Weekend Holidays During Methylphenidate Use in ADHD Children: A Randomized Clinical Trial

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ABSTRACT

Objective: The aim of this study was to assess whether weekend drug holidays during methylphenidate (MPH) administration would change the efficacy and tolerability to the medication in male children with Attention-Deficit Hyperactivity Disorder (ADHD).

Methods: In a 28-day, double-blind study, children with diagnoses of ADHD were randomized to receive BID MPH for 7 days a week (n = 21) or to receive BID MPH on weekdays and a placebo on weekends (n = 19). Parents completed the Conners’ Abbreviated Rating Scale (ABRS) to assess ADHD symptoms and the Barkley’s Side Effect Rating Scale (SERS) to assess side effects on weekends. Teachers completed the ABRS on each Monday after weekends.

Results: Both groups showed a significant reduction on the ABRS over time as the dose was increased. However, the group difference in the ABRS scores was not statistically significant, either on weekend parent ratings (at the endpoint, \( p = 0.41 \); effect size = 0.26) or on teachers’ ratings (at the endpoint, \( p = 0.99 \); effect size = 0.002). The omission of MPH on weekends was associated with significantly less severity of insomnia (\( F = 3.96, \text{d.f.} = 1, p = 0.05 \)) and a trend for less interference on appetite (\( F = 3.18, \text{d.f.} = 1, p = 0.08 \)).

Conclusion: Our findings suggest that weekend holidays during MPH administration reduce the side effects of insomnia and appetite suppression without a significant increase in symptoms, either on weekends or in the first school day after them. Possible explanations for these findings (rate-dependent response or impact of demands of the environment) are discussed in this paper.

INTRODUCTION

Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most commonly recognized and treated psychiatric disorders of childhood, affecting 3%–6% of school-age children (Rohde et al. 1999). It is associated with morbidity and disability across the life cycle and has a severe social impact in terms of financial cost, family stress, harm to academic activities, and negative effects on self-esteem (Barkley et al. 1990a; NIH 2000).

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Many studies have clearly documented the short-term effectiveness of stimulants (methylphenidate and amphetamine) in reducing the symptoms of ADHD, as well as in improving the functioning of several other domains (Greenhill et al. 2001; American Academy of Pediatrics 2001; Spencer et al. 1996). Methylphenidate (MPH) is the most widely prescribed stimulant by psychiatrists in the United States (Zarin et al. 1998), and it is the only stimulant medication available in Brazil. The National Institute of Mental Health (NIMH) Collaborative Multisite Multimodal Treatment Study of Children with ADHD (MTA) verified the long-term effectiveness of methylphenidate (MPH) in a 14-month randomized clinical trial (The MTA Cooperative Group 1999).

MPH is well tolerated by most patients. Barkley et al. (1990b) studied the frequency and the severity of 17 side effects that were suspected to be associated with MPH in a double-blind, placebo-controlled study. The medication was assessed at doses of 0.3 and 0.5 mg/kg, twice a day, in 83 children with ADHD. Only 4 of 17 items (loss of appetite, insomnia, stomach pains, and headache) showed a dose-related increase, suggesting that some of the putative side effects may be manifestations of the disorder itself, rather than an adverse response to medication.

A drug holiday is a medication-free period during its systematic use. The omission of MPH on weekends (i.e., a withdrawal of the drug each Saturday and Sunday) is a common method for establishing a drug holiday (Taylor 1994; Coffey 1997). This is based on the assumption that weekends without medication might reduce side effects of the medication in some children without a clinically significant reduction in efficacy. For example, the reduction of the appetite-suppressant effect of MPH could lead to an increased consumption of calories, preventing an undesired weight loss, while the carryover of beneficial effects at school may render the medication less essential at home, where the demands on attention are less. Although the strategy of implementing weekend holidays during MPH use is controversial in the USA, it has been recommended in some countries (Schmidt 2002). In addition, clinical experience indicates that some parents prefer to stop MPH during weekends, even when the medication is recommended for use 7 days a week and is effective. For example, in the long-term follow-up of children in a clinical trial of Concerta™ (McNeil Consumer & Specialty Pharmaceuticals, Fort Washington, PA) 27% of the families elected to have weekend holidays without medication (Wolraich et al. 2001). Hazell et al. (1996), assessing 788 parents through a retrospective study, documented that trials without stimulants were commonly found during school holidays in some regions in Australia.

We are not aware of any previous study that has been designed to specifically address the effectiveness of weekend holidays during MPH use. Greenhill et al. (2001) have evaluated ADHD children in a double-blind titration study, in which a placebo, low, medium, and high doses of MPH were used randomly during 28 days (including 4 weekends). The results suggested that active medication on the weekend was associated with clinical improvement, according to the parents’ report. However, this study used a complex daily dose-switching methodology even on weekends, which is different from the real-world office practice, where MPH is used as a continuous treatment on both days of the weekend.

The main objective of the present study was to verify whether there would be a clinically significant reduction in effectiveness when weekend MPH holidays were implemented in children with ADHD. Based on the literature, our main hypotheses were that weekend MPH holidays would:

1. decrease the effectiveness of the overall treatment regime and
2. reduce side effects associated with the medication.

**MATERIAL AND METHODS**

**Sample**

The sample was ascertained from the ADHD outpatient clinic at the Child and Adolescent Psychiatric Division of Hospital de
Clinicas de Porto Alegre (HCPA). The HCPA is the university hospital of the Federal University of Rio Grande do Sul. Porto Alegre is the capital of Brazil's southernmost state, with a population of 1,800,000 inhabitants.

The inclusion criteria were:

a. ADHD diagnosis according to the DSM-IV criteria (American Psychiatric Association 1994);
b. age between 6 and 14 years;
c. male sex;
d. education level between the 1st and 8th elementary grade.

The exclusion criteria were:

a. presence of significant neurological or clinical disease;
b. presence of bipolar disorder or substance abuse/dependence disorder;
c. use of any psychiatric medication in the last 6 months, including MPH;
d. estimated IQ lower than 70.

The IQ was estimated based on the vocabulary and block design subtests of the Wechsler Intelligence Scale—third edition (WISC-III) (Wechsler 1991), administered by a trained psychologist (Sattler 1988).

Parents provided written, informed consent, and children or adolescents provided verbal assent to participate. This investigation was approved by the Ethical Committee of the HCPA (approved as an IRB by the Office for Human Research Protections, United States of America—IRB 00000921).

Diagnostic procedures

The diagnoses of ADHD and comorbid disorders were based on a three-stage process:

a. evaluation with a semistructured interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiological Version—K-SADS-E) (Orvaschel 1985), modified to assess DSM-IV criteria and administered to the parents by trained assistants. Interrater reliability for the ADHD diagnosis was evaluated previously (Kappa coefficient = 0.94, \(p < 0.001\)) (Polanczyk et al. 2003);
b. revision of each diagnosis derived through the K-SADS-E in a clinical committee chaired by an experienced child psychiatrist (L.A.R.); and
c. clinical evaluation of ADHD and comorbid conditions using DSM-IV criteria by a child psychiatrist who previously received the results of the K-SADS-E.

Interviews with parents (usually the mother) and the child or adolescent were conducted. Information about the symptoms in the school environment were obtained through the use of the Attention Problems scale of the CBCL (Child Behavior Checklist)-Teacher Report Form (TRF) (Achenbach 1991), which includes items related to ADHD behaviors in the classroom. When a diagnostic disagreement occurred in the three-stage process, priority was given to diagnoses derived from clinical interviews (Rohde 2002).

Study design

A randomized, double blind, parallel-group design was used. Patients were randomized to one of the two groups, based on a computer-derived algorithm (EPIINFO.06) (Dean et al. 1995). During weekdays of the trial, both groups received MPH. On weekends, one group received a placebo, and the other group continued to use methylphenidate.

Pharmacological intervention

The initial dose of MPH was 0.3 mg/kg/day on the first week. The dose was raised to 0.50 mg/kg/day on the second week and to 0.70 mg/kg/day on the third and fourth weeks, unless the emergence of adverse effects prevented the increase. MPH was administered orally, in individual doses, twice a day, after breakfast and lunch (James et al. 2001). Both methylphenidate and placebo pills were of the same shape and color. A 1-week supply of pills was provided for each patient in blister packs labeled with their names, date, time of administration, and schedule. Compliance was checked by counting the unused pills returned in the
blister packs at the end of each week. The MPH and placebo pills were supplied by Novartis Pharmaceuticals (São Paulo, Brazil) at no cost and without restrictions, but no additional funding was requested or received from Novartis or any other commercial entity.

Assessment of efficacy and side effects

The primary efficacy assessment was the change from baseline on the 10-item Conners’ Abbreviated Rating Scale (ABRS) (Conners and Barkley 1985). The ABRS is a valid and reliable instrument frequently used as a primary outcome measure in clinical trials of ADHD. Items are rated on a 0 (Not at all) to 3 (Very Much) scale, so the 10-item instrument yields scores from 0 to 30. Both parents and teachers completed the same form of the ABRS to provide a measure of effectiveness in two settings. Before the beginning of the 4-week double-blind protocol, parent and teacher interviews were used to obtain responses to each item on the ABRS. During the trial, parents completed the ABRS about weekend behavior on every Monday (7th, 14th, 21st, and 28th days) of the protocol. Teachers completed the ABRS about school behavior during the first day after the weekends (Mondays). Parents were clearly instructed to focus their assessment on ADHD symptoms during the previous weekend when completing the ABRS. Regarding teachers’ assessment, they were interviewed on each Monday at the end of the school day, and they were requested to focus their assessment on ADHD symptoms during only that school day when completing the ABRS.

In addition, parents completed the Barkley’s Side Effect Rating Scale (SERS) to assess side effects on weekends. The SERS is a 17-item scale of putative side effects of the stimulants. The severity of each symptom is scored from 0 to 9 (Barkley et al. 1990b). Recent investigations have used two general scores:

a. the number of symptoms and
b. severity of symptoms (James et al. 2001).

Data analyses

Baseline patient demographic characteristics, IQ, and ADHD symptoms in the two groups were compared using the $\chi^2$ test or the Fisher’s Exact Test (categorical variables) and the Student $t$ test (continuous variables). For the ABRS and the SERS, the effects of treatment group assignment at the endpoint (4th week) were assessed by the Student $t$ test. Comparisons between pretreatment and endpoint scores on both scales in each group (intragroup comparisons) were performed using the paired Student $t$ test. In addition, an effect of treatment group assignment over time as the dose was increased was also examined by repeated-measures analysis of variant (ANOVA).

An unbiased estimate of the effect size (ES) was computed for the total score on the ABRS, according to the method suggested by Cohen (1998). An effect size of > 0.80 is considered large, between 0.50 and 0.80 is considered moderate, and < 0.20 is considered small.

Although no parent ratings were missing, some teacher ratings (8.5%) were missed because of either the child’s absence from school on a specific day of evaluation or a school holiday in 1 of the 4 Mondays of the protocol. Because ABRS teacher scores for the 5 days of evaluation followed a linear distribution, we used linear interpolation to estimate the missing data (Altman 1991). A significance level of 5% was set for the study. All tests were two-tailed.

RESULTS

Pretreatment patient characteristics

The sample was comprised of 40 children and adolescents, 21 in the group to which MPH was administered on the weekend (MPH group) and 19 in the group that received a placebo on the weekend (placebo group). All families of children that fulfilled inclusion and exclusion criteria were accepted to participate in the study. The children’s demographic characteristics, IQ, type of ADHD, and basal scores in attention-problem scales of the TRF and the CBCL are presented in Table 1. No significant between-group difference was found in any of these measures. In addition, there was no significant between-group difference in the prevalence of comorbidities. The main comorbidity in both groups was disruptive behavior
disorder (conduct or oppositional defiant disorder) (MPH group = 57.2%; Placebo group 57.9%).

Adherence to protocol

Only 7 of 160 blister packs were returned with unused pills. Four (4) of these were from 3 of the subjects in the weekend MPH group, and 3 were from 2 of the subjects in the weekend placebo group. In the MPH group, 1 patient did not receive the second dose on Thursday of the second week, another patient forgot to take the second dose on Sunday of the third week and both doses on Monday of the fourth week (the last day of the protocol), and a third patient did not receive both doses on Sunday of the third week. In the placebo group, 1 patient forgot to take the morning dose on Monday of the second week and the other patient did not receive doses on two weekdays. None of the findings in the analyses reported below were significantly modified by the exclusion of this subject.

Ratings in the ABRS

No significant between-group difference was detected on the basal ABRS for teacher or parent ratings. For both sources, the two groups showed a significant reduction on ABRS scores between pretreatment and endpoint evaluations (Parents: MPH group: \( t = 4.26, \text{d.f.} = 20, p < 0.001 \); Placebo group: \( t = 5.51, \text{d.f.} = 18, p < 0.001 \); Teachers: MPH group: \( t = 7.74, \text{d.f.} = 20, p < 0.001 \); Placebo group: \( t = 13.75, \text{d.f.} = 18, p < 0.001 \)). The change from baseline to end-of-treatment was greater for the teacher ratings (\( ES_{\text{MPH}} = 1.69; ES_{\text{placebo}} = 3.01 \)) than for the parent ratings (\( ES_{\text{MPH}} = 0.93; ES_{\text{placebo}} = 1.23 \) (see Figs. 1a and 1b). However, no significant difference was detected on endpoint ABRS ratings between the MPH and the placebo group (Parents: end point: \( t = -0.83; \text{d.f.} = 38; p = 0.41 \); effect size = 0.26; Teachers: \( t = 0.01; \text{d.f.} = 38; p = 0.99 \); effect size = 0.002).

METHYLPHENIDATE USE IN CHILDREN WITH ADHD

<table>
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<th>TABLE 1. Demographic Characteristics, IQ, ADHD Type and Basal Scores on CBCL and TRF Attention Problem Scale in Both Groups</th>
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<td>Characteristics(^{a,b})</td>
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<td>Age (years)</td>
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<td>Estimated IQ</td>
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<td>Monthly Family Income:(^c)</td>
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<td>Basal T-score in the attention problem scale—CBCL</td>
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Note: ADHD = Attention-Deficit Hyperactivity Disorder; MPH = methylphenidate; CBCL = Child Behavior Checklist; TRF = Teacher Report Form;

\(^a\) = mean and standard deviation (in parentheses) are reported for continuous variables;

\(^b\) = no significant difference between groups in any variable assessed;

\(^c\) = Monthly family income was calculated according to the following formula: total monthly income received by all members of the family (expressed in number of minimum wages) divided by the number of persons in the family [a value lower than 0.7 (approximately U$ = 68 per family member per month) is usually an indicator of poverty in Brazil].

Disorder (conduct or oppositional defiant disorder) (MPH group = 57.2%; Placebo group 57.9%).
FIG. 1. A: Mean parental scores in the Conners Abbreviated Rating Scale (ABRS) are presented for the weekends in the group that received methylphenidate on the weekends (MPH) and the group that received a placebo on the weekends. Although both groups showed a significant decrease on parental ABRS scores between baseline and endpoint ($p < 0.001$), no effect was detected for group assignment at the endpoint ($p = 0.41$; effect size = 0.26).

B: Mean teacher scores in the ABRS are shown for the first school day after the weekends in both groups. Again, no effect was detected for group assignment at the endpoint ($p = 0.99$; effect size = 0.002).
Repeated-measures ANOVAs yielded significant effects of time as the dose was increased on both parent and teacher ratings in the ABRS, but no significant effect was detected for group assignment or for the interaction between time and group assignment (data not shown but available upon request).

**Parent ratings in the SERS (tolerability at home during the weekend)**

Barkley’s Side Effect Rating Scale (SERS) provides two scores: the number of adverse effects reported (SERS-N) and the mean severity of reported adverse effects (SERS-S). Repeated-measures ANOVAs yielded significant effects of time as the dose was increased in parent ratings in the SERS-N (F = 4.43, d.f. = 4, p = 0.002) and SERS-S (F = 8.11, d.f. = 4, p < 0.001). However, no significant effect was detected for group assignment for SERS-N (F = 2.04, d.f. = 1, p = 0.16) or for SERS-S (F = 0.02, d.f. = 1, p = 0.89), and for the interaction between dose and group assignment for SERS-N (F = 1.64, d.f. = 4, p = 0.17) or for SERS-S (F = 1.67, d.f. = 4, p = 0.16).

Since previous investigations have demonstrated that decreased appetite and insomnia are two of the best-documented side effects when using MPH (Barkley et al. 1990b; Vitiello 2001), we also assessed the effect of group assignment on these two side effects. In an analysis of insomnia, a significant effect was detected for group assignment (F = 3.96, d.f. = 1, p = 0.05). No significant effect was found for time as the dose was increased (F = 0.37, d.f. = 4, p = 0.83) and for the interaction between dose and group assignment (F = 0.60, d.f. = 4, p = 0.66) (see Fig. 2a). When only scores between the two groups at the endpoint were assessed, a trend for an effect of group assignment was verified (t = −1.87, d.f. = 37.71, p = 0.07). In the analysis of decreased appetite, a trend for significance was detected for group assignment (F = 3.18, d.f. = 1, p = 0.08). A significant effect was detected for time as the dose was increased (F = 3.20, d.f. = 4, p = 0.02), but no significant effect was found for the interaction between dose and group assignment (F = 1.17, d.f. = 4, p = 0.33) (see Fig. 2b). An analysis of the scores between the two groups at the endpoint revealed a trend for an effect of group assignment (t = −1.9, d.f. = 38, p = 0.07).

**DISCUSSION**

The primary finding of this investigation of the clinical practice of using weekend “holidays” as part of a regime of MPH to treat ADHD was that the 5-day/week MPH regime with weekend holidays resulted in a significant reduction in insomnia and a trend toward the reduction in decreased appetite, compared to the 7-day/week MPH regime without a weekend holiday. This was achieved without a significant decrease in parents’ account (rating) of the efficacy of the MPH regime with a weekend holiday. In addition, it is important to note that teachers’ ratings on ADHD symptoms on each Monday after the weekend were not also significantly increased by the MPH regime with a weekend holiday.

Conventional wisdom and clinical experience suggest that substituting a placebo for even a single day leads to a return of symptoms, so the persistence of low ratings of ADHD symptoms on the weekends for the MPH regime with weekend holidays is unexpected. For example, Greenhill et al. (2001) assessed ADHD children on 4 weekends in a 28-day titration trial of placebo and low, medium, and high doses of MPH. Although this study implemented a complex daily dose-switching schedule that is very different from real-world practice, findings suggested that tit rates of MPH were significantly different from the placebo on the weekend. Therefore, we will address possible explanations for our findings and some limitations of this study that may account for the lack of between-group differences in parent ratings of ADHD symptoms.

Pharmacodynamic studies of MPH clearly documented the short duration of efficacy of MPH, which usually diminishes approximately within 4 hours after the last dose (Swanson et al. 1978; Swanson et al. 1998). Thus, a carryover effect of weekday treatment over a 2-day weekend is not expected. However, Swanson et al. (2002) recently documented that, despite the large effect of MPH on behavior in the class-
FIG. 2. A: Mean parental scores on the severity of insomnia are presented for weekends for the group that received methylphenidate on the weekends (MPH) and the group that received a placebo on the weekends. A significant effect was detected for group assignment ($p = 0.05$), but an effect of time as the dosage was increased was not found ($p = 0.83$). B: mean parent scores for the severity of decreased appetite are shown for the weekends in both groups. A trend for a significant effect was detected for the group assignment ($p = 0.08$), and an effect of time as the dosage was increased was found ($p < 0.02$).
room, the effect on playground behavior was small or insignificant. Thus, the context established by the home setting on the weekend may have created conditions in which the effects of MPH are minimal or insignificant, because children may have been involved in play activities much of the time.

There are some recent neurobiological data that might support these findings. Although some clinical reports have indicated that stimulants exert the same qualitative effect on all subjects, recent preclinical investigations with mice have frequently suggested that stimulants work in a rate-dependent manner (Anderson et al. 2002). In clinical studies, Volkow et al. (2002) recently used positron emission tomography (PET) in a study to estimate the increase of extracellular dopamine after oral administration of MPH. Although there was a considerable degree of individual variation, the findings suggested that there were smaller dopamine changes in subjects with low, than in those with high, dopamine cell activity. In addition, Mattay et al. (1996) evaluated the effects of d-amphetamine administered, using PET scan measures of blood flow during the performance of neuropsychological tasks. They were able to demonstrate that clinical doses of the stimulant increased only regional blood flow in the brain region activated by the task. These findings suggest that MPH and amphetamines may not produce direct effects on specific brain regions, but instead may integrate and facilitate neural activity in segregated brain circuits elicited by environmental stimulation (Swanson et al. 2002). Thus, it is reasonable to suggest that during the weekend, when networks related to the ADHD neurobiology might be less demanded, differences between a drug and a placebo would be more difficult to detect.

The lack of difference between the groups on weekends in our study might also be related more to the expectations of parents than to neurobiological aspects. It is possible that parental tolerance of ADHD symptoms on weekends might be higher than on weekdays. In this regard, cultural differences may contribute to our findings. In Brazil, parents may be more concerned about ADHD symptoms when they interfere with school activities than when they interfere with behaviors at home. In addition, Schachar et al. (1997) documented that parents’ knowledge of the improvement of their children’s symptoms at school might impact on their ratings of their children’s behavior at home. Thus, parental scores in ABRS on weekends might be low and clinically indistinguishable between the two groups, because both of them improved significantly during weekdays resulting from MPH, and a halo effect produced a persisting effect on the weekend.

It is possible that the overall medication regimes of the study were ineffective. This is discounted because there were improvements from baseline that were about the expected size (large effects sizes; ES > 0.80) for both groups (MPH and placebo) either for teacher ratings or for parent ratings, based on the large literature on the effects of MPH (Klassen et al. 1999). The absence of a difference between the groups could be associated with problems of sample size (Type II error). However, parental ABRS mean scores for the 4 weekends were quite similar in both groups (effect size between groups at endpoint = 0.26), indicating that increasing the sample size would not make a superiority of MPH appear.

Some limitations of this study should be also acknowledged. First, we only assessed ADHD boys. Thus, our findings may not generalize to females with the disorder. Second, parents rated the weekend behavior of children on the Monday following the weekend. After using the medication on Monday, the children could have improved and the parents might have remembered less about the weekend symptoms. However, most of the parents in the study worked all day on Mondays, and all the children were at school; therefore, the assessment performed on this day tends to not be affected by a halo effect related to symptoms on a Monday itself. Furthermore, it is expected that if major symptoms were present on the weekend, they would not suffer the impact of a recall-bias only one day later. Even so, a more sensitive design might acquire ratings of behavior and objective measures during the weekend itself, instead of retrospectively after the weekend. To capture a broader range of situations at home, ratings
and objective measures could be obtained in the morning and afternoon of each weekend day, when the physiological effects of MPH are expected. In addition, scales assessing home compliance and/or peer interaction might have had a higher sensitivity to detect problems on weekends than the ABRS. Third, MPH and placebo pills were of the same shape and color, but they were not matched for taste. Thus, there is a chance that children in the MPH weekend holiday group had realized that they were receiving a placebo instead of MPH on the weekends. However, the expected impact of this potential flaw would have been of increasing differences on the parental ratings between groups (what did not occur), because families received a full explanation of the protocol to sign the informed consent.

In clinical practice, physicians might have to use MPH weekend holidays with children who have significant side effects, such as important insomnia or decreased appetite or with those who have much more prominent symptoms at school than at home. The results of this study provide some empirical support for this clinical practice. It is important to note that we are not advocating that weekend MPH holidays should be the rule, but that this strategy might be considered in those specific cases.

Recent findings from the MTA study have suggested that MPH doses of about 38 mg/day might be more associated with long-term side effects than expected in the past (e.g., growth suppression). Growth suppression effects of MPH might be mediated by reduced calorie consumption, and insomnia might be associated with a dyssynchrony of growth hormone secretion during the initial stages of sleep (Howrie 1987; Vgontzas et al. 1999). Thus, the manifestation of growth suppression may require an accumulation of effects on eating and sleep that may be avoided or minimized with weekend holidays.

**CONCLUSIONS**

In conclusion, our findings suggest that weekend MPH holidays in male ADHD children were not associated with a significant decrease in short-term efficacy, and they might reduce two important MPH side effects (decreased appetite and insomnia) during the weekend. Further studies on the effects of weekend holidays during the use of MPH and other stimulants to treat ADHD children and adolescents are needed.

**REFERENCES**


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