Brief Report

A Post Hoc Subgroup Analysis of an 18-Day Randomized Controlled Trial Comparing the Tolerability and Efficacy of Mixed Amphetamine Salts Extended Release and Atomoxetine in School-Age Girls with Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Background: Because the scientific literature on the pharmacotherapy of attention-deficit/hyperactivity disorder (ADHD) is almost entirely based on the results of studies in samples consisting primarily of boys, much is unknown about the treatment response in girls.

Objective: This post hoc analysis compared the efficacy, tolerability, and time course of the effect of mixed amphetamine salts extended release (MAS XR) and atomoxetine in school-age girls with ADHD.

Methods: This was an intent-to-treat subanalysis of the data from girls enrolled in a multicenter, 18-day, randomized, double-blind, parallel-group, forced dose-titration, laboratory school study enrolling boys and girls aged 6 to 12 years with ADHD. The study compared the efficacy, tolerability, and time course of the effect of increasing doses of MAS XR (10, 20, and 30 mg/d) and atomoxetine (0.5 and 1.2 mg/kg per day). The laboratory school sessions were organized in cycles to include 12 hours of observation. Efficacy measures included the SKAMP (Swanson, Kotkin, Agler, M-Flynn, and Pelham) deportment rating subscale, the SKAMP attention rating subscale, and academic testing (number of math problems attempted and answered correctly). Adverse events were assessed throughout the study period. Tolerability and efficacy measures were assessed during laboratory school visits on days 7, 14, and 21.

Results: This subanalysis included 57 girls (median age, 9 years; 49.1% white, 22.8% black, 17.5% Hispanic) with a diagnosis of ADHD, combined subtype. Twenty-six girls were randomized to receive MAS XR and 31 were randomized to receive atomoxetine. Mean SKAMP deportment and attention subscale scores in the 2 groups were similar at baseline. Mean changes from baseline were significantly greater for MAS XR compared with atomoxetine on the SKAMP deportment score (–0.48 vs –0.04, respectively; $P < 0.001$) and SKAMP attention score (–0.45 vs –0.05; $P < 0.001$). The time course of medication effect, based on change from baseline in SKAMP deportment scores, indicated 12-hour efficacy for MAS XR at hours 2, 4.5, 7, 9.5, and 12 (all time points, $P < 0.01$ vs baseline) but not for atomoxetine. At the end of the study, both treatment groups had a significant increase from baseline in the mean number of math problems attempted and answered correctly ($P < 0.001$). Girls who received MAS XR attempted significantly greater numbers of problems compared with those who received atomoxetine ($P = 0.04$). Both MAS XR and atomoxetine were well tolerated. The most frequently occurring treatment-related adverse events in girls receiving MAS XR were decreased

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appetite (40.7%), upper abdominal pain (29.6%), insomnia (25.9%), and headache (14.8%). The most frequently occurring treatment-related adverse events in girls receiving atomoxetine were somnolence (28.1%), upper abdominal pain (15.6%), vomiting (15.6%), nausea (12.5%), and decreased appetite (12.5%).

Conclusion: This post hoc analysis in a subpopulation of girls with ADHD, combined subtype, found that 18-day treatment with MAS XR was significantly more effective than atomoxetine in terms of ratings of classroom behavior, attention, and academic productivity. (*Clin Ther*. 2006;28:280–293)

Key words: girls, attention-deficit/hyperactivity disorder, ADHD, Adderall XR, amphetamine, stimulant, laboratory school study, atomoxetine, Strattera, nonstimulant.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) has an estimated prevalence of 4% to 12% among school-age children and is reported to be more common in boys than in girls.[1] Although the male-to-female ratio for ADHD has ranged from 6:1 to 9:1 in clinical samples, the ratio in community-based population studies has ranged from 2:1 to 3:1.[2] Similarly, national surveys in the general US population have reported that boys are ~3 times more likely than girls to have a diagnosis of ADHD and to receive treatment for this condition.[3] Reviewing data from the US National Ambulatory Medical Care Survey for 1995–1999, Robison et al[4] reported that a diagnosis of ADHD was recorded at an estimated 14,402,090 office-based visits involving children aged 5 to 18 years; 74.2% of the patients were boys and 25.8% were girls. A larger proportion of girls (18.7%) in this sample was receiving no treatment compared with boys (13.9%), suggesting that undertreatment tends to occur more often among girls with ADHD than among boys with ADHD.

Despite these differences, girls and boys with ADHD have similar clinical correlates[5–8] and patterns of familiality.[7] Several direct comparative studies have found no consistent clinical differences between girls and boys with ADHD with regard to core symptom severity or social functioning.[6,9,10] These studies found, however, that compared with boys with ADHD, girls with ADHD exhibited significantly lower rates of rule-breaking (0.6% girls vs 2.4% boys) and other externalizing behaviors (12.9% girls vs 21.4% boys), and that these differences may play a role in the less frequent identification and referral of girls with ADHD.[6] Some evidence suggests the existence of subtype-specific gender differences.[10,11] Specifically, Graetz et al[11] detected gender differences with regard to core ADHD symptoms among children with ADHD of the combined and hyperactive/impulsive subtypes. For example, significantly greater proportions of boys with ADHD of the hyperactive subtype were rated as being impaired compared with girls with this ADHD subtype in terms of peer interactions (40.0% vs 9.5% respectively; $P = 0.01$) and schoolwork difficulties (42.5% vs 9.5%; $P = 0.008$). However, among children with ADHD of the inattentive subtype, girls had significantly higher scores on the Child Behavior Checklist Scale for social problems compared with boys (4.2 vs 3.1, respectively; $P = 0.03$). These data suggest that gender differences in both the presentation and level of impairment associated with ADHD may be subtype specific.

In the study by Robison et al,[4] stimulant medication was the most common treatment prescribed for ADHD in both sexes (42%). Psychostimulants are the currently recommended first-line pharmacotherapy for ADHD in children.[12] This recommendation is based on the results of numerous studies conducted over several decades that consistently reported the beneficial effect of psychostimulant therapy, as evidenced by rapid reductions from baseline in core ADHD symptoms.[13,14] As in trials of older immediate-release psychostimulant agents,[14–16] clinical trials of newer, long-acting formulations of methylphenidate and mixed amphetamine salts have generally indicated comparable improvements from baseline in ratings of core ADHD symptoms such as hyperactivity and inattention within hours of dosing.[14,17,18] More recently, improvements in core ADHD symptoms similar to those with psychostimulants have been described in school-age children after 1 week of treatment with the nonstimulant agent atomoxetine, a selective norepinephrine reuptake inhibitor.[19,20] The improvements in ADHD symptoms with these 2 types of agents appear to be similar; however, many aspects of atomoxetine's onset, magnitude, and duration of effect remain to be elucidated.

Because the scientific literature on the pharmacotherapy of ADHD is almost entirely based on the results of studies in samples consisting primarily of boys,[7] much is unknown about the specific treatment response in girls. One of the conclusions of the Na-