

Methylphenidate treatment in children with attention deficit hyperactivity disorder and comorbid social phobia

Pavel Golubchik^{a,d}, Jonathan Sever^{a,d} and Abraham Weizman^{b,c,d}

The aim of this study was to assess the response of social phobia (SP) symptoms to methylphenidate (MPH) treatment in children with attention deficit hyperactivity disorder (ADHD). Twenty-one ADHD patients with SP, aged between 8 and 18 years, received 12 weeks of MPH treatment. The severity of SP symptoms were assessed by the Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA), and the severity of ADHD symptoms was assessed by the ADHD Rating Scale at baseline and at endpoint. MPH treatment was associated with a significant decrease in the ADHD Rating Scale scores ($P < 0.0001$) and in the total LSAS-CA scores ($P = 0.013$), as well as the school-related items of LSAS-CA ($P = 0.011$). A significant correlation was found between the reductions in ADHD score and total LSAS-CA score ($P = 0.038$), especially in school-related SP. The improvement in ADHD symptoms because of MPH treatment correlates with a parallel improvement in SP.

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most prevalent neuropsychiatric disorder in pediatric population, causing difficulties in academic performance and in emotional and adaptive functioning and is associated with increased rates of comorbid anxiety and mood disorders (Kashani and Orvaschel, 1988; Biederman *et al.*, 1991; Pliszka, 1992; Lewinsohn *et al.*, 1997).

Social anxiety disorder, also known as social phobia (SP), is a common, disabling anxiety disorder that is characterized by excessive fear and/or avoidance of social situations and often co-occurring with ADHD (Solanto *et al.*, 2009). There are few studies on the nature of this comorbidity and its treatment. In children with ADHD, the presence of social and emotional problems results in more missed school days and higher rates of healthcare utilization (Classi *et al.*, 2012). Both ADHD symptoms (inattention, hyperactivity, or both) and poorer social competence show negative associations with cognitive outcomes (Ramos *et al.*, 2013). Thus, deficits in some aspects of executive function may account for the social problems often experienced by youth with ADHD (Tseng and Gau, 2013).

Methylphenidate (MPH) treatment reduces socially disruptive behavior in ADHD children (Campbell-Meiklejohn *et al.*, 2012). Although MPH has agonistic dopamine and norepinephrine activity and is the treatment of choice in ADHD, little is known about its influence on comorbid anxiety disorders in ADHD pediatric populations and particularly on SP.

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^aChild and Adolescent Outpatient Clinic, ^bResearch Unit, Geha Mental Health Center, ^cFelsenstein Medical Research Center, Sackler Faculty of Medicine, Tel Aviv University, Petah Tikva and ^dSackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Correspondence to Pavel Golubchik, MD, Child and Adolescent Outpatient Clinic, Geha Mental Health Center, 1 Helsinki St, PO Box 102, Petah Tikva 4910002, Israel

Tel: + 972 3 9258270; fax: + 972 3 9523598;
e-mail: pavelgo@gmail.com

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Most of the studies that evaluated the response to MPH of children suffering from anxiety and ADHD reported mixed results (Tannock *et al.*, 1995; Abikoff *et al.*, 2005; Goetz *et al.*, 2007; Bedard and Tannock, 2008; Ter-Stepanian *et al.*, 2010; Masi *et al.*, 2012). SP is especially prevalent and a frequently comorbid condition in primary school-age children with ADHD, and causes significant impairment in school, family, and social functioning as compared with children without anxiety disorder or ADHD (Lee *et al.*, 2012). MPH has been found to normalize the neural activity and to be associated with some improvements in emotional recognition and in social adaptation (Williams *et al.*, 2008). Monotherapy with atomoxetine – a selective norepinephrine uptake inhibitor approved for the treatment of ADHD (Geller *et al.*, 2007) in children and adults with ADHD – effectively improves the symptoms of both ADHD and comorbid social anxiety disorder (Adler *et al.*, 2009; Ravindran *et al.*, 2009).

The present study aimed to examine the effect of 3 months of treatment with MPH on comorbid SP in ADHD children. We hypothesized that, in ADHD children, improvement in ADHD symptoms would be associated with a parallel improvement in SP severity of pediatric patients suffering from ADHD/SP.

Methods

Participants

Twenty-one children with ADHD and comorbid SP, aged between 8 and 18 years, were identified in an outpatient

clinic at the Geha Mental Health Center, Petah Tikva, Israel. All children met the DSM-IV-TR ADHD and SP criteria established by a semistructured clinical interview, Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman *et al.*, 2000), of both children and their parents.

The severity of ADHD was assessed by the ADHD Rating Scale (ADHD-RS) (Dupaul *et al.*, 1998), whereas the severity of SP was assessed by the Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA) (Masia-Warner *et al.*, 2003), which was completed by parents' self-reporting. Children with a history of or with current organic brain syndrome, substance abuse, mental retardation, bipolar disorder, or suicidal ideation were excluded from the study.

All participants attended regular schools during their study and were from similar socioeconomic status. All children were psychostimulant naïve and were referred for ADHD assessment by either a pediatrician or a school consultant or were brought by their parents. SP was diagnosed by a child psychiatrist at the outpatient clinic. The study was approved by the Geha Mental Health Center Review Board and the Israeli Ministry of Health Board for Human Clinical Studies. All participants and their parents gave their written informed consent for participation in the study.

Procedure

Diagnosis

The diagnoses of DSM-IV-TR ADHD and SP were established following an interview according to the guidelines of K-SADS (Kaufman *et al.*, 2000) that was conducted by a board-certified senior child and an adolescent psychiatrist (P.G. or J.S.).

The severity of ADHD was assessed with the ADHD-RS (Dupaul *et al.*, 1994). The severity of SP symptoms was assessed by the LSAS-CA (Masia-Warner *et al.*, 2003). Only patients with an LSAS-CA score above the cutoff point of 23 were included in the study, as their cutoff represented the best balance of sensitivity and specificity for distinguishing between individuals with SP and typically developed controls (Masia-Warner *et al.*, 2003).

Measures

Rating scales

ADHD Rating Scale (Dupaul *et al.*, 1998): It is a clinician-rated scale with one item for each of the 18 DSM-IV-TR symptom criteria for ADHD. The severity for each item is rated on a scale between 0 (not present) and 3 (severe). The overall minimal possible score on the questionnaire is 0 and the maximal score is 54. In this study, it was used as a clinician-administered, semistructured parent-child interview during the first and the last (3 months later) visits intended to monitor the severity of ADHD symptoms.

Liebowitz Social Anxiety Scale for Children and Adolescents (Masia-Warner *et al.*, 2003): It is used to assess the severity of SP. The scale assesses the range of social interaction and performance in situations that may cause individuals with social anxiety to fear and/or to avoid. It is also an established measurement tool used by researchers to evaluate the efficiency of various anti-SP treatments, including pharmacological interactions. The modified social anxiety scale for children and adolescents includes 24 items. Each item consists of a given situation, the severity of the anxiety (0–3 = none, mild, moderate, severe), and the rate of avoidance (0–3 = never, occasionally, often, usually). School-related items include 1, 2, 3, 5, 7, 10, 11, 13, 14, 15, 16, and 24.

Treatment

All eligible patients received a daily dose of 0.5–1.0 mg/kg of MPH treatment, but the daily dose did not exceed 60 mg/day. At baseline (time 0, before initiating the treatment) and at endpoint (12 weeks later), the patients were assessed using the ADHD-RS and LSAS-CA.

The safety and tolerability of treatment were evaluated throughout the study by spontaneous self-report of adverse effects by the participants or their parents. The participants could report the side effects through telephone at any time during the 12-week study period.

Statistical analysis

Two-tailed, paired Student's *t*-test and Spearman's correlation test were used as appropriate. All results are expressed as mean ± SD.

Results

Age and sex

Twenty-one children and adolescents (18 boys and three girls), aged 11.8 ± 2.3 years, were included in this open-label 12-week study.

As expected, significant reductions in the ADHD-RS scores were obtained in the total group ($N = 21$) following MPH treatment; ADHD-RS 1 (baseline) versus ADHD-RS 2 (endpoint) scores were 32.5 ± 8.4 versus 24.0 ± 8.0 , respectively ($t = 5.5$, $df = 20$, $P < 0.0001$).

Similarly, significant decreases in the total LSAS-CA scores were obtained following MPH treatment in the total group ($N = 21$); LSAS-CA 1 (baseline) versus LSAS-CA 2 (endpoint) scores were 54.3 ± 22.6 versus 51.1 ± 21.7 , respectively ($t = 2.71$, $df = 20$, $P = 0.013$).

School-related items from the LSAS-CA improved significantly between baseline and endpoint: 33.7 ± 18.0 versus 31.4 ± 16.0 , respectively ($t = 2.8$, $df = 20$, $P = 0.011$). LSAS-CA items unrelated to school also improved slightly between baseline and endpoint: 19.7 ± 8.7 versus 18.7 ± 7.9 ,

respectively, but the change did not reach statistical significance ($t = 1.8$, $d.f. = 20$, $P = 0.088$).

Correlation

A significant correlation was found between the improvement in total LSAS-CA score and the improvement in ADHD symptoms [Spearman's correlation $r = 0.45$ (95% confidence interval 0.029–0.74), $N = 21$, $P = 0.038$].

Discussion

This study aimed to evaluate the MPH efficacy on both ADHD and SP symptoms in ADHD patients with comorbid SP. As expected, significant alleviation in ADHD symptoms was demonstrated following a 12-week MPH treatment, as reflected by the changes in the ADHD-RS scores ($P = 0.0001$). Almost all patients demonstrated an improvement in their ADHD symptoms, independent of the SP severity. However, following MPH treatment, a significant improvement was found in the SP levels as assessed by the total LSAS-CA scores.

When comparing school-related items in the LSAS-CA, at baseline and after 12-week MPH treatment, significant reductions were detected, whereas LSAS-CA items not related to school were not altered significantly. Such marked improvement in school-related SP symptoms may be ascribed to the effect of MPH on school performance, academic achievement, and self-efficacy leading to improvement in social functioning of the individual (Abikoff *et al.*, 2005) and to reduction in SP.

Not surprisingly, positive correlation was found between the improvements in ADHD symptoms and school-related SP symptoms. Similar results were previously reported in a study by Whalen *et al.* (1989) in which it was demonstrated that MPH treatment improved the peer status of hyperactive children, enhanced their social status, and increased the rate of nomination of hyperactive boys as 'best friends, cooperative, and fun to be with'.

Conzelmann *et al.* (2009) found that blunted emotional reactivity is pronounced in ADHD patients. They pointed out that MPH normalized social cognition, which is frequently impaired in those patients (Conzelmann *et al.*, 2011).

Such relationships may be explained by a common underlying pathogenic mechanism of ADHD and SP. The frequent co-occurrence of ADHD and SP in general and the parallel improvement in both syndromes following MPH treatment, as shown in our study, indicate that ADHD-related behavior may result in social problems. This may occur when there is a deficiency in social information processing that may lead to disruption in social cognition (Nijmeijer *et al.*, 2008; Uekermann *et al.*, 2010). Williams *et al.* (2008) investigated children and adolescents with ADHD using event-related potentials. They performed an evaluation before treatment with

MPH and again 4 weeks later and found that MPH treatment is associated with some improvements in emotional recognition. In contrast, untreated ADHD children may display social cognition deficits that may lead to lack of sufficient insights into others' emotions (Yuill and Lyon, 2007). Such putative improvement in social interaction following MPH treatment may be relevant to a parallel improvement in SP.

Considering the neurobiological dimension, social cognition impairments in ADHD may be because of dysfunction in the brain regions that are critically involved in social cognition and interaction. The increased level of distractibility and impaired executive function and attention in ADHD children may lead to insecure or anxious attachment and as a result to development of SP (Finzi-Dottan *et al.*, 2006). Thus, MPH-related improvement in social cognition may contribute to alleviation of SP. However, the relationship between SP and deficit in social cognition and emotional recognition is as yet unclear. Nevertheless, in our study, the alleviation of ADHD achieved by MPH treatment was accompanied by a parallel relief in SP.

MPH treatment in our study was well tolerated and safe; none of the participants reported intolerable side effects that would cause termination of the MPH treatment. These findings are consistent with previous studies that demonstrated the safety of stimulant treatment in ADHD pediatric patients with comorbid anxiety disorders (Diamond *et al.*, 1999; Abikoff *et al.*, 2005).

Limitations

The main limitations of our study are the open-label design, the relatively small sample size ($N = 21$), the relatively short treatment duration (12 weeks), and the lack of long-term follow-up. It is possible that, with a longer treatment duration, improvement would be obtained in SP symptoms that are unrelated to school as well.

An additional limitation is the lack of subjective reports. Subjective reports from parents, teachers, and the children themselves should be collected in a future study to complement the objective reports on reductions in the total LSAS-CA and school-related LSAS-CA scores following 3 months of treatment with MPH. Such subjective data would support the real world/clinical significance of the two-point and three-point reduction in the scores for total and school-related LSAS-CA items, respectively, especially in view of the large variance observed with these measures.

Conclusion

It appears that MPH treatment may be safe and effective in ADHD patients suffering from SP. It seems that, in ADHD/SP children, SP symptoms related to school situations respond better to short-term MPH treatment compared with the symptoms that are unrelated to school.

Large-scale, double-blind studies are needed to substantiate our findings. Studies comparing MPH monotherapy with MPH + CBT or MPH + selective serotonin reuptake inhibitors are required to reveal the best therapeutic option in this complex population.

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Conflicts of interest

There are no conflicts of interest.

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