The Effectiveness of Short- and Long-Acting Stimulant Medications for Adolescents With ADHD in a Naturalistic Secondary School Setting
William E. Pelham, Bradley H. Smith, Steven W. Evans, Oscar Bukstein, Elizabeth M. Gnagy, Andrew R. Greiner and Margaret H. Sibley
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What is This?
Between 70% and 80% of children diagnosed with ADHD continue to exhibit core ADHD symptoms and related impairments in adolescence (Bagwell, Molina, Pelham, & Hoza, 2001; Barkley, Fischer, Edelbrock, & Smallish, 1990; Edwards, Barkley, Laneri, Fletcher, & Metevia, 2001; Kent et al., 2011; Sibley et al., 2012). As with children, Central Nervous System stimulant medication is often the first-line approach to treating adolescents with ADHD—it is easily accessible, affordable, and offers immediate symptom relief in up to 70% to 85% of recipients (Findling et al., 2011; Greenhill et al., 2002; Pliszka, 2007; Smith, Waschbusch, Willoughby, & Evans, 2000). Compared with children, there are fewer studies of stimulant medication for adolescents with ADHD (Smith et al., 2000). Existing studies demonstrate that medication delivered in analogue settings clearly produces an acute effect on teen academics (Evans et al., 2001) and disruptive behavior (Smith et al., 1998). Parents also report that stimulant medication produces improvements in their adolescents’ ADHD symptoms (Findling et al., 2011). These studies establish the efficacy of stimulant medication for teens. However, less is known about the effectiveness of this approach as a treatment in real-world settings. The complicated nature of the secondary school environment and documented adolescent nonadherence with stimulant medication may undermine the exportability of this approach.

Medication studies that rely on parent-reported outcomes and analogue settings have limitations. Parents may possess biases and their reports may not detect weekly changes in adolescent behavior. Of principal concern is the presence of a halo effect for ADHD symptom ratings (Hartung et al., 2010) and parents’ limited opportunities to directly observe their teenage children (Steinberg & Morris, 2001). Furthermore, analogue settings allow for careful medication assessments, but controlled conditions (Evans et al., 2001; Smith et al., 1998) may not elicit an adolescent’s typical behavior or impairments. Medication may be
efficacious in some daily activities but not others, limiting the external validity of standardized analogues. Perhaps most importantly, adolescents with ADHD are known to resist stimulant medication (Charach & Gajaria, 2008; Marcus, Wan, Kenner, & Olfsen, 2005; McCarthy et al., 2009; Perwien, Hall, Swensen, & Swindle, 2004). Analogue studies do not account for nonadherence. Therefore, they do not accurately assess the true effectiveness of stimulant medication in adolescents.

The current study is a placebo-controlled, cross-over investigation of the effectiveness of short- and long-acting stimulant medications for adolescents with ADHD. The study was conducted in each adolescent’s natural school environment. Measures of efficacy and adherence were collected using school records, direct observation, and teacher ratings. We hypothesized that across domains, adolescents would show an equally positive response to short- and long-acting stimulant medications compared with placebo. However, we believed that these effects would be smaller than previously reported in analogue studies. We also hypothesized that medication adherence would be stronger for the long-acting than the short-acting formulation.

Method
Participants
Participants (N = 30) were recruited from a sample of adolescents with ADHD who previously or currently attended outpatient services at the Western Psychiatric Institute and Clinic. Adolescents ranged in age from 12 to 17 years (M = 14.1). Participants were 10% female, 87% Caucasian, and possessed a median family income of US$36,000. School setting was as follows: public middle (n = 12), public high (n = 11), private (n = 6), and vocational (n = 1). All participants met Diagnostic and Statistical Manual of Mental Disorders (3rd ed., revised; American Psychiatric Association, 1987) diagnostic criteria for ADHD, 42% for oppositional/defiant disorder (ODD), 25% for a learning disability, and 17% for conduct disorder (CD). Diagnosis was made from parent and teacher rating scales and structured parent interviews. Exclusionary criteria included a full scale IQ < 80, history of seizures, severe side effects, or other medical problems that would contraindicate stimulant medication, and current or historical drug/alcohol abuse. Participants and parents signed IRB-approved informed consent. Six participants provided insufficient data for study inclusion. Six participants possessed only medication adherence data.

Procedure
Participants were randomly assigned to one of three medication conditions for each 12-week grading period: short-acting methylphenidate (MPH; t.i.d.), long-acting pemoline (q.a.m.), or placebo (q.a.m.). MPH doses were based on the recommendation from these previously conducted medication assessments. The afternoon dose of MPH was half the morning and noon dose (maximum dose: 30 mg in a.m., 30 mg at noon, and 15 mg in p.m.). Pemoline doses were about 5.6 times higher than MPH (Pelham, Greenslade et al., 1990), with a maximum daily dose of 112.5 mg q.a.m. In the pemoline condition, participants began at 37.5 mg and were titrated upward to the target dose with increases every 2 days. Side effects ratings were collected and dosing changes were decided by the clinic and medication directors. Medication was placed in opaque capsules, dispensed in childproof bottles, and divided by dosing schedule (e.g., morning, noon, afternoon).

Side-effect ratings were completed at 3-week intervals for the duration of each medication condition (i.e., school marking period). Participants mailed ratings and adherence calendars to the clinic. Adolescents, parents, teachers, and school administrators were asked to report abrupt deterioration in functioning. If deterioration was the result of a medication change, the dose was discontinued and the adolescent began the next randomized condition. At least two teachers (morning and afternoon) were selected for each adolescent to complete brief behavioral ratings 3 times per grading period. Grades were collected from the school. Participants and parents visited the clinic at the end of each grading period to complete standardized rating scales.

Measures
Grades. We obtained adolescents’ report cards and computed grade-point averages (GPA; on a 0-4 scale with 4 indicating “A” and 0 indicating failure) for each marking period. When report cards were unavailable (n = 6), teachers’ reports of the student’s class grade was used.

ADHD symptoms and academic impairment. Teachers completed the IOWA Conners Rating Scale (Pelham, Milich, Murphy, & Murphy, 1989) at 3-week intervals for each grading period. Inattention/Overactivity (I/O) and Oppositional/Defiant (O/D) subscale scores were computed across teachers for each participant in each drug conditions. Teachers also completed the Impairment Rating Scale (IRS; Fabiano et al., 2006), which measures impairment in domains such as peer and teacher relationships, academics, and self-esteem. Teachers also completed items regarding the adolescents’ academic habits (e.g., prepared for class, took notes, on time).

Adherence. Percentage of doses taken was the index of adherence. Medication adherence was computed using pill counts and adherence calendars. When calendars were unreturned, pill counts alone were used. Four participants offered adherence data for only two conditions.
Satisfaction. Parents and adolescents completed 10-point Likert-type ratings of their satisfaction with each drug condition. Ratings ranged from 1 (very bad, don’t want to take in future) to 10 (very good, want to take in future), with 5 being neutral. These ratings were used to evaluate global satisfaction with the medication, including its effects and dosing schedule.

Results

Measures of efficacy were analyzed using a repeated-measures ANOVA with placebo, MPH, and pemoline conditions. Follow-up pairwise contrasts were conducted as appropriate.

Grades. There was no significant effect of drug condition on GPA. Means showed an improvement from placebo ($M = 1.63$, $SD = 0.79$) in both medication conditions ($M$s = 1.92, 1.97, $SD$s = 0.63, 0.81 for MPH and pemoline, respectively) with effect sizes of 0.4. Clinical improvement occurred for slightly more than half the sample: 11 students improved their GPA by at least a letter grade in at least one drug condition, but most GPAs remained in the “D” range.

ADHD symptoms and impairment. MPH (see Table 1) produced a significant improvement in I/O, $F(1, 16) = 4.61, p < .05$, and a marginal effect for the O/D rating, $F(1, 16) = 3.26, p = .09$. Teachers’ ratings of impairment showed no significant effects of drug in any domains. On teachers’ ratings of academic habits, there was a significant medication effect for note-taking, $F(2, 16) = 3.79, p < .05$, and marginal effects for turning in assignments, $F(2, 16) = 4.86, p = .06$, and class preparation, $F(2, 16) = 4.04, p = .06$. Pairwise comparisons (see Table 1) revealed that MPH produced the significant effect for note-taking, while both medication conditions produced marginal effects for class preparedness and on-time work completion.

Adherence. Pemoline was contrasted with MPH t.i.d. ($n = 23$; see Table 2). Pemoline adherence did not differ from morning MPH dose. There were significant differences between morning and noon, $F(1, 20) = 9.5, p < .01$, and afternoon, $F(1, 20) = 16.1, p < .01$, MPH doses. Mean adherence rates were 92.2% ($SD = 12.5$%) for pemoline, 96.0% ($SD = 5.9$%) for morning MPH, 76.4% ($SD = 31.4$%) for noon MPH, and 69.0% ($SD = 27.6$%) for afternoon MPH.

Satisfaction. A 3 (drug: placebo, MPH, pemoline) × 2 (rater: parent, adolescent) ANOVA was conducted for satisfaction ratings (see Table 1). Results showed a significant effect of drug, $F(2, 46) = 4.99, p < .05$, with no effect for rater or the interaction. Across raters, the MPH condition was significantly superior to placebo, $F(1,23) = 7.7, p < .05$, and pemoline, $F(1, 23) = 5.71, p < .05$. The highest ratings were given by parents in the MPH condition.

Table 1. The Effect of Stimulant Medication on School Performance

<table>
<thead>
<tr>
<th>Rating</th>
<th>Placebo</th>
<th>MPH t.i.d.</th>
<th>MPH t.i.d.</th>
<th>Pemoline</th>
<th>Pemoline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M(SD)$</td>
<td>$M(SD)$</td>
<td>$M(SD)$</td>
<td>$M(SD)$</td>
<td>$d^a$</td>
</tr>
<tr>
<td>Inattention/overactivity</td>
<td>4.61 (2.16)</td>
<td>3.45 (1.47)**</td>
<td>.53</td>
<td>4.15 (2.18)</td>
<td>.21</td>
</tr>
<tr>
<td>Oppositional/defiant</td>
<td>2.09 (1.83)</td>
<td>1.45 (1.52)**</td>
<td>.35</td>
<td>2.09 (2.55)</td>
<td>.00</td>
</tr>
<tr>
<td>Peer relations$^b$</td>
<td>2.19 (1.69)</td>
<td>1.72 (1.11)</td>
<td>.28</td>
<td>1.97 (1.64)</td>
<td>.13</td>
</tr>
<tr>
<td>Teacher relations$^b$</td>
<td>1.41 (1.47)</td>
<td>1.08 (0.69)</td>
<td>.22</td>
<td>1.26 (1.18)</td>
<td>.15</td>
</tr>
<tr>
<td>Academics$^b$</td>
<td>2.75 (1.49)</td>
<td>2.68 (1.00)</td>
<td>.04</td>
<td>2.30 (1.26)</td>
<td>.30</td>
</tr>
<tr>
<td>Overall impairment$^c$</td>
<td>1.63 (1.07)</td>
<td>1.42 (0.64)</td>
<td>.20</td>
<td>1.57 (1.14)</td>
<td>.06</td>
</tr>
<tr>
<td>Prepared for class$^d$</td>
<td>73.4 (19.3)</td>
<td>85.2 (10.8)**</td>
<td>.63</td>
<td>88.1 (9.7)**</td>
<td>.79</td>
</tr>
<tr>
<td>Notes taken$^d$</td>
<td>66.5 (20.5)</td>
<td>85.7 (12.9)**</td>
<td>.95</td>
<td>76.3 (28.8)</td>
<td>.48</td>
</tr>
<tr>
<td>Assignments on time$^d$</td>
<td>86.2 (15.0)</td>
<td>97.8 (3.2)**</td>
<td>.80</td>
<td>97.3 (2.6)**</td>
<td>.73</td>
</tr>
<tr>
<td>Adolescent satisfaction</td>
<td>4.46 (2.70)</td>
<td>5.08 (2.72)</td>
<td>.23</td>
<td>4.38 (2.53)</td>
<td>-.03</td>
</tr>
<tr>
<td>Parent satisfaction</td>
<td>3.83 (2.82)</td>
<td>7.58 (1.88)</td>
<td>1.33</td>
<td>4.64 (2.78)</td>
<td>.29</td>
</tr>
</tbody>
</table>

$^a$Represents Cohen’s $d$ standardized effect size difference from placebo.

$^b$Ratings ranged from 0 (no problem) to 6 (extreme problem).

$^c$Ratings ranged from 0 (none) to 3 (severe).

$^d$Teachers estimated the percentage of time that adolescents completed notes, were prepared for class, and turned in assignments on time.

Significantly different from placebo, $^*p < .10$. $^{**}p < .05$.

Table 2. Pemoline Versus MPH t.i.d. Medication Adherence

<table>
<thead>
<tr>
<th></th>
<th>Pemoline (%)</th>
<th>MPH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 25%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25%-49%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50%-74%</td>
<td>14.3</td>
<td>0</td>
</tr>
<tr>
<td>75%-89%</td>
<td>4.8</td>
<td>12.5</td>
</tr>
<tr>
<td>90%-100%</td>
<td>81.0</td>
<td>87.5</td>
</tr>
</tbody>
</table>

Note: MPH = methylphenidate.

$^1n = 21.$

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Discussion

Primary findings of this study are as follows: (a) short-acting MPH, but not long-acting pemoline, led to statistically significant improvements in ADHD symptoms and note-taking habits when compared with placebo; (b) there were small, but clinically significant benefits of both formulations for GPA, ODD symptoms, and academic habits; (c) long-acting pemoline led to stronger adherence than short-acting MPH, particularly in noon and afternoon doses; and (d) there was greater satisfaction with short-acting MPH than long-acting pemoline and placebo.

The results of this study suggest that stimulant medication produces some gains in the secondary school setting (see Table 1). However, these benefits were smaller than reported in previous MPH and pemoline studies with adolescents that were conducted in controlled treatment settings (Evans et al., 2001; Riggs, Thompson, Mikulich, & Whitmore, 1996; Smith et al., 1998). This finding is slightly surprising as a similar study we conducted with elementary school children found equivocal stimulant medication effects for naturalistic and analogue settings (Pelham et al., 2002). The organizational structure of secondary schools creates a challenge for measuring behavioral change (Evans, Allen, Moore, & Strauss, 2005) because students spend little time in the presence of each teacher and teachers can offer limited resources to individual students. Thus, it is possible that our low response to medication is a measurement issue—teachers may not notice behavioral change. On the other hand, compared with analogue settings and elementary schools, secondary schools possess greater activity variability, more factors that influence academics, and more challenging academic tasks (Eccles, 2004). In this setting, behavioral changes produced by stimulant medication may be insufficient to create meaningful improvements in functioning.

It is also possible that the medication effects found in our previous analogue studies (Evans et al., 2001; Smith et al., 1998) were enhanced by co-occurring behavioral treatment (Sibley et al., 2011). Combined therapy can enhance medication effects (Carlson, Pelham, Milich, & Dixon, 1992). Therefore, in secondary schools, pairing behavioral interventions (e.g., Evans, Schultz, DeMars, & Davis, 2011) with stimulant medication may improve response. Adolescents with ADHD are a population with a historically poor treatment response (e.g., Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Evans, Serpell, Schultz, & Pastor, 2007). Therefore, we believe that when stimulant medication is prescribed, behavioral interventions should always be implemented as conjunctive therapy.

The smaller medication effects produced in this study may also stem from adolescent nonadherence. Refusing and resisting stimulant medication is a documented, adolescent-specific problem (Charach & Gajaria, 2008; Marcus et al., 2005; McCarthy et al., 2009; Perwien et al., 2004). The controlled conditions associated with analogue settings afford near-perfect medication adherence. However, our effectiveness study produced much lower adherence rates (see Table 2), especially in the short-acting MPH condition. Adolescent satisfaction ratings were far lower than those completed by parents (see Table 1). In fact, most adolescents indicated that they preferred placebo to long-acting pemoline, and only slightly preferred short-acting MPH to placebo. These data suggest that nonadherence is a critical issue among teens with ADHD that likely damps stimulant medication effectiveness. Interventions are needed to improve adherence in adolescents who show evidence of acute response to these medications.

The limitations of this study should be considered. First, our sample size was small and missing data interfered with our ability to conduct more comprehensive analyses of medication effects. Second, the long-acting medication delivered in this study was pemoline, which is no longer commercially available. The purpose of pemoline’s inclusion was to observe the impact of long-acting medication on adherence, and we believe our study still represents a valid pursuit of this question as pemoline is shown to possess equivalent effects and side effects to other commercially available stimulant medications, including MPH (Pelham, greenslade et al., 1990). Finally, the majority of our outcome measures were derived from teacher report, which may not always be valid in the secondary school setting (Evans et al., 2005).

In sum, stimulant medication appears less effective in secondary schools than in analogue settings. Improving medication adherence in teens and coupling stimulant medication with conjunctive behavior therapy in secondary schools may improve medication response. It is our hope that future work will develop exportable interventions that address these needs. There are promising pharmacological and behavioral interventions for adolescents with ADHD (Smith et al., 2000), but more work is needed to create effective and accessible treatment packages.

Declaration of Conflicting Interests

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References


Bios

William E. Pelham, PhD, is a Professor of Psychology and Psychiatry at Florida International University. He directs the FIU Center for Children and Families and is Chair of the FIU Psychology Department.

Bradley H. Smith directed the adolescent program at the University of Pittsburgh Medical Center ADD Program from 1993 to 1996. He is currently an associate professor in the Department of Psychology at the University of South Carolina, where his research and teaching focuses on after-school and summer programs, which are based on the STP.

Steven W. Evans, PhD, is a professor of psychology and co-director of the Center for Intervention Research in Schools at Ohio University. His research focuses on treatment development and evaluation research for adolescents with ADHD and related problems.

Oscar Bukstein is Professor of Psychiatry at the University of Texas Health Science Center.

Elizabeth M. Gnagy is currently a Research Scientist in the Center for Children and Families at Florida International University.

Andrew R. Greiner is a Research Scientist at the Florida International University Center for Children and Families.

Margaret H. Sibley, PhD, is an Assistant Professor of Psychiatry at Florida International University with a primary appointment at the interdisciplinary Center for Children and Families. Her work addresses the diagnosis and treatment of ADHD in adolescence.