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Short-Term Side Effects of Stimulant Medication Are Increased in Preschool Children with Attention-Deficit/Hyperactivity Disorder: A Double-Blind Placebo-Controlled Study

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ABSTRACT

Preschool children with attention-deficit/hyperactivity disorder (ADHD) (27 boys, 5 girls, mean age 4 years 10 months) participated in a double-blind placebo-controlled crossover drug study to assess the side effects of methyphenidate. Children received twice daily, for at least 1 week each, placebo, 0.3 mg/kg methylphenidate, and 0.5 mg/kg methylphenidate. Side effects were monitored by a parent rating scale designed for medication studies. In general, methylphenidate was tolerated relatively well, with no children withdrawing because of adverse effects. Of 17 childhood behaviors usually associated with side effects, 8 behaviors showed significant changes, generally at the higher dose of methylphenidate. Interestingly, 3 of the side effects were associated with improved behavior. The number of side effects appeared higher than what is usually reported in a population of school-age children, but few parents reported them as being severe. Severe side effects were reported in less than 10% of the sample, with approximately as many reports of severe effects on placebo as on low and high doses of the medication. The results indicate that methylphenidate has a relatively low toxicity in preschool children (over the first 7–10 days), that some behavioral changes that might be viewed as side effects of methylphenidate are actually normal behaviors or ADHD behaviors in preschool children (e.g., sociability), that these "side-effect" behaviors are more common in preschool than school-age children, that some "side effects" of methylphenidate are associated with improvements in behavior, and that preschool and school-age children may have different side effects of methylphenidate (e.g., mood changes and anxiety).

METHYLPHENIDATE IS BY FAR the most widely prescribed medication for the treatment of attention-deficit/hyperactivity disorder (ADHD). It has demonstrated effectiveness in school-age ADHD children in enhancing on-task behavior, academic achievement, and peer relationships and in reducing the number of negative behaviors evidenced (Barkley 1996, Rapoport and Castellanos 1996). In addition, there is

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growing evidence of similar effectiveness of methylphenidate with preschool children (Monteiro Musten et al., 1997). The positive effects of methylphenidate notwithstanding, there is limited information on the side effects of methylphenidate derived from double-blind placebo-controlled experiments, and these are available regarding school-age but not preschool-age children (Barkley et al. 1990b, DuPaul et al. 1996). Considering that 34% of pediatricians and 15% of family physicians report prescribing stimulants to preschoolers with ADHD (Wolraich et al. 1990), additional research with the younger age group is important.

In order to determine the actual incidence of side effects with methylphenidate, Barkley and colleagues (1990) compared the percent occurrence and severity level of the 17 most commonly reported short-term side effects of two doses of methylphenidate (0.3 and 0.5 mg/kg) and placebo in a triple-blind study. Their results indicated that 4 side effects occurred significantly more in children receiving medication than in those receiving placebo: decreased appetite, insomnia, stomachaches, and headaches.

DuPaul et al. (1996) compared self-reports, teacher reports, and parent reports of side effects experienced by 9- to 15-year-old children receiving methylphenidate, and parents did not report a significant increase in side effects relative to placebo. These side effects may be of sufficient magnitude and concern to warrant removing some children from medication treatment. However, contrary to popular media reports (*Time Magazine*, 1989), most side effects are reported to be transient and subside following titration of dosage (Barkley 1977, Werry and Sprague 1974).

Interestingly, studies that look at reports of side effects while subjects are receiving placebo suggest that many side effects attributed to stimulants may really be symptoms of ADHD. Barkley and colleagues (1990b) found 72% of subjects reported side effects while taking placebo, with the most common being irritability (18%), anxiety, (12%), proneness to crying (10%), and insomnia (7%). Others have reported similar results (Fine and Johnston 1993, Conners 1975).

The purpose of the present study was to assess the occurrence and severity of side effects during short-term treatment of preschool-age ADHD children. In light of the increasing numbers of diagnoses in lower age group, it appears important that both the positive and negative impact of medication be determined.

METHODS

Subjects

One hundred and nine children (all outpatients) between the ages of 4 and 6 years were recruited from the Children's Hospital of Eastern Ontario, or referred directly by local physicians over a period of 2 years. At initial contact, 43 families chose not to participate in this study, while 66 families agreed to participate and completed the assessment. Fifty-four children met all the following criteria:

1. Diagnostic and Statistical Manual of Mental Disorders—Revised (DSM-III-R, American Psychiatric Association 1987) criteria for a diagnosis of ADHD assessed by parent reports in the Diagnostic Interview for Children and Adults—Parents (DICA-P) (Herjanic and Reich 1982, Reich et al. 1982).
2. Parents completed the Swanson, Nolan, and Pelham Checklist (SNAP) (Johnston et al. 1985, Pelham and Bender 1982). Items included on the SNAP allow for a DSM-III-R diagnosis. Criterion for inclusion was a score greater than 1 on 8 out of the 14 DSM-III-R items.
3. A standard score greater than or equal to 80 on the Peabody Picture Vocabulary Test (PPVT) (Dunn and Dunn 1981) if the subject spoke only English, or a score of greater than or equal to 72 if the subject was bilingual.
4. A score equal to or above 1.5 SD above the age and sex mean on the Hyperactivity Index of the Conners Parent Rating Scale—Revised (CPRS-R, Conners 1989).
5. Attention span of less than 88 seconds on the parent-supervised attention task. This criterion is 1.5 SD above the mean attention span achieved by normal children on this task (Pisterman et al. 1989, 1990a).
5. Subjects were neither attending nor entering grade 1 at the time of assessment or throughout the duration of their participation in the study.
6. Parents and children were fluent in English.

7. Subjects did not have any sensory or physical disabilities, developmental disorders (e.g., autism), neurologic disease, or obvious central nervous system dysfunction as assessed by a pediatrician.
8. Subjects who had received methylphenidate were considered for the study if they had received methylphenidate for less than 6 months and if the daily dosage administered was less than the mean of dosages used in the current study. Medication was withdrawn for 48 hours prior to the initial assessment and resumed only if the child did not meet the inclusion criteria or if the parents chose not to participate in the study (n = 2).

Procedures

Screening procedures. Screening assessments were conducted over a period of three sessions. Parents were contacted by telephone and given information regarding the study. Following informed consent, parents attending session 1 were given a written description of the study and were interviewed using the computerized version of the semi-structured Diagnostic Interview for Children and Adolescents—Parent Interview and the Family Demographics questionnaire (Multi-Health Systems Inc., ©1990, Washington University).

Treatment procedures. Each subject received 7–10 days of treatment with placebo, low-dose methylphenidate, and high-dose methylphenidate. Dosage was determined by the weight of the child (0.3 mg/kg and 0.5 mg/kg). Parents were instructed to administer the doses twice a day, once at breakfast and at lunch. The order of treatment was fully randomized and was prepared by the pharmacy department with subjects and parents, research, and medical personnel kept blind to the order. At the end of each treatment period, the child and parent attended two consecutive sessions. Parents were instructed to administer the child's medication at least one half-hour prior to the session. In one session, cognitive tasks were administered to the child, and rating scales for demographics, symptom outcome, and side effects were administered to the parent. In the other session, parent and child engaged in an interactive task. The order of these sessions was randomized across subjects and treatment conditions. Treatment compliance was determined by counting the number of pills returned to the researcher at the end of each treatment period. Unused medication was returned to the pharmacy department at the hospital for disposal.

Medications. Two doses (0.3 mg/kg and 0.5 mg/kg) of methylphenidate hydrochloride and a lactose placebo were prepared by the pharmacy at the Children's Hospital of Eastern Ontario to the nearest 2.5 mg and administered in orange capsules (Size 16, Eli Lilly Company) in order to disguise the difference in taste between placebo and medication. Each dose was administered twice daily (BID).

Design. All subjects participated in all treatment conditions in a double-blind, drug-placebo crossover design using a placebo and two doses of methylphenidate. In cases where subjects were receiving methylphenidate before the commencement of the study, medication was withdrawn 48 hours before the initial assessment. Six possible blocks of treatment orders (PLH, PHL, LPH, LHP, HPL, HLP) were presented, with the order of treatment randomized within each block.

Measures. The Side Effects Rating Scale (SERS) (Barkley 1981, Barkley 1990, Barkley et al. 1990b, Table 2) was administered to the parents and was used to assess symptoms reported to be associated with methylphenidate treatment. The SERS uses a 10-point Likert-type scale ranging from absent (0) to severe (9) in order to assess the presence and severity of side effects spanning somatic, psychological, and social domains, and has been demonstrated to be sensitive to the effects of methylphenidate (Barkley et al. 1990b).

RESULTS

Of the 54 children who met the inclusion criteria, the parents of 13 children refused methylphenidate treatment. A total of 41 children proceeded to the treatment phase of the study, following parent feedback and informed consent for medication. Of these, 32 children (27 boys and 5 girls) completed the treatment regimen, 4 children withdrew from treatment, and 5 children lacked complete questionnaires following one or more of the treatment conditions. Table 1 compares subjects who completed the protocol with those whose parents declined treatment despite meeting inclusion criteria. The mean age of the parents was 32;

they were generally high-school graduates; and the combined family income was approximately $42,000 (Canadian). Twenty-six percent of the children were living in single-parent homes. All of the single parents were receiving social assistance at the time of the assessment and treatment. Family income and parents' ages were not correlated significantly with inclusion variables.

Comorbidity. All participants met the clinical criteria for a diagnosis of ADHD based on the DICA–Parent Semi-Structured Interview. None of the children met the criteria for diagnoses of mood disorders, obsessive-compulsive disorders, overanxious disorder, somatization disorder, or psychotic symptoms. Oppositional-defiant disorder and conduct disorder were diagnosed as present in 84% and 19%, respectively, of the children with ADHD. A group of children also were reported to exhibit all the symptoms of separation anxiety disorder (39%) but did not meet the criteria based on the duration of the symptoms.

The results were analyzed to permit interpretation of both the number of children affected by methylphenidate and the change in the number of symptoms and their severity at each dose. The SERS was subdivided into three groups of side effects reflecting Temperament, Somatic and Sociability. In addition, each of the 17 side effects was examined individually. The subjects' mean severity ratings for the three subgroups along with each of the 17 parent-reported side effects were submitted to analyses of variance with repeated measures across each treatment condition. The percent occurrence and the severity of each side effect was calculated as well. Finally, the percentage of subjects improving and worsening relative to placebo was calculated, and the differences were assessed using the sign test (Tabachnick and Fidell 1989).

Table 2 reveals that the Total Temperament, Total Somatic, and Total Sociability each showed significant effects across treatment conditions. On average, methylphenidate was demonstrated to have positive effects on preschoolers' Temperament and a negative effect on Somatic complaints and Sociability. Subsequent pairwise comparisons using Tukey's procedure indicated that in each case a medication effect was evident only with the high dose, with the placebo and the low dose showing no significant differences (Tabachnick and Fidell 1989).

Out of the 17 possible side effects, 11 symptoms showed significant effects across treatment conditions. Irritable, Anxious, Insomnia, and Sad/unhappy decreased in severity, whereas Nightmares, Decreased appetite, Drowsiness, and Uninterested in others increased. Subsequent pairwise comparisons using Tukey's procedure indicated that in each case only the high-dose treatment was responsible for the effect, with the exception of Decreased appetite, in which the low dose also resulted in significant change.

The number of children (percentage) experiencing each side effect was calculated across each medication condition and is reported in Table 3. Significant effects were found with Irritable, Sad/unhappy, Anxious, Nightmares, Decreased appetite, Drowsiness, Talks less with others, and Uninterested in others. In each case, dosage effects occurred only between placebo and 0.5 mg/kg, with the exception of Decreased appetite, in which all three conditions differed from one another. The statistically significant medication effects indicate that the proportion of children experiencing Irritability, Anxiety, and Insomnia decreased,

TABLE 1. CHARACTERISTICS OF TREATMENT COMPLETERS AND TREATMENT REFUSERS: INCLUSION CRITERIA

	Treatment completed (N = 31)	*Treatment refused (N = 13)*	
Inclusion criteria			*F (1, 42)*
Age (months)	58.1 ± 6.5	55.6 ± 5.9	1.4
PPVT (standard score)	99.7 ± 14.4	102.3 ± 16.2	0.4
DICA symptoms (number)	12.0 ± 1.5	10.8 ± 2.0	4.7*
SNAP symptoms (number)	11.5 ± 1.9	9.6 ± 2.8	6.6*
Conners Hyperactivity Index (T-score)	84.6 ± 10.00	67.8 ± 20.3	13.8**
Attention task-supervised (sec)	30.4 ± 10.4	36.2 ± 32.5	0.3

*$p < 0.05$; **$p < 0.001$.
Data are reported as mean ± standard deviation.

whereas there was an increase in the percentage of children experiencing difficulty on the measures of Sad/unhappy, Nightmares, and Decreased appetite.

Side effects rated at seven or above were considered to be severe (Barkley et al. 1990b, DuPaul et al. 1996). Few parents reported side effects as being severe; nevertheless, more children were reported to be experiencing severe side effects than has been found with school-aged populations (Barkley et al. 1990b,

TABLE 2. NUMBER OF ADVERSE EFFECTS IN ADHD PRESCHOOLERS TREATED WITH VARIOUS DOSES OF METHYLPHENIDATE

	Number of adverse effects				
Adverse effects	*Placebo*	*Low dose methylphenidate 0.3 mg/kg*	*High dose methylphenidate 0.5 mg/kg*	*F (2, 60)*	
		Temperament			
Irritable	3.50 ± 2.5	3.68 ± 3.0	1.13 ± 2.0	14.87***	Placebo > High Low > High
Sad/unhappy	1.88 ± 2.7	1.91 ± 2.4	3.88 ± 2.8	9.02***	Placebo < High Low < High
Prone to crying	2.69 ± 3.0	2.91 ± 2.9	2.19 ± 2.6	0.96	
Anxious	2.88 ± 2.6	2.56 ± 2.5	0.36 ± 1.3	16.13***	Placebo > High Low > High
Euphoric/unusually happy	0.44 ± 1.1	0.59 ± 1.3	0.22 ± .9	0.84	
Total	11.38 ± 9.1	11.65 ± 7.0	7.76 ± 5.6	4.76*	Placebo > High Low > High
		Somatic			
Insomnia, trouble sleeping	2.78 ± 2.8	2.38 ± 2.5	1.09 ± 1.7	8.69***	Placebo > High Low > High
Nightmares	0.84 ± 1.7	0.78 ± 1.5	2.25 ± 2.4	5.77**	Placebo < High Low < High
Stares a lot or daydreams	1.44 ± 2.1	1.13 ± 1.5	1.88 ± 2.7	1.17	
Decreased appetite	0.56 ± 1.2	2.28 ± 2.6	4.03 ± 2.9	17.94***	Placebo < Low Placebo < High Low < High
Stomachaches	0.84 ± 1.5	1.13 ± 2.0	0.45 ± 1.2	1.98	
Headaches	0.53 ± 1.2	0.72 ± 1.7	1.34 ± 2.3	2.1	
Drowsiness	0.53 ± 1.6	0.55 ± 1.1	2.88 ± 3.0	13.14***	Placebo < High Low < High
Bites fingernails	0.66 ± 1.9	0.69 ± 2.2	0.56 ± 1.2	0.05	
Dizziness	0 ± 0	0.06 ± .4	0.06 ± .4	1	
Tics or nervous movements	0.06 ± .4	0.07 ± .4	0.33 ± 1.4	1.03	
Total	8.25 ± 6.1	9.77 ± 8.5	14.88 ± 11.0	5.54**	Placebo < High Low < High
		Sociability			
Talks less with others	0.69 ± 1.6	1.03 ± 2.0	1.75 ± 2.6	2.31	
Uninterested in others	1.00 ± 1.7	0.73 ± 1.2	3.41 ± 2.8	17.94**	Placebo < High Low < High
Total	1.69 ± 3.1	1.77 ± 2.8	4.88 ± 3.5	12.49***	Placebo < High Low < High

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
Data are means ± standard deviations.

Rapoport and Castellanos 1996). In most cases, severe side effects were reported in less than 10% of the sample, with approximately as many side effects being reported as severe in children receiving placebo as in those receiving low and high doses of medication. Differences in the rates of reported severity were evident for Irritable, Decreased appetite, Drowsiness, and Uninterested in others. However, post hoc analyses revealed that placebo and low dose differed from high dose only for the percentage of subjects reported to experience Decreased appetite and Drowsiness. No effects were detected by the post hoc analyses for Irritable and Uninterested in others.

TABLE 3. PERCENTAGE OF SUBJECTS DISPLAYING EACH ADVERSE EFFECT DURING MEDICATION CONDITIONS

Side effect	*Placebo*	*Low dose methylphenidate 0.3 mg/kg*	*High dose methylphenidate 0.5 mg/kg*	*F (2, 60)*	
		Temperament			
Irritable	81	75	38	11.39***	Placebo > High
% severe	6	22	3	3.33*	Low > High
Sad/unhappy	47	56	84	7.39***	Placebo < High
% severe	9	3	19	1.13	Low < High
Prone to crying	56	66	56	.74	
% severe	16	12	6	1.17	
Anxious	66	72	12	26.89***	Placebo > High
% severe	9	9	3	.66	Low > High
Euphoric/unusually happy	19	25	6	2.44	
% severe	0	0	0	—	
		Somatic			
Insomnia or trouble sleeping	59	62	41	5.44*	Placebo > High
% severe	12	6	0	2.07	Low > High
Nightmares	28	31	62	5.51**	Placebo < High
% severe	0	0	6	2.07	Low > High
Stares a lot or daydreams	47	47	53	.22	
% severe	6	0	9	1.42	
Decreased appetite	25	56	81	15.37***	Placebo < Low
% severe	0	6	22	5.57**	Placebo < High Low < High
Stomachaches	31	38	22	1.28	
% severe	0	3	0	1.00	
Headaches	18.75	21.88	37.50	2.72	
% severe	0	3.13	6.25	1.00	
Drowsiness	12.50	25.00	65.63	13.05**	Placebo < High
% severe	3.13	0.00	15.63	3.81*	Low < High
Bites fingernails	12.50	15.63	28.13	1.42	
% severe	3.13	6.25	0.00	1.52	
Dizziness	0.00	3.13	3.13	1.00	
% severe	0.00	0.00	0.00	—	
Tics or nervous movements %	3.13	9.38	12.50	1.42	
% severe	0.00	0.00	3.13	1.00	
		Sociability			
Talks less with others	21.88	34.38	50.00	3.92*	Placebo < High
% severe	3.13	3.13	9.38	.79	
Uninterested in others	31.25	37.50	75.00	8.18***	Placebo < High
% severe	0.00	0.00	12.50	4.43*	Low < High

*$p < .05$; **$p < .01$; ***$p < .001$.

TABLE 4. PERCENTAGE OF CHILDREN WHO IMPROVED, DETERIORATED, AND SHOWED NO CHANGE IN DIFFERENT TREATMENT CONDITIONS

Variables		*Clinical change with low-dose (0.3 mg/kg) and high-dose (0.5 mg/kg) of methylphenidate treatment*			
		% Improved	*% Deteriorated*	*% No change*	*Significance (p)*
		Temperament			
Irritable	P-L	41	41	19	1.00
	L-H	47	66	16	0.02
	P-H	72	12	16	0.001
Sad/unhappy	P-L	25	31	44	0.81
	L-H	19	16	16	0.01
	P-H	16	69	16	0.01
Prone to crying	P-L	31	28	41	1.00
	L-H	41	25	35	0.38
	P-H	41	34	25	0.84
Anxious	P-L	41	31	28	0.68
	L-H	69	3	28	0.001
	P-H	66	3	31	0.001
		Somatic			
Euphoric/unusually happy	P-L	12	16	72	1.00
	L-H	25	6	69	0.11
	P-H	19	6	75	0.29
Insomnia or trouble sleeping	P-L	25	28	47	1.00
	L-H	47	6	47	0.01
	P-H	53	6	41	0.001
Nightmares	P-L	12	16	72	1.00
	L-H	22	53	25	0.06
	P-H	19	53	28	0.05
Stares a lot or daydreams	P-L	31	22	47	0.63
	L-H	31	34	344	1.00
	P-H	38	28	34	0.66
Decreased appetite	P-L	12	50	38	0.01
	L-H	22	56	22	0.04
	P-H	9	75	16	0.001
Stomachaches	P-L	19	34	47	0.33
	L-H	34	9	56	0.06
	P-H	19	34	47	0.33
Headaches	P-L	9	12	78	1.00
	L-H	16	28	56	0.42
	P-H	16	25	59	0.58
Drowsiness	P-L	6	15	78	0.45
	L-H	19	56	25	0.02
	P-H	9	62	28	0.001
Bites fingernails	P-L	6	12	81	0.68
	L-H	16	28	56	0.42
	P-H	12	28	59	0.27
Dizziness	P-L	0	3	97	1.00
	L-H	0	0	32	—
	P-H	0	3	97	1.00
Tics or nervous movements	P-L	0	6	94	0.5
	L-H	3	12	84	0.38
	P-H	3	12	84	0.38
		Sociability			
Talks less with others	P-L	12	22	66	0.55
	L-H	28	34	38	0.82
	P-H	16	38	46	0.14
Uninterested in others	P-L	22	16	62	0.77
	L-H	12	72	16	0.001
	P-H	12	62	25	0.002

Determination of the number of symptoms or the relative severity of side effects across treatment conditions does not reveal individual patterns of side effects, an important clinical consideration. The sign test (Tabachnick and Fidell 1989) was performed to identify the percentage of children whose side effects worsened, ameliorated, or did not change with ech treatment condition, compared with placebo and between dosages. Table 4 reports the percentages of children in each response category for each placebo-dose comparison. A placebo/low-dose difference was found only with Decreased appetite.

Behavioral changes from low-dose to high-dose treatment were reported for five symptoms: Irritable, Sad/unhappy, Insomnia, Decreased appetite, and Drowsiness. Irritable and Insomnia were reported to have remained the same or improved for most of the children. Fifty to sixty percent of the children were reported to have worse side effects with increasing dose on the remaining symptoms of Sad/unhappy, Decreased appetite, and Drowsiness.

The placebo/higher-dose analyses revealed significant changes with Irritable, Sad/unhappy, Anxious, Insomnia, Nightmares, Decreased appetite, and Drowsiness. Examination of the proportions indicated that one-half to three-quarters of the children were reported to have improved on symptoms of Irritable, Anxious, and Insomnia. However, the remaining symptoms were reported to have become worse for the same proportion of children.

In general, whereas Decreased appetite appeared to have been the side effect that increased most in being experienced by over half the children receiving both doses, Irritable and Insomnia seemed to improve with medication. The data further suggest that more children experienced an increased severity of side effect symptoms following the higher dose relative to both placebo and the lower dose.

DISCUSSION

In general, this study confirms for the preschool-age group the body of literature reporting relatively mild side effects occurring with methylphenidate treatment in school-aged boys. Perhaps one of the most interesting findings is that preschoolers display a high rate of behaviors often regarded as side effects while receiving placebo. This may simply reflect a developmental difference, since others have reported that preschool-age children are more symptomatic in general, compared with school-age children (Barkley 1990, Palfrey 1985, Campbell et al. 1982). A comparison between the results of the present study and the results obtained by Barkley (Barkley 1996) and his colleagues (Barkley et al. 1990b) underlines this finding. The preschoolers in the current study showed more of these "side effect" behaviors than is generally reported with their school-age counterparts, even while receiving placebo.

Barkley and his colleagues found that 72% of school-age subjects self-reported having side effects while receiving placebo (Barkley et al. 1990b), and others have reported a similar phenomenon with teachers' reports (DuPaul et al. 1996). In the current study, 97% of the preschoolers were reported to experience some side effects while receiving placebo. While Barkley reported the most common side effects with school-age children receiving placebo to be irritability (18%), anxiety (12%), proneness to crying (10%), and insomnia (7%), the corresponding figures in the current study are irritability (81%), anxiety (66%), proneness to crying (56%), and insomnia (59%). In fact, only tics/nervous movements and dizziness were reported in less than 10% of the subjects while they were receiving placebo. Together, these findings may reflect the aforementioned developmental difference, or that parents and teachers of preschoolers may mistake ADHD symptoms for side effects. Finally, the fact that preschoolers are less able than older children to articulate their internal states may also add to this apparent increase in rate of symptomatology.

The present findings on sociability and emotionality differ from the somatic complaints evidenced in the school-age group and merit discussion. This social dampening effect reported by parents is of some concern, especially considering claims that methylphenidate is used as a "chemical billy club" (Dockx 1988) or "straitjacket" (McCartney 1988). While it is desirable to decrease the occurrence of negative, disruptive, and aggressive behaviors, the reduction of positive prosocial behaviors may hinder children socially (Coie et al. 1990). The effects of methylphenidate on sociability are unclear in the literature (Henker and Whalen 1989, Hinshaw and McHale 1991, Whalen 1989, Whalen and Henker 1991). Some investigators report

methylphenidate to have a positive effect on sociability (Barkley and Cunningham 1979, Pelham et al. 1987, Schleifer et al. 1975); others report methylphenidate to have a negative effect on sociability (Buhrmester et al. 1992, Cantwell and Carlson 1987, Whalen et al. 1979b, Rie et al. 1976); while still others find methylphenidate to have no effect (Barkley 1985, Hinshaw et al. 1989, Pelham and Bender 1982, Wallander et al. 1987). One possible interpretation of the decrease in sociability and the increase in solitary play may be that methylphenidate is successful in increasing the attention span of preschoolers, resulting in sustained on-task behavior.

It has been demonstrated that ADHD boys tend to be more talkative and socially active than normal controls (Buhrmeister et al. 1992, Copeland 1979, Pelham and Bender 1982, Whalen et al. 1978, 1979b) and have an unusually high desire for social interaction (MacDonald 1988); however, they tend to be socially inept and lacking in prosocial skills (Milich and Landau 1982, Whalen and Henker 1985). Therefore, parents may be used to the high level of activity observed in their ADHD preschooler and misinterpret their child's ability to concentrate on a task for a sustained time as a decrease in sociability. This interpretation is supported by the results obtained by Monteiro Musten et al. (1997), who demonstrated the efficacy of methylphenidate in increasing on-task behavior in preschoolers. As a result, parents may be observing a normalization of social interest and behavior. It must be kept in mind, though, that research suggests that a reduction in social interaction may be an improvement in the social functioning of ADHD children because of the high incidence of impulsive, disruptive, and aggressive behaviors that are manifested in their social engagements (Buhrmeister et al. 1992, Coie et al. 1990, Hinshaw and McHale, 1991, Whalen and Henker 1991).

Previous research has suggested that mild dysphoria is a common side effect of stimulant medication (Gittelman-Klein et al. 1976, Rapoport 1979), and stimulants have been demonstrated to increase negative affect and elevate levels of anxiety and sadness in some ADHD children (Buhrmester et al. 1992, Conners and Taylor 1980, Hinshaw et al. 1989, Whalen et al. 1978, 1989, 1990, 1981). This is of some concern because dysphoria has been demonstrated to have a negative effect on peer acceptance (Burhmeister et al. 1992). On this point, the findings of the current study are mixed. While sadness increased in our preschool population as a function of stimulant treatment, both irritability and anxiety decreased. It is possible that this represents a developmental difference in response to methylphenidate. Alternatively, another interpretation is that while methylphenidate is successful in improving the sustained attention of ADHD preschoolers, it does not substantially affect their mood. As a result, the decrease in activity level and problematic behaviors allows for parents to become more aware of their child's mood. This might be expected to be more negative in comparison with siblings or peers and is more easily observed when one considers emotional reactivity to frustrating events evidenced by preschool ADHD children (Barkley et al. 1990b, Campbell 1990).

Children with ADHD have been reported to experience more medication-related dysphoria while engaging in small structured activities (Whalen et al. 1979b, Hinshaw et al. 1989), whereas observations in more open action-oriented settings, such as classrooms or playgrounds, do not reveal this effect (Hinshaw et al. 1989, Pelham et al. 1987, Whalen et al. 1987). In cases where preschoolers are more likely to be engaged in small constrained activities (structured by the primary caregiver) than to be engaged in play activities in open settings, medication-related dysphoria might be more likely to be observed. In any case, the decrease in anxiety and irritability as a function of treatment with stimulant medication is encouraging.

CONCLUSIONS

The findings from the present investigation are limited in several ways. First, the age group of the population under investigation (4–6 years) may have interfered with the parents' ability to detect medication side effects, because preschoolers cannot always articulate medication-related sensations. This may partially account for both the higher level of behavioral side effects reported, and the higher variability observed in comparison with older ADHD children. Furthermore, there is evidence that the reported severity and oc-

currence of side effects resulting from methylphenidate can be affected by who is reporting them, with self-reports resulting in the highest level of side effects (DuPaul et al. 1996).

Second, the dosages used in the current study are relatively conservative in comparison with the dosages commonly used in a clinical setting (i.e., up to 1.0 mg/kg, see Rapoport and Castellanos 1996). This may explain why most of the medication effects were detected primarily between placebo and the higher dose.

Third, the design of the study did not include reversal of treatment conditions (ABA) or a control group. It is possible, as discussed above, that the high rate of behaviors reported as side effects in a placebo condition may have instead been behaviors associated with the disorder itself.

Finally, the restricted time range in the present investigation may have distorted the possible rates of side effects. Clinical practice reveals that in some patients, some side effects that are evident early in treatment may dissipate with time, whereas others surface only after prolonged use.

Despite its limitations, this controlled investigation demonstrates that preschoolers with ADHD show generally mild side effects while taking methylphenidate over a 7- to 10-day period. The side effects appear to be somewhat more severe and more variable than those generally observed in school-age children with ADHD, and the side effects tended to be less somatic and more behavioral in nature. The high number of side effects reported in the placebo condition suggests that some behaviors classified as side effects may simply reflect a developmental difference in behavior patterns between preschoolers and older children.

Future research should employ multiple observers, a wider range of doses, and a longer time period. Considering the potential benefits of methylphenidate and the limitations in treatment modalities for preschoolers with ADHD, methylphenidate should be considered a reasonable intervention with this population.

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