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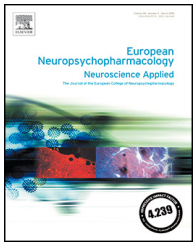

Combined fluvoxamine and extended-release methylphenidate improved treatment response compared to fluvoxamine alone in patients with treatment-refractory obsessive-compulsive disorder: A randomized double-blind, placebo-controlled study

Huirong Zheng[a,*], **Fujun Jia**[a], **Hongying Han**[b], **Shibin Wang**[a], **Guangquan Guo**[a], **Dongming Quan**[a], **Gang Li**[a], **Huiyan Huang**[c]

[a] *Guangdong Mental Health Center, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Affliated School of Medicine of South China University of Technology, No. 123 Huifu Xi Road, Guangzhou 510180, Guangdong, PR China*
[b] *Department of Psychiatry, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, PR China*
[c] *Pharmacy Department of Guangdong General Hospital, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, PR China*

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Abstract
More effective, tolerable interventions for treatment-refractory obsessive-compulsive disorder (OCD) are needed. Preliminary findings encourage optimism that methylphenidate augmentation may be of benefit in the treatment of OCD. To test modulator methylphenidate (MPH) of extended-release formulations (MPH-ER) a safe and effective add-on therapy for refractory OCD, a pilot randomized, placebo-controlled, double-blind trial was conducted at an outpatient, single-center academic setting. Participants included 44 adults with serotonin reuptake

* Corresponding author.
E-mail address: hgm198103@163.com (H. Zheng).

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inhibitor (SRI) treatment-refractory OCD and receiving a stable fluvoxamine pharmacotherapy with Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores higher than 20. Data were analyzed in the intention-to-treat sample. All subjects were randomized into two parallel groups to receive fluvoxamine (250 mg daily) plus MPH-ER (36 mg daily) or fluvoxamine (250 mg daily) plus identical placebo tablets under double-blind conditions and followed for 8 weeks. Forty-four patients (29 [66%] men), with a mean (SD) age of 24.7 (6) years participated; with a mean (SD) duration of episode 5.7 (3) were randomized and forty-one finished the trial. In the intention-to-treat analysis, the improvement in the Y-BOCS total score and Y-BOCS obsession subscale score was more prominent in the fluvoxamine and MPH-ER group compared with those receiving placebo ($P < .001$). Additionally, cumulative response rates were higher in the MPH-ER vs placebo groups (59% vs 5%; $P < .001$). MPH-ER was well tolerated; No subjects dropped out due to side effects. In summary, combined treatment with MPH-ER demonstrated an enhanced clinical rate of response compared to placebo. Further trials should examine MPH-ER efficacy in a larger sample

1. Introduction

Obsessive compulsive disorder (OCD) is characterized by distressing obsessions (intrusive recurrent thoughts) and compulsions (repetitive ritualized behavior) that interfere with normal function (Association, 2013). It affects approximately 1.3% of the population in any given year and up to 2.7% over the course of their lifetime (Kessler et al., 2012). OCD causes substantial morbidity: 60% of individuals with moderate OCD and 80% of those with severe OCD report severe role impairment in home management, work, relationships, and social functioning (Ruscio et al., 2010). Also, OCD causes significant impairments of executive function including deficits in a attention (Benzina et al., 2016).

First-line medications include selective serotonin reuptake inhibitors (SSRIs) and clomipramine, which are mostly used in OCD in higher doses than those required to treat depression in order to obtain clinical benefits (Soomro et al., 2008). Varied individual response rates to SSRIs as well as the possible benefit of augmentation therapy with other agents such as antipsychotics further implicate the role of other neurobiologic factors in pathophysiology of OCD (Veale et al., 2014). However, approximately 30% of patients receive no meaningful benefit from the best available treatments, and many of those who are judged to be treatment responders continue to have significant residual symptoms. The antipsychotic augmentation is also associated with a substantial side-effect burden (Bloch et al., 2006). In extreme cases, profoundly affected patients turn to invasive treatments such as deep brain stimulation (Greenberg et al., 2010). Also, remission rarely occurs in severe cases. New treatments are urgently needed. In a recent review, Koran and Aboujaoude suggested many patients with OCD who respond partially or not at all to first-line medications and cognitive behavioral therapy approaches need additional treatments necessary, including optional stimulants treatment (Koran and Aboujaoude, 2017).

While most first-line pharmacotherapy targets serotonergic modulatory neurotransmission, convergent evidence suggests that dysregulation of the neurotransmitter dopamine may contribute to the pathophysiology of OCD (Koo et al., 2010). In this regard, dysregulation of the cortico-striatal-thalamocortical (CSTC) may be a key component, as disruption of dopamine transmission has been reported in several studies of patients with OCD (Denys et al., 2013; Pauls et al., 2014). Additionally, imaging studies suggest the presence of a complex imbalance in the dopamine system in OCD patients (Perani et al., 2008; Sesia et al., 2013).

Methylphenidate of extended-release formulations (MPH-ER) is a dopamine reuptake inhibitor, and as a stimulant drug, remains the most widely used pharmacological agent in the treatment of children and adolescents with attention-deficit/hyperactivity disorder (ADHD) (Brault and Lacourse, 2012; Maia et al., 2014). The therapeutic effects of MPH-ER in the treatment of ADHD appear to be elicited primarily through an inhibition of the presynaptic dopamine transporter (Volkow et al., 1999, 2002a), with a minor influence on the noradrenaline transporter. This action will amplify neurotransmission by increasing synaptic cleft residence time of impulse-released dopamine (Volkow et al., 2002b). Alternatively, others have proposed that dopamine re-uptake inhibition by methylphenidate attenuates dopaminergic tone attenuates dopaminergic tone by increasing stimulation of presynaptic inhibitory autoreceptors (Seeman and Madras, 2002). Preliminary data suggest that methylphenidate decreased checking compulsion symptoms which are comorbid with ADHD (Gurkan et al., 2010). In addition, a case series reports that adjunctive MPH-ER can reduce self-reported and objective inattention and hoarding symptoms (Rodriguez et al., 2013), that may also be of benefit in OCD (King et al., 2017).

A recent case study reported methylphenidate attenuates dopaminergic tone augmentation in adolescent female OCD with ADHD. A 15-year-old woman with Y-BOCS score of 24, the patient was treated with 25 mg of methylphenidate, in addition to sertraline 300 mg daily. After 8 weeks, the Y-BOCS score of the patient declined to 11, indicating a promising response to the treatment. And 18 month follow-up of the patient also showed improvements in OC symptoms (King et al., 2017). These findings encourage optimism that methylphenidate interventions may be of benefit in the treatment of refractory OCD; however, to the best of our knowledge, no controlled studies have addressed its efficacy

in treatment of moderate-to-severe OCD. The aim of the present double-blind, placebo-controlled trial was to assess the efficacy as well as tolerability of MPH-ER augmentation in treatment of refractory OCD.

2. Methods and materials

All study procedures were approved by the Guangdong General Hospital Human Investigations Committee. This trial was registered on ClinicalTrials.gov (identifier: NCT02194075).

2.1. Subjects

From October 2013 to December 2016, 248 subjects were screened by print and internet advertisements, community outreach, and physician referrals. Screening consisted of clinical interview; baseline clinical ratings (as detailed below); physical examination; blood chemistries, and electrocardiography. Inclusion criteria were a primary DSM-IV diagnosis of OCD, determined by a board-certified psychiatrist and confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-I-CV). The other inclusion criteria included treatment with fluvoxamine at a stable effective dose for ≥ 8 weeks (by patient report); failure of at least 1 previous adequate-dose SSRI trial (by patient report and/or past clinical records); total score ≥ 20 in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS); low-dose stable benzodiazepine use were permitted; ongoing psychotherapy of ≥ 12 weeks duration (analogously to the continuation of stable medication) were permitted to better reflect the therapeutic profile of refractory patients in clinical practice, but the initiation of new psychotherapy were not permitted after initiation of the study.

After describing the details of the study to interested and eligible subjects, written informed consent was obtained in accordance with the procedures set by the Guangdong General Hospital Institutional Review Board. Exclusion criteria were: prior exposure to methylphenidate; a clinical or SCID-I-CV diagnosis of a psychotic disorder; attention deficit hyperactivity disorder (ADHD), autism, or substance abuse or dependence within the past 6 months; a history of a seizure disorder or other major neurologic disease or of psychosurgery; suicidality or psychiatric instability that made participation potentially unsafe, in the evaluating psychiatrist's judgment; pregnancy or breastfeeding; any unstable medical condition. Comorbid unipolar major depressive disorder, anxiety disorders, skin picking disorder, hoarding, and tic disorders were permitted.

2.2. Intervention procedures

This trial was an 8-week, double-blind, randomized, placebo-controlled trial of adjunctive fixed-doses of MPH-ER to fluvoxamine and placebo were dispensed in identical-appearing tablets therapy in OCD. The allocation to parallel groups was determined by pre-randomized codes generated by a computer. Coded treatments were allocated sequentially to subjects in order of their registration for the trial. During the study, the randomization list was held securely and none of the research personnel, who enrolled, assessed, and treated the patients, were aware of the patient assignments until the study was concluded. The use of concomitant rescue medications during the treatment trial was restricted to the use of alprazolam up to 1.2 mg day. Following evaluation and informed consent, all subjects were randomized into two parallel groups to receive fluvoxamine (250 mg daily) plus placebo or fluvoxamine (250 mg daily) plus MPH-ER (36 mg daily) under double-blind conditions. The MPH-ER initial dosage was 18 mg/day for the initial 4 weeks of the study followed by 36 mg/day for the rest of the trial course. Biweekly assessments consisted of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989), Hamilton Depression Rating Scale (HDRS; 17-item version was used for analysis) (Hamilton, 1960), and Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959), as well as clinical checks for safety and evaluation of side effects using clinical interview and the Physical Symptom Checklist (Clyde, 1986). Response rate was defined as a 25% improvement in Y-BOCS score for partial response and $\geq 35\%$ improvement for full response.

2.3. Safety and side effects assessments

Vital signs and weight were measured at baseline and at each visit in addition to a 12-lead ECG performed at baseline, and at weeks 4 and 8, if any cardiac complaints were present. A physical examination was administered at baseline and week 8, or upon early termination. Side effects were assessed at baseline and at biweekly assessments by clinical interview and the Physical Symptom Checklist. The adverse effects checklist was a 25-item questionnaire covering a broad range of complaints.

2.4. Statistical analysis

According to the pilot randomized placebo-controlled design, the sample size was calculated to allow a detection of 30% difference in improvement between methylphenidate and placebo group. Under the assumption of a significant level of 0.05 with a power of 0.80, a minimal sample size of 34 with 17 subjects in both groups was determined. Estimating a drop-out rate of 20%, we decided to recruit 22 participants for each group. SPSS software version 20.0 (IBM SPSS, IBM Corp, Armonk, NY) was used to complete the analysis. Safety analyses were performed using descriptive statistics and frequency distribution of dropouts. Demographic and clinical characteristics between the two groups were compared using T test (for continuous variables), chi-squared test or Fisher's exact test (for categorical variables). All outcome results used Intent-to-Treat (ITT) analyses. Continuous YBOCS scores were analyzed using a mixed effects model and simple effect analysis (2-tailed, $\alpha = 0.05$). The primary outcomes included improvement in Y-BOCS score and the clinical response rate. Response rate was defined as a 25% improvement in Y-BOCS score for partial response and $\geq 35\%$ improvement for full response.

The secondary outcome measures, including change in obsessions (Y-BOCS-obsessions), change in compulsions (Y-BOCS-compulsions), change in HDRS, change in HARS, and adverse side effects, were also analyzed using mixed effects models, with treatment group, time, and time $\times$ treatment group as predictors.

3. Results

3.1. Subject

The recruitment and flow of subjects is summarized in the CONSORT diagram in Fig. 1. The most common reasons for nonparticipation were insufficient refractoriness (especially underdosing of fluvoxamine), unstable medication, and unwillingness to participate in a blinded study. Forty four subjects with treatment-refractory OCD were consented. Two early dropouts occurred in the MPH-ER group and were included in analysis. One occurred at week 2 after randomization (due to interference by his symptoms that made attending regular appointments difficult) and the second occurred

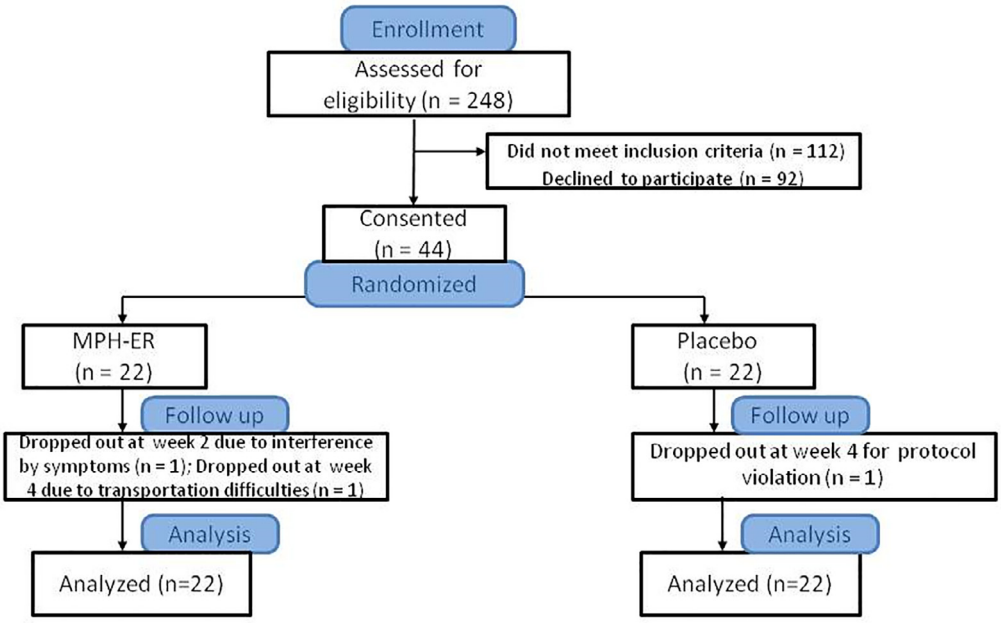

Fig. 1 Patient Recruitment, Randomization, and Flow in Pilot Study (MPH-ER = methylphenidate of extended-release formulations).

Table 1 Comparison of baseline clinical and demographic characteristics between the two treatment groups.

Variable	MPH-ER($n = 22$)		Placebo($n = 22$)		p-value
	Mean	SD	Mean	SD	
Age, (y)	26.2	6.2	25.2	6.6	.63
Sex,(n)					
Male,(n)	16		13		
Female,(n)	6		9		.34
Education, (y)	13.1	2.5	14.2	2.3	.14
Onset age,(y)	17.9	4.4	20.1	5.9	.17
Duration of episode (y)	6.3	4.2	5.0	2.8	.23
Chronic course >7(y),n(%)	8 (37)		5 (23)		.56
MDD, n(%)	4 (18)		3 (14)		
GAD, n(%)	1(5)		1(5)		
Tics, n(%)	1(5)		0		
SPD, n(%)	0		2 (9)		
Y-BOCS baseline score	23.9	3.2	25.0	3.3	.25
Obsessions	12.7	2.8	12.7	2.3	.95
Compulsions	11.5	2.6	12.3	3.5	.44
HDRS baseline score	12.4	5.0	12.9	5.1	.75
HARS baseline score	15.4	6.8	13.7	5.7	.38

Abbreviations: MPH-ER = methylphenidate of extended-release formulations, HARS = Hamilton Anxiety Rating Scale, HDRS = 17-item Hamilton Depression Rating Scale, Y-BOCS = Yale-Brown Obsessive Compulsive Scale, MDD = Major Depressive Disorder, GAD = Generalized Anxiety Disorder, Tics = Tic Disorder, SPD = Skin Picking Disorder, SD = Standard Deviation.

at week 4 (who could not attend the biweekly clinic appointments because of travel). One patient dropped out of the placebo group at week 4 (due to a protocol violation; he stopped taking his medications for a period of several days). Concomitant comorbidities, age, gender, age of onset, and other characteristics are summarized in Table 1.

3.2. Primary outcomes

3.2.1. Analyses of change in Y-BOCS scores over time

The baseline Y-BOCS total scores did not differ significantly between the two groups ($t = -1.16$, $p = .25$).The mixed effects model, using time and treatment group as

Table 2 Comparison of change scores in mixed-model statistical analyses between the two treatment groups.

Variable	MPH-ER ($n=22$)		Placebo ($n=22$)		Time		Treatment		Time × Treatment	
					F	*p*	*F*	*p*	*F*	*p*
Y-BOCS										
Baseline	23.9	3.2	25.0	3.3						
8 week	17.2	3.4	23.1	3.6	10.1	<.001	83.0	<.001	4.1	.003
Y-BOCS-obsessions										
Baseline	12.7	2.8	12.7	2.3						
8 week	7.2	3.1	12.9	3.4	8.1	<.001	68. 8	<.001	11.2	<.001
Y-BOCS-compulsions										
Baseline	11.5	2.6	12.3	3.5						
8 week	9.9	3.7	10.5	3.6	2.3	.061	12.9	<.001	.9	.449
HDRS										
Baseline	12.4	5.0	12.9	5.1						
8 week	6.3	2.9	11.0	5.8	5.5	<.001	13.9	<.001	1.2	.322
HARS										
Baseline	15.4	6.8	13.7	5.7						
8 week	11.1	5.2	16.1	5.2	.5	.712	3.9	.048	2.9	.023

Note: Y-BOCS = Yale-Brown Obsessive Compulsive Scale, HDRS = 17-item Hamilton Depression Rating Scale, HARS = Hamilton Anxiety Rating Scale, MPH-ER = methylphenidate of extended-release formulations.

categorical effects, indicated that there was a statistically significant difference in a main effect of group, time, and time × treatment group interaction between the two groups in change in Y-BOCS scores from baseline to study end (Table 2). Simple effect analysis revealed that from the second week, the MPH-ER + fluvoxamine group showed a significant decrease in Y-BOCS scores compared to MPH-ER + placebo ($F=8.16$, $p=.005$); Adjustment for gender and age, or onset age did not change the results. Change in Y-BOCS scores over time for the two treatment groups is graphically depicted in Table 2 and Fig. 2A.

3.2.2. Rate of change in response

At week 8, there were 8 of 22 (36.4%) partial responders in the MPH-ER group by the a priori definition of a 25% improvement from baseline Y-BOCS (using last observation carried forward for dropouts) and 1 of 22 (4.6%) partial responders in the placebo group. This difference approached statistical significance in the overall sample ($\chi^2_{\ 1}=5.03$, $P=.025$). By a more stringent criterion for full response of 35% improvement from baseline, there were 5 responders (22.7%) in the MPH-ER group and 0 in the placebo group met full response criteria at study end. Examination of the 13 responders in MPH-ER group (by the 25% improvement criterion) did not reveal obvious clinical correlates of responder status.

3.3. Secondary outcomes

3.3.1. Y-BOCS obsession subscale score

The baseline Y-BOCS obsession subscale score did not differ significantly between the two groups ($t=-0.19$, $p=.85$). The mixed effects model showed the effect of group, time and time × treatment group interaction significant difference between the two groups in Y-BOCS obsession subscale score from baseline to study end (Table 2). After 4 weeks, the MPH-ER + fluvoxamine group showed a significant decrease in Y-BOCS obsession subscale scores compared to MPH-ER + placebo group ($F=10.45$, $p=.001$); Change in Y-BOCS obsession subscale scores over time for the two treatment groups is graphically depicted in Fig. 2B.

3.3.2. Y-BOCS compulsion subscale score

The baseline Y-BOCS compulsion subscale scores did not differ significantly between the two groups($t=-1.037$, $p=.31$). In a mixed model analysis, changes in Y-BOCS compulsion subscale scores showed a main effect of treatment between-group differences (main effect of treatment venue, $F(1,210)=12.98$, $P<.001$), but no effects of time or interactions in the compulsion subscale (Fig. 2C).

3.3.3. Depression and anxiety scores

Depression and anxiety scores were low to moderate at baseline and showed substantial change across the 8 weeks of treatment. The HDRS decreased in both placebo- and MPH-ER- treated groups, though a statistically significant difference existed between groups. There were significant main effects of treatment and time on HDRS scores (main effect of treatment venue, $F(1,210)=13.92$, $P<.001$; time venue, $F(1,210)=5.5$, $P<.001$). Changes in HARS scores also showed between-group differences on significant main effect of treatment and time × group interaction. After 6 weeks, The time × treatment interaction approached significance ($F=4.71$, $P=.031$). At end point, The MPH-ER + fluvoxamine group shows a significantly decrease in HARS scores compared to MPH-ER + placebo group ($F=8.27$, $p=.004$). The change in the severity of anxiety in OCD presented in Table 2. And the improvement in comorbid anxiety symptoms was positively correlated with the improvement in OCD symptoms after controlling

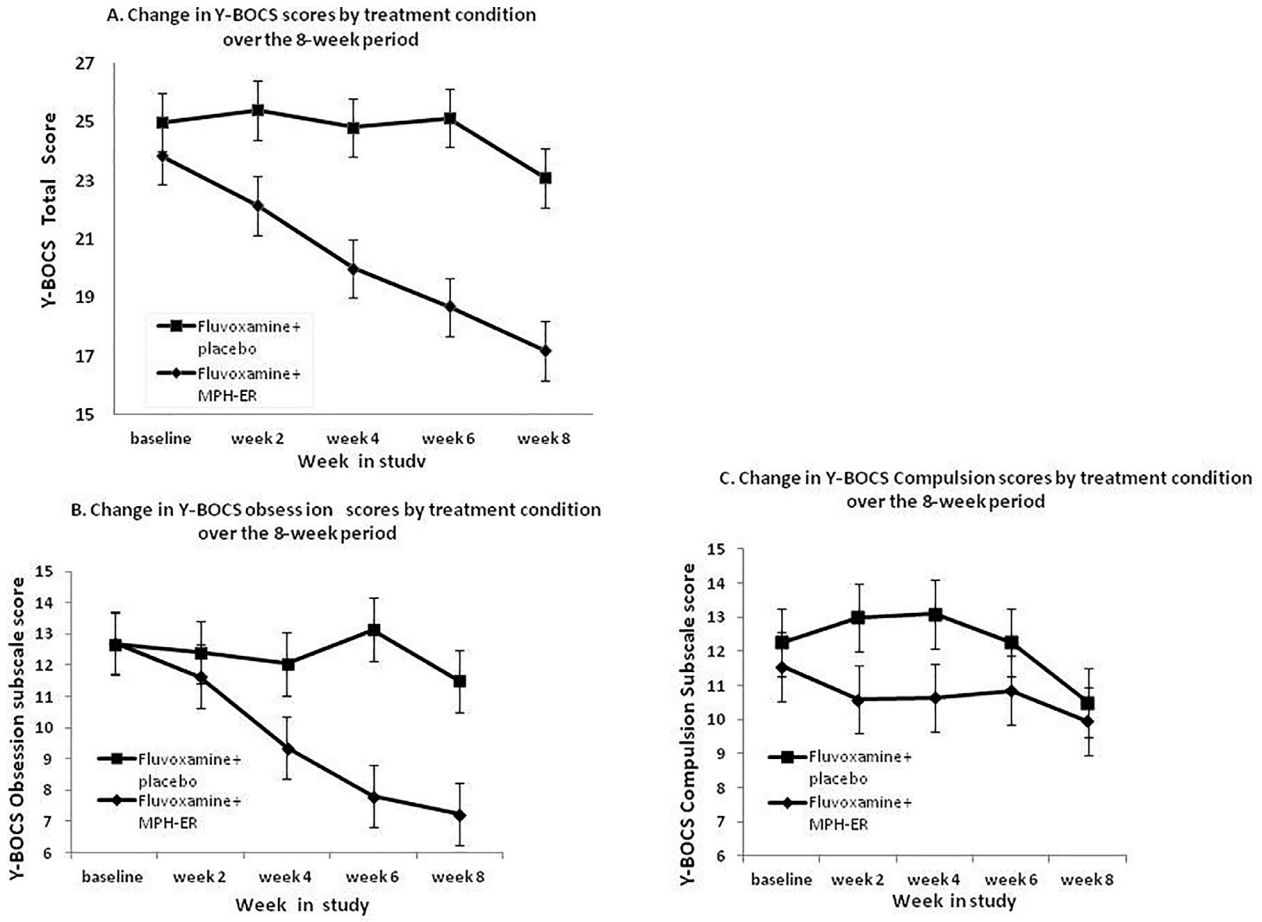

Fig. 2 Y-BOCS total scores, Y-BOCS obsession scores and YBOCS compulsion scores by treatment condition over the 8-week period. Changes shown in Y-BOCS total scores (A),Y-BOCS obsession scores (B) and Y-BOCS compulsion scores (C) by treatment condition over the 8-week period. Error bars indicate SE.
Abbreviation: MPH-ER = methylphenidate of extended-release formulations; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

the gender, age and age of onset (HARS, $n = 22$, $r = 0.495$, $P = .031$).

3.3.4. Safety and side effects

Overall, MPH-ER was well tolerated. No subjects dropped out due to physical side effects. Two measured symptoms were more frequent in MPH-ER-treated patients: palpitations (3 MPH-ER vs 1 placebo) and headaches (2 MPH-ER vs 0 placebo). One subject in MPH-ER group felt significant palpitations in the first week, but did not exceed the normal heart rate. The pounding heartbeat dissipated in a week, and there was no recurrence. A second subject with depression, and a history of headache from a work-related accident was assigned to the MPH-ER group. He had moderate headaches persisted throughout the study period, though the subject chose not to drop out before study completion. In contrast, many measured physical symptoms were reported more frequently in placebo-treated than in MPH-ER-treated patients (e.g., constipation: 3 MPH-ER vs 4 placebo; poor memory: 1 MPH-ER vs 5 placebo; insomnia: 1 MPH-ER vs 2 placebo), and many others did not differ between groups. There were no nervous system side effects and disturbance of consciousness, by clinical criteria.

4. Discussion

Our study is the first randomized, double-blind, placebo-controlled trial aimed to explore the possible efficacy of MPH-ER as an augmentation therapy compared to fluvoxamine monotherapy in treatment of patients with established refractory OCD. The object of the study was to test the hypothesis that MPH-ER augmentation of fluvoxamine treatment is well tolerated and may be proposed as an effective therapeutic strategy to improve outcome in OCD. Patients in both groups were followed for 8 weeks, and their response to treatment was evaluated using the Y-BOCS. Our results showed a significant reduction in total Y-BOCS and its obsession subscale scores of patients in the MPH-ER group, compared to the control group, during the course of trial. This improvement occurred in the earlier stage of the MPH-ER therapy. The patients' obsessions symptoms considerably improved, which may be attributed to the MPH-ER augmentation leading to dopaminergic and noradrenergic activation of frontal cortical structures (Brem et al., 2014). This, in turn, may have led to patients being better able to identify dysfunctional obsessional beliefs, and apply set-shifting strategies that reduce focus on obsessional content. As compulsive behavior often results from obsessional beliefs, the

response to compulsions may be later than the improvement of obsessions, requiring longer period of follow up, and improve learning associated with exposure-based approaches. This controlled study also showed that anxiety scores improved along with those of total Y-BOCS and obsession versus comparison groups. We did not find group differences in other clinical measures or side effects. Overall, we observed a significant and clinically meaningful treatment effect (versus a placebo) with MPH-ER, as evidenced by change in the Y-BOCS total score, Y-BOCS obsession score and compulsion score.

To date, a very limited number of studies have suggested stimulants might be especially useful in OCD patients. A double-blind study reported an improvement with D-amphetamine or caffeine augmentation in treatment-resistant OCD patients. At the end of week 1, 6 of 12 D-amphetamine subjects (50%) and 7 of 12 caffeine subjects (58%) were responders. At week 5, the responders' mean Y-BOCS score decreases were, for the D-amphetamine group, 48% (range, 20—80%); and, for the caffeine group, 55% (range, 27—89%) (Koran et al., 2009). Our findings on OCD outcomes are generally consistent with the literature, as they suggest that OCD symptoms fast improve with stimulants treatment (King et al., 2017; Koran and Aboujaoude, 2017). This potentially gives guidance to the clinicians on the use of MPH-ER to achieve faster response in adult OCD patients, but it is hard to draw conclusions about remission rates over a longer period of time based on our findings.

The literature also suggests that methylphenidate is effective in relieving depression with the rapid onset of response within 4 weeks or earlier (Buhagiar and Cassar, 2007; Lavretsky et al., 2006, 2015). The findings on depressive symptoms outcomes in the present study are not markedly different. Our results also showed that with MPH-ER treatment anxiety may decrease along with the coresymptoms of OCD. It is noteworthy that the significant decrease in anxiety scores occurred not within the first 4 weeks but later in the treatment. Since the improvement in comorbid anxiety symptoms was correlated with the improvement in OCD symptoms, we considered that reductions in anxiety symptoms were not an independent factor for the outcome. Another possibility is that decreases in anxiety symptoms might also reflect the improvement with MPH-ER in social, academic, and behavioral areas, which is an impaired aspect of OCD, as some of the authors reported in adult studies with OCD (Nakao et al., 2014; Pauls et al., 2014).

There are several limitations of our study. Firstly, due to the limited duration of follow up, this potentially gives guidance to clinicians on the use of MPH-ER to achieve faster response in OCD adults, but does not answer how remission rates might vary over time compared to fluvoxamine and placebo. Future studies of MPH-ER augmentation should systematically explore longer periods of treatment. Secondly, the age at onset of OCD in our sample included over 20 years and under 20 years (see Table 1), although such retrospective numbers are prone to recall bias. It is increasingly appreciated that childhood-onset and adult-onset OCD may be genetically and etiologically distinct (van Grootheest et al., 2005). It may be that certain treatments will prove to be more efficacious in one or the other of these populations. Due to the small size of our sample and the imprecision of retrospective report of symptom onset, a stratified analysis based on onset was not possible in our sample; this should be addressed in future studies. Additionally, due to the use of methylphenidate, we excluded subjects with prior history of substance abuse and attention deficit hyperactivity disorder that may limit generalizability of the results.

5. Conclusion

Our study is the first comprehensive and well-controlled study to address the MPH-ER augmentation potential to enhance OCD clinical outcomes. The evidence shows that the combination of fluvoxamine and MPH-ER has a higher and faster response rates than fluvoxamine plus placebo, while no additional adverse events was found with combination treatment. The improved efficacy of combined treatment has significant clinical implication for refractory OCD and this encourages more research and clinical trials.

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Conflict of interest

All authors report no biomedical financial interests or potential conflicts of interest.

Contributors

HZ and FJ designed the study and wrote the protocol. HZ drafted the manuscript and completed a first version of the article. HYH and SW undertook the statistical analyses. GG, DQ and GL played an important role in the acquisition of clinical data. HH acquired and analyzed actigraphic data. All authors contributed to interpretations of the results of the pilot trial, revised the manuscript and approved the final version of the paper.

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