Article

A Placebo-Controlled Study of Guanfacine in the Treatment of Children With Tic Disorders and Attention Deficit Hyperactivity Disorder

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Objective: This study evaluated the efficacy and safety of guanfacine in treating children with tic disorders and attention deficit hyperactivity disorder (ADHD).

Method: Subjects from a specialty tic disorders clinic were randomly assigned to receive 8 weeks of treatment with guanfacine or placebo under double-blind conditions. Follow-up visits occurred every 2 weeks for safety monitoring and dose adjustment.

Results: Thirty-four medication-free subjects (31 boys and three girls with a mean age of 10.4 years) with ADHD, combined type, and a tic disorder participated. After 8 weeks of treatment, guanfacine was associated with a mean improvement of 37% in the total score on the teacher-rated ADHD Rating Scale, compared to 8% improvement for placebo. Nine of 17 subjects who received guanfacine were blindly rated on the Clinical Global Improvement scale as either much improved or very much improved, compared with none of 17 subjects who received placebo. The mean score on the parent-rated hyperactivity index improved by 27% in the guanfacine group and 21% in the placebo group, not a significant difference. On the Continuous Performance Test, commission errors decreased by 22% and omission errors by 17% in the guanfacine group, compared with increases of 29% in commission errors and of 31% in omission errors in the placebo group. Tic severity decreased by 31% in the guanfacine group, compared to 0% in the placebo group. One guanfacine subject with sedation withdrew at week 4. Guanfacine was associated with insignificant decreases in blood pressure and pulse.

Conclusions: Guanfacine appears to be a safe and effective treatment for children with tic disorders and ADHD.

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The stimulants methylphenidate and d-amphetamine (1) and the mixed preparation of d, l-amphetamine (2) are first line agents for the treatment of attention deficit hyperactivity disorder (ADHD). Despite the impressive track record for the stimulants in the treatment of ADHD, they fail in 25% of patients due to lack of efficacy or the emergence of unwanted side effects (3). For example, numerous case reports have observed the emergence or worsening of tics after exposure to stimulants (4–6). The de novo onset of tics has also been documented in placebo-controlled, multiple-dose stimulant trials that excluded children with tic disorders (7, 8). In contrast, Gadow and colleagues (9) reported no increase in tics in their placebo-controlled study of methylphenidate in a group of 34 children with ADHD and a tic disorder. Similarly, Castellanos et al. (10) studied multiple doses of methylphenidate and d-amphetamine in 20 children with ADHD and a tic disorder and reported only a modest increase in tics. However, three subjects showed a clinically significant increase in tics while taking a stimulant, which prompted discontinuation of the medication.

The impact of methylphenidate on tics was evaluated in five boys with ADHD and a tic disorder (11). In that study, there was a significant decline in tics when long-term treatment with methylphenidate was withdrawn. Law and Schachar (12) followed 72 stimulant-treated children for up to a year (range=1–12 months). Approximately 20% (N=10) of the 51 subjects without preexisting tics demonstrated an emergence of tics, and a third of the 21 subjects with preexisting tics showed worsening. Another study showed no mean change in tic severity in 27 subjects with ADHD and a tic disorder for up to 2 years of treatment with methylphenidate (13). However, four children required a neuroleptic or clonidine to manage their tic symptoms. Collectively, these findings indicate that not all children with a tic disorder will show an increase in tics when treated with a stimulant. Nonetheless, a subgroup of children with preexisting tics and a subgroup with no prior history of tics will show unacceptable level of tics upon exposure to a stimulant.

When stimulants fail, clinicians turn to nonstimulant medications. Only a handful of randomized, controlled trials have been conducted with nonstimulants in ADHD.

Desipramine was superior to placebo in two studies (14, 15). Due to concerns about alterations in cardiac conduction, however, many clinicians are reluctant to use desipramine (16). The novel antidepressant bupropion was found to be equivalent to methylphenidate in one study (17) and superior to placebo in another (18). Pindolol was compared to placebo and methylphenidate in a crossover trial (19) and produced moderate improvement. The emergence of nightmares (N=3) and hallucinations (N=3), however, prompted the discontinuation of the pindolol treatment arm. Feigin and colleagues (20) evaluated the efficacy of deprenyl in children with ADHD and a tic disorder in a placebo-controlled, crossover study. Deprenyl was superior to placebo in the first arm of the study. However, the group who received placebo first followed by deprenyl showed no treatment effect.

The α_2-receptor agonist clonidine has been used in the treatment of tic disorders and ADHD for more than 20 years (21). The findings from controlled studies, however, have been somewhat inconsistent, with three studies showing benefit (22–24) and two reporting negative results (15, 25). Nonetheless, the use of clonidine in children is increasing (26), suggesting that clinicians find it useful for a range of behavior problems.

Guanfacine is a newer α_2-adrenergic receptor agonist that differs from clonidine in several ways. First, it is less sedating and has a longer duration of action than clonidine (27). The longer duration of action may make guanfacine more convenient to use with children and adolescents. Second, guanfacine has been shown to improve prefrontal cortical function in nonhuman primates (28). This finding is of interest given the importance of the prefrontal cortex in ADHD (29). Three open-label guanfacine studies involving a total of 36 children have been published (30–32). In these studies, guanfacine showed promising effects on ADHD outcomes and on tics in the subset of 18 children with tics. The purpose of the placebo-controlled study reported here was to evaluate the safety and efficacy of guanfacine in the treatment of children and adolescents with ADHD and tic disorders.

Method

Design

This study was a randomized, double-blind, placebo-controlled trial of parallel groups. After completing the screening procedures and a 7- to 14-day washout period, subjects were randomly assigned to receive either guanfacine or placebo for 8 weeks.

Setting and Subjects

The subjects were recruited from the Tic Disorders Clinic of the Yale Child Study Center. Before study entry, each child was seen for a detailed clinical evaluation by an interdisciplinary team consisting of a child psychiatrist, a child psychiatric nurse specialist, and/or a psychologist. The diagnoses of a tic disorder and ADHD were made on the basis of this clinical interview. Potentially appropriate subjects were referred to the investigators for further assessment. After obtaining written informed consent from parents and assent from children, subjects were screened for eligibility. Both boys and girls were eligible for the study. Entry criteria included age between 7 and 15 years, a DSM-IV diagnosis of ADHD (any type), a DSM-IV tic disorder (any type), and a score of ≥1.5 standard deviation units for age and gender on the 10-item Conners hyperactivity index (33) rated by the teacher or a parent. To be eligible, children had to be enrolled in the same school for at least a month before entry, with no planned change in school placement for at least 10 weeks after entry.

Exclusion criteria included evidence of current major depression, generalized anxiety disorder, separation anxiety disorder, or psychotic symptoms (based on all available information); WISC-R IQ <70; and a prior adequate trial of guanfacine (dose of ≥1.5 mg/day for at least 2 weeks). Subjects had to be free of all psychotropic medication for at least 2 weeks and free of any significant medical problem. Children with moderate or more severe tic symptoms (Yale Global Tic Severity Scale [34] total tic score >22) or significant obsessive-compulsive symptoms (Children's Yale-Brown Obsessive Compulsive Scale [35] total score >15) were also excluded because of their likely need for pharmacological treatment targeting these symptoms.

Procedures

Screening and baseline assessment. The screening included routine laboratory tests, ECG, measurement of lying and standing pulse and blood pressure, height and weight measurement, medical history, and a physical examination. A structured diagnostic interview was not used, but an experienced clinician (L.S., P.B.C., or Y.S.K.) conducted a joint parent and child interview to screen for anxiety, depression, and psychosis. This interview was not intended to provide a psychiatric diagnosis but to identify children with pressing comorbid conditions who could be referred for appropriate treatment. The DSM-IV diagnosis of ADHD was based on a review of the ADHD Rating Scale with the parent (36) and queries about age at onset and duration of symptoms and impairment. Confirmation that the child's ADHD symptoms interfered with classroom performance was obtained from review of the ADHD Rating Scale completed by the teacher (37), as well as from telephone contact with the teacher. Past and current severity of tics and obsessive-compulsive symptoms were also assessed in a joint parent-child interview during which the Yale Global Tic Severity Scale and the Children's Yale-Brown Obsessive Compulsive Scale were administered by an experienced clinician (L.S.).

During the telephone contact, the teacher was told that the child was being screened for a medication study and that ratings would be requested throughout the study. For subjects who had more than one teacher, one teacher was nominated to complete the ratings. Teachers were not paid for their participation. To account for attenuation on pretreatment teacher and parent ratings, as well as on the clinicians' ratings of tics and obsessive-compulsive symptoms, measures were collected twice before subjects were randomly assigned to study groups. Similarly, to limit practice effects, the Continuous Performance Test (38) was also repeated at screening and baseline visits. For each of these measures, the mean of the two pretreatment ratings became the baseline score.

Medication. Before study entry, parents were advised on how to taper the child's current ineffective medication. The method of tapering the current medication depended on the medication class. For example, stimulants were tapered rapidly, whereas nortriptyline and clonidine were tapered more slowly. At the screening visit, parents were given a blister pack containing placebo capsules and instructed to give one capsule three times per day. Based on the family's schedule and length of time since discontinuation of the previous medication, the placebo washout period lasted 7–14 days (mean=11.6, SD=2.9). At the randomization

visit, parents were given another blister pack and instructed to continue administering one capsule three times per day. For subjects assigned to receive guanfacine, the placebo capsules were gradually replaced with active drug beginning with a single 0.5 mg dose at bedtime (the morning and afternoon doses remained placebo). On day 4, the morning dose of placebo was replaced with a 0.5 mg dose of guanfacine, and on day 8, the afternoon placebo dose was replaced with a 0.5 mg of guanfacine. A telephone session with the parent was scheduled in the first week, and follow-up visits occurred every 2 weeks. During the follow-up visits, the primary clinician, who was blind to the subject's study group, reviewed side effects and made dose adjustments. A second, blinded clinical evaluator assessed therapeutic response and collected ratings from the parents and teachers every 4 weeks. From study day 15 to 28, upward adjustment of the medication was made at the discretion of the primary blinded clinician, on the basis of the subject's clinical response and/or possible side effects. The maximum allowable dose was 4 mg/day in three divided doses. Dose increases were not allowed after study day 28, but dose reductions to manage side effects were allowed at any time during the study.

Outcome Measures

The ADHD Rating Scale (37) is an 18-item measure of inattention and hyperactive/impulsive symptoms derived from DSM-IV. Each symptom was scored by the child's teacher from 0 to 3 (0=never [or rarely], 1=sometimes, 2=often, and 3=very often). The scale yields three scores: an inattention score and a hyperactive/impulsive score (range=0–27 for each score) and a total score (range=0–54).

The Clinical Global Impression global improvement score compares current symptom severity to baseline severity (39, 40). A score of 1 corresponds with very much improved and 2 with much improved, 3 denotes minimal change, and 4 represents no change. Scores of 5, 6, or 7 indicate deterioration (minimally worse, much worse, or very much worse, respectively). In this study, the clinician who was blind to the subject's study group used this scale to rate global improvement in ADHD symptoms after an endpoint interview with the parent and the child and, if possible, a telephone conversation with the teacher during the week before the child's final study visit. A score of much improved or very much improved, reflecting meaningful improvement in ADHD symptoms both at school and at home, was counted as a positive response.

The hyperactivity index of the Parent Conners Questionnaire is a 10-item rating scale in which each item is rated from 0 to 3 (range=0–30). Norms are available, and the scale has been used in other medication studies (33, 40).

The Yale Global Tic Severity Scale is a semistructured clinical interview designed to measure current tic severity (34). The scale yield three summary scores: total motor score (range=0–25), total phonic score (range=0–25), and total tic score (the sum of the motor and phonic scores). The Yale Global Tic Severity Scale also contains an impairment scale (range of scores=0–50), which measures the overall burden caused by the tics. Because the score on the impairment scale is unlikely to change over brief periods of time, it was not used in this study.

The Children's Yale-Brown Obsessive Compulsive Scale is a clinician-rated instrument for the measurement of severity of obsessive-compulsive symptoms (35). Obsessions and compulsions are rated on five separate scales yielding three summary scores: an obsessions score (range=0–20), a compulsions score (range=0–20), and a total score (range=0–40).

The Continuous Performance Test is a computer-administered and -scored measure of sustained visual attention and motor response inhibition (37). The test takes about 15 minutes to administer and yields measures of omissions, commissions, and reaction time. Norms are available for the test. The test has been used to evaluate drug response.

Adverse effects were systematically assessed at each visit by the primary clinician using a modified version of the Systematic Assessment for Treatment of Emergent Events (SAFTEE) (41). The assessment for adverse effects also included questions about concomitant medications and concurrent illness. Lying and standing pulse and blood pressure were measured at baseline and every 2 weeks during the trial with an automated blood pressure machine. Height and weight measurements were repeated at midpoint and endpoint, and routine laboratory tests and the ECG were repeated at endpoint. ECGs were read by faculty members in the Department of Pediatric Cardiology of the Yale University School of Medicine.

Data Analysis

Analyses were based on an intent-to-treat principle, with the last observation carried forward for subjects with missing data. Repeated measures analysis of variance (ANOVA) was used to evaluate quantitative variables such as scores on the ADHD Rating Scale, the hyperactivity index, the Continuous Performance Test, and the Yale Global Tic Severity Scale. Planned group comparisons of the change from baseline to endpoint on these measures were analyzed with t tests. To evaluate the effect of guanfacine on blood pressure and pulse, we conducted a series of repeated measures ANOVAs to examine differences between groups across time and change from a lying to a standing position. We also examined data from each subject to identify any clinically meaningful change in blood pressure after exposure to guanfacine. A clinically meaningful change was defined as a decrease of 10 mm Hg (approximately one standard deviation in pediatric populations) in the child's lying systolic or diastolic blood pressure from baseline at any visit (42). Categorical variables such as the proportion of responders and the frequency of side effects in each group were evaluated by chi-square analyses on contingency tables. Statistical significance for all analyses was set at alpha=0.05 (two-tailed test).

Results

Fifty subjects were screened for the study. Ten were ineligible because they did not meet study criteria, and six eligible subjects declined to participate. Thus, 34 subjects (31 boys and three girls) entered the study and were randomly assigned to receive either guanfacine (N=17) or placebo (N=17). The children ranged in age from 7 to 14 years (mean=10.4, SD=2.01); 29 were Caucasian, two were African American, two were Hispanic, and one was Asian. Approximately one-third of the subjects (N=11) had no prior medication treatment; the remaining two-thirds (N=23) had at least one prior treatment trial with a stimulant. Of the 23 with prior treatment, 19 reported a history of increased tics while taking stimulant medication.

Twenty subjects met the DSM-IV criteria for Tourette's disorder, 12 met the criteria for chronic motor tic disorder, and two had a history of stimulant-induced tic disorder (i.e., did not meet the duration criterion). All subjects met the DSM-IV criteria for ADHD, combined type. At baseline, the percentage of male subjects, mean age, mean IQ, and mean scores on various outcome measures were similar across the two groups. Table 1 shows the subjects' characteristics at baseline.

TABLE 1. Baseline Demographic and Clinical Characteristics of 34 Subjects With Tic Disorders and ADHD in an 8-Week Placebo-Controlled Trial of Guanfacine

Characteristic	Mean	SD
Age (years)	10.4	2.0
ADHD Rating Scale score	35.8	8.8
Parent Conners Questionnaire hyperactivity index score	17.6	4.5
Yale Global Tic Severity Scale total score [a]	15.3	6.7
Body weight (lb)	86.1	27.3

[a] Two subjects with scores of 0 were not included.

Treatment Effects

A two-factor (treatment and visit) ANOVA with repeated measures on visit (baseline, midpoint, and endpoint) was used to evaluate the effect of guanfacine on teacher ratings on the ADHD Rating Scale. A significant interaction between visit and treatment was observed for the inattention score ($F=8.56$, df=2, 64, $p=0.005$), the hyperactive/impulsive score ($F=5.51$, df=2, 64, $p=0.006$), and the total score ($F=7.83$, df=2, 64, $p=0.001$). For secondary outcomes, the repeated measures ANOVA was performed for scores from the baseline and endpoint visits. A significant interaction of visit and treatment was also found for the total tic score of the Yale Global Tic Severity Scale ($F=4.04$, df=2, 30, $p=0.05$). The interaction of visit and treatment for the parent-rated hyperactivity index was not significant.

After 8 weeks of treatment, the guanfacine group showed a 37% drop in the total score on the ADHD Rating Scale completed by the teacher, compared to an 8% drop in the placebo group ($t=3.61$, df=32, $p<0.001$) (Table 2). On clinician-rated change in ADHD symptoms (rated on the Clinical Global Impression global improvement scale), nine of 17 subjects in the guanfacine group were rated much improved or very much improved, compared to none of 17 in the placebo group ($p<0.001$, Fisher's exact test). Guanfacine was also associated with a 31% drop in the total tic score of the Yale Global Tic Severity Scale, compared with 0% improvement in the placebo group ($t=2.02$, df=30, $p=0.05$). The 27% improvement from baseline on the parent-rated hyperactivity index for the guanfacine group was not significantly different from the 21% improvement in the placebo group.

On the Continuous Performance Test, guanfacine was associated with a 22% and 17% improvement in the number of commission and omission errors, respectively. In contrast, the placebo group showed a 29% increase in commission errors and a 31% increase in omission errors ($t=2.70$, df=31, $p=0.01$ for commission errors; $t=2.12$, df=31, $p=0.04$ for omission errors).

Medication Dose

The dose of guanfacine ranged from 1.5 mg to 3.0 mg/day. The most common guanfacine dose schedule was 1.0 mg (8:00 a.m.), 0.5 mg (3:00 p.m.), and 1.0 mg (8:00 p.m.). The modal dose for placebo was 1 mg t.i.d.

Side Effects

No serious side effects were observed. There were no alterations in laboratory test results, and no subject showed a clinically meaningful change in cardiac conduction. One subject in the guanfacine group withdrew from the study at week 4 due to sedation. Six other subjects also complained of mild sedation, which relented with continued treatment or dose decrease. Three subjects reported midsleep awakening during the dose escalation period. This effect was transient in two subjects and persistent, although tolerable, in the third subject. Other complaints included dry mouth (N=4), constipation (N=2), and loss of appetite in the morning (N=2). These complaints were most common in the first 4 weeks of treatment, during the dose adjustment phase. None of these side effects was significantly more frequent in the guanfacine group than in the placebo group. There were no significant changes in weight from baseline to endpoint in either group and no significant differences between groups in weight change.

To evaluate cardiovascular effects, we first compared the standing blood pressure and pulse measurements at 1 minute and 3 minutes visually and by ANOVA. If no differences were detected, the two standing blood pressure measurements were averaged. Next, we used ANOVA to test for a difference between groups in the change from lying to the mean standing blood pressure. There was no significant difference between groups, suggesting that guanfacine did not produce an orthostatic decline in blood pressure. Last, a repeated measures ANOVA on lying and standing blood pressure and pulse measurements across treatment groups and the three visits showed no differences (Table 3, Figure 1). In the subject-by-subject case review, a drop of one standard deviation in lying systolic or diastolic blood pressure was shown at one visit by six subjects in the guanfacine group and two subjects in the placebo group, a nonsignificant difference ($p=0.11$, Fisher's exact test). Most of the six guanfacine-treated subjects showed the decrease in blood pressure at the week 4 visit, which is consistent with the decline in mean values (Figure 1). No subject showed a reduction in blood pressure of one standard deviation at more than one visit.

Discussion

To our knowledge, this is the first controlled study of guanfacine in children with ADHD. The results suggest that it is a safe and effective treatment for children with ADHD and a coexisting tic disorder. The 37% improvement observed by classroom teachers is lower than the 50%–60% improvement reported in stimulant trials (43), but is similar (14) or better (18) than the level of improvement observed in other nonstimulant studies. Given that prior treatment with stimulants failed in two-thirds of the subjects in the current study, the results reported here may not be comparable to the findings of other nonstimulant trials. These findings also raise questions about the

TABLE 2. Baseline and Endpoint Values for Primary and Secondary Outcome Measures of Subjects With Tic Disorders and ADHD in an 8-Week Placebo-Controlled Trial of Guanfacine

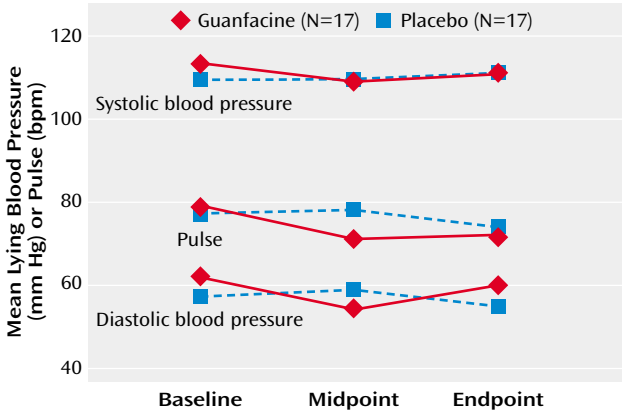
Measure	Subjects Receiving Guanfacine (N=17)				Subjects Receiving Placebo (N=17)				Comparison of Endpoint Means			Effect Size[a]
	Baseline		Endpoint		Baseline		Endpoint					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	t	df	p	
ADHD Rating Scale (teachers' ratings)												
Total score	37.2	8.4	23.6	13.6	34.4	9.3	31.7	11.2	2.80	32	<0.01	1.23
Inattention score	19.6	5.0	12.8	7.2	16.9	4.8	15.4	5.4	3.79	32	<0.01	1.06
Hyperactive/impulsive score	17.6	5.5	10.8	8.1	17.4	7.2	16.3	8.1	2.98	32	<0.01	0.90
Parent Conners Questionnaire hyperactivity index score	17.3	3.9	12.7	6.7	17.9	5.2	14.1	5.3	0.82	32	n.s.	0.18
Yale Global Tic Severity Scale total score[b]	15.2	6.6	10.7	7.0	15.4	7.0	15.4	5.5	2.02	30	0.05	0.67
Continuous Performance Test score												
Omissions[c]	23.7	17.4	19.6	18.8	20.6	17.4	26.9	27.1	2.12	31	0.04	0.60
Commissions	45.2	58.5	35.4	51.0	28.7	28.9	36.9	43.1	2.70	31	0.01	0.41

[a] Mean change in score for guanfacine group minus change for the placebo group, divided by the standard deviation at baseline for the whole study group.
[b] N=15 in guanfacine group (two subjects with scores of 0 throughout the trial were not included).
[c] N=16 in guanfacine group.

TABLE 3. Baseline, Midpoint, and Endpoint Resting Blood Pressure and Pulse Measurements of Subjects with Tic Disorders and Attention Deficit Hyperactivity Disorder in an 8-Week Placebo-Controlled Trial of Guanfacine

Time Point and Measure	Subjects Receiving Guanfacine (N=17)		Subjects Receiving Placebo (N=17)	
	Mean	SD	Mean	SD
Baseline				
Blood pressure				
Systolic (mm Hg)	113.0	10.6	109.3	10.1
Diastolic (mm Hg)	62.2	8.4	57.6	7.4
Pulse (bpm)	78.9	9.8	77.0	11.3
Midpoint				
Blood pressure				
Systolic (mm Hg)	108.6	9.7	109.2	12.8
Diastolic (mm Hg)	54.4	9.1	58.9	8.8
Pulse (bpm)	70.6	8.3	77.7	10.6
Endpoint				
Blood pressure				
Systolic (mm Hg)	110.8	11.0	110.6	12.7
Diastolic (mm Hg)	59.4	12.0	54.4	11.2
Pulse (bpm)	73.4	13.4	71.1	10.8

FIGURE 1. Baseline, Midpoint, and Endpoint Lying Blood Pressure and Pulse of Subjects With Tic Disorders and ADHD Who Received Guanfacine or Placebo



utility of combining guanfacine with a stimulant. In patients with Tourette's syndrome and ADHD, this combination might permit lower doses of the stimulant. Furthermore, guanfacine could provide protection against increased tics. Questions about these effects can be answered only with further study.

The 31% improvement in tics in this study is lower than that found in some (44), but not all (45, 46), neuroleptic studies. This improvement rate is remarkably similar to that found in a large controlled study of clonidine in Tourette's syndrome, which showed a 26% difference in improvement between the active drug and placebo groups (24). Because our study included patients with only mild to moderate tics, it is not clear from these results whether guanfacine would also be effective for more severe tics. Nonetheless, the fact that these subjects showed improvement in tics suggests that guanfacine may be particularly useful in the treatment of children with ADHD in the presence of comorbid tics.

Our failure to observe a significant between-group difference in scores on the parent-rated hyperactivity index may be due to the small size of the study groups. In addition, when this index has been used as a measure of symptom change in stimulant studies, the percentage of improvement in parents' ratings is often lower than that in teachers' ratings (3). In the present study, nine of the 17 guanfacine-treated children were blindly rated by clinicians as much improved or very much improved, compared to none of the 17 children in the placebo group. Although this determination was partly based on input from teachers (telephone contact and ADHD Rating Scale scores), parents were the primary informants. Thus, the hyperactivity index may not have captured the positive behavioral change observed by parents.

The gains reported by teachers were evident in the change in the scores on the ADHD Rating Scale inattention and hyperactive/impulsive subscales, as well as in the total score. These findings suggest that the improvements observed in the classroom were not simply due to calming or sedative effects. The positive effects on attention were

further supported by improved performance on the Continuous Performance Test in the guanfacine group.

Animal studies have established that guanfacine improves prefrontal cortical function through direct action on postsynaptic α_{2A}-receptors located in the prefrontal cortex. For example, single photon emission computed tomography studies in young monkeys have shown that systemic guanfacine administration increases blood flow in the prefrontal cortex, without altering regional cerebral blood flow in the posterior cortical areas (28). Single-cell recording studies in monkeys performing working memory tasks have shown that α_2-receptor agonists can increase the delay-related activity of prefrontal cortical neurons (47). In addition, guanfacine infusion directly into the prefrontal cortex in young or aged monkeys improves working memory without evidence of hypotension or sedation (48, 49).

The more potent hypotensive effects of clonidine are likely due to its action at imidazoline I_1-receptors in the brainstem (50). In contrast, guanfacine has only weak affinity for I_1-receptors. The sedative effects of α_2-receptor agonists are the result of inhibitory effects on noradrenergic locus ceruleus neurons (51) and direct effects in the thalamus (52). Clonidine is 10 times more potent than guanfacine in reducing locus ceruleus firing and inhibiting norepinephrine release (53). Clonidine also has a higher affinity than guanfacine for α_{2B}-receptors, which are prominent in the thalamus. Thus, the cognitive-enhancing effects of guanfacine can be dissociated from sedative and hypotensive actions in the brain.

Limitations

The relatively small size of the study group made it difficult to determine predictors of drug response. In addition, the study group was ascertained from a specialty clinic, which could limit the generalizability of the findings. Indeed, two-thirds of the subjects had already failed one or more stimulant trials owing to a reported increase in tics, an inadequate response, or both. Future studies including larger groups of children with ADHD, both with and without tic disorders, are warranted.

Another limitation of the study is that the baseline assessment did not include a structured diagnostic interview. However, the diagnoses of ADHD and tic disorders were made after a systematic clinical evaluation by an interdisciplinary team with expertise in assessing these disorders (54). Another team of experienced clinicians confirmed the diagnoses in the study screening procedure by means of a detailed evaluation of tic, ADHD, and obsessive-compulsive symptoms. Finally, each child was screened for symptoms of comorbid anxiety, depression, and thought disorder, and subjects with prominent symptoms were excluded.

Clinical Implications

Adult studies have reported a 12- to 23-hour half-life for guanfacine (27), which suggests that it could be administered on a twice-daily schedule. The results of this study suggest that guanfacine is well tolerated when given three times a day. In the absence of pharmacokinetic data in pediatric samples, a thrice daily schedule appears appropriate. On the basis of the observation that sedative and hypotensive effects occurred early in treatment, dosing should start low and move upward slowly, with frequent clinical monitoring when the medication is initiated. Mid-sleep awakening occurred in a few subjects, and clinicians should be watchful for this adverse effect. Hypomania was not observed in this study (55).

Published practice guidelines recommend baseline and follow-up ECG for children treated with clonidine (56), although ECG monitoring was not recommended in a recent statement by the American Heart Association (57). We did not detect any ECG changes in this study, but recommendations concerning ECG monitoring remain uncertain at present. Abrupt withdrawal of clonidine can produce a rebound increase in blood pressure (58). Perhaps because of its longer half-life, guanfacine appears not to have this liability (59). Nonetheless, precipitous withdrawal of guanfacine is probably unwise. Blood pressure monitoring is warranted for patients treated with guanfacine, particularly during the dose adjustment phase.

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