003-2472-4591
In Soo Heo https://orcid.org/0000-0003-3236-5744
Hee-jung Yoon https://orcid.org/0000-0001-9860-4774
Hyung Mo Sung https://orcid.org/0000-0002-2396-3358
Jonghun Lee https://orcid.org/0000-0002-3581-5029
Won-Myong Bahk https://orcid.org/0000-0002-0156-2510

REFERENCES

1. Spijker J, Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA. *Functional disability and depression in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Acta Psychiatr Scand 2004;110:208-214.*
2. Russo M, Mahon K, Burdick KE. *Measuring cognitive function in MDD: emerging assessment tools. Depress Anxiety 2015;32:262-269.*
3. Zuckerman H, Pan Z, Park C, Brietzke E, Musial N, Shariq AS, *et al. Recognition and treatment of cognitive dysfunction in major depressive disorder. Front Psychiatry 2018;9:655.*
4. Fabbri C, Serretti A. *Genetics of treatment outcomes in major depressive disorder: present and future. Clin Psychopharmacol Neurosci 2020;18:1-9.*
5. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, *et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905-1917.*
6. Crown WH, Finkelstein S, Berndt ER, Ling D, Poret AW, Rush AJ, *et al. The impact of treatment-resistant depression on health care utilization and costs. J Clin Psychiatry 2002;63:963-971.*
7. Nelson JC, Pikalov A, Berman RM. *Augmentation treatment in major depressive disorder: focus on aripiprazole. Neuropsychiatr Dis Treat 2008;4:937-948.*
8. Fabbri C, Serretti A. *How to utilize clinical and genetic information for personalized treatment of major depressive disorder: step by step strategic approach. Clin Psychopharmacol Neurosci 2020;18:484-492.*
9. Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, editors. *Psychopharmacology: the fourth generation of progress. New York:Raven Press;1995. p.1081-1097.*
10. Chen LC, Chen YH, Bai YM, Chen TJ, Chen MH, Su TP. *Antidepressant resistance in adolescents with major depressive disorder: a nationwide longitudinal study. J Affect Disord 2020;262:293-297.*
11. McIntosh D, Kutcher S, Binder C, Levitt A, Fallu A, Rosenbluth M. *Adult ADHD and comorbid depression: a consensus-derived diagnostic algorithm for ADHD. Neuropsychiatr Dis Treat 2009;5:137-150.*
12. Faraone SV, Biederman J. *What is the prevalence of adult ADHD? Results of a population screen of 966 adults. J Atten Disord 2005;9:384-391.*
13. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, *et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry 2006;163:716-723.*
14. Adler LA, Barkley RA, Wilens TE, Ginsberg DL. *Differential diagnosis of attention-deficit/hyperactivity disorder and comorbid conditions. Prim Psychiatr 2006;13:1-14.*
15. Sobanski E. *Psychiatric comorbidity in adults with attention-deficit/hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci 2006;256 Suppl 1:i26-i31.*
16. Torgersen T, Gjervan B, Rasmussen K. *ADHD in adults: a study of clinical characteristics, impairment and comorbidity. Nord J Psychiatry 2006;60:38-43.*
17. Bond DJ, Hadjipavlou G, Lam RW, McIntyre RS, Beaulieu S, Schaffer A, *et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder. Ann Clin Psychiatry 2012;24:23-37.*
18. Sternat T, Mohamed M, Furtado M, Canzonieri A, Armata RS, Epstein I, *et al. SSRI treatment response may predict undetected attention deficit hyperactivity disorder in depressed patients. In: Anxiety and Depression Association of America (ADAA) Annual Conference; Mar 31-Apr 3, 2016; Philadelphia, USA.*
19. Sternat T, Katzman MA. *Neurobiology of hedonic tone: the relationship between treatment-resistant depression, attention-deficit hyperactivity disorder, and substance abuse. Neuropsychiatr Dis Treat 2016;12:2149-2164.*
20. Alexander SJ, Harrison AG. *Cognitive responses to stress, depression, and anxiety and their relationship to ADHD symptoms in first year psychology students. J Atten Disord 2013;17:29-37.*
21. Kooij SJ, Bejerot S, Blackwell A, Caci H, Casas-Brugué M, Carpentier PJ, *et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC Psychiatry 2010;10:67.*
22. Ginsberg Y, Quintero J, Anand E, Casillas M, Upadhyaya HP. *Underdiagnosis of attention-deficit/hyperactivity disorder in adult patients: a review of the literature. Prim Care Companion CNS Disord 2014;16:PCC.13r01600.*

23. Zetterqvist J, Asherson P, Halldner L, Långström N, Larsson H. *Stimulant and non-stimulant attention deficit/hyperactivity disorder drug use: total population study of trends and discontinuation patterns 2006-2009. Acta Psychiatr Scand 2013;128:70-77.*
24. Gabriel A, Violato C. *Adjunctive atomoxetine to SSRIs or SNRIs in the treatment of adult ADHD patients with comorbid partially responsive generalized anxiety (GA): an open-label study. Atten Defic Hyperact Disord 2011;3:319-326.*
25. Bech P. *Struggle for subtypes in primary and secondary depression and their mode-specific treatment or healing. Psychother Psychosom 2010;79:331-338.*
26. Miller IW, Bishop S, Norman WH, Maddever H. *The modified Hamilton Rating Scale for Depression: reliability and validity. Psychiatry Res 1985;14:131-142.*
27. Heo S, Kim JH, Joung YS, Lee WI, Kim JJ, Sohn SH, *et al. Clinical utility of the Korean version of the WHO adult attention-deficit/hyperactivity disorder self-report scale screener. Psychiatry Investig 2018;15:325-329.*
28. Jeon SW, Han C, Ko YH, Yoon SY, Pae CU, Choi J, et al. *Measurement-based treatment of residual symptoms using Clinically Useful Depression Outcome Scale: Korean validation study. Clin Psychopharmacol Neurosci 2017;15:28-34.*
29. Park JY, Kim JH. *Korean version of the Sheehan Disability Scale (SDS): reliability and validity. Korean J Clin Psychol 2010;29:73-81.*
30. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. *The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 1987;334:1-100.*
31. Chang Z, D'Onofrio BM, Quinn PD, Lichtenstein P, Larsson H. *Medication for attention-deficit/hyperactivity disorder and risk for depression: a nationwide longitudinal cohort study. Biol Psychiatry 2016;80:916-922.*
32. Findling RL. *Open-label treatment of comorbid depression and attentional disorders with co-administration of serotonin reuptake inhibitors and psychostimulants in children, adolescents, and adults: a case series. J Child Adolesc Psychopharmacol 1996;6:165-175.*
33. Gammon GD, Brown TE. *Fluoxetine and methylphenidate in combination for treatment of attention deficit disorder and comorbid depressive disorder. J Child Adolesc Psychopharmacol 1993;3:1-10.*
34. Patkar AA, Masand PS, Pae CU, Peindl K, Hooper-Wood C, Mannelli P, *et al. A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of methylphenidate in outpatients with treatment-resistant depression. J Clin Psychopharmacol 2006;26:653-656.*
35. Carpenter LL, Milosavljevic N, Schecter JM, Tyrka AR, Price LH. *Augmentation with open-label atomoxetine for partial or nonresponse to antidepressants. J Clin Psychiatry 2005;66:1234-1238.*
36. Kratochvil CJ, Newcorn JH, Arnold LE, Duesenberg D, Emslie GJ, Quintana H, *et al. Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety symptoms. J Am Acad Child Adolesc Psychiatry 2005;44:915-924.*
37. Bushe C, Day K, Reed V, Karlsdotter K, Berggren L, Pitcher A, *et al. A network meta-analysis of atomoxetine and osmotic release oral system methylphenidate in the treatment of attention-deficit/hyperactivity disorder in adult patients. J Psychopharmacol 2016;30:444-458.*
38. Zimmerman M, Chelminski I, McGlinchey JB, Posternak MA. *A clinically useful depression outcome scale. Compr Psychiatry 2008;49:131-140.*
39. Zimmerman M, Posternak MA, McGlinchey J, Friedman M, Attiullah N, Boerescu D. *Validity of a self-report depression symptom scale for identifying remission in depressed outpatients. Compr Psychiatry 2006;47:185-188.*