Acute Impact of Immediate Release Methylphenidate Administered Three Times a Day on Sleep in Children with Attention-Deficit/Hyperactivity Disorder

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Objective To determine the impact of immediate release Ritalin, given three times a day, on sleep quality and quantity in medication-naïve, newly diagnosed children with attention-deficit/hyperactivity disorder (ADHD).

Methods Children (aged 6–12) rigorously diagnosed with ADHD (n = 21) underwent multiple measurement assessments (i.e., actigraphy, sleep diary, and questionnaires) during a 1-week baseline and then during a 3-week blinded randomized medication trial.

Results Although the medication was effective in reducing ADHD symptoms, analyses of actigraphy and sleep diary data found statistically and clinically significant changes in the children’s total sleep time and sleep onset latency in the medication compared to the no medication conditions. No effects on sleep were found based on the sleep questionnaire.

Conclusions Physicians and parents are encouraged to closely monitor children’s sleep when treating ADHD with stimulant medication.

Key words ADHD; children; medication; sleep.
Beyer, & Finkleson, 2002; Greenhill, Halperin, & Abikof, 1999; Schachar, Tannock, Cunningham, & Corkum, 1997; Waschbusch & Hill, 2003). Of the known side-effects of MPH treatment, sleep disruption is potentially one of the most deleterious for both children and their families.

Rather than getting sleepy and lethargic, children deprived of sleep typically display restlessness, irritability, and become easily frustrated (Anstead, 2000; Dahl, 1996). Complete or partial sleep loss negatively affects children’s executive (e.g., planning, organization, and problem solving), cognitive (e.g., attention and inhibition) and behavioral (e.g., irritability, low frustration tolerance) functioning (Dahl, 1996; Fallone, Acebo, Arndt, Seifer, & Carskadon, 2001; Randazzo, Muehlbach, & Schweitzer, 1998; Sadeh, Gruber, & Raviv, 2002, 2003). Moreover, child sleep problems have been associated with increased family stress and have even been linked to increased rates of child abuse (Stores, 1996). Furthermore, the daytime sequelae of sleep deprivation can closely resemble ADHD and may exacerbate or mimic existing symptoms (Van der Heijden, Smits, & Gunning, 2005).

There have been a number of systematic reviews of the literature on sleep characteristics of children with ADHD (Ball & Koloin, 1995; Bullock & Schall, 2005; Cohen-Zion & Ancoli-Israel, 2004; Corkum, Tannock, & Moldofsky, 1998; Cortese, Konoval, Yateman, Mouren, & Lecendreux, 2006; Owens, 2005; Van der Heijden et al., 2005). These reviews concur that parents of children with ADHD report more sleep problems than do parents of typically developing children (~5-fold increase), with the most frequent concerns being difficulties initiating sleep (including bedtime resistance), shortened sleep duration, and increased number of night awakenings. Greater day-to-day variability in sleep patterns in children with ADHD has also been found (Gruber, Sadeh, & Amiram, 2000). However, parental reports of sleep problems in children with ADHD have not been consistently confirmed using objective measures such as polysomnography (PSG; multiple physiologic variables are recorded during an overnight sleep study) or actigraphy (measurement of motor activity using an accelerometer-based device that resembles a small wristwatch). Previous reviews have attributed these inconsistencies to methodological and measurement issues, with the most significant being small sample sizes, inconsistent and suboptimal diagnostic criteria for both ADHD and sleep disturbances, and ambiguity regarding the medication status of participants.

Failure to address medication status and medication history is perhaps one of the most problematic and confounding of these methodological issues, since it allows for confusion between sleep problems associated with ADHD and those associated with current or previous drug treatments. Current treatment with stimulant medication has, in fact, been identified as a predictor of parental reports of sleep problems (Corkum, Moldofsky, Hogg-Johnson, Humphries, & Tannock, 1999; Mick, Biederman, Jetton, & Faraone, 2000; Sadeh, Pergamin, & Bar-Haim, 2006; Stein, 1999). Given the large number of children being treated with stimulant medication and its potential effects on sleep, it is critical to understand the consequences for children with ADHD of sleep changes resulting from treatment with stimulant medication.

In both acute and long-term clinical trials, parents have listed sleep problems as one of the most common and persistent side-effects of stimulant medication (Charach, Ickowicz, & Schachar, 2004; Schachar et al., 1997). The research conducted to date has mostly examined the impact of BID stimulant medication. In a BID dosing pattern, medication is given twice daily; in the morning and at lunchtime. With a half-life of ~4 hr after the last dose, the assumption is that circulating MPH would be below threshold for behavioral effects by typical bedtimes (~8 hr after the last dose). There have been inconsistent findings in regard to the impact of BID MPH on sleep in children with ADHD. For example, some research has found no differences or minimal clinically significant differences in sleep between medicated and nonmedicated conditions (Tirosh, Sadeh, Munvez, & Lavie, 1993) whereas others have found significant differences, particularly in terms of delayed sleep onset and total sleep time (Schwartz et al., 2004).

There is very little research on the impact of adding a third, late-afternoon dose of MPH, as in the currently recommended TID dosing regime, despite the fact that the third dose falls within 3–4 hr of typical bedtimes. To date, only two studies, involving a total of 37 children between them, have systematically attempted to compare the effects of BID and TID dosing schedules on sleep during an acute medication trial (Kent, Blader, Koplewicz, Abikoff, & Foley, 1995; Stein et al., 1996). Approximately, half of the participants studied had been previously treated with stimulant medication, and the impact of prior treatment remains unknown. Although the studies found minimal impact on sleep using TID dosing schedule compared to BID, the authors of both studies noted that their research designs were inadequately powered to detect differences in the side-effects of BID and TID dosing, if they did in fact exist. Thus, to date, very little is known about TID medication regimes.
on sleep. In a recent double-blind, crossover trial, Sangal et al. (2006) compared a newly approved nonstimulant medication, atomoxetine (given BID) with TID MPH. They found significant increased sleep onset latency in the MPH group relative to baseline and compared to the atomoxetine group, and a decrease in night awakenings in the MPH group.

The goal of the current investigation was to assess sleep quantity and quality in children rigorously diagnosed with ADHD before and after initiation of TID treatment with immediate release methylphenidate (MPH IR). Sleep was evaluated using multiple measures including actigraphy, sleep diaries, and questionnaires during a baseline period (prior to medication), and during an acute three-week, blinded medication trial. Our study recruited only newly diagnosed, medication-naïve children, who were rigorously diagnosed with ADHD using strict, evidence-based assessment procedures (as outlined by Pelham, Fabiano, & Massetti, 2005). We hypothesized that the administration of TID MPH would result in sleep disruption, particularly increased sleep latency and decreased sleep duration.

**Method**

**Sample**

Twenty-eight children (20 males, eight females) between the ages of 6 and 12 were recruited to participate in the study. Recruitment and enrolment occurred between March 2004 and October 2006 through referrals from a specialty ADHD Clinic at a community hospital in a mid-sized Canadian town. At the ADHD Clinic, each child underwent a rigorous diagnostic assessment conducted by an interdisciplinary team of practitioners (clinical psychologists, school psychologists, and pediatricians), which included parent and teacher semi-structured diagnostic interviews, questionnaires, observations, and a psycho-educational assessment. Approval was granted by the hospital and university research ethics boards and written parental and child verbal assent were gained prior to participation.

**Participant Selection**

Inclusion criteria required that participants: (a) be stimulant medication-naïve, (b) meet DSM-IV criteria for one of the three ADHD subtypes, (c) receive a recommendation to initiate a trial of MPH following the assessment, and (d) have parents/caregivers who agreed to initiate a stimulant medication trial through the clinic pediatrician. Children were excluded if they: (a) had an IQ <1 SD below the mean on the Wechsler Intelligence Scale for Children–IV (WISC-IV), (b) had a known neurological, metabolic, or seizure disorder, (c) were currently taking other psychotropic medications or medications for sleep disturbances, (d) evidenced symptoms of an intrinsic sleep disorder [i.e., sleep apnea, restless leg syndrome (RLS)/PLMS]) or a sleep-onset disorder based on parent report, or (e) reached criteria for another mental health disorder that was considered primary to the ADHD diagnosis (e.g., autism). Children with ADHD and comorbid conditions were not excluded.

**Materials**

**Conners’ Parent and Teacher Rating Scale-Revised (Short Form)—(CRS-R: S)**

The CRS-R: S is a standardized behavior rating system completed by parents and teachers to assess problem behaviors in children ages 3–17 (Conners, Parker, Sitarenios, & Epstein 1998a,b). The Conners’ Parent Rating Scale-Revised (Short Form) (CPRS-R: S) and the Teacher Rating Scale-Revised (Short Form) (CTRS-R: S) consist of items comprising scales that tap both externalizing and internalizing symptomology. We examined scores for the overall ADHD Index, as well as the Inattentive, Hyperactive/Impulsive and Oppositional subscales.

**Actigraphy**

Basic Mini-Motionlogger actigraphs (AMI Inc., New York, USA) were used to measure motor activity and to assess sleep quality using an accelerometer-based device, resembling a small wristwatch. Actigraphic data provide valid and reliable estimates of sleep and wake patterns and are used to measure sleep quality variables such as sleep latency, continuity, and duration (Acebo et al., 1999; Sadeh, Hauri, Kripke, & Lavie, 1995; Tryon, 2004). Actigraphs have been shown to have a high rate of agreement with PSG (the gold standard of sleep evaluation) and to distinguish effectively between sleep disturbed children and controls (Morgenthaler et al., 2007). These actigraphs employ a piezoelectric beam sensor, with a fixed sensitivity of 2–3 Hz to detect accelerations greater than 0.1 G. With a 32 K memory and a sampling rate of 10 Hz, data can be collected for up to 22 days after initialization and downloaded in zero-crossing (ZC) mode through an auto-interface into ACT operational software. Scoring of sleep data in ACTION W2 (AW2) used a validated sleep algorithm developed by Sadeh, Sharkey, and Carskadon (1994).
Sleep Diary

Sleep diaries completed by parents are widely used in clinical settings and have been found to have good face validity, high internal consistency, and good agreement with videotapes of children’s sleep (Wiggs & Stores, 1995). The diary allowed for the collection of information using identical questions for each day during the baseline and acute medication trial. The diary has been used in previous research (Corkum et al., 1999, Corkum, Tannock, Moldofsky, Hogg-Johnson, & Humphries, 2001).

Sleep Disturbances Scale for Children (SDSC)

The SDSC (Bruni et al., 1996) is a 26-item norm-referenced questionnaire in which parents rated the frequency of various childhood sleep problems from 1 (never) to 5 (daily). The SDSC yields a total sleep problem index and six sleep problem scales (i.e., disorders of initiating and maintaining sleep, sleep breathing disorders, disorders of arousal, sleep–wake transition disorders, disorders of excessive somnolence, and sleep hyperhydrosis). The scale has been found to have satisfactory internal consistency, adequate test–retest reliability, and to be a valid measure of discrimination between controls and clinical groups, and sensitive to treatment (Bruni et al., 1996). The version used in the current study requested parents to respond based on their perceptions of their child’s sleep over the previous week, rather than the 6 month time frame typically used when administering this sleep questionnaire.

Procedures

One week of baseline data were collected followed by a 3-week medication trial with random assignment of the children to one of three medication-dosing schedules. The original fully randomized schedule was modified after a pilot study conducted prior to the current study indicated that children receiving a moderate dose before the low dose of MPH reported more side-effects and were more likely to stop taking the third dose (4 p.m.) of medication. Participants followed a standardized clinical blind medication trial protocol for MPH IR (Ritalin) administered by one of the two ADHD Clinic pediatricians. This consisted of one week of baseline, placebo, low and moderate MPH dose condition. Children weighing 25 kg or less received 5 and 10 mg doses, while children over 25 kg received 10 and 15 mg doses. Children received medication TID (8 a.m., 12 p.m., and 4 p.m.).

Each of the 3 weeks of the medication trial began on a Saturday morning and concluded on the following Friday night. A pharmacy local to the ADHD Clinic prepared both the placebo and active medication (the tablets were powdered and packaged into gelatin capsules to prevent identification of the contents). The child, the family, school personnel, and the study investigators were unaware of the randomization schedule. This information was only made available to the pediatrician and the pharmacist. The families were in contact with their pediatrician only if concerns arose regarding medication side-effects.

Children wore an actigraph on their nondominant wrist for each week of the research protocol and were advised to remove it only for “rough play,” contact sports or bathing/swimming. The parent most familiar with the child’s bedtime and waking routines was instructed to complete the sleep diary just after the child went to sleep and after he/she woke up each day. The questionnaires were completed at the end of each week.

Statistical Analysis

The Statistical Package for Social Science (SPSS 14.0) was used for all analyses. In the current study, we found changes on the order of 1 SD between nonmedicated and medicated conditions (effect size of 2.42), which represents excellent power to detect differences with the current sample size. Repeated measures ANOVA (with medication status as the repeated measure and $\alpha = .05$) was used to examine the effect of medication on the dependent variables. Data from the actigraph and sleep diary were considered complete and therefore valid if a minimum of five of the 7 days of data per week were successfully collected. Data were considered invalid and therefore excluded from the analyses if one or more of the following criteria were met: (a) physiological or environmental sleep conditions were atypical (e.g., illness, sleep over); (b) the child or parent deviated from the medication trial (e.g., took medication BID rather than TID); or (c) data were not collected by the parents (e.g., forgot to put actigraph on the child and/or forgot to complete the sleep diary).

Results

Of the 28 children recruited to participate in this study, seven children were excluded in the final data analyses for the following reasons: actigraphic problems (i.e., data failure/loss of actigraph/refusal to wear actigraph) ($n = 5$), withdrawal of consent due to marital discord ($n = 1$), and decision immediately prior to the medication trial to try alternative medication ($n = 1$). The final sample ($n = 21$)
ranged in age from 6 years, 1 month to 12 years, 1 month, and had a mean age of 8 years, 6 months (SD = 19.53 months). There were 15 males and six females. In terms of ADHD subtype, 11 were diagnosed with combined type, two with hyperactive–impulsive type and eight with inattentive type. Of the sample, 29% were diagnosed with a comorbid-learning disability and 10% were diagnosed with a comorbid oppositional defiant disorder. None of the children received a comorbid diagnosis of a conduct disorder, or an internalizing disorder (e.g., anxiety, depression). Participants had full scale IQs in the Average range (M = 94.67, SD = 10.73) on the WISC-IV. All participants were Caucasian and based on scores from the Hollingshead Two-Factor Index of Social Position (Hollingshead, 1958) the sample consisted of predominantly middle-class families (mean score = 3.29, SD = 1.01, Level III). Participant characteristics are presented in Table I.

**Efficacy of Stimulant Medication**

Repeated measures ANOVAs indicated that TID MPH was effective at reducing ADHD symptoms at both home and school (Table II). There was a significant time effect for the ADHD Index on both the CTRS [F(3,18) = 6.85, p = .003, η² = .55] and the CPRS [F(3,18) = 6.15, p = .005, η² = .51]. Contrast analyses found that the no medication conditions (placebo and baseline) differed from the medication conditions, and that there was no dose effect (i.e., low and moderate dose were both effective in reducing ADHD symptoms). Examination of the mean t-scores indicated that the scores in the no medication conditions fell in the moderately or markedly

### Table I. Participant Characteristics and Comorbidities

| Characteristics | Mean (SD) |
|-----------------|-----------|
| Age (months)    | 8 years, 6 months (19.53 months) |
| IQ (Full Scale Standard Score on WISC-IV) | 94.67 (10.73) |
| Diagnoses No. of participants (%) | |
| ADHD-combined type | 11 (52) |
| ADHD-hyperactive-impulsive type | 2 (10) |
| ADHD-inattentive type | 8 (38) |
| Learning disabilities | 6 (29) |
| Oppositional defiant disorder | 2 (10) |
| Conduct disorder | 0 (0) |
| Generalized anxiety disorder | 0 (0) |
| Depression | 0 (0) |

### Table II. T-Scores from Conners' Parent (CPRS) and Teacher (CTRS) Rating Scales

| Scale | Baseline Mean (SD) | Placebo Mean (SD) | Low dose Mean (SD) | Moderate dose Mean (SD) | F-value | Sign | Effect size (η²) | Contrasts |
|-------|-------------------|-------------------|-------------------|-----------------------|---------|------|----------------|-----------|
| CPRS  |                   |                   |                   |                       |         |      |                |           |
| ADHD  | 68.90 (11.98)     | 69.38 (10.23)     | 63.05 (13.89)     | 62.14 (14.11)         | 6.15    | 0.005| .51            | B = PL, PL ≠ LD, LD = MD |
| InA   | 67.19 (12.84)     | 68.19 (12.01)     | 62.86 (13.51)     | 61.05 (13.43)         | 5.51    | 0.007| .48            | B = PL, PL ≠ LD, LD = MD |
| Hyp-Imp | 65.43 (14.67)  | 64.00 (15.39)     | 58.95 (19.52)     | 59.67 (19.83)         | 1.64    | 0.22 | .22            | B = PL, LD = MD |
| Opp   | 61.00 (13.87)     | 62.38 (13.93)     | 55.57 (13.01)     | 55.24 (12.39)         | 2.40    | 0.10 | .26            | B = PL, LD = MD |

ADHD, ADHD Index; InA, DSM-IV: Inattentive Scale; Hyp-Imp, DSM-IV Hyperactive–Impulsive scale; Opp, Oppositional scale; B, baseline; PL, placebo; LD, low dose; MD, moderate dose.
atypical range (above 65 or 70, respectively), whereas the scores in the medication conditions were in the mildly atypical (60–65) or typical (50–60) ranges. All the other scales of interest on the CTRS were significantly reduced during the medication conditions, whereas one of three scales showed significant reduction on the CPRS. However, there was a nonsignificant trend in the same direction for two CPRS scales.

**Actigraphy**

Consistent with our hypothesis, sleep disruption during the medication conditions was found based on actigraphy data (Table III). Repeated measures ANOVAs found a significant reduction in total sleep time \( F(3,18) = 7.22, p < .001, \eta^2 = .86 \), with children sleeping an average of 57 min less when on medication compared to no medication conditions. This reduction in total sleep time was primarily accounted for by significant changes in sleep onset latency \( F(3,18) = 10.69, p < .001, \eta^2 = .64 \), which increased from an average of 26 min when in the no medication conditions to 65 min when taking medication. The remaining difference in total sleep time was accounted for by a nonsignificant change in the children’s bedtime, which occurred later in the medication conditions.

The children awakened at the same time in all conditions \( F(3,18) = 1.13, p = .36, \eta^2 = .16 \). There were no changes in the children’s frequency of awakening during sleep \( F(3,18) = .63, p = .60, \eta^2 = .10 \) nor was the children’s sleep efficiency changed \( F(3,18) = .17, p = .92, \eta^2 = .03 \). Also, there was no change in the mean activity during sleep or variability in sleep activity \( F(3,18) = 1.19, p = .34, \eta^2 = .17 \) and \( F(3,18) = .71, p = .56, \eta^2 = .11 \), respectively.

Examination of the times for lights out, sleep onset and sleep offset indicated that the children were being put to bed around 9:15–9:30 p.m. and were waking just before 7 a.m. During the no medication conditions the children slept for \( \sim 9 \) hr and 20 min, whereas during the medication condition they slept \( \sim 8 \) hr and 20 min.

**Sleep Diary**

The findings from the sleep diary were very similar to those from actigraphy (Table IV). Parents reported that children slept less during the night and evidenced increased sleep onset latency while on medication \( F(3,18) = 17.65, p < .001, \eta^2 = .75; F(3,18) = 8.05, p < .001, \eta^2 = .57, \) respectfully), but did not awaken more during the night \( F(3,18) = .46, p = .71, \eta^2 = .07 \). Again, there was no dose effect (i.e., low dose and moderate dose had a similar impact on sleep). Compared to the actigraphy data, parents reported slightly earlier times for lights out (9:00–9:15 p.m.) and sleep onset times (9:30–10:00 p.m.), whereas they reported later wake times (\( \sim 7:15 \) a.m.). Bedtime resistance did not

## Table III. Actigraph Data for the Baseline Week and 3 Weeks of the Acute Medication Trial

| Scale                        | Baseline Mean (SD) | Placebo Mean (SD) | Low dose Mean (SD) | Moderate dose Mean (SD) | F-value | Sig. | Effect size \( \eta^2 \) | Contrasts |
|------------------------------|--------------------|-------------------|--------------------|-------------------------|---------|-----|--------------------------|-----------|
| Total sleep time             | 497.26 (40.70)     | 495.65 (47.52)    | 444.49 (36.42)     | 434.57 (48.01)          | 7.22    | .000 | .86                      | B = PL    |
|                             |                    |                   |                    |                         |         |     |                          | PL ≠ LD   |
|                             |                    |                   |                    |                         |         |     |                          | LD = MD   |
| Sleep onset latency          | 29.19 (15.42)      | 23.07 (18.04)     | 63.93 (37.93)      | 66.91 (38.28)           | 10.69   | .000 | .64                      | B = PL    |
|                             |                    |                   |                    |                         |         |     |                          | PL ≠ LD   |
|                             |                    |                   |                    |                         |         |     |                          | LD = MD   |
| Wake after sleep onset       | 58.85 (31.05)      | 57.59 (33.56)     | 55.81 (29.96)      | 53.29 (28.17)           | .63     | .60  | .10                      | B = PL = LD = MD |
| Sleep efficiency             | 89.39 (3.49)       | 89.51 (6.10)      | 88.95 (6.07)       | 89.43 (5.38)            | .17     | .92  | .03                      | B = PL = LD = MD |
| Activity mean                | 13.43 (6.88)       | 12.20 (4.20)      | 12.76 (3.76)       | 11.77 (4.04)            | 1.19    | .34  | .17                      | B = PL = LD = MD |
| Activity SD                  | 27.59 (5.45)       | 28.37 (6.08)      | 29.11 (6.29)       | 27.26 (7.09)            | .71     | .56  | .11                      | B = PL = LD = MD |
| Lights out                   | 21.05:35 (0:55:31) | 21:13:57 (0:51:07)| 21:29:43 (1:15:41)| 21:23:29 (0:51:27)      | 2.37    | .10  | .28                      | B = PL = LD = MD |
| Sleep onset                  | 21:34:06 (0:56:27) | 21:38:43 (0:55:58)| 22:36:22 (1:17:14)| 22:29:44 (0:49:19)      | 22.98   | .000 | .79                      | B = PL |
|                             |                    |                   |                    |                         |         |     |                          | PL ≠ LD   |
|                             |                    |                   |                    |                         |         |     |                          | LD = MD   |
| Sleep offset                 | 6:56:58 (0:48:46)  | 6:56:38 (0:51:21) | 6:52:47 (0:58:40)  | 6:46:58 (0:39:43)       | 1.13    | .36  | .16                      | B = PL = LD = MD |

Total sleep time, number of minutes scored as sleep from sleep onset to sleep offset; sleep onset latency, minutes from lights out to first episode of sleep (first 20 min block with >19 min scored as sleep); wake after sleep onset, number of minutes awake between sleep onset and sleep offset; sleep efficiency, 100 x sleep minutes/onset–offset duration; activity mean, mean activity score (counts/epoch); activity SD = standard deviation of activity mean; lights out, time parent indicated that the child’s bedroom lights were turned out and child was expected to fall asleep; sleep onset, time that sleep onset started; sleep offset, time that child awoke.

**Sleep Diary**

The findings from the sleep diary were very similar to those from actigraphy (Table IV). Parents reported that children slept less during the night and evidenced increased sleep onset latency while on medication \( F(3,18) = 17.65, p < .001, \eta^2 = .75; F(3,18) = 8.05, p < .001, \eta^2 = .57, \) respectfully), but did not awaken more during the night \( F(3,18) = .46, p = .71, \eta^2 = .07 \). Again, there was no dose effect (i.e., low dose and moderate dose had a similar impact on sleep). Compared to the actigraphy data, parents reported slightly earlier times for lights out (9:00–9:15 p.m.) and sleep onset times (9:30–10:00 p.m.), whereas they reported later wake times (\( \sim 7:15 \) a.m.). Bedtime resistance did not
The present study sought to determine the impact of immediate release Ritalin (MPH IR), given TID during an acute medication trial, on sleep quality and quantity in medication-naïve, newly diagnosed children with ADHD. Sleep was evaluated using multiple measures including actigraphy, sleep diary, and a sleep questionnaire. A significant reduction in total sleep time and increased sleep onset latency was found based on both the actigraphic data and sleep diary data, but not the questionnaire data.

The children participating in the current study were reported by their parents and teachers to evidence significant reduction in ADHD behaviors while on TID MPH IR compared to the baseline and placebo conditions. Based on the ADHD Index of the CPRS and CTRS, the mean t-score was reduced from the markedly/moderately atypical to the typical/mildly atypical ranges when the children were on medication. A review of individual cases indicated that all children experienced a significant reduction in their ADHD symptoms while on medication. For some children, improvement was found primarily on the Inattention scale while for others improvement was noted on the Hyperactive-Impulsive scale or the ADHD Index.

Table IV. Sleep Diary Data for the Baseline Week and Three Weeks of the Acute Medication Trial

| Scale             | Baseline Mean (SD) | Placebo Mean (SD) | Low dose Mean (SD) | Moderate dose Mean (SD) | F-value | Sig. | Effect size ($\eta^2$) | Contrasts |
|-------------------|--------------------|-------------------|-------------------|------------------------|---------|-----|----------------------|-----------|
| Time in bed       | 586.76 (36.63)     | 585.97 (42.42)    | 547.12 (33.05)    | 547.56 (33.74)         | 17.65   | .000 | .75                  | B = PL, PL ≠ LD, LD = MD |
| Sleep onset latency| 23.09 (12.86)      | 24.71 (15.15)     | 52.10 (32.29)     | 51.14 (30.34)          | 8.05    | .001 | .57                  | B = PL, PL ≠ LD, LD = MD |
| Night awakenings  | 0.24 (0.27)        | 0.16 (0.20)       | 0.25 (0.45)       | 0.23 (0.30)            | 0.46    | .71  | .11                  | B = PL, PL ≠ LD, LD = MD |
| Bedtime resistance| 26.26 (14.31)      | 29.42 (15.37)     | 32.44 (25.77)     | 30.13 (17.13)          | 0.72    | .56  | .11                  | B = PL, PL ≠ LD, LD = MD |
| Lights out        | 21.02 (0.56:45)    | 21.13 (0.55:16)   | 21.15 (0.59:15)   | 21.15 (0.51:07)        | 1.41    | .27  | .08                  | B = PL, PL ≠ LD, LD = MD |
| Sleep onset       | 21.25 (0.56:32)    | 21.37 (0.52:42)   | 22.02 (1.78:18)   | 22.00 (0.57:05)        | 7.52    | .002 | .56                  | B = PL, PL ≠ LD, LD = MD |
| Sleep offset      | 7:14:46 (0:38:46)  | 7:20:35 (0:49:05) | 7:15:57 (0:42:28) | 7:07:36 (0:35:29)      | 1.50    | .25  | .20                  | B = PL, PL = MD, LD = MD |

Time in bed, minutes from lights out to awake time; Sleep onset latency, minutes from lights out to sleep; night awakenings, number of times child awoke during night; bedtime resistance, minutes from first call for bed to getting into bed; lights out, time the lights were turned out in child’s bedroom and child was expected to go to sleep; sleep onset, time child was reported to fall asleep; sleep offset, time child was reported to wake up.

Table V. Sleep Disturbances Scale for Children Data for the Baseline Week and Three Weeks of the Acute Medication Trial

| Scale     | Baseline Mean (SD) | Placebo Mean (SD) | Low dose Mean (SD) | Moderate dose Mean (SD) | F-value | Sig. | Effect size ($\eta^2$) | Contrasts |
|-----------|--------------------|-------------------|-------------------|------------------------|---------|-----|----------------------|-----------|
| DIM       | 56.86 (11.38)      | 57.71 (11.65)     | 59.76 (12.13)     | 62.05 (17.07)          | 1.21    | .36 | .17                  | N/A       |
| SDB       | 53.10 (13.58)      | 52.76 (12.63)     | 53.71 (12.96)     | 52.14 (12.32)          | 1.20    | .34 | .17                  | N/A       |
| DA        | 54.33 (12.93)      | 52.81 (14.10)     | 51.00 (11.92)     | 51.67 (12.50)          | 1.81    | .18 | .23                  | N/A       |
| SWTD      | 60.71 (15.32)      | 54.71 (17.21)     | 57.14 (15.55)     | 55.86 (15.02)          | 2.40    | .10 | .29                  | N/A       |
| DOES      | 52.76 (10.32)      | 53.86 (12.07)     | 51.38 (12.92)     | 52.24 (13.24)          | 0.76    | .53 | .13                  | N/A       |
| SHY       | 54.10 (11.81)      | 50.43 (8.47)      | 50.43 (8.68)      | 49.86 (7.26)           | 2.13    | .13 | .26                  | N/A       |
| Total     | 58.42 (12.56)      | 54.89 (12.83)     | 55.40 (12.92)     | 58.02 (12.23)          | 2.02    | .15 | .25                  | N/A       |

DIM, disorders of initiating and maintaining sleep; SDB, sleep breathing disorders; DA, disorders of arousal; SWTD, sleep-wake transition disorders; DOES, disorders of excessive somnolence; SHY, sleep hyperhydrosis; Total, total score.
clinical judgement as well as the data collected on the CPRS and the CTRS, the medication used in the current study was thought to be effective in treating ADHD symptoms in this sample of 21 children.

Despite the fact that the children were reported by their teachers and parents to display reduced ADHD symptoms, there were significant negative changes in the children’s sleep as a result of medication. Based on the results of the actigraphy data, children during the medication conditions were sleeping ~57 min less per night than during the no medication conditions. This reduction in sleep time is not only statistically significant, but also represents a clinically significant change from 9 hr, 20 min per night to 8 hr, 20 min per night. This is particularly noteworthy given recent research that has demonstrated that reduced sleep duration is associated with poorer academic, behavioral and cognitive performance (Dahl, 1996; Fallone et al., 2001; Sadeh et al., 2002). Moreover, it has been demonstrated that even a reduction of 1 hr per night can have detrimental effects on daytime functioning (Sadeh et al., 2003).

This reduction in total sleep time was accounted for primarily by increased sleep onset latency. It is important to note that the children’s sleep latency was not atypical during the no medication conditions (i.e., they fell asleep within 30 min from lights out) but would be considered clinically significant during medication conditions (i.e., taking ~65 min to fall asleep). The majority of studies that have examined the impact of stimulant medication on sleep using objective measures have been conducted using BID dosing. The results of these studies have been inconclusive (Schwartz et al., 2004; Tirosh et al., 1993). The two previously studies, which compared TID and BID MPH (Kent et al., 1995; Stein et al., 1996) had serious methodological limitations thus rendering their findings uninterruptible. However, our findings were very consistent with those by Sangal et al. (2006), who found that children taking TID MPH IR took on average 69 min to fall asleep compared to 30 min at baseline and 42 min on a nonstimulant medication for ADHD.

Delayed sleep onset is particularly problematic when the child cannot accommodate for this shift by sleeping later in the morning. We found that the children continued to wake at the same time despite their later sleep onset time. This is not surprising as the children have to wake up at set times for school during the weekdays as well as for scheduled activities on the weekends. We were not able to separate out weekdays from weekends as this would result in invalid actigraphic data (i.e., less than the recommended five nights of data; Acebo et al., 1999). Our finding of later sleep onset is not novel, as many studies have reported this; however, in previous research this finding is often attributed to the ADHD diagnosis rather than as a result of treatment for ADHD.

An important finding of our research is that the quality of sleep did not seem to be affected by medication. Once the children fell asleep they were no more likely to wake up during the night regardless of their medication status and their sleep efficiency was similar across all conditions. There was a nonsignificant trend in the data indicating that the children may have been put to bed slightly later during the weeks they were on active medication. This could account for the remaining difference between total sleep time during the medication conditions compared to the no medication conditions once sleep onset was accounted for. A plausible explanation for this could be that the children stalled a bit more during medication weeks as they were not as tired.

The fact that findings can differ based on the data collection methods has been reported numerous times in the literature (Corkum et al., 1998). It has been demonstrated that subjective measures (i.e., questionnaires, sleep diaries) rather than objective measures (i.e., actigraphy, PSG) are more likely to find significant differences in sleep in children with ADHD compared to typically developing children. On the surface, our findings appear to be inconsistent with this previously noted difference between objective and subjective measures, as we found similar results based on actigraphy and sleep diary but not on the sleep questionnaires completed by parents. We believe that this finding is most likely due to the nature of the sleep questionnaire in that each scale is quite diverse and taps into a range of potential sleep problem areas. For example, the Disorders of Initiating and Maintaining Sleep Subscale (DIM) is comprised of seven items, which collect information on total sleep time, sleep onset latency, bedtime resistance, and night awakenings. Based on the results of the actigraphy and sleep diary data, we found changes in some of these areas (i.e., sleep duration and sleep onset latency) but not in other areas (i.e., bedtime resistance and night awakenings); potentially resulting in an overall nonsignificant finding on the scale. This is an important finding as it underscores the need to carefully select research and clinical measures, which are sensitive to the changes that need to be monitored.

Although the results of the current study are robust, there are a number of limitations that must be considered.
when interpreting the results. Our power to detect differences in sleep across the conditions was very strong; however, our small and relatively homogenous sample (e.g., Caucasian, rural, middle class, low rates of comorbidity) makes it difficult to generalize our findings to all children with ADHD being treated with stimulant medication. For example, we do not know if our findings would generalize to children of other ethnicities or children with comorbidities such as anxiety, depression, and conduct disorders. Also, we need to determine if some children are more at risk for developing sleep problems and if so, what factors are associated with this increased risk (e.g., preexisting sleep problems, family history of sleep problems, and comorbidity). The current sample was screened for preexisting sleep problems such as sleep apnea, RLS/PLMD, and parasomnias; however, screening was based on information gathered from a semi-structured parent interview rather than from PSG sleep studies. A large heterogeneous sample in terms of ethnicity and comorbidity as well as a rigorously screened sample in terms of preexisting sleep problems will be needed to address the above-noted issues.

Another significant limitation is our lack of knowledge about whether our findings during the acute trial would persist over time. This is a difficult question to address given the logistic and ethical issues associated with long-term follow-up. However, sleep disruption has been reported as a reason for discontinuing medication in long-term trials (Charach et al., 2004). Also, we do not know if medication adjustments in terms of dosage and timing of administration would change the negative effects on sleep. Given that in the current study both low and moderate doses of TID MPH IR resulted in similar levels of sleep disruption, this may indicate that dosing might not significantly change these negative effects. The number of doses given per day may also result in different degrees of sleep impairment, however, both BID and TID doses have been demonstrated to result in some sleep problems albeit these are potentially greater with TID dosing. There is also limited information on how long-acting medications such as Concerta might affect sleep, although it seems reasonable to assume that the impact would be similar to TID MPH IR given that both are the same medication and both exert their behavioral effects over a similar length of time (although they are released differently).

Our results demonstrated that sleep quantity changed (i.e., reduced total sleep and increased sleep onset latency), however, we did not find any evidence for changes in the quality of sleep (i.e., no changes in activity level, number of minutes awake from sleep onset to offset or sleep efficiency). In order to fully understand the potential underlying changes in sleep architecture (i.e., sleep stages), which may result from stimulant medication, it would be necessary to conduct PSG studies. The few that have been conducted in recent years have resulted in inconsistent findings most likely due to methodological issues such as using between subjects design (Sadeh et al., 2006).

Future research needs to determine whether sleep is disrupted in children with ADHD, as is often concluded, or whether sleep is disrupted due to other confounding variables such as treatment of ADHD with stimulant medication. In favor of the argument for an iatrogenic impact is the fact that there is a lack of specificity of sleep problems to ADHD, there have been few significant findings of differences in sleep between medication-naive children with ADHD compared to typically developing children, and a number of studies have found that medication and comorbidity significantly predict sleep problems in this population (Corkum et al., 1999; Mick et al., 2000; Stein, 1999).

Another area for future research is in determining whether medication results in restricted sleep duration or whether it results in a phase shift or potentially both. Determining if children treated with stimulant medication sleep longer in the morning, if given the opportunity, would be the first step. A comparison of weekday versus weekend wake times or school year versus holiday wake times could be conducted. Also, it needs to be determined what the daytime consequences are for this reduction in sleep time. Potentially a reduction of 1 hr per night could have significant impact on adaptive functioning, learning, and behavior (Sadeh et al., 2003). However, these negative effects may be masked by continued treatment with stimulant medication.

Also important for future research is the need to determine the impact on sleep of long-acting stimulant medications. This need is underscored by the fact that current practice parameters recommend long-acting medications, such as Concerta, for the treatment of ADHD (AACAP, 2007) and the fact that we do not have any systematic research evaluating the impact on sleep of these long-acting medications.

Based on the findings from the current study, we would encourage physicians and parents to closely monitor children’s sleep when treating ADHD with stimulant medication and to carefully weigh the benefits of improved behavioral functioning while on medication against the potential negative consequences of sleep.
disruption over the longer term. There has been a significant shift in medication practices for ADHD to using a TID or long-acting stimulant medication, rather than a BID dosing schedule, as well as a reduced emphasis on “drug holidays.” If the child is experiencing sleep problems, the benefits of the third dose of medication/long-acting medication and need for “drug holidays” should be re-considered in light of the potential impact sleep disruption has on daytime functioning.

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