

Original Article

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Safety outcomes of selective serotonin reuptake inhibitors in adolescent attention-deficit/hyperactivity disorder with comorbid depression: *the ASSURE study*†

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Abstract

Background. Attention deficit-hyperactivity disorder (ADHD) is related to depressive disorder, and adolescents with both present poor outcomes. However, evidence for the safety of concomitantly using a methylphenidate (MPH) and a selective serotonin reuptake inhibitor (SSRI) among adolescent ADHD patients is limited, a literature gap aimed to address through this investigation.

Methods. We conducted a new-user cohort study using a nationwide claims database in South Korea. We identified a study population as adolescents who were diagnosed both ADHD and depressive disorder. MPH-only users were compared with patients who prescribed both a SSRI and a MPH. Fluoxetine and escitalopram users were also compared to find a preferable treatment option. Thirteen outcomes including neuropsychiatric, gastrointestinal, and other events were assessed, taking respiratory tract infection as a negative control outcome. We matched the study groups using a propensity score and used the Cox proportional hazard model to calculate the hazard ratio. Subgroup and sensitivity analyses were conducted in various epidemiologic settings.

Results. The risks of all the outcomes between the MPH-only and SSRI groups were not significantly different. Regarding SSRI ingredients, the risk of tic disorder was significantly lower in the fluoxetine group than the escitalopram group [HR 0.43 (0.25–0.71)]. However, there was no significant difference in other outcomes between the fluoxetine and escitalopram groups.

Conclusion. The concomitant use of MPHs and SSRIs showed generally safe profiles in adolescent ADHD patients with depression. Most of the differences between fluoxetine and escitalopram, except those concerning tic disorder, were not significant.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) carries a significantly increased risk for comorbidity with a wide range of psychiatric disorders (Reale *et al.*, 2017). In particular, ADHD is closely related to depressive disorder, with the latter indicating a 16–26% prevalence in the former (Sonnby, Åslund, Leppert, & Nilsson, 2011). Several previous studies have explored this high comorbidity rate as well as the biological linkage or causality and its clinical outcomes (Biederman *et al.*, 2008; Posner *et al.*, 2014; Riglin *et al.*, 2021). Children with both ADHD and depression have been found to be more impaired in their academic and social functioning than children with ADHD alone (Blackman, Ostrander, & Herman, 2005). Thus, the American Academy of Pediatrics recommends that clinicians assess children and adolescent patients with newly diagnosed ADHD for depression (Wolraich *et al.*, 2019).

As treatment, adolescents diagnosed with both ADHD and depression concomitantly take ADHD medications and antidepressants according to the clinical guidelines (Cheung *et al.*, 2018). Fluoxetine and escitalopram, two types of a selective serotonin reuptake inhibitor (SSRI), are the only antidepressants approved by the US Food and Drug Administration (FDA) for child and adolescent major depressive disorder (MDD) (Boaden, Tomlinson, Cortese, & Cipriani, 2020). In the UK, only fluoxetine is licensed for child and adolescent

MDD (Boaden *et al.*, 2020). However, the clinical hurdles for the use of antidepressants are concerns about adverse drug reactions such as suicidal behavior since the ‘black box warning’ issued by the FDA in 2004 (Jick, Kaye, & Jick, 2004). In previous research, the risk of suicidal behavior in patients aged 10 to 19 years increased after they began taking antidepressants (Jick *et al.*, 2004). Since then, an increasing number of studies have questioned the methodological rigor of the FDA analysis (Fornaro *et al.*, 2019). Further, antidepressants have been associated with an increased rate of manic symptoms, atrial fibrillation, and gastrointestinal symptoms (Fenger-Grøn *et al.*, 2019; Goldsmith, Singh, & Chang, 2011; Murphy, Segarra, Storch, & Goodman, 2008), and the augmentation of a SSRI with a methylphenidate (MPH) is believed to affect serotonin syndrome and MPH addiction (Ishii, Tatsuzawa, Yoshino, & Nomura, 2008; Van Waes, Ehrlich, Beverley, & Steiner, 2015). Nonetheless, evidence for the safety evaluation of concomitant ADHD medications and antidepressants use among in adolescents is sparse.

Based on the above, we aimed to evaluate the safety of the concomitant use of SSRIs, the first recommended drug for adolescent depression, in ADHD patients using MPHs through a comparative effectiveness research to establish real-world evidence for such medication use safety. Furthermore, we aimed to execute a head-to-head study comparing the safety outcomes between the SSRI types – fluoxetine and escitalopram.

Methods

Study design and database

This is a retrospective observational cohort study, which used a nationwide administrative claims database in South Korea [Health Insurance Review and Assessment service (HIRA)] from Jan 2016 to Mar 2021. The HIRA database contains complete health information for the Korean population, including anonymized personal identifiers, demographics, diagnoses, and information on medical procedures and medications in the national reimbursement lists. The HIRA database was standardized to Observational Medical Outcomes Partnership common data model (OMOP-CDM) version 5.3.

The study protocol was pre-specified before execution and registered with the EU Post-Authorization Studies register under EUPAS44893 (see Supplement 1). According to this protocol, the study package for the entire process was released in an online repository for transparency of analyses (<https://github.com/ABMI/Assure>). Analyses of de-identified data were performed in accordance with local laws and regulation and with approval from respective scientific and ethics committees (Ajou University Medical Center Institutional Review Board: AJIRB-MED-EXP-21-88).

Study population and exposure

All detailed code lists are presented in Table S1 (see Supplement 2). For the study population, we identified adolescent (aged 10–19 years) MPH users with ADHD and depressive disorder diagnoses. To avoid any bias from database left censoring, we excluded patients who had been enrolled in the database for less than 1 year before the index date. Patients who had non-stimulant ADHD prescriptions (atomoxetine, bupropion, clonidine) were also excluded. The population was divided into four study groups: the MPH-only group, MPH plus SSRIs group (SSRI group), MPH plus fluoxetine group (fluoxetine group), and MPH plus

escitalopram group (escitalopram group). As described in the study protocol (see Supplement 1), we also performed a sertraline analysis. However, we could not execute a confounder adjustment due to the small sample size, so it was excluded from this study.

The MPH-only group was defined as patients who were prescribed an MPH for the first time according to their medical history. This group was limited to antidepressant-naïve patients only. The SSRI group was defined as patients who were exposed to both an MPH and a SSRI for the first time in their treatment, to the exclusion of those prescribed antidepressants other than SSRIs. The fluoxetine and escitalopram groups were defined as patients who were prescribed fluoxetine or escitalopram only without other SSRIs in the SSRI group. The schematic visualization for the study groups is presented in the Figure S1 (see Supplement 3).

The index date was defined as the date of first MPH prescription for the MPH-only group. For the SSRI, fluoxetine, and escitalopram groups, it was defined the date of first concomitant prescription of a MPH and any SSRI, fluoxetine, or escitalopram, respectively.

Outcomes and follow-up

All outcomes were defined based on their diagnostic codes according to SNOMED-CT classification (Table S1 in the Supplement 2). The primary outcomes were neuropsychiatric events, which included psychosis, tic disorder, mania, sleep disorder, suicide, and ADHD-related hospitalization. ADHD-related hospitalization was defined as any hospitalization with the presence of an ADHD diagnosis and individual psychotherapy without hospitalization in the previous 2 weeks. The secondary outcomes were arrhythmia, hypertension, seizure, traumatic injury, tremor, headache, and gastrointestinal events (abdominal pain, constipation, nausea/vomiting). All study outcomes were limited to new-onset events in the database except traumatic injury, gastrointestinal events, and ADHD-related hospitalization. We also validated our results through analysis, using respiratory tract infection as a negative control outcome.

Patients were followed up to the last date of assigned treatment [as treated (AT) approach], the date of last observation in the database, the date of occurrence of the endpoint, and the date of censoring. Each treatment was considered continued if the patient received their new prescription within 30 days of the last date of the previous prescription. Treatment discontinuation was defined as the last prescription at which no more prescriptions were given within 30 days, and the discontinued date was defined as the 30 days after the last administration (the grace period of 30 days). Censoring events were defined as events wherein patients were exposed to another therapy (i.e. patients in the MPH-only group were considered censored when exposed to a SSRI and the SSRI group was considered censored when the SSRI or MPH treatment were discontinued).

Statistical analysis

All variables were denoted as frequency and percentage. Propensity score (PS) was calculated for estimating empirical equipoise which can assess feasibility of comparison (Alexander *et al.*, 2013) and adjusting the effects of bias from confounders between the two study groups. We defined two groups as comparable when their empirical equipoise was greater than 70%. We used L1 regularized logistic regression to estimate the PS including all the available characteristics in the database. All variables

were dichotomized, and all missing variables were considered not present. Study groups were matched in 1:1 pair based on the PS and an absolute standardized mean difference (aSMD) was assessed to describe the balance of covariate distribution. For all outcomes, the incidence rates (IR) were estimated. The Cox proportional hazards model was used to develop an outcome model for calculating hazard ratios (HRs) with 95% confidence intervals (CI). Only the treatment was included as a covariate of the Cox model. The Kaplan–Meier curve and Log-rank tests were used to derive cumulative incidence and compare between-group differences. $p < 0.05$ was defined as statistically significant. A subgroup analysis was performed to determine whether the results differed according to sex.

Sensitivity analyses

We conducted sensitivity analysis in the following analytic settings: PS adjustment method, follow-up strategy, and study population. We varied PS adjustment methods from 1:1 PS matching to 1: maximum (1: n) matching or stratification with 5 strata. We also varied our follow-up strategy to intention-to-treat (ITT) for estimating the effect of being assigned to a given treatment regardless of non-adherence (Smith, Coffman, & Hudgens, 2021). In the ITT strategy, patients were limited to those observed for 1 year and followed up to the study period (1 year) or the occurrence of the outcome. Additionally, we varied two definitions related to the study groups. First, we included only patients who were simultaneously prescribed an MPH and a SSRI; however, in the sensitivity analysis, we permitted a 30-day gap between MPH and SSRI. The index date was based on the first prescription of SSRI, with the MPH prescription falling within 30 days before the first SSRI prescription. Second, to assess the generalizability of our results, we expanded our study groups from MPH users to patients who used ADHD medications including MPHs, atomoxetine, bupropion, and clonidine.

All analyses were performed using R, version 4.1.0, and its open-source statistical packages, including the Observational Health Data Sciences and Informatics analytic packages.

Results

Cohort characteristics

This analysis covered 9663 patients, 6746 of whom were assigned to the SSRI groups and 2917 to the MPH-only group (Fig. 1; Table S1 in the Supplement 3). The SSRI groups were divided into the escitalopram group ($n = 3364$) and the fluoxetine group ($n = 2381$). The study group pairs were compatible for comparison with empirical equipoise of above 70% (Figure S3 in the Supplement 2).

The baseline characteristics of the overall study population before and after propensity score matching are reported in Table 1. After propensity score matching, all baseline characteristics between the MPH-only and SSRI groups among 2650 matched pairs were balanced (all aSMD < 0.10 ; Table 1). The male proportions between these groups were 56.6 and 57.9%, respectively. Anxiety disorder was a common comorbidity in both groups, at 28.6 and 28.4%, respectively. Anticholinergics and antipsychotics were the most commonly prescribed medications for both groups (26.5 and 27.5% for anticholinergics; 21.9 and 22.8% for antipsychotics). The mean dose of initial methylphenidate prescription was 17.4 ± 15.1 mg and 17.4 ± 12.7 mg in the SSRI and MPH-only groups, respectively (aSMD < 0.01).

In the comparison within SSRI types – the fluoxetine group *v.* the escitalopram group – all baseline characteristics were balanced (all aSMD < 0.10 ; Table 1). Specifically, the male proportions were 47.3% and 47.7% for the fluoxetine and escitalopram groups, respectively. Anxiety disorder was 24.6 and 23.7%, and anticholinergics and antipsychotics were commonly prescribed between these groups as well. Anxiolytics accounted for 15.9 and 14.0% for each group. The mean dose of initial methylphenidate prescription was 16.2 ± 11.2 and 16.7 ± 12.1 mg in the fluoxetine and escitalopram groups, respectively (aSMD = 0.04).

Outcome assessment

The risks of all the outcomes were not significantly different between the SSRI and MPH-only groups (Table 2; Fig. 2). Specifically, the incidence rates were 37.59/1000 PYs and 36.63/1000 PYs [HR 1.04 (0.66–1.65)], respectively for psychosis, 0.89/1000 PYs and 2.13/1000 PYs for suicide, and 23.26/1000 PYs and 12.91/1000 PYs [HR 1.85 (0.95–3.80)] for ADHD-related hospitalization. Detailed number of events, person-years and incidence rates are presented in Table S2 (see Supplement 3). The negative control outcome did not show statistical significance in any analysis setting including sensitivity analyses.

In the comparison between SSRI types, there were significant differences in tic disorder (Table 2; Fig. 2). The fluoxetine group showed lower risk of tic disorder than the escitalopram group [IR 41.72/1000PYs, 71.80/1000 PYs, respectively; HR 0.60 (0.37–0.95)]. Suicide and hypertension could not be assessed due to no outcome in the study groups. The remaining outcomes did not show any statistically significant differences.

In the subgroup analyses, all the comparisons between the SSRI and MPH-only male subgroups showed no significant differences; however, there was a significant difference in tic disorder between the fluoxetine and escitalopram male groups [HR 0.35 (0.17–0.65)] (Fig. S3; Table S4, S5 in the Supplement 3). For the female subgroup, there were significant differences in ADHD-related hospitalization [HR 6.14 (1.13–114.03)] and nausea and vomiting [HR 4.4 (1.45–19.01)] between the SSRI and MPH-only groups (Table S3 in the Supplement 3). Unlike the male subgroup, there was no difference in the risk of tic disorder between the fluoxetine and escitalopram female subgroups [HR 0.73 (0.30–1.72); Fig. 3].

Sensitivity analyses

Balances between the study groups in all the sensitivity analyses are presented in Figure S3 and S4 (see Supplement 3). In all analyses, the maximum value of aSMD was under 0.10. The overall sensitivity analysis results are shown in Table S6 and S7 (see Supplement 3). For the comparison between SSRI and MPH-only groups, no consistent results were confirmed by the various sensitivity analysis settings.

Between the fluoxetine and the escitalopram groups, however, the fluoxetine group showed a lower risk of tic disorder than the escitalopram group with consistency and significance (Table S7 in the Supplement 3). Figure 3 shows the results of sensitivity and subgroup analyses for tic disorder.

Discussion

In this nationwide retrospective cohort study, we extensively compared the risk of neuropsychiatric, cardiovascular, and other

Table 1. Comparisons of baseline characteristics, comorbidities, and concomitant drugs in adolescent ADHD patients with depression after propensity score matching

Characteristics	SSRI (n = 2650)	MPH-only (n = 2650)	aSMD	Fluoxetine (n = 1820)	Escitalopram (n = 1820)	aSMD
Socio-demographics, n (%)						
Male	1500 (56.6)	1534 (57.9)	0.03	860 (47.3)	869 (47.7)	0.01
10–14 years	1161 (43.8)	1186 (44.8)	0.02	638 (35.1)	647 (35.5)	0.01
15–19 years	1489 (56.2)	1464 (55.2)	0.02	1182 (64.9)	1173 (64.5)	0.01
Race, Korean	2650 (100.0)	2650 (100.0)	0.00	1820 (100.0)	1820 (100.0)	0.00
Index year, n (%)						
2017	511 (19.3)	517 (19.5)	0.01	344 (18.9)	369 (20.3)	0.03
2018	583 (22.0)	621 (23.4)	0.03	483 (26.5)	481 (26.4)	0.00
2019	778 (29.4)	780 (29.4)	0.00	530 (29.1)	520 (28.6)	0.01
2020	778 (29.4)	732 (27.6)	0.04	463 (25.4)	450 (24.7)	0.02
Psychiatric comorbidity, n (%)						
Anxiety disorder	758 (28.6)	752 (28.4)	0.01	447 (24.6)	431 (23.7)	0.02
Autism spectrum disorder	69 (2.6)	68 (2.6)	0.00	36 (2.0)	41 (2.3)	0.02
Conduct disorder	241 (9.1)	220 (8.3)	0.03	119 (6.5)	122 (6.7)	0.01
Intellectual disability	128 (4.8)	123 (4.6)	0.01	66 (3.6)	57 (3.1)	0.03
Medication use, n (%)						
Anticholinergics	702 (26.5)	729 (27.5)	0.02	594 (32.6)	553 (30.4)	0.05
Antiepileptics	134 (5.1)	129 (4.9)	0.01	81 (4.5)	87 (4.8)	0.02
Antipsychotics	581 (21.9)	603 (22.8)	0.02	398 (21.9)	390 (21.4)	0.01
Anxiolytics	225 (8.5)	232 (8.8)	0.01	289 (15.9)	255 (14.0)	0.05
Methylphenidate dose (mg)						
Mean (s.d.)	17.4 (15.1)	17.4 (12.7)	0.00	16.2 (11.2)	16.7 (12.1)	0.04

ADHD, attention-deficit/hyperactivity disorder; PS, propensity score; MPH, methylphenidate; SSRI, selective serotonin reuptake inhibitor; aSMD, absolute standardized mean difference; FLX, fluoxetine; ECP, escitalopram.

safety outcomes according to the presence or types of SSRIs use in adolescent ADHD patients with depressive disorder. We found that the concomitant use of MPHs and SSRIs showed safe profiles in the study population. In the head-to-head comparison for fluoxetine and escitalopram, most of the differences in safety were not significant. However, the risk of tic disorder was significantly higher in the escitalopram than the fluoxetine group with consistency in all analytic settings.

There is a lack of published data on the medication safety of concomitant MPH and SSRI use for adolescent patients. In our study, suicide showed no definite risk observed between the SSRI and the MPH-only groups. Our results align with Chen et al.'s nationwide longitudinal study, in which they observed no risk of suicidal behavior related to ADHD medication, both before and after adjustment for antidepressants (Chen et al., 2014). Although antidepressants were reported to have an effect on suicide (Jick et al., 2004), a study found that ADHD diagnosis was not influenced by the impact of SSRI initiation on suicide risk (Lagerberg et al., 2022). Further, impulsivity associated with suicide was related to unintentional accident outcomes such as fractures (Chen et al., 2017).²¹ As with suicide risk, we did not find differences in traumatic injury risk between SSRI and MPH-only groups.

Our finding of no difference in the risk of new-onset manic symptoms between MPH-SSRI combination use, and

MPH-only use are consistent with those of Chang, Saxena, Howe, and Simeonova (2010). Stimulants and SSRIs should be carefully prescribed for adolescents with risk factors, such as a history of antidepressant-induced mania, psychosis, and a family history of bipolar disorder (Goldsmith et al., 2011). The pharmacological mechanism of MPHs is associated with the risk of psychotic symptoms and disorders (Tost, Alam, & Meyer-Lindenberg, 2010). However, antidepressants have possible beneficial effects on psychosis (Bykowsky et al., 2019). Although our study did not explore these possible protective effects, the results showed no difference in the risk of psychosis between the concomitant use of MPHs and SSRIs and the use of MPH only.

For sleep disorder, sleep initiation and maintenance are affected by antidepressants; that is, some antidepressants can improve sleep (Wilson & Argyropoulos, 2005), while others may worsen sleep disorders like REM sleep disorder and nightmares (Wichniak, Wierzbicka, Wałęcka, & Jernajczyk, 2017). In our study, the concomitant use of MPHs and SSRIs showed no sleep disorder risk.

Our study also showed no significant difference in tic disorder between MPH-only and SSRIs groups. MPHs have been reported to have an effect on tic symptoms in children with ADHD, but tic symptoms induced by SSRIs are a rare adverse effect (Gadow,

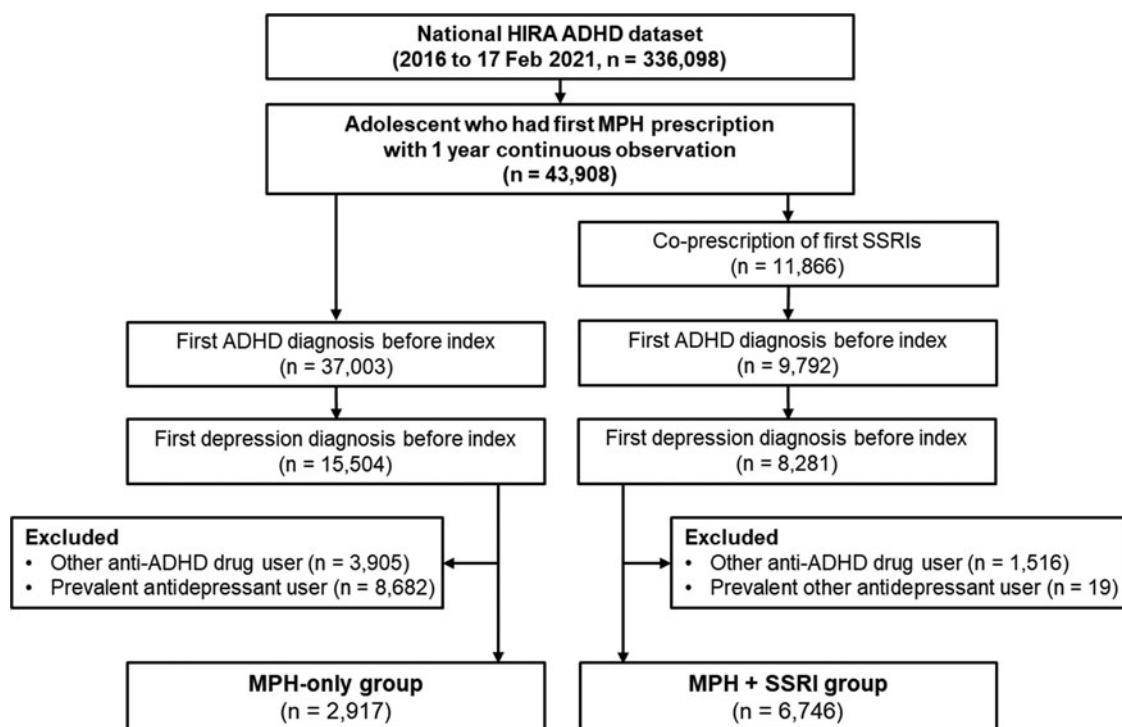


Fig. 1. Flow diagram between the SSRI and the MPH-only groups.

Table 2. Risk of outcome events between the SSRI and the MPH-only group or between the fluoxetine and escitalopram groups

Outcomes	Incidence rate [§]		HR (95% CI)	Incidence rate [§]		HR (95% CI)
	SSRI (n = 2650)	MPH-only (n = 2650)		Fluoxetine (n = 1820)	Escitalopram (n = 1820)	
Primary endpoints						
Mania	20.38	11.88	1.71 (0.85–3.67)	21.25	21.35	1.04 (0.50–2.19)
Psychosis	37.59	36.63	1.04 (0.66–1.65)	40.38	32.34	1.33 (0.76–2.38)
Sleep disorder	62.44	43.29	1.41 (0.96–2.12)	67.32	63.56	1.07 (0.70–1.65)
Suicide	0.89	2.13	0.41 (0.02–4.28)	1.39	0.00	NA
Tic disorder	57.62	52.07	1.13 (0.77–1.67)	32.00	75.84	0.43 (0.25–0.71) [‡]
Hospitalization [†]	23.26	12.91	1.85 (0.95–3.80)	12.63	22.49	0.57 (0.24–1.28)
Secondary endpoints						
Arrhythmia	4.52	10.71	0.43 (0.13–1.21)	1.40	4.49	0.32 (0.02–2.51)
Abdominal pain	3.55	2.14	1.79 (0.35–12.88)	5.58	1.49	4.03 (0.60–78.80)
Constipation	9.78	17.24	0.60 (0.27–1.28)	9.79	11.94	0.88 (0.31–2.44)
Headache	12.48	11.79	1.11 (0.51–2.51)	19.64	16.49	1.28 (0.58–2.88)
Hypertension	0.90	5.34	0.17 (0.01–1.07)	0.00	2.99	NA
Nausea vomiting	22.33	14.97	1.60 (0.85–3.17)	16.85	20.95	0.86 (0.39–1.86)
Seizure	51.19	55.14	0.69 (0.37–1.28)	21.33	22.85	0.91 (0.44–1.89)
Traumatic injury	4.44	4.27	1.11 (0.29–4.48)	4.20	1.49	3.05 (0.39–61.57)
Tremor	12.88	14.03	0.92 (0.43–1.99)	9.82	19.70	0.52 (0.20–1.28)
Negative control outcome	9.92	5.34	1.85 (0.67–5.87)	5.58	2.99	1.90 (0.37–13.69)

MPH, methylphenidate; SSRI, selective serotonin reuptake inhibitor; FLX, fluoxetine; ECP, escitalopram; [§]Incidence rate were calculated as case per 1000 person-years; HR, hazard ratio; CI, 95% confidence interval; [‡]statistically significant; [†]Hospitalization indicates a hospitalization with the presence of an ADHD diagnosis; Negative control outcome indicates respiratory tract infection.

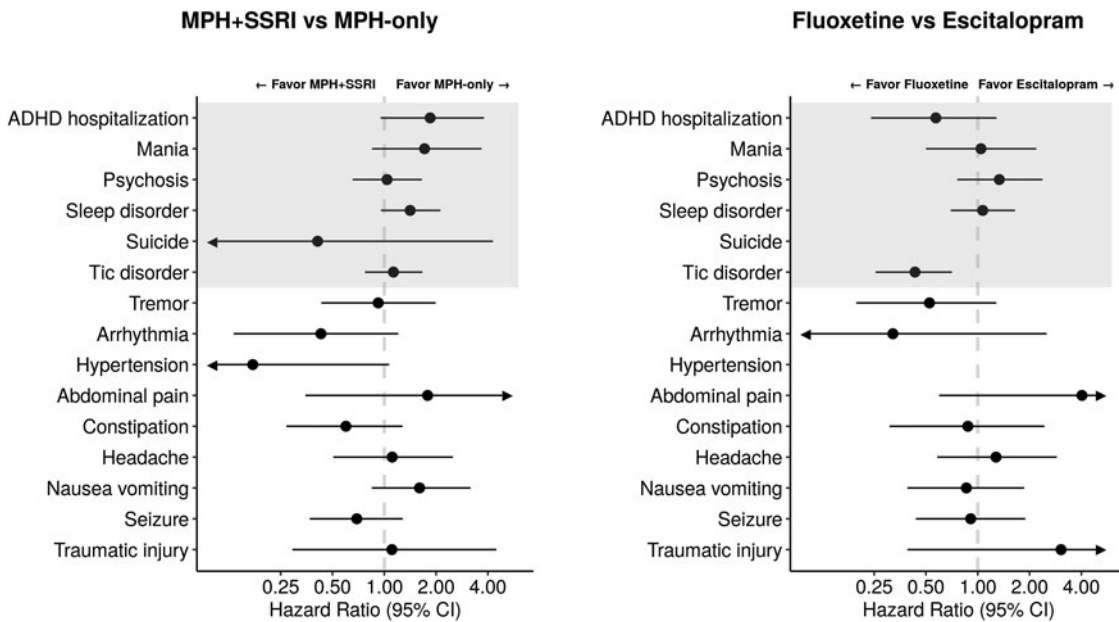


Fig. 2. Forest plots of outcome estimates from analyses which compared the SSRI v. the MPH-only groups and the fluoxetine v. the escitalopram groups. Red shading is neuropsychiatric events, and the red dot and line means statistically significant.

Sverd, Sprafkin, Nolan, & Ezor, 1995; Kayhan, Uguz, Kayhan, & Toktaş, 2014). Similarly, MPHs have been linked to risk of seizure and headache (Man et al., 2020; Pan et al., 2022), while antidepressants generally have a low risk (Montgomery, 2005; Walker, Walker, Robertson, & Stansfeld, 1998). In this study, the concomitant use of MPHs and SSRIs did not show higher seizure or headache risk than MPH-only use. On the other hand, both antidepressants and MPHs have been associated with drug-induced tremor (Frei & Truong, 2022). However, our findings showed that no difference in the risk of tremor between the SSRI and MPH-only groups. Since drug-induced tremor shows dose-dependent exacerbation, further studies considering SSRI doses are needed (Baizabal-Carvalho & Morgan, 2022).

Some studies suggest an association between MPH-SSRI concomitant use and arrhythmia and raise concerns about this combination. Moreover, antidepressant treatment has been associated with a higher risk of atrial fibrillation (Fenger-Grøn et al., 2019). However, there was no significant difference in the risk of arrhythmia and hypertension between the SSRI and MPH-only groups. Furthermore, because hypertension is more common in people over the age of 55 years, results related to hypertension risk require confirmation through a study considering other age groups (Wang et al., 2020).

Further, our findings showed no difference in the risk of gastrointestinal symptoms between MPH-SSRI concomitant use and MPH alone. Although antidepressants increase the risks of gastrointestinal symptoms, such symptoms are usually transient (Murphy et al., 2008).

For ADHD-related hospitalization, we found no difference between SSRIs and MPH-only groups. Previous studies on co-morbid ADHD and obsessive-compulsive disorder suggest that treating both disorders concurrently can be beneficial (Cabarkapa, King, Dowling, & Ng, 2019). We found that SSRIs do not exacerbate ADHD symptoms, although we could not identify whether it was beneficial to treat comorbidity or not. Overall, our findings suggest that the concomitant use of SSRIs and MPHs

is not significantly riskier than MPHs alone for neuropsychiatric, cardiovascular, and other safety issues.

Our subgroup analysis by sex showed no difference in most safety outcomes in females using SSRIs and MPHs together, except for the increased risk of nausea and vomiting and ADHD-related hospitalization. Consistent with our finding on nausea and vomiting, Romero-Acosta et al., found that girls reported more somatic symptoms such as stomach-ache than did boys (Romero-Acosta et al., 2013). However, gastrointestinal symptoms are usually transient. In addition, because outcome counts for ADHD-related hospitalization in female group were less than 10, it was challenging to determine whether the concomitant use of MPHs and SSRIs was risky or not. Sex differences in the symptoms of ADHD are well documented in the literature (Arnett et al., 2015). However, with respect to ADHD medication safety, previous studies considering sex differences are limited (Kok, Groen, Fuermaier, & Tucha, 2020). Sex-related differences in pharmacokinetics, immunological, and hormonal factors might be a potential explanation, but still, further studies are needed to confirm our results.

A previous study reported no significant difference between fluoxetine and escitalopram treatments with regard to efficacy and adverse events (Patris et al., 1996). Similarly, except for tic disorder, we observed no difference in the risk of adverse events between escitalopram and fluoxetine groups (Oh, Zupan, Gross, & Toth, 2009). Tic disorder is a rare adverse event of SSRI whose pathophysiology is imperfectly known, although an indirect dopaminergic inhibition through serotonergic mediation has been proposed (Altindag, Yanik, & Asoglu, 2005). In our study, the fluoxetine group showed a lower risk of tic disorder than the escitalopram group, and other sensitivity analyses showed consistent results. In line with our finding, Revet et al., showed the possibility of an opposite direction of association for tic disorder between fluoxetine and escitalopram, although there was no statistical significance (Revet et al., 2020). Contrary to escitalopram, fluoxetine antagonizes 5-HT_{2C} receptors (Opal et al., 2014; Pogorelov et al., 2017). Considering that tic disorder

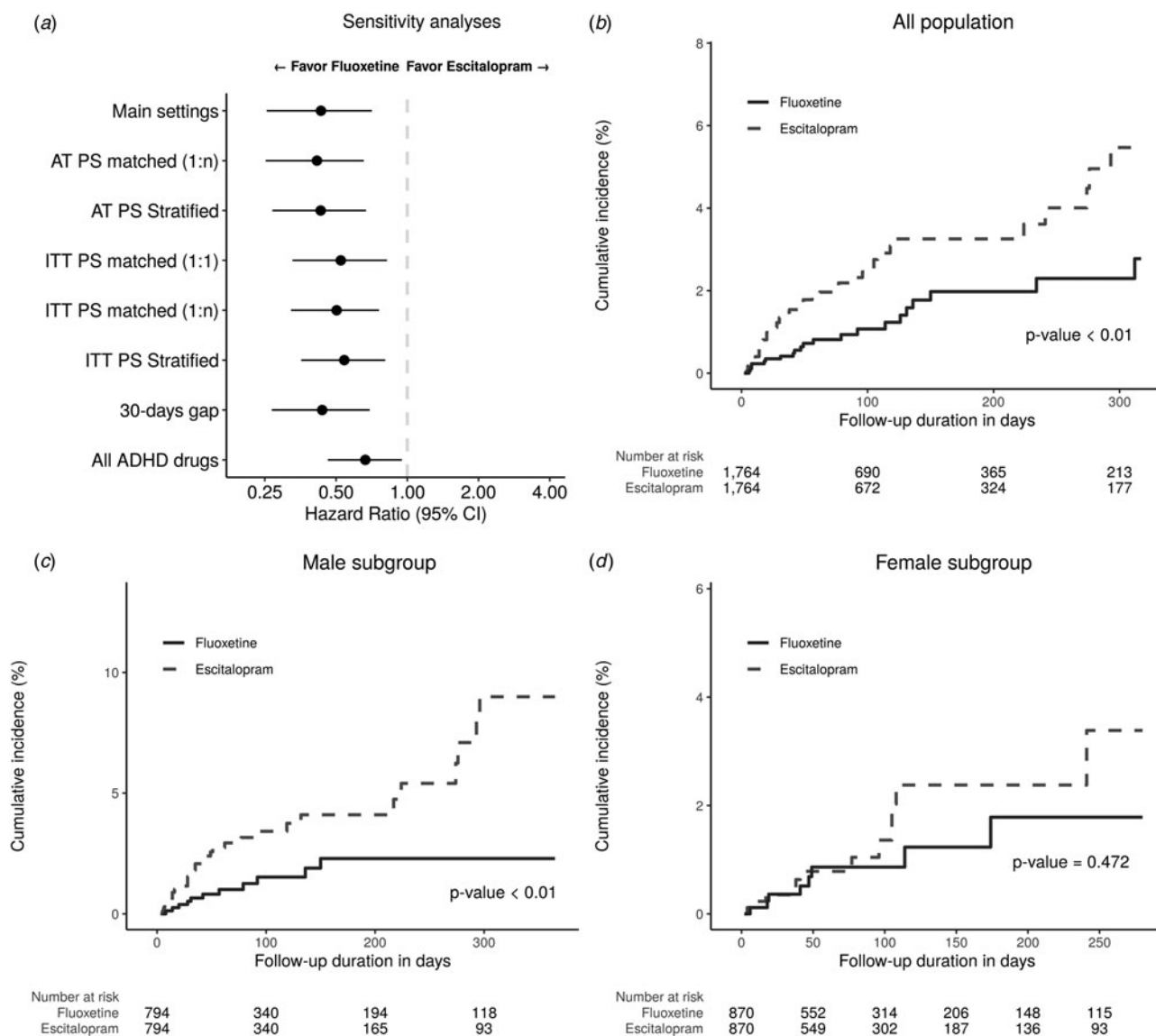


Fig. 3. Comparison of tic disorder between the fluoxetine and escitalopram groups. (a) Results of sensitivity analyses for tic disorder (Red dot and line means statistically significant) (b) Kaplan-Meier plot for tic disorder between fluoxetine and escitalopram groups (c) Kaplan-Meier plot for tic disorder in the male subgroup (d) Kaplan-Meier plot for tic disorder in the female subgroup. MPH, methylphenidate; SSRI, selective serotonin reuptake inhibitor; AT, as treated; PS, propensity score; ITT, intention-to-treat; ADHD, attention-deficit/hyperactivity disorder; CI, 95% confidence interval.

is related to dopamine, dopamine action through 5-HT_{2C} receptors may have caused a difference between fluoxetine and escitalopram. Specifically, a rodent study showed that 5-HT_{2C} receptor antagonists might be efficacious in treating movement disorders caused by dopamine signaling and in potentiating the antidepressant and anxiolytic effects of SSRIs by reducing anxiety and depression-like behavior (Demireva et al., 2020). Overall, there is no difference in most of the adverse events between fluoxetine and escitalopram when used in combination with a MPH, but further studies on tic disorder are needed to verify this.

Our study used a population-based cohort study using claims data. Despite randomized controlled trials (RCTs) being the gold standard, advantages of the cohort study such as larger samples and longer follow-up time could be an alternative to RCTs. Considering confounding factors as the limitation of the cohort study, we applied large-scale propensity score adjustments including one-to-one propensity score matching, variable-ratio

propensity score matching, and propensity score stratification to reduce the effects of confounding factors.

Limitations

This study has some limitations. First, we did not perform a clinical evaluation considering ADHD type and severity or depressive disorder at baseline. This was because capturing the symptoms of ADHD or depressive disorder directly was challenging due to the nature of the claims data. This limitation may have led to a bias in the difference in disease severity at baseline. However, by including the incident diagnosis of depressive disorder in both groups, we conducted the study with an empirical equipoise of more than 70% between the groups. In addition, we attempted to minimize the confounding bias by introducing a large-scale propensity score, which we calculated using all the variables we could capture, and a negative control outcome to validate our results.

Second, since this was a code-based analysis, the possibility of errors due to misclassification of variables cannot be ruled out. However, this is a limitation of all retrospective observational studies using database. Therefore, we evaluated the overall consistency of the results by performing analyses with the strictest definitions and various sensitivity settings. For example, in the study group definition, we confirmed whether the overall results were consistent through analysis by changing the MPH-user group to the ADHD-medication-user group and by changing the interval between MPH and SSRI from 0 to 30 days. In addition, the definition of most outcomes is also limited to incident cases, and only outcomes that could occur repeatedly for independent reasons were allowed. Also, adverse events not reaching the status of a case were not captured. Despite the above limitations, this remains the first large-scale retrospective cohort study to evaluate the safety of concomitant SSRI and MPH use in adolescents diagnosed with both ADHD and depressive disorder.

Conclusion

In conclusion, our findings suggest no difference in the risk of neuropsychiatric, cardiovascular, and other adverse events between the concomitant use of MPHs and SSRIs and MPH-only use. Considering this result, SSRIs may be a favorable treatment option for mood symptoms in ADHD patients using MPHs. Moreover, we found no difference in most of adverse events between fluoxetine and escitalopram in terms of SSRI selection, but caution may be required for tic disorder. Further collaborative investigations are still needed to clarify the association with each safety outcome according to ethnicity.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291723000120>.

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