An Open Study of Adjunct OROS-Methylphenidate in Children and Adolescents Who Are Atomoxetine Partial Responders: I. Effectiveness

Timothy E. Wilens, M.D., Paul Hammerness, M.D., Linsey Utzinger, B.A., Mary Schillinger, B.A., Anna Georgiopoulos, M.D., Robert L. Doyle, M.D., MaryKate Martelon, M.P.H., and Kerry Brodziak, B.A.

Abstract

Objective: This study evaluated the effectiveness of adding OROS methylphenidate (MPH) to children who are partial responders to atomoxetine (ATMX) in the treatment of attention-deficit/hyperactivity disorder (ADHD).

Methods: This is a two-phase, 7-week, open study in children aged 6–17 years. Phase I initiated ATMX for a minimum of 4 weeks. Phase II entered partial responders to ATMX and added up to 54 mg of OROS MPH to their regimen. Subjects were assessed on multiple outcomes, including ADHD, executive functioning, and adverse effects. All analyses were intent to treat, with last observation carried forward.

Results: Fifty subjects who were partial responders to ATMX were treated with the combination therapy, with 41 subjects completing the entire protocol. There was a 40% reduction in their ADHD Rating Scale from the start of phase II through the end of study (from 21.14 ± 9.9 to 12.8 ± 9.7 , $t = 6.5$, $p < 0.0001$). In addition, there was a clinically significant reduction in the Clinical Global Index of ADHD severity from moderate to mild ADHD (start of phase II, 3.7; end of phase II, 2.7, 27%, $t = 6.5$, $p < 0.0001$), as well as improvements in executive functioning.

Conclusion: These results suggest that OROS MPH added to the regimen of partial responders to ATMX improves ADHD and executive functioning, necessitating further controlled trials.

Introduction

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a neurobehavioral and heterogeneous disorder of multiple etiologies (Goldman et al. 1998). It is a major clinical and public health problem because of its associated co-morbidity and disability in children, adolescents, and adults (Wilens et al. 2002). Hyperactivity and impulsivity have been correlated directly with impairment and social dysfunction, and longitudinally may predict more aggressive and delinquent behaviors (Loney et al. 1981; Loney et al. 1983). The cognitive symptoms of ADHD appear early in life and are refractory to change (Fischer et al. 1990; Seidman et al. 1997), persisting with diminution of hyperactivity and impulsivity over time (Hart et al. 1995). This further highlights the importance of the cognitive disturbances within ADHD.

There is an extensive literature regarding the generalized cognitive deficits described in ADHD in which disturbances in attention, memory systems, and executive function (EF) and their interaction emerge as important elements of these disturbances (for review, see Schachar et al. 1995; Halperin 1996; Lyon 1996; Pennington et al. 1996). Children with

ADHD are heterogeneous in their neuropsychological findings: Subaverage or relatively weak performance on various tasks of vigilance, verbal learning, memory, and EFs such as set shifting, planning and organization, complex problem solving, and response inhibition (Barkley et al. 1992; Grodzinsky et al. 1992; Schachar et al. 1995; Seidman et al. 1997). EF has been linked to ADHD by nature of the self-regulation and dysfunction in information processing in ADHD (Schachar et al. 1995; Pennington and Ozonoff 1996). Although variably defined, EF generally refers to “mental control” processes that are “proactive” and include interference control, effortful and flexible organization, and strategic planning, which include anticipatory and goal-oriented “preparedness to act” (Denckla 1989; Pennington and Ozonoff 1996).

Among medication treatments for ADHD, atomoxetine (ATMX) and the stimulants are Food and Drug Administration (FDA) approved and remain among the first-line agents (Wilens et al. 2000; Greenhill et al. 2002; Pliszka et al. 2006). An extensive short-term literature indicates that stimulants and nonstimulants diminish behaviors prototypical of ADHD, including motoric overactivity, impulsivity, and inattentiveness (for review, see Pliszka et al. 2006). Although clearly

effective for ADHD, some cognitive and social operations are not fully responsive to monotherapy with these agents. Most ADHD children continue with clinically significant symptoms while under treatment (Swanson et al. 2001). For instance, only 30–50% of youths have >50% reduction in their symptoms with stimulants alone. Similarly, approximately one half to two thirds of children and adolescents with ADHD respond favorably to ATMX (Michelson et al. 2002), and the reported effect size in children and adolescents is between 0.6 and 0.7 (Faraone et al. 2004), resulting in persistent symptoms and impairment in some youth.

What is becoming increasingly recognized is the impairment associated with residual psychopathology and the need to optimize treatment. As part of a longitudinal study, we previously reported that the majority of ADHD youths failed to achieve “normalization” over 4 years (defined by the non-ADHD control group) in their ADHD symptoms. Also, a lack of normalization of ADHD symptoms was associated with academic failure, interpersonal and family dysfunction, and general social dysfunction (Biederman et al. 1998). Given the increasingly recognized notion of impairment of ADHD with residual symptoms (Rappaport et al. 1994; Biederman et al. 1998; Swanson et al. 2001) and the importance of targeting treatment to normalize function (and symptoms) of ADHD, the combination of two treatments makes conceptual sense in addressing ADHD in some youths.

One combination increasingly used clinically in ADHD is stimulants plus ATMX. For example, chart reviews and use data suggest that up to one third of prescriptions of ATMX in the United States are in combination with a stimulant (IMS Health data) (Adler et al. 2006). Despite this degree of combined pharmacotherapy of stimulants and ATMX, surprisingly little data are available. One small case series in 4 subjects reported a favorable outcome (Brown 2004). A small pilot study was presented (Carlson et al. 2007) using ATMX and OROS methylphenidate (MPH). In 25 children who did not respond to stimulants, ATMX was titrated to full dose for 4 weeks, at which point subjects not to be considered “responders” were randomized to receive ATMX + OROS MPH ($n = 9$) or placebo ($n = 12$) for an additional 6 weeks, resulting in no significant differences between groups. While helpful, the small sample size receiving ATMX + OROS MPH and preselection of subjects who were resistant to previous stimulant trials and retested on MPH limits the findings.

The potential use of ATMX and stimulants may be of value to youths with residual symptoms such as ADHD or EF dysfunction. To this end, we studied openly the use of OROS MPH adjunctly in children and adolescents who were partial responders to ATMX. Based on the mechanistic differences in ATMX and OROS MPH (Wilens 2006) coupled with the growing literature of concomitant treatments, we hypothesized that the combination of OROS MPH plus ATMX would be superior to ATMX alone for ADHD. We secondarily hypothesized that aspects of cognitive functioning such as EF would be improved specifically with the addition of OROS MPH compared to ATMX alone.

Methods

Subjects

Eligible subjects had a diagnosis of ADHD by clinical interview confirmed by structured psychiatric interview. Ex-

cluded from the study were potential subjects who were on other psychotropic medications, had clinically significant chronic medical condition(s) (including history of structural cardiac defects or cardiovascular symptoms) (Gutgesell et al. 1999), had clinically significant abnormal baseline laboratory values, were pregnant or nursing females, had mental retardation (intelligence quotient [IQ] <70), had organic brain disorders, or had untreated seizure disorders. Likewise, youth with a lifetime diagnosis of psychosis, bipolar disorder, schizoaffective disorder or schizophrenia, or a current (past 30 days) diagnosis(es) of unipolar depression, panic or generalized anxiety disorder, or Tourette’s disorder were also excluded. Subjects with a recent history (e.g., 3 months) of a substance use disorder were not enrolled. Subjects with a clinical history of a partial response to ATMX or MPH were included; conversely, those with a history of no response or intolerable adverse effects (AEs) to either ATMX or MPH were excluded for ethical reasons. The study was approved by the Massachusetts General Hospital Institutional Review Board. Parents of subjects provided informed consent and all subjects 12 and older provided assent.

Clinical trial

The study was an open 4-week treatment of ATMX with partial ADHD responders completing a subsequent 3-week study of adjunct OROS MPH. After screening for ADHD, youths underwent a full structured psychiatric, neuropsychological, and clinical interview. Eligible ADHD youths who had been washed out from their previous treatment (if any) were then started on ATMX openly for a minimum of 4 weeks; then partial responders received OROS MPH in addition to ATMX for 3 additional weeks.

Definition of partial response. We chose partial response criteria that were conceptually similar to those of a study of ATMX partial responders $\pm$ OROS MPH (Carlson et al. 2007). Carlson et al. placed subjects on ATMX in addition to a placebo at the start of phase I. At the end of phase I, subjects with a Clinical Global Impression–Improvement (CGI-I) rating of 1 or 2 (much or very much improved) remained on placebo and ATMX in phase II, whereas subjects who continued to have substantial symptoms were either given a placebo or OROS MPH and ATMX in phase II. Of the 25 subjects enrolled, 4 were dropped due to adverse events, perceived lack of efficacy, and physician decision; 4 remained on ATMX plus placebo; 9 were randomly assigned to ATMX plus OROS MPH; and 8 were randomly assigned to ATMX plus placebo (Carlson et al. 2007).

We further expanded these criteria. For ethical reasons, subjects in our study who received ATMX with intolerable adverse effects or no response (CGI-I of 4–7, none or worse) were not eligible for further treatment with OROS MPH and were discontinued from the protocol. Similarly, subjects with a CGI-I of 1 (very much improved) and Clinical Global Impression–Severity (CGI-S) rating of ≤ 2 (borderline mentally ill) were not eligible for further treatment and were discontinued from the protocol.

Dosing. McNeil provided all doses of OROS MPH. On the basis of published controlled data (Michelson et al. 2001; Michelson et al. 2002) as well as manufacturer and FDA recommendations, ATMX was initiated using a weight-based

nomogram at 0.5 mg/kg per day to be administered initially at bedtime with a snack for 2 weeks and then increased to 1.4 mg/kg per day (or 100 mg maximum) divided into either daily (a.m.) or twice daily dosing (a.m. and p.m. dosing) based on tolerability. Subjects who were already on a stable regimen of ATMX and manifested a partial response to ATMX were eligible to bypass phase I and enter directly into phase II of the trial and placed on OROS MPH. OROS MPH was titrated openly in 18-mg increments weekly to a target dose of 54 mg, the maximum dose recommended by the FDA at the start of the study. Medication could be adjusted downward if the subject developed greater than or equal to moderate AEs due to the treatment. Medical compliance was assessed by pill counts at each follow-up visit and was >80% for all subjects.

Assessments

At baseline/screening and each week thereafter, all subjects had efficacy measures (ADHD), vital signs, and adverse effects assessed. At the beginning and end of each study period (or at last study visit for premature discontinuation), all subjects had EF assessment and an electrocardiogram (ECG).

All diagnostic assessments were made using *Diagnostic and Statistical Manual of Mental Disorder*, 4th edition (DSM-IV)-based (American Psychiatric Association 1994) structured interviews by raters with bachelor's or master's degrees in psychology who had been extensively trained and supervised by the senior investigators (T.W., J.B.). Psychiatric assessments for subjects under 18 years old relied on the DSM-IV Kiddie Schedule for Affective Disorders–Epidemiologic Version (KSADS-E) (Ambrosini 2000) and were based on independent interviews with the primary caregivers. For every diagnosis, information was gathered regarding the ages at onset and offset and treatment history.

ADHD Rating Scale (ADHD RS). Our main dependent variable was the ADHD Rating Scale (DuPaul 1990; DuPaul et al. 1998), which assessed each of the individual symptoms of ADHD in DSM-IV (0–3 on a scale of severity). Psychometric properties have been established in children shown to be sensitive to stimulant and atomoxetine drug effects (DuPaul 1990; DuPaul et al. 1998; Faries et al. 2001) and have been used in clinical trials to demonstrate efficacy for ADHD. The time frame of the ADHD RS was the past week. An unblinded investigator assessed the ADHD RS IV.

As a secondary outcome, we also collected the CGI Ratings (National Institute of Mental Health 1985), a widely used scale that measures the overall severity and improvement. We used two subscales: the CGI-S (1 = not ill, to 7 = extremely ill) and the CGI-I (1 = very much improved, to 7 = very much worse).

Behavioral Rating Inventory of Executive Functioning (BRIEF). The BRIEF was a secondary outcome and was completed by most youths. The BRIEF is a reliable and valid behavior rating scale of EF in children and adolescents (Gioia et al. 2000; Gioia et al. 2002; Mahone et al. 2002; Vriezen et al. 2002). The BRIEF is an 86-item questionnaire for parents and teachers of children ages 5–18 years that enables professionals to assess EF behaviors in the home and school environments. Specific subdomains that make up the BRIEF include the ability to: (1) Initiate behavior; (2) inhibit competing actions or stimuli; (3) select relevant task goals, plan, and organize a

means to solve complex problems; (4) shift problem-solving strategies when necessary; (5) monitor and evaluate one's own behavior; (6) organize one's materials and space; (7) modulate one's emotional responses; and (8) hold stimuli in working memory. The test–retest correlations were at least 0.8 for the indexes. The T scores on test–retest were also carried out and indicated the stability of the T scores over 2- to 3-week intervals, supporting the notion that repeating the BRIEF would have no significant variability expected due to the instrument itself (Gioia et al. 2000).

Statistical analysis

Using conservative estimates (effect size of 0.5 versus baseline; dropout rate of 15%; 80% power; 0.05 level of significance), we calculated that a total number of 40 children would be necessary for our study. For the purposes of our main aim to examine the effectiveness of adjunct OROS MPH in ATMX partial responders, we included in our analyses only those subjects who were entered into phase II ($n=50$; see Fig. 1). In these 50 subjects, all analyses were intent to treat (at least one dose of OROS MPH) with last observation carried forward. Differences between the ADHD RS, BRIEF scores, and vital signs at the start and end of each phase were analyzed using paired *t*-tests. The nonparametric Wilcoxon signed-rank test was used to analyze differences in the CGI-S scales. McNemar's test was used to assess differences in the binary variables that estimated improvement at the end of each phase. *t*-Tests and chi-squared tests were used to determine differences between included, added, and dropped subjects. An alpha level of 0.05 was used to assert statistical significance; all statistical tests were two-tailed. Data are presented as mean $\pm$ standard deviation (SD) unless otherwise stated. We calculated all statistics using STATA 10.0.

Results

In all, 82 subjects were exposed to ATMX and 50 were exposed to the combination of ATMX and OROS MPH. Demographic features of the sample that entered into phase II are presented in Table 1. The subjects were predominantly male subjects with mainly the combined subtype of ADHD. A large minority (44%) had previous medication exposure, and oppositional defiant disorder was the most common lifetime co-morbidity (37%).

Of the 50 subjects enrolled into phase II, 40 started at baseline, whereas 10 were already on ATMX and entered directly into the beginning of phase II (Fig. 1). There were no differences between subjects who started at baseline compared to those who directly entered phase II on demographic variables including co-morbidity; however, those 10 subjects who were previously on ATMX had a higher ADHD RS scores (29.1) than those who began the study at baseline and were placed on ATMX (19.15; $t = -3.1, p < 0.01$). There was no difference in the ADHD RS at the end of phase II between those who were added at the start of phase II and those who began at baseline on ATMX ($t = -0.5, p > 0.05$). There were no meaningful differences in outcomes for the ADHD RS and the CGI-S scores between the total sample and the sample that began at baseline.

Of the 50 subjects entered into phase II, 41 subjects completed the protocol (8 subjects had adverse events and 1 subject dropped because of a physical illness unrelated to

FIG. 1. Subject disposition for all subjects who signed a consent form.

medication). There were no differences between included and dropped subjects in phase II on any baseline demographic variables, including co-morbidity. However, there was a clinically and statistically significant difference in CGI-S with dropped subjects having a higher last observed score (3.7)

TABLE 1. DEMOGRAPHIC FEATURES AND COMORBIDITY OF SAMPLE THAT BEGAN PHASE II ($N=50$)[†]

	Mean $\pm$ SD or N (%)
Age	9.3 $\pm$ 2.5
Sex	
Male	38 (76)
Female	12 (24)
ADHD Subtype	
Combined type	27 (54)
Inattentive type	19 (38)
Hyperactive/impulsive type	4 (8)
Prior Medication Treatment	22 (44)
Lifetime Comorbidity	
Disruptive disorders	
Oppositional defiant disorder	20 (40)
Conduct disorder	2 (4)
Mood disorders	
Major depression	1 (2)
Anxiety disorders	
Panic disorder	1 (2)
Agoraphobia	4 (8)
Social phobia	5 (10)
Specific phobia	7 (14)
Obsessive compulsive disorder	1 (2)
General anxiety disorder	3 (6)
Separation anxiety disorder	9 (18)
Substance use disorders	0 (0)

[†]Subjects entered into phase II if they had taken atomoxetine (ATMX) for at least four weeks and were partial responders to ATMX.

ADHD, attention-deficit/hyperactivity disorder.

than those who completed the study (2.5; $t = -3.1$, $p < 0.05$). The mean weight-corrected doses of ATMX at the beginning and end of phase II was 1.1 mg/kg per day and for OROS MPH was 1.0 mg/kg per day.

ADHD-Rating Scale. We first examined our primary outcome, the ADHD RS (Fig. 2). Compared to baseline, at the end of phase I there was a 44% reduction in subjects' ADHD RS (baseline, 34.3 ± 8.4 ; end of phase I, 9.2 ± 8.7 ; $t = 11.11$, $p < 0.0001$). ATMX partial responders ($n = 50$) who entered into phase II and were treated with OROS MPH had an additional clinically and statistically significant 40% reduction in the ADHD RS (start of phase II, 21.14 ± 9.9 ; end of phase II, 12.8 ± 9.7 ; $t = 6.5$, $p < 0.0001$).

Clinical Global Impression. We also examined response to treatment using the categorical CGI-S and CGI-I (Fig. 3). For the CGI-S, there was a clinically and statistically significant improvement from the start of phase II (4.5, markedly/moderately ill) to the end of phase II (2.7, borderline mentally ill/mildly ill; $t = 6.5$, $p < 0.0001$) for ATMX partial responders ($n = 50$). Using a categorical assessment of response, there was no significant difference in the percent of subjects with much to very much improvement on the CGI-I between entry into phase II and the study end (65% and 78%; $\chi^2 = 2.8$, $p = 0.10$; $n = 40$).

BRIEF Subscales. We also examined the effects of combined treatment using an instrument sensitive to clinical features of EF, the BRIEF (Table 2). Only 38 subjects completed the BRIEF (mean age 9.4 ± 2.7). There were significant improvements in EF at the end of phase I as well as at the end of phase II. Compared to baseline, subjects who received ATMX alone manifested significantly improved scores on all of the BRIEF subscales, including shifting, initiation, working memory, planning/organizing, and organization of material ($ps < 0.05$). Compared to the start of phase II, subjects who received ATMX + OROS MPH resulted in clinically and statistically significant improvements in 8 of the 9 BRIEF subscales,

FIG. 2. Mean Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) scores. Start of phase II versus end of phase II ($t = 6.5$; $p < 0.0001$). Subjects were entered into phase II if they had taken atomoxetine (ATMX) for at least 4 weeks and were partial responders to ATMX. All analyses were intent to treat with last observation carried forward. OROS MPH = OROS methylphenidate.

including inhibition, initiation, working memory, planning/organizing, organization of material, and monitoring. Of note, the combination of ATMX + OROS MPH resulted in all of the mean BRIEF subscales improving to within one standard deviation of a mean of 50 suggestive of “normalization.”

Safety/tolerability. There were no serious adverse events. There were no clinically meaningful changes in ECG, cardiovascular vital signs, or blood chemistries associated with the combination. Side effects were generally tolerable, with insomnia, headache, appetite loss, and irritability most commonly reported on the combined regimen.

Discussion

The results of this open study of adjunct OROS MPH in ATMX partial responders indicate improved outcome for core ADHD symptoms. Likewise, we secondarily found improved

clinically related aspects of EF. While limited by the study design, these data suggest that the combination of stimulants plus ATMX may be beneficial in the treatment of ADHD and associated EF related deficits and warrants further study under controlled conditions.

Our current data are similar to a prior reported case series of 4 children who previously had an impartial response to monotherapy with either a stimulant or ATMX (Brown 2004). These children were placed on stimulants with ATMX added ($n = 2$) or on ATMX with stimulants added. Improvements in ADHD and across a “wide range of symptoms” were noted in subjects.

Our current study lacked a MPH-only comparator. Of interest, in comparing our data for ADHD and EF outcome in the combined group to ongoing trials of MPH alone in a similar group of youths (Wilens 2008), we found that our combined group had improved ADHD symptom score reductions, a higher percentage of responders, and more improvement in

FIG. 3. Mean Clinical Global Impressions–Severity (CGI-S) scores. Start of phase II versus end of phase II ($t = 6.5$; $p < 0.0001$). Subjects were entered into phase II if they had taken atomoxetine (ATMX) for at least 4 weeks and were partial responders to ATMX. All analyses were intent to treat with last observation carried forward. OROS MPH = OROS methylphenidate.

TABLE 2. SUBSCALES OF THE BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTIONING (BRIEF)[†]

Subscale	Baseline	At the start of phase II (ATMX + MPH)	End of phase II (ATMX + MPH)
Inhibition	63	60	55
Shifting	57	54	51*
Initiation	66	59	53***
Working memory	73	66	59***
Emotional control	55	53	52
Plan/organize	67	63	56***
Organization of material	63	59	55**
Monitor	65	62	56***

[†]The BRIEF was completed by 38 subjects (50% were on stimulants prior to study entry).

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

ATMX, atomoxetine; MPH, methylphenidate.

clinical features of EF than associated with ATMX alone. While limited, these observations derived from historical data suggest that the combination of ATMX + OROS MPH resulted in an additive effect over ATMX or MPH alone. Clearly, further controlled studies comparing ATMX or MPH alone and in combination are necessary to validate these observations.

Our data add to a small literature on combined pharmacotherapy (Pataki 1993; Wilens et al. 1995; Wilens et al. 2008). The limited controlled data on combined regimens shown useful for ADHD include stimulants and tricyclic antidepressants (Pataki et al. 1993), ATMX (Carlson et al. 2007), or alpha agonists (Kurlan 2002; Hazell et al. 2003; Palumbo et al. 2008). In four of these controlled studies, the combinations resulted in improvements in ADHD over those with stimulants alone. Moreover, in addition to improved co-morbid conditions (e.g., tics), improved cognition and complex problem solving were reported (Pataki et al. 1993; Kurlan 2002).

In the current study, we also found intriguing findings with improved EF outcome in those receiving ATMX + OROS MPH that exceeded ATMX alone. Not only was there stepwise improvement in EF with ATMX alone and then in combination with OROS MPH, but the combination resulted in scores of EF that were within 0.5 SD of normalization of EF. Our findings, if supported in further work, may suggest specific improvements in EF that may be associated with the combination of agents that may have somewhat different mechanisms of action (Wilens 2006). Whereas ATMX is a highly selective noradrenergic agent, MPH has more mixed catecholaminergic effects (Wilens 2008). These mechanistic differences may account for our observed improvements in clinical aspects of EF on the BRIEF. Moreover, we have noted improved EF on the combination of ATMX + OROS MPH compared to our historical data on MPH alone (Wilens 2008). While preliminary in nature, these findings warrant further examination given an emerging literature highlighting the importance of EF and residual ADHD symptoms in ADHD (Swanson et al. 2001; Biederman et al. 2004).

There are a number of methodological limitations to our study. Because the study was open in nature, there may have been bias in our observations of outcome. The relatively small sample size may have underestimated our findings. For ethical reasons and to approximate clinical practice, we used an *a priori* definition of partial response. However, our definition of ATMX partial responders has not been validated. We excluded youths with significant current psychiatric comorbidity, restricting the generalization of the findings to more co-morbid, clinically relevant populations. We did not include a group who received a placebo, MPH, or ATMX alone, limiting our ability to ascribe our findings of the combination compared to a placebo, MPH, or ATMX alone. We also did not collect information on the duration of treatment prior to entrance into the study. For subjects entering into phase I, we relied on a minimum of 4 weeks on ATMX that may have been inadequate. We also included subjects who entered directly into phase II who were already on ATMX for clinical reasons and manifested a partial response, which may have confounded our results. For measurement of executive functioning, we relied on the self-report of children and adolescents with the assistance of their parents and caregivers on a clinical scale of executive functioning, the BRIEF, instead of repeated neuropsychological testing.

Despite these limitations, this study is clinically relevant because in patients with some improvement in symptoms and functional impairment on ATMX, OROS MPH appears to add to the overall outcome of ADHD. Similarly, for youths with more extensive putative executive function deficits, the combination of ATMX and MPH may be helpful. Prior to specific recommendations, further examination of safety and tolerability issues on the combination (see Hammerness et al., 2009) and replication of efficacy data under controlled conditions with adequate comparators are necessary.

Disclosures

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Address correspondence to:

Timothy E. Wilens, M.D.

*Pediatric Psychopharmacology Unit
Massachusetts General Hospital, YAW 6A*

55 Fruit Street

Boston MA 02114

E-mail: twilens@partners.org