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A Prospective Open Trial of Guanfacine in Children with Pervasive Developmental Disorders

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Abstract

Objective:

A common complaint for children with pervasive developmental disorder (PDD) is hyperactivity. The purpose of this pilot study was to gather preliminary information on the efficacy of guanfacine in children with PDD and hyperactivity.

Methods:

Children with PDD accompanied by hyperactivity entered the open-label trial if there was a recent history of failed treatment with methylphenidate or the child did not improve on methylphenidate in a multisite, placebo-controlled trial.

Results:

Children (23 boys and 2 girls) with a mean age of 9.03 (±3.14) years entered the open-label trial. After 8 weeks of treatment, the parent-rated Hyperactivity subscale of the Aberrant Behavior Checklist (ABC) went from a mean of 31.3 (±8.89) at baseline to 18.9 (±10.37) (effect size = 1.4; $p < 0.001$). The teacher-rated Hyperactivity subscale decreased from a mean of 29.9 (±9.12) at baseline to 22.3 (±9.44) (effect size = 0.83; $p < 0.01$). Twelve children (48%) were rated as Much Improved or Very Much Improved on the Clinical Global Impressions– Improvement. Doses ranged from 1.0 to 3.0 mg/day in two or three divided doses. Common adverse effects included irritability, sedation, sleep disturbance (insomnia or midsleep awakening), and constipation. Irritability led to discontinuation in 3 subjects. There were no significant changes in pulse, blood pressure, or electrocardiogram.

Conclusions:

Guanfacine may be useful for the treatment of hyperactivity in children with PDD. Placebo-controlled studies are needed to guide clinical practice.

Introduction

Pervasive Developmental Disorders (PDDs), such as autistic disorder, Asperger's disorder, and PDD-not otherwise specified (NOS), are chronic conditions of early childhood onset defined by varying degrees of social impairment, delayed and deviant language, and repetitive behavior (*Diagnostic and Statistical Manual of Disorders*, 4th edition, Text Revision; DSM-IV-TR; American Psychiatric Association, 2000). The PDDs are often accompanied by motor restlessness, overactivity, distractibility, and disruptive behavior (Lecavalier et al., in

press). For some children with PDD, these symptoms may be severe enough to warrant pharmacotherapy. Indeed, expert clinicians and researchers ranked the stimulants and α2-adrenergic agonists as the two most appropriate medication groups for treating children with developmental disabilities and hyperactivity (Rush and Francis 2000). Despite the opinion of these experts, however, the empirical support for the use of these medications in PDD is limited.

The stimulants are first-line treatments for typically developing children with inattention, hyperactivity, and impulsiveness. Of the currently available stimulants, methylphenidate is the most commonly used. Data from the Multimodal Treatment Study of ADHD (MTA) indicate that 75% of typically developing children with attention-deficit/hyperactivity disorder (ADHD) benefit from methylphenidate during both short- and long-term treatment (MTA Cooperative Group 1999; Greenhill et al. 2001). To date, only a handful of stimulant trials in children with PDD and hyperactivity have been undertaken (Aman et al. 2003). The Research Units on Pediatric Psychopathology (RUPP) Autism Network recently completed a multisite trial in children with PDD accompanied by hyperactivity and showed that methylphenidate was superior to placebo (RUPP Autism Network 2005). Compared to typically developing children with ADHD, however, the magnitude of response to methylphenidate was modest and there was a relatively high frequency of adverse events leading to discontinuation. When stimulants are not successful in reducing the primary symptoms of ADHD, clinicians turn to nonstimulant medications such as clonidine, guanfacine, atomoxetine, or desipramine (Scahill et al. 2001; Spencer et al. 2001; TS Study Group 2001; Michelson et al. 2002). Although each of these compounds has been evaluated in one or more placebo-controlled trials in typically developing children with ADHD, none of these nonstimulant medications has been well studied in children with PDD and hyperactivity.

The α2 agonist clonidine has been used in the treatment of overactivity and impulsiveness in children for over 2 decades (Leckman et al. 1991; TS Study Group 2001). The chief drawback of clonidine is sedation (Jaselkis et al. 1992; TS Study Group 2001). Guanfacine is a newer α2 adrenergic agonist that appears to be less sedating than clonidine and, therefore, may be better tolerated. The plasma half-life of guanfacine in healthy adults is 10–30 hours compared with 4–10 hours for clonidine. This longer duration of action may promote better compliance due to the need for less frequent dosing and may protect against the rebound effects associated with abrupt discontinuation of clonidine (Leckman et al. 1986). In addition, animal studies show that guanfacine improves prefrontal cortical function in nonhuman primates, without sedation further supporting differentiation of these pharmacological effects (Avery et al. 2000). The only two published placebo-controlled trials of guanfacine in pediatric populations provide somewhat inconsistent results. Scahill et al. (2001) showed that guanfacine was superior to placebo on teacher-rated ADHD measures in children with tic disorders and ADHD. The medication was also helpful in reducing tics. Cummings et al. (2002) reported no benefit over placebo in children with Tourette syndrome. However, this trial involved a small sample and did not specifically target ADHD symptoms. To date, there is only a retrospective report of guanfacine in developmentally disabled children. This report showed a modest benefit for guanfacine, although, once again, target symptoms were not clearly specified (Posey et al. 2004). The purpose of the present study is to collect prospective pilot data on the safety and effectiveness of guanfacine in the treatment of children with PDD and hyperactivity.

Methods

Design

This was a multisite, 8-week, prospective, open-label trial of guanfacine in children with PDD and high levels of hyperactivity and distractibility. The trial was designed as companion study to a mulitsite, placebo-controlled trial of methylphenidate in children with PDD and hyperactivity conducted by the RUPP Autism Network (2005). Subjects entered the guanfacine study by one of two pathways: (1) If there was a recent history of failed treatment with methylphenidate and all other entry criteria for the RUPP methylphenidate study were met; (2) if the child did not improve on methylphenidate in the RUPP multisite study. Eligible subjects were boys and girls between the ages of 5 and 14 years; DSM-IV diagnosis of PDD (PDD-NOS, Asperger's disorder, autistic disorder) based on a DSM-IV clinical diagnosis and corroborated by the Autism Diagnostic Interview-Revised (Lord et al. 1997) accompanied by clinically significant symptoms of ADHD (i.e., impulsiveness and hyperactivity) as evidenced by a score of at least Moderate (≥ 4) on the Clinical Global Impressions (CGI) Severity score for ADHD symptoms. Subjects also had to have an average score of 1.7 on the parent-rated or teacher-rated hyperactive-impulsive items of the SNAP-IV (Swanson et al. 2001; http://adhd. net). (This SNAP threshold is approximately 1.2 SD above the mean for typically developing children (Swanson et al. 2001). This relatively low threshold was set because some items on the SNAP imply use of language and often do not apply to children with PDD. (Indeed, these items were consistently left blank by some parents and teachers.) Other entry criteria required a mental age of at least 18 months as measured by any one of the following tests: the Slosson Intelligence Test, the Wechsler Intelligence Scale for Children (when possible), or by the Revised Leiter International Intelligence Test or the Mullen Scales of Early Development (Slosson 1983; Wechsler 1991; Mullen 1995; Roid and Miller 1997).

Procedures

Following a detailed screening that included medical, psychiatric, and developmental assessments, eligible children were enrolled via one of the pathways mentioned above. Subjects were seen weekly for the first 4 weeks to evaluate response and tolerability and then seen every other week until week 8. Visits included vital signs, height and weight, and a systematic review of adverse events. Efficacy ratings were collected at baseline and every 4 weeks.

Measures:

The primary outcome measures were the parent-rated Hyperactivity subscale of the Aberrant Behavior Checklist (ABC) and the Improvement item of the CGI scale (CGI-I). The Hyperactivity subscale of the ABC contains 16 items that reflect hyperactivity and impulsive behavior (Aman et al. 1985) and was designed to measure change in treatment studies and has been normed in developmentally disabled populations (Marshburn et al. 1992; Brown et al. 2002). Higher scores reflect greater symptom severity. The ABC also contains several other subscales on the basis of factor analysis including: Irritability, Social Withdrawal, Stereotypy, and Inappropriate Speech. These scales have also been used to measure change in clinical trials for children with autism (RUPP Autism Network 2002).

The CGI-I is a commonly used 7-point scale designed to reflect overall change (Guy 1976). In this study, a research clinician trained to reliability used all available information to judge whether there was any change from baseline. If so, the change was rated as positive (Minimally Improved, Much Improved, Very Much Improved) or negative (Minimally Worse, Much Worse, or Very Much Worse). Ratings of Much Improved or Very Much Improved were used to define a positive clinical response with all other responses used to define inadequate response.

Other important outcomes included the teacher-rated Hyperactivity subscale of the ABC and the parent- and teacher-rated SNAP-IV. The SNAP-IV is an 18-item scale based on the DSM-IV symptoms of ADHD (Swanson et al. 2001). It has been used as a measure of change in clinical trials in typically developing children with ADHD (MTA Group 1999), but less commonly in children with PDD.

Medication

The medication regimen was determined by body weight. Children below 25 kg started with 0.25 mg at bedtime and increased to 0.25 mg bid on day 4. Thereafter, dosage increases were made in 0.25-mg increments, approximately every fourth day as tolerated, to a maximum of 3.5 mg per day, given on a tid schedule (e.g., 8 am, 2 pm, and 8 pm). For children ≥ 25 kg, the guanfacine dose schedule was similar, but starting with 0.5 mg at night and increases in 0.5 mg increments. The maximum dose for these children was 5.0 mg/day on a tid schedule. There were no planned dose increases after week 5. Medication decreases to manage adverse effects were permitted at any time.

Results

Twenty seven subjects met eligibility criteria at baseline. However, 2 subjects, who did not improve on methylphenidate in the multisite trial, declined further study treatment. Thus, 25 subjects (mean age = 9.03 ± 3.14) entered the open-label trial. Of these, 14 entered directly due to recently failed treatment with methylphenidate; the other 11 did not show improvement with methylphenidate during the multisite trial. The sample included 92% boys (n = 23); 72% (n = 18) were Caucasian, 24% (n = 6) were African-American, and 4% (n = 1) were Hispanic. Table 1 presents demographic and clinical characteristics of the study sample.

Characteristic	*n (%)*
Boys	23 (92)
Caucasian	18 (72)
Black	6 (24)
Hispanic	1 (4)
Diagnosis	
Autistic disorder	7 (28)
PDD-NOS	18 (72)
	Mean (SD)
Age	9.0 ± 3.14
IQ	50.9 (31.56)
Vineland	
COM	54.7 ± 27.0
DLS	42.9 ± 20.9
SD	51.9 ± 15.2

PDD = Pervasive developmental disorder; NOS = not otherwise specified; SD = standard deviation; COM = Communication; DLS = Daily Living Skills.

Table 1. Baseline Clinical Characteristics of Children with PDD in Guanfacine Trial

On the basis of data from Brown et al. (2002), the population mean on the ABC Hyperactivity subscale for developmentally disabled children receiving developmental disabilities services in the age group of this trial was 12.92 ± 11.70. As shown in Table 2, the mean score of 31.2 ± 8.77 on the parent-rated ABC Hyperactivity subscale in this sample was nearly 2 SD above the population mean (Brown et al. 2002). Tables 2 and Table 3 show the results on the parent- and teacher-rated ABC subscales, respectively. The parent-rated Hyperactivity declined 40% from 31.2 at baseline to 18.9 at the endpoint. This endpoint score is below 1 SD above the normative value and equals a pre- and post-treatment effect size of 1.4 (mean change from baseline to endpoint divided by the SD at baseline). Similarly, the teacher-rated Hyperactivity subscale declined 25% from 29.9 at baseline to 21.9 at endpoint for an effect size of 0.83. As shown in Table 2, parents rated significant reductions on the Irritability, Stereotypic Behavior, and Social Withdrawal subscales. By contrast, although teacher ratings were similar to parent ratings in severity at baseline, teachers reported modest improvements on these same measures at the endpoint.

Subscale	*Baseline (SD)*	*Endpoint (SD)*	*Change score*	*% change*	*t-test*	*p value*
Hyperactivity	31.2 (8.77)	18.9 (10.37)	12.3	39%	5.4	<0.001
Irritability	17.4 (13.17)	11.5 (8.28)	5.9	34%	2.75	0.01[a]
Social withdrawal	12.7(10.06)	7.6 (5.69)	5.1	40%	3.05	<0.01[a]
Stereotypy	8.8 (5.76)	5.4 (4.83)	3.4	39%	3.28	<0.01[a]
Inappropriate speech	5.0 (4.40)	4.3 (5.14)	0.7	14%	0.64	0.53

SD = Standard deviation.
[a]$p < 0.05$ after correction for multiple comparisons.

Table 2. Parent-Rated Aberrant Behavior Checklist Subscale Scores Pre- and Post-Treatment

Subscale	*Baseline (SD)*	*Endpoint (SD)*	*Change score*	*% Change*	*t-test*	*p value*
Hyperactivity	29.9(10.09)	21.9 (9.56)	8.0	27%	3.4	<0.01
Irritability	16.8 (10.57)	14.4 (8.92)	2.4	14%	1.48	0.15
Social withdrawal	13.0 (12.20)	11.8 (10.38)	1.2	9.2%	0.92	0.37
Stereotypy	7.5 (5.35)	6.6 (5.48)	0.9	12%	1.12	0.27
Inappropriate speech	5.1 (4.36)	6.0 (4.34)	-0.9	-18%	1.13	0.27

SD = Standard deviation.

Table 3. Teacher-Rated Aberrant Behavior Checklist Subscale Scores at Pre- and Post-Treatment

Table 4 shows parent- and teacher-rated change on the SNAP-IV scale. There is good agreement between parents and teachers on all SNAP-IV scales, although the magnitude of change was greater on parent ratings. Using all available data, the clinician rated 12 of 25 (48%) children as Much Improved or Very Much Improved at week 8. Two subjects withdrew due to lack of efficacy.

In doses ranging from 1.0 mg/day to 3.0 mg/day in two or three divided doses, guanfacine was well tolerated. There were no serious adverse effects. Common adverse events included sedation ($n = 10$), irritability ($n = 7$), sleep disturbance (e.g., insomnia or midsleep awakening) ($n = 6$), increased aggression or self-injury ($n = 4$), decreased appetite ($n = 4$),

constipation (n = 3), perceptual disturbance (n = 2) (defined as visual distortion of size and distance), and agitation (n = 1). Several of these adverse effects occurred in the same subjects. Three subjects withdrew prematurely due to irritability (being moody, tearful, and easily frustrated) (see Table 5). Systolic blood pressure showed a mean decline of about 7 points at 4 weeks, but returned to baseline by week 8 (see Fig. 1). Diastolic blood pressure remained stable throughout the 8-week trial (see Fig. 2). There were no clinically significant changes in the electrocardiogram taken at week 8 compared to the endpoint, as determined by a pediatric cardiologist at each site.

Discussion

This prospective, open-label trial in children with PDD accompanied by hyperactivity and impulsive behavior showed that guanfacine was associated with a 39% improvement over

Subscale	*Baseline (SD)*	*Endpoint (SD)*	*Change score*	*% change*	*t-test*	*p value*
Parent						
Total	35.5 (8.21)	22.7 (10.02)	12.8	36%	5.98	<0.0001
Inattention	18.2 (5.05)	12.4 (5.56)	5.8	32%	4.90	<0.0001
Hyperactivity	17.3 (4.44)	10.2 (5.40)	7.1	41%	6.27	<0.0001
Teacher						
Total	33.1 (10.43)	27.2 (10.44)	5.9	18%	2.71	0.01
Inattention	16.9 (6.76)	14.2 (5.97)	2.7	16%	2.46	0.02
Hyperactiviry	16.2 (5.30)	13.0 (5.85)	3.2	20%	2.67	0.01

SD = Standard deviation.

Table 4. Parent and Teacher Snap-IV Scores at Baseline and 8 Weeks

Adverse event[a]	*n (%)*	*Study termination*
Sedation	7 (28)	
Irritability	7 (28)	3
(moody, tearful, easily frustrated)		
Sleep disturbance	6 (24)	
(insomnia or mid-sleep awakening)		
Aggression or self-injury	4 (16)	
Tiredness	3 (12)	
Decreased appetite	2 (8)	
Constipation	2 (8)	
Talkativeness	1 (4)	
Perceptual disturbance	2 (8)	1 (with agitation)
(altered sense of size and distance)		

[a]Several subjects experienced more than one adverse event.

Table 5. Probable Drug-related Adverse Event Reported by Parents During 8-Week Study

baseline on the parent-rated ABC Hyperactivity subscale and SNAP-IV scales. This 12-point improvement on the parent-rated ABC Hyperactivity subscale was virtually identical to the magnitude of change observed in the placebo-controlled trial of risperidone in children with

autism (RUPP Autism Network 2002). However, the subjects in that risperidone trial had more serious behavioral problems, as evidenced by much higher scores on the ABC Irritability subscale. It is not clear that children with hyperactivity accompanied by high levels of tantrums, aggression, or self injury (i.e., behaviors captured on the Irritability subscale) would show the same magnitude of improvement with guanfacine as that observed with risperidone (RUPP Autism Network 2002). The level of improvement on parent-rated ADHD symptoms observed in this open-label study with guanfacine was slightly less than the parent-rated improvement in an open-label trial comparing methylphenidate and atomoxetine in typically developing children with ADHD (Kratochvil et al. 2002). In that study, children were randomly assigned to methylphenidate or atomoxetine for 10 weeks and each medication was associated with a 50% improvement compared to baseline.

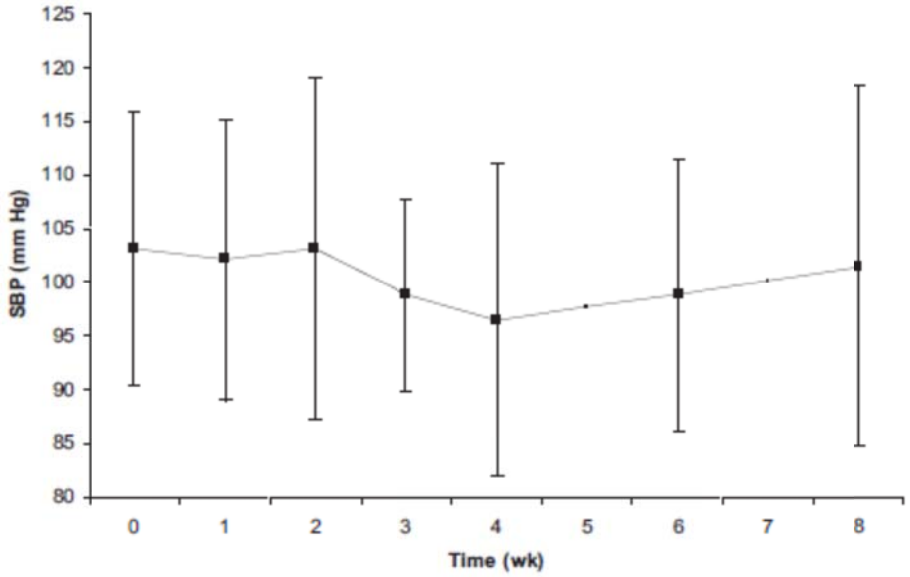

FIG. 1. Systolic blood pressure for entire sample across 8 weeks of guanfacine trial.

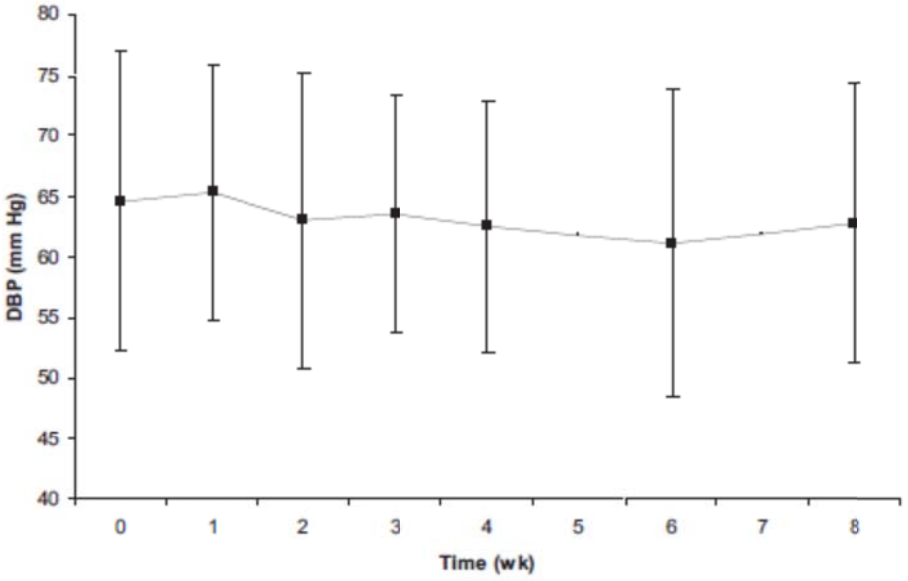

FIG. 2. Diastolic blood pressure for entire sample across 8 weeks of guanfacine trial.

Guanfacine was also associated with improvements on teacher ratings, although of lesser magnitude than parent ratings. This pattern of response by the informant was remarkably similar to the results in the RUPP Autism Network methylphenidate study (RUPP Autism Network, in press). One possible explanation for the lower magnitude of response by teachers in these studies of children with PDD and hyperactivity is the variability of classroom placements in this population. Children in special education classrooms with high teacher-to-student ratios may have greater structure and different standards for acceptable behavior. By contrast, the abnormal behavior of children with PDD in mainstream classes may be more noticeable and elicit different responses on rating scales from regular classroom teachers. This study was not large enough to examine teacher rating according to classroom type.

Although gains were largest in the domains of hyperactivity and impulsiveness, gains were also observed on parent ratings of irritable and explosive behavior, stereotypies, and social interaction. The improvements in explosive behavior and stereotypies is not surprising given that a prior study in children with tic disorders showed improvements in impulsive behavior and tics (Scahill et al. 2001). The improvement on the parent-rated Social Withdrawal scale, which partially reflects interest in others and positive response to interaction from others, is not easily explained. If replicated by other studies, the observed improvement in social interaction may be the natural consequence of decreased involvement in stereotypic behavior. However, these ancillary benefits reflected in parent ratings are tempered by the fact that the teacher ratings did not show similar benefits. The Social Withdrawal also contains items that describe a lack of energy. Given that sedation was a noticeable adverse effect in this study, it is interesting to note that "lack of energy" did not seem to influence parental perceptions of social behavior on this scale.

Sedation, sleep disturbance, and irritability were adverse effects that required dose reduction, dose adjustment, or discontinuation in some cases. Effects on blood pressure and pulse were modest and appeared to diminish over time. To manage sleep disturbance, research clinicians redistributed the doses by giving higher doses prior to bedtime or by changing the time of the bedtime dose (generally moving it closer to actual bedtime). Increased irritability, which occurred in 7 subjects, appeared to be dose related because dose reduction resulted in resolution in 3 cases, was self-limited in 1 case, and led to discontinuation in 3 cases. Parents described this irritability as "grouchy," "easily frustrated—even tearful," although not typically explosive. This adverse event was not reported in the either of the controlled studies in children with tic disorders (Scahill et al. 2001; Cummings et al. 2002), suggesting that children with PDD may be more vulnerable to this effect.

The results of this study are generally consistent with the findings by Scahill et al. (2001) and more encouraging than the retrospective report of 80 children with PDD (Posey et al. 2004). In that report, guanfacine was judged to be effective in 23% (19 of 80) subjects as measured by a score of Much Improved or Very Much Improved on the CGI-I. Comparison of our current results with the findings from Posey et al. (2004) is hampered by the retrospective nature of that report and the less specific target symptoms for the medication in that case series.

Guanfacine is an α2 adrenergic agonist that shares some pharmacological features with clonidine (Newcorn et al. 2003). Clonidine was presumed to enhance prefrontal function indirectly by decreasing the firing of presynaptic noradrenergic receptors in the locus coeruleus (LC). This reduced firing by LC neurons exerts a regulatory effect on norepinephrine function and decreases arousal. Animal and human studies over the past 2 decades, however, have shown

that guanfacine can have direct effects on prefrontal function via postsynaptic effects in prefrontal regions (Arnsten and Li 2004). This action may contribute to direct enhancement of prefrontal function, resulting in decreased distractibility, impulsiveness, and overactivity (Arnsten and Li 2004). Although the results of this pilot study cannot directly confirm this mechanism, these results do suggest that guanfacine may be a useful alternative for the treatment of hyperactivity in children with PDD. Large-scale, placebo-controlled studies are needed to guide clinical practice.

The findings of this study need to be interpreted with due consideration of the limitations. First, this was a small study comprised of children with PDD who were nonresponders to methylphenidate. Whether these generally positive results would be observed in a similar sample of children with PDD but no prior history of stimulant failure is not clear and warrants further study. Simply stated, the findings of this pilot trial may only be relevant to patients who have shown an inadequate response to stimulant treatment. Second, there was no placebo control. The absence of a placebo control makes it difficult to be certain that the observed improvements are attributable to the study medication or to nonspecific factors, such as the clinical attention that comes with study participation or the passage of time. In the absence of placebo control, it is not possible to adjust the study results for these nonspecific factors. Finally, the trial was relatively short term. Thus, we can not make any statements about the long-term effectiveness or tolerability of guanfacine in this population.

In conclusion, the results of this study suggest that guanfacine may be a useful treatment for hyperactivity in children with PDD who do not show improvement with methylphenidate. In this clinical population, guanfacine appears to better tolerated than clonidine (Jaselkis et al. 1992). Guanfacine should be started at low doses and increased gradually to avoid adverse effects, particularly sedation. Although modest, effects on blood pressure appear to be most evident early in treatment during the dose-adjustment phase. Therefore, close monitoring of pulse and blood pressure is indicated early in treatment. Sleep disturbance, usually in the form of midsleep awakening, occurred in 6 of these 25 cases. This observation suggests that sleep history should be established at baseline and monitored during treatment. The management of sleep disturbance appears to be somewhat individualized, but shifting the time of the last dose or the distribution of doses was a successful strategy in some cases.

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Disclosures

Dr. Scahill has affiliations with Janssen Pharmaceutica, Pfizer, and Bristol-Myers Squibb. Dr. Aman has affiliations with Janssen Pharmaceutica, Eli Lilly, Forest Labs, and Abbott. Dr. Arnold has affiliations with Eli Lilly, McNeil, Novartis, Noven, Shire, Sigma Tau, and Targacept. Dr. McDougle has affiliations with AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen Pharmaceutica, PediaMed Pharmaceuticals, and Pfizer, Inc. Dr. McCracken has affiliations with Janssen Pharmaceutica, Eli Lilly, Abbott, Bristol Myers Squibb, Shire, Wyeth, Pfizer, Cephalon, and McNeil. Dr. Posey has affiliations with Eli Lilly & Company, Pfizer, and Janssen. Drs. Tierney, Dziura, Young, Shah, Ghuman, Ritz, and Vitiello have no financial relationships with for-profit enterprises to disclose.

References

Aman MG, Buican B, Arnold LE: Methylphenidate treatment in children with borderline IQ and mental retardation: Analysis of three aggregated studies. J Child Adoles Psychopharmacol 13:27–38, 2003.

Aman MG, Singh NN, Stewart AW, Field CJ: The Aberrant Behavior Checklist: A behavior rating scale for the assessment of treatment effects. Am J Ment Deficiency 89:485–491, 1985.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association, 2000.

Arnsten AFT, Li BM: Neurobiology of executive functions: Catecholamine influences on prefrontal cortical functions. Biol Psychiatry, 2004.

Avery R, Franowicz JCS, Studholme C, van Dyck CH, Arnsten AFT: The alpha-2A adrenoceptor agonist, guanfacine, increases regional cerebral blood flow in dorsolateral prefrontal cortex and improves accuracy in monkeys performing a spatial working memory task. Neuropsychopharmacol 23:240–249, 2000.

Brown EC, Aman MG, Havercamp SM: Factor analysis and norms for parent ratings on the Aberrant Behavior Checklist–Community for young people in special education. Res Devel Disabil 23:45–60, 2002.

Chakrabarti S, Fombonne E: Pervasive developmental disorders in preschool children. JAMA 285:3093–3099, 2001.

Cummings DD, Singer HS, Krieger M, Miller TL, Mahone EM: Neuropsychiatric effects of guanfacine in children with mild Tourette syndrome: A pilot study. Clin Neuropharmacol 25:325–332, 2002.

Greenhill LL, Swanson JM, Vitiello B, Davies M, Clevenger W, Wu M, Severe JB, Arnold LE, Abikoff HB, Conners CK, Elliott G, Hechtman L, Hinshaw SP, Hoza B, Jensen PS, Kraemer HC, March JS, Newcorn JH, Pelham WE, Wells K, Wigal T: Impairment and deportment responses to different methylphenidate doses in children with ADHD: The MTAtitration. J Am Acad Child Adolesc Psychiatry 40:180–187, 2001.

Jaselskis CA, Cook EH Jr, Fletcher KE, Leventhal BL: Clonidine treatment of hyperactive and impulsive children with autistic disorder. J Clin Psychopharmacol 12:322–327, 1992.

Kratochvil CJ, Heiligenstein JH, Dittman R, Spencer TJ, Biederman J, Wernicke J, Newcorn JH, Casat C, Milton D, Michelson D: Atomoxetine and methylphenidate treatment in children with ADHD: A prospective, randomized, open-label trial. J Am Acad Child Adolesc Psychiatry 41:776–784, 2002.

Lecavalier L. Behavioral and emotional problems in young people with pervasive developmental disorders: Relative prevalence, effects of subject characteristics, and empirical classification. J Autism Develop Disorders Aug. 2, 2006; [E pub ahead of print].

Lord C, Pickles A, McLennan J, Rutter M, Bregman J, Folstein S, Fombonne E, Leboyer M, Minshew N: Diagnosing autism: Analyses of data from the Autism Diagnostic Interview. J Autism Develop Disord 27:501–517, 1997.

Marshburn EC, Aman MG: Factor validity and norms for the Aberrant Behavior Checklist in a community sample of children with mental retardation. J Autism Develop Disord 22:357–373, 1992.

Michelson D, Allen AJ, Busner J, Casat C, Dunn D, Kratochvil C, Newcorn J, Sallee FR, Sangal RB, Saylor K, West S: Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: A randomized, placebo-controlled study. Am J Psychiatry 159: 1896–1901, 2002.

MTA Cooperative Group: A 14-Month randomized clinical trial of treatment strategies for attentiondeficit/hyperactivity disorder. Arch Gen Psychiatry 56:1073–1086, 1999.

Mullen E: The Mullen Scales of Early Learning. Circle Pines (Minnesota), American Guidance Service, 1995.

Newcorn JH, Schulz KP, Halperin JM: Adrenergic agonists: Clonidine and guanfacine. In: Pediatric Psychopharmacology: Principles and Practice. Edited by Martin A, Scahill L, Charney DS, Leckman JF. New York, Oxford, pp 264–273, 2003.

Posey DJ, Puntney JI, Sasher TM, Kem DL, McDougle CJ: Guanfacine treatment of hyperactivity and inattention in pervasive developmental disorders: A retrospective analysis of 80 cases. J Child Adolescent Psychopharmacol 14:233–241, 2004.

Research Units on Pediatric Psychopharmacology (RUPP) Autism Network: Risperidone in children with autism and serious behavioral problems. N Engl J Med 347:314–321, 2002.

Research Units on Pediatric Psychopharmacology (RUPP) Autism Network: Methylphenidate in children with PDD and hyperactivity. Arch Gen Psychiatry 62:1266–1274, 2005.

Roid GH, Miller LJ: Leiter International Performance Scale–Revised: Examiner's Manual. In: Leiter International Performance Scale–Revised. Edited by Roid GH, Miller LJ. Wood Dale (Illinois), Stoelting Co., 1997.

Rush AJ, Francis A: Expert Consensus Guideline Series: Treatment of psychiatric and behavioral problems in mental retardation (special issue). Am J Mental Retardat 105:159–228, 2000.

Scahill L, Chappell PB, Kim YS, Schultz RT, Katsovich L, Shepherd E, Arnsten AFT, Cohen DJ Leckman JF: Guanfacine in the treatment of children with tic disorders and ADHD: A placebo-controlled study. Am J Psychiatry 158:1067–1074, 2001.

Slosson RL: Slosson Intelligence Test. East Aurora (New York), Slosson Educational Publications, 1983.

Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB, Clevenger W, Davies M, Elliott G, Greenhill LL, Hechtman L, Hoza B, Jensen PS, March JS, Newcorn JH, Owens L, Pelham WE, Schiller E, Severe J, Simpson S, Vitiello B, Wells CK, Wigal T, Wu M: Clinical relevance of the primary findings of the MTA: Success rates based on severity of ADHD and ODD symptoms at the end of treatment. J Am Acad Child Adolesc Psychiatry 40:168–179, 2001.

Wechsler D: Manual for the Wechsler Preschool and Primary Scale for Children–Revised. San Antonio (Texas), Psychological Corporation, 1989. Wechsler D. Manual for the Wechsler Intelligence Scale for Children–Third Edition. San Antonio (Texas), Psychological Corporation, 1991.