

An Open-Label, Prospective Study of Guanfacine in Children with ADHD and Tic Disorders

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Objectives: To evaluate the efficacy and safety of guanfacine in children with attention-deficit hyperactivity disorder (ADHD) and tic disorders.

Material and Method: Twenty-five medication-free subjects (23 males and 2 females), aged 7-16 (mean=10.6±2.0) years participated in an 8-week open-label guanfacine study. Subjects were recruited from a specialty clinic for children with tic disorders over a four-year period. Eligibility criteria included presence of ADHD (any type), a tic disorder (any type), and being medication free for two weeks. Outcome measures included the Hyperactivity Index of the Conners Parent Questionnaire, the teacher-rated ADHD Rating Scale, and the Yale Global Tic Severity Scale (YGTSS).

Results: All subjects met criteria for ADHD (combined type N=22; predominantly inattentive type N=3) and a tic disorder (Tourette's Disorder N=20; chronic motor tic disorder N=5). At an average dose of 2.0 ± 0.6 mg/day, guanfacine was associated with mean improvement of 27% on the Hyperactivity Index (N=25; t=4.61; p<0.001), 32% on the total score of the teacher-rated ADHD Scale (N=19; t=5.27; p<0.001), and 39% on the total tic severity scale (N=19; t=4.17; p<0.001). Mild and statistically insignificant decreases in blood pressure and pulse were observed in the sample as a whole. Five subjects had endpoint systolic blood pressure below 1 SD from their age and gender norms. **Conclusion:** Results of this open-label study add to the growing data base on the safety and efficacy of guanfacine in children with ADHD and tic disorders.

KeyWord: Guanfacine, Attention-deficit hyperactivity disorder, Tic disorders, Children

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Stimulant medications, such as methylphenidate, d-amphetamine, and l-amphetamine, are first-line agents for treatment of attention-deficit hyperactivity disorder (ADHD)⁽¹⁾. However, treatment with stimulant medication fails in as many as 20-30 % of children, due to lack of efficacy or untoward effects⁽²⁾. A recurring clinical observation associated with stimulant treatment is the emergence or worsening of tics⁽³⁻⁵⁾. De novo emergence of tics in children with no prior history of tics has been reported to be as high as 10-38 % in controlled studies^(6,7). A one-year prospective methylphenidate study that included 72 children with ADHD

reported the emergence of tics in approximately 20% (N=10) of the 51 subjects without pre-existing tics and a worsening of tics in a third (N=7) of the 21 subjects with pre-existing tics⁽⁸⁾. The emergence or exacerbation of tics prompted dose reduction or discontinuation in 8 cases. In a series of 5 cases of ADHD and Tourette's syndrome studied on and off methylphenidate, Riddle and colleagues observed that tics decreased when stimulant was withdrawn and increased when it was reinitiated⁽⁹⁾. By contrast, the use of stimulants in children with ADHD and tic disorder was evaluated in two placebo-controlled crossover studies⁽¹⁰⁻¹¹⁾. A worsening of tics was observed in only a small percentage of children, while stimulants were beneficial in majority of cases. In conclusion, some of children with

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ADHD and a tic disorder can tolerate stimulant treatment. However, it is clear that stimulants can worsen tics in some children in this clinical population. At present, it is not possible to predict which children with ADHD and a tic disorder will show exacerbation of tic symptoms when exposed to stimulant medications.

Given the above considerations, several investigators have evaluated the efficacy of non-stimulant medications in children with ADHD and a tic disorder⁽¹²⁻¹⁴⁾. The α -2 adrenergic agonist, clonidine was introduced for the treatment of tics over twenty years ago⁽¹⁵⁾. Clonidine was shown to be effective in the treatment of tics in one controlled study⁽¹⁶⁾, though was not superior to placebo in another study⁽¹⁷⁾. Efficacy of clonidine in the treatment of ADHD has also been inconsistent^(14,18,19). The largest study of clonidine in the treatment of ADHD to date was a multisite study by the Tourette's Syndrome Study Group⁽²⁰⁾. In that study of 136 children with ADHD and a tic disorder, clonidine was compared to placebo, methylphenidate alone, and the combination of methylphenidate and clonidine. All active treatments were superior to placebo. Furthermore, no treatment was associated with a mean increase in tics. Clonidine and the combination of clonidine and methylphenidate was well tolerated with no serious side effects. The most common side effects of clonidine are sedation and irritability^(16,20).

Guanfacine is a newer α -2 agonist developed for the treatment of hypertension similar to clonidine. Compared with clonidine, guanfacine has longer plasma half-life and is less sedating than clonidine⁽²¹⁻²³⁾. Unlike clonidine, which is a non-selective agonist of α -2a, -2b, and 2c-adrenergic receptors, guanfacine is more selective to α 2a-adrenergic receptors⁽²⁴⁾. This selectivity of action may explain the less frequent sedative effects of guanfacine compared to clonidine⁽²⁵⁾. The use of guanfacine in child psychiatry has received increasing clinical attention. However clinical studies in children are limited. Two open-label trials of guanfacine in the treatment of ADHD, involving 28 children and adolescents, offer preliminary evidence regarding the effectiveness of guanfacine in ADHD^(26,27). In another open trial of 10 youngsters aged 8 to 16 years with ADHD and a tic disorder, Chappell et al reported that guanfacine was associated with a significant decrease in motor and phonic tic severity as well as commission errors and omission errors on the Continuous Performance Test (CPT)⁽²⁸⁾. However, parent-rated impulsiveness was not significantly improved. Our group recently completed the first double-blind, placebo-controlled trial involving 34 children⁽²⁹⁾. In that study,

guanfacine (N=17) was superior to placebo (N=7) on global measures of improvement, teacher-rated ADHD symptoms, Commission Errors and Omission Errors on CPT, and clinician-rated tic severity. The change in the Conners Hyperactivity Index rated by parents was not different across treatment groups. Taken together, these four studies provide data on 55 children treated with guanfacine (17 subjects received placebo). Although guanfacine appeared safe and well tolerated in these studies, the total sample size remains small and insufficient to guide practice. The purpose of the present study is to provide additional data on the effectiveness and tolerability of guanfacine in children with ADHD and a tic disorder.

Material and Method

Design:

The design was an 8-week, open-label study in which guanfacine was given in gradually increasing doses. The subjects were recruited from the Tic Disorder Clinic of the Yale Child Study Center. Prior to the study, each subject was seen for clinical evaluation by an interdisciplinary team consisted of a child psychiatrist, a child psychiatric nurse specialist, and/or a psychologist. To be eligible, subjects had to be between 7 and 16 years, have a clinical diagnosis of ADHD (any type), and a tic disorder (any type)⁽³⁰⁾, and be medication-free. Potentially eligible subjects were referred to investigators and screened for eligibility for the placebo-controlled trial. Subjects who did not meet severity or other entry criteria for the placebo-controlled trial (N=4), those who declined to participate in the placebo-controlled study (N=8), and placebo non-responders from the placebo-controlled study (N=13) participated in this open-label study. Thus, in all 25 subjects (23 male and 2 female) participated. Following the initial screening and a medication-free period of at least two weeks, baseline measures were collected. Subjects were seen for at least 2 follow up visits in 8 weeks study period.

Guanfacine Dosing

Guanfacine was started at 0.5 mg at bedtime and gradually increased in increments of 0.5 mg every 4 days up to 0.5 mg three times per day (morning, afternoon, and bedtime), as tolerated. Further increases in 0.5 mg increments every four to five days to a maximum of 4.0 mg/day over a four-to five-week period were made on a flexible basis according to clinical response and side effects.

Measures

ADHD symptoms were evaluated with the Conners Parent Questionnaire completed by parent⁽³¹⁾ and the ADHD Rating Scale-completed by teachers⁽³²⁾. Tic symptoms were evaluated with Yale Global Tic Severity Scale (YGTSS)⁽³³⁾ rated by an experienced clinician (LS).

Conners Parent Questionnaire is a 48-item rating scale including 10-item Hyperactivity Index. Each item is rated 0 to 3. The 10-item Hyperactivity Index (range 0-30) was used to evaluate parental impression of changes in ADHD-related symptoms.

ADHD Rating Scale consists of 18 items (9 for inattention and 9 for hyperactivity/impulsivity). Each item is rated 0-3. The scale yields three scores, including Inattention score (0-27), Hyperactivity/Impulsivity score (3-27) and the total score (0-54).

YGTSS is a semi-structured clinical interview for measuring tic severity that has been used as a measure of change in several studies. The scale rates the number, frequency, intensity, complexity and interference of motor and phonic tics separately as well as the over all impairment due to tics. The YGTSS yields four scores: Total Motor (0-25); Total Phonic (0-25); Total Tic (0-50) and Impairment (0-50). Because the Impairment scale is unlikely to show change over short periods, only Total Motor, Total Phonic and Total Tic scores were used in this study.

Blood pressure and pulse were also recorded on each subject at each visit. Side effects were assessed at each visit using a modified version of the SAFTEE⁽³⁴⁾.

Data Analysis

Analyses were based on the intent to treat principle with last observation carried forward for missing data. Analysis of changes in all measured scores at baseline and the endpoint were performed using a paired *t*-test.

Results

The 25 subjects (23 males and 2 females) had a mean age of 10.6 ± 2.0 years (range 7 to 16 years). Twenty subjects met criteria for Tourette s Disorder and 5 met criteria for chronic motor tic disorder. All 25 subjects met DSM-IV criteria for ADHD. Of these, 22 children were diagnosed with the Combined type and the other 3 subjects were diagnosed with the Inattentive type. Seven subjects dropped out due to lack of efficacy (N=3), sedation (N=1), and lost to follow up (e.g., family moved) (N=3). For these 7 subjects, data from their first follow up visit was carried forward to endpoint. The average dosage of guanfacine at the endpoint was 2.0 ± 0.6 mg/day (range of 1-3 mg/day).

Outcome Measures

Table 1 shows baseline and endpoint scores on clinical outcome measures. The number of subjects changes slightly due to missing data. For example, six subjects participated during the summer months and the teacher ratings were not available. The YTGSS were missing on six subjects. All measures available to analyze using paired *t*-test showed significant change from baseline with *p* value <0.001.

Table 1. Baseline and endpoint values for parent, teacher and clinician ratings

Measure	N	Baseline Mean \pm SD	Endpoint Mean \pm SD	Decrease Mean \pm SD	Percent Change	<i>t</i> score	<i>p</i> value
Parent Hyperactivity Index	25	15.48 \pm 4.71	11.36 \pm 4.90	4.12 \pm 4.89	26.61	4.61	<0.001
Teacher ADHD							
Inattention	19	17.10 \pm 6.88	12.26 \pm 6.38	4.84 \pm 6.03	28.30	3.50	<0.001
Hyperactivity/ Impulsivity	19	15.32 \pm 8.78	9.79 \pm 6.94	5.53 \pm 4.25	36.10	5.67	<0.001
Total	19	32.42 \pm 13.37	22.05 \pm 11.38	10.37 \pm 8.57	31.99	5.27	<0.001
YGTSS							
Total Motor	19	10.26 \pm 4.00	6.68 \pm 4.55	3.58 \pm 4.35	34.89	3.59	<0.001
Total Phonic	19	8.84 \pm 5.67	4.95 \pm 4.47	3.89 \pm 4.74	44.00	3.58	<0.001
Total Tic	19	19.05 \pm 7.98	11.63 \pm 7.48	7.42 \pm 7.76	38.95	4.17	<0.001

Adverse Events and Blood Pressure Effects

Twelve of 25 subjects reported one or more side effects during the course of the eight-week trial. These included headache (N=4), stomachache (N=4), tiredness (N=3), irritability (N=3), sleep disturbances (N=3), and dizziness (N=3). Side effects were generally mild and managed by dose reduction or were self limiting. Only one subject discontinued treatment due to sedation.

Post-baseline blood pressure measurements were missing in two subjects. In 13 subjects, baseline measurements were taken by an automated blood pressure machine, which was not available at endpoint. In the 10 subjects for whom baseline and endpoint data were comparable, systolic blood pressure, diastolic blood pressure, and pulse (mean \pm SD) at baseline decreased from 103.2 ± 9.5 mmHg, 68.2 ± 9.2 mmHg, 84.6 ± 7.1 per minute to 98.7 ± 11.5 mmHg, 67.0 ± 9.3 mmHg, and 80.5 ± 11.2 per minute at endpoint, respectively (Table 2). This nearly 5 point drop in systolic pressure and the 1 point drop diastolic pressure were not statistically significant and were less than one standard deviation (approximately 10 mmHg for this age group)⁽³⁵⁾. Using all available data, we identified 5 of 23 subjects (missing data N=2) with a one standard deviation drop (10mm Hg) in blood pressure during the study period. The drop was in systolic blood pressure in all 5 cases and was observed on only one post-baseline measurement. This was accompanied by a complaint of dizziness in one subject. Dose reduction was undertaken in two subjects, which was followed by resolution of dizziness in the one case and the subnormal blood pressure in both cases. The guanfacine dose was maintained in the other three subjects showing the one standard deviation drop with return of normal blood pressure at subsequent visit.

Discussion

This study adds to the growing, but still modest, pediatric data-base on the effectiveness and toler-

ability of guanfacine for the treatment of ADHD. Guanfacine was associated with a 27% reduction in the parent-rated Conners Hyperactivity Index, which was statistically significant and remarkably similar to the magnitude observed in our placebo-controlled study⁽²⁹⁾. In each of these studies, however, parent-rated improvement was lower than what was reported by Horrigan and Barnhill⁽²⁷⁾ on the same measure in their open-label guanfacine trial in children with ADHD without a comorbid tic disorder. Whether guanfacine may be more beneficial for children with ADHD uncomplicated by a tic disorder awaits further study.

Guanfacine was also associated with a 32% drop in the teacher-rated ADHD Rating Scale, and a 39% decrease in the YGTSS Total Tic score. This level of improvement is similar in magnitude to other nonstimulant medications in ADHD⁽¹²⁾ and to what we found in our placebo-controlled guanfacine study⁽²⁹⁾. It is, however, lower than the improvement typically reported in stimulant studies⁽³⁶⁾. The significant improvement on both Inattention and the Hyperactivity/Impulsivity subscales in the current study suggests that guanfacine may be effective for hyperactivity/impulsive symptoms as well as inattention. In addition to pre-synaptic α -2 adrenergic activity, which may explain the positive effects on hyperactivity and impulsiveness, animal studies suggest that guanfacine binds to post-synaptic α -2a receptors in prefrontal cortex⁽²⁴⁾. This action of guanfacine, which appears to distinguish guanfacine from clonidine, may account for improvement in attention span observed by teachers.

The 39% improvement on tic severity is similar to the effect documented in the placebo-controlled guanfacine study⁽²⁹⁾ and to results from the largest placebo-controlled study of clonidine for the treatment of tics⁽¹⁶⁾. It should be noted, however, that the tic severity was generally mild in the current sample. Therefore, it is difficult to predict whether guanfacine would be effective for more severe tics.

Table 2. Blood Pressure and Pulse Changes for Subjects with Manual Measurements

Measure	N	Baseline Mean \pm SD	Endpoint Mean \pm SD	Decrease Mean \pm SD	t score	p value
Systolic BP	10	103.2 \pm 9.5	98.7 \pm 11.5	4.5 \pm 8.6	1.66	0.05-0.1
Diastolic BP	10	68.2 \pm 9.2	67.0 \pm 9.3	1.2 \pm 7.8	0.48	> 0.5
Pulse	10	84.6 \pm 7.1	80.5 \pm 11.2	4.1 \pm 14.7	0.88	0.2-0.5

As in previous studies, the present study shows guanfacine to be safe and well tolerated by children as young as seven years of age when given on a three times per day schedule. Whether these findings can be extrapolated to younger children is not clear. The mean change in blood pressure was modest for most subjects. However, 5 of 25 subjects had a reduction in blood pressure that fell to one standard deviation below the population mean for gender and age at some point in the trial. Two subjects required dose reduction. Thus, although guanfacine appears safe, blood pressure and pulse should be monitored during the dose adjustment phase. In the present study, electrocardiograms were not done in every subject. The practice of routine electrocardiogram for α 2 agonists remains controversial. It is recommended in some practice guidelines⁽³⁷⁾, but not by others⁽³⁸⁾.

There are two important limitations with this study. First, the study did not have a placebo group. As noted above, however, the findings are highly consistent with the results of the placebo-controlled trial. Thus, this study replicates the finding of the earlier placebo-controlled study. Secondly, this study evaluated the treatment effects of guanfacine in a relatively small sample of children with ADHD and tic disorders for a short-term period of time. Nonetheless, it is worthy to note that the sample size in this study is larger than any of the previous open-label studies and provides useful information on the use of this medication in children with ADHD and tic disorders.

In conclusion, stimulants remain the drug of choice for the treatment of children with ADHD. For children who do not respond to stimulant medication or who show an unacceptable level of tics on a stimulant, other nonstimulant medications should be considered. Data from large-scale surveys indicates that the α -2 agonists are commonly used in the pediatric population⁽³⁹⁾ and may be on the rise⁽⁴⁰⁾. Despite this trend, the level of empirical support for clonidine and guanfacine remains modest⁽³⁹⁾. Guanfacine is relatively new to child psychiatry with the first reports appearing only in recent years. Indeed, efficacy and safety data are limited to three small open label studies, one controlled study and a few case reports⁽⁴¹⁾. The findings of this study offer additional data on the use of guanfacine in children with ADHD and tic disorders and the additional guidance on the clinical management of this medication in the pediatric population. Additional research is needed to confirm these results and to evaluate the efficacy of guanfacine in other clinical populations such as children with pervasive devel-

opmental disorders with prominent problems of hyperactivity, impulsiveness and inattention.

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การใช้ยา guanfacine รักษาเด็กที่มีภาวะซน-สมาธิสั้น (ADHD) ร่วมกับ tic disorders

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วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพและความปลอดภัยของ guanfacine ในการรักษาเด็กที่มีภาวะซน-สมาธิสั้น (ADHD) ร่วมกับ tic disorders

วัสดุและวิธีการ: เป็นการศึกษาผลการรักษาด้วย guanfacine แบบ open-label ระยะเวลา 8 สัปดาห์ ในผู้ป่วยเด็ก อายุ 7-16 ปี จำนวน 25 คน ที่รับการรักษาในคลินิกเฉพาะโรค tic disorders ผู้ป่วยที่เข้าร่วมในการศึกษาได้แก่ผู้ป่วย ADHD ที่มี tic disorders ร่วมด้วย และไม่ได้ได้รับการรักษาด้วยยาใดๆ เป็นระยะเวลาอย่างน้อย 2 สัปดาห์ การวัดผลการรักษาใช้ Hyperactivity Index ของแบบประเมิน Conners Parent Questionnaire, ADHD Rating Scale ที่ประเมินโดยครู และ Yale Global Tic Severity Scale (YGTSS)

ผลการศึกษา: ผู้ป่วยทุกรายมีลักษณะทางคลินิกครบตามเกณฑ์การวินิจฉัย ADHD (22 รายเป็นชนิด combined และ 3 ราย เป็นชนิด predominantly inattentive) และ tic disorder (20 รายเป็น Tourette's disorder และ 5 รายเป็น chronic motor tic disorder) พบว่า guanfacine ในขนาดเฉลี่ย 2.0 ± 0.6 มก. ต่อวัน มีประสิทธิภาพในการลด Hyperactivity Index ที่ประเมินโดยพ่อแม่ลงร้อยละ 27 (N=25; $t=4.61$; $p<0.001$) ลด ADHD Rating Scale ที่ประเมินโดยครูลงร้อยละ 32 (N=19; $t=5.27$; $p<0.001$) และลด YGTSS ลงร้อยละ 39 (N=19; $t=4.17$; $p<0.001$) ค่าความดันโลหิตและชีพจรของผู้ป่วยโดยรวมมีการเปลี่ยนแปลงลดลงเล็กน้อยอย่างไม่เป็นนัยสำคัญทางสถิติ มีผู้ป่วย 5 รายที่มีความดันโลหิตลดลงมากกว่า 1 ค่าความเบี่ยงเบนมาตรฐานตามอายุและเพศ

สรุป: การศึกษาครั้งนี้ทำให้ได้ข้อมูลเพิ่มเติมเกี่ยวกับประสิทธิภาพและความปลอดภัยของ guanfacine ในการรักษาเด็กที่มีภาวะ ADHD ร่วมกับ tic disorders