Clonidine for Attention-Deficit/Hyperactivity Disorder: I. Efficacy and Tolerability Outcomes

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ABSTRACT

Objective: To determine the efficacy and safety of clonidine, used alone or in combination with methylphenidate, in treating attention-deficit/hyperactivity disorder (ADHD).

Method: A 16-week, randomized, double-blind, placebo-controlled clinical trial was conducted in 122 children, ages 7 to 12, with any subtype of ADHD, randomly assigned to clonidine, methylphenidate, clonidine in combination with methylphenidate, or placebo according to a $2^2$ factorial design. In two successive 4-week titration periods, clonidine (or matching placebo) and added methylphenidate (or matching placebo) were adjusted to optimal doses and then continued for 8 weeks. The primary efficacy outcome was changed from baseline to week 16 on the Conners Teachers Abbreviated Symptom Questionnaire. Secondary outcomes included the Conners Abbreviated Symptom Questionnaire for Parents and the Children's Global Assessment Scale.

Results: On the Conners Teachers Abbreviated Symptom Questionnaire, clonidine was not found to improve ADHD symptoms, whereas subjects treated with methylphenidate showed significant improvement compared to those not treated with methylphenidate. Subjects treated with clonidine had greater improvements on the Conners Abbreviated Symptom Questionnaire for Parents and Children’s Global Assessment Scale, but also a higher rate of sedation compared with subjects not treated with clonidine.

Conclusions: Based on the Conners Teachers Abbreviated Symptom Questionnaire, methylphenidate offers the best combination of efficacy and tolerability for ADHD. Clonidine was well tolerated despite the frequency of sedation and did offer some benefit.


Clonidine is an $\alpha_2$-agonist U.S. Food and Drug Administration–approved only for hypertension in adults. The tablet form of clonidine has a duration of action of 3 to 5 hours with a half-life of 12 to 16 hours.

Previous studies have suggested that clonidine may be useful as a potential treatment for youths with attention-deficit/hyperactivity disorder (ADHD). Clonidine is used to target not only ADHD symptoms but also tics, insomnia, and explosivity. Commonly reported side effects with clonidine are sedation, hypotension, and dizziness. There are limited safety data and some controversy about potential increases in cardiovascular risks associated with clonidine. Clonidine is often prescribed and dosed after dinner or at bedtime for its sedating effects. However, the effects on ADHD symptom reduction, beyond sedation, are unclear.

Despite its use, clonidine has yet to be comprehensively studied in primary ADHD. A randomized, double-blind, placebo-controlled clinical trial of the safety and efficacy of clonidine, alone and in combination with methylphenidate, was conducted in 136 children with Tourette’s syndrome and comorbid...
ADHD (TACT Trial). Results from this study demonstrated that both methylphenidate and clonidine were efficacious for ADHD symptoms with a similar magnitude of effect, and the combination of methylphenidate and clonidine was most effective. Clonidine was associated with sedation, but there was no evidence of cardiac toxicity. However, the TACT Trial results are difficult to extrapolate to primary ADHD because treatment with clonidine in the TACT Trial was targeted to the treatment of both tics and ADHD. Therefore, further information regarding the safety and efficacy of clonidine in children with ADHD is needed to help guide clinicians in making more informed treatment choices. Thus, we conducted a multicenter, randomized, double-blind, placebo-controlled study of clonidine, methylphenidate, and clonidine plus methylphenidate in children with primary ADHD. The study was designed primarily to determine the safety and efficacy of clonidine, given alone or in combination with methylphenidate, for the treatment of ADHD in children. More important, it was designed to replicate the TACT Trial design and treatments to facilitate comparisons between the two databases.

**METHOD**

**Subjects**

Children ages 7 to 12 years of any race and ethnic background and in school were enrolled. Each subject met DSM-IV criteria for ADHD of any subtype. All of the subtypes were included to maintain consistency with the study design of the TACT Trial. The Diagnostic Interview Schedule for Children (ASQ-Teacher), Iowa Conners Teacher Rating Scale, ASQ-Parent, Iowa Conners Parent Rating Scale, and the Wechsler Individual Achievement Test III (WISC-III) were administered (WISC-III, vocabulary and block design subtests), the parent self-report rating scales were explained, and the procedures of the study were reviewed. The study coordinator visited each subject’s school to obtain agreement from the designated teacher (for older children with multiple teachers, one teacher in a major course was selected) and principal to explain teacher self-report rating scales and to review the procedures of the study, including the activities of the classroom observers (see below). All of the investigators, study coordinators, teachers, parents, and participants were blinded to the treatment assignments.

After successful screening, a baseline (week 0) evaluation visit occurred within 2 weeks. At this time, the following visits were performed: Conners Abbreviated Symptom Questionnaire for Teachers (ASQ-Teacher), Iowa Conners Teacher Rating Scale, Conners Abbreviated Symptom Questionnaire for Parents (ASQ-Parent), the Conners Continuous Performance Task, the Children’s Global Assessment Scale (CGAS), and the Wechsler Individual Achievement Test III (WISC-III) screeners. Systematic classroom observations of the subject’s behavior by a trained, independent observer also took place. Classroom observers were trained at the State University of New York at Buffalo under the supervision of Dr. Pelham. In addition, vital signs were assessed and an electrocardiogram (ECG) was performed.

At the baseline visit, subjects were randomly assigned by the CTCC to receive methylphenidate alone (MPH), clonidine alone (CLON), combined methylphenidate and clonidine (COMB), or placebo (PBO). The computer-generated randomization plan included stratification by center (investigator) and sexual maturity status (prepubertal: Tanner stages I–II; pubertal: Tanner stages III–V). Blocking was used to ensure approximate balance among the treatment groups within each stratum. Only the programmer in the
Biotostatistics Center who generated the plan and the pharmacist in the Pharmacy Center who packaged and labeled the drug were aware of the treatment assignments. Treatment assignments were not revealed to the subjects or investigators until the entire study was completed and the database was officially locked. Each site was supplied with sealed envelopes that contained their subjects’ treatment assignments in the event that such information was needed for emergent medical care. Unblinding did occur for two subjects due to a severe allergic reaction that resulted in an emergency department visit, which was later determined not to be related to study medication, and prolonged QTc intervals for which an echocardiogram followed, which was normal.

Subjects entered a double-blind treatment period for 16 weeks that consisted of an 8-week dose titration period (4 weeks for clonidine, then 4 weeks for methylphenidate) and an 8-week maintenance dose period. There was an initial 4-week dose titration period for clonidine (0.1 mg scored tablets or matching placebo tablets). Subjects continued to receive clonidine (or matching placebo) on entering the subsequent 4-week dose titration period for methylphenidate (or matching placebo) powder packaged in gelatin capsules equivalent to 5-mg strength. For both medications, an individualized, flexible dose titration procedure was used, which was designed to reproduce standard clinical practice and to allow the determination of an optimal dose for each subject. Optimal dose was defined as the one that allowed the subject to reach a level of school functioning considered good, with no further room for improvement, with an acceptable level of side effects and representing a meaningful clinical change from baseline. As guides to medication dose titration, approximately every 3 days the teacher telephoned or faxed to the site a completed ASQ-Teacher and a side effects rating scale (modified from Pelham16) to include possible adverse effects of clonidine. To achieve a general level of consistency across sites, an ASQ-Teacher score of 5 (the normal childhood population mean3) was considered an approximation to help the investigator determine when there was no further room for improvement. The maximum allowable daily drug doses were 60 mg for methylphenidate and 0.6 mg for clonidine.

Methylphenidate: Method of Administration. Methylphenidate was administered as immediate-release methylphenidate (5-mg capsules) or matching placebo capsules. Dosing was initiated with one capsule (5 mg) before school. After 3 days, adding an additional 5-mg capsule at lunchtime was allowed. These doses were adjusted to optimal effect based on regular reports provided by the teacher and parents. The daily dose was allowed to increase by one 5 mg capsule every 3 school days. If ADHD symptoms were worse than the baseline state or were a problem later in the day, then a third 5 mg dose was added after school. The doses were administered at 7:00 A.M., 11:00 A.M., and 3:00 P.M. Although three-times-daily dosing was considered optimal for the study, if an afternoon dose was problematic, then it was allowed to be dropped. The dose titration was continued until either the optimal dose or the maximum dose of 0.6 mg/day was reached.

Clonidine: Method of Administration. Clonidine was administered as brand-name Catapres (0.1-mg scored tablets) or matching scored placebo tablets. Dosing was initiated with ½ tablet at bedtime. The dose was increased by ½ tablet every 3 days initially using a three-times-daily dosing schedule (before school, after school, bedtime). A fourth dose (lunchtime) could be added if needed due to waning efficacy or to reduce side effects (e.g., sedation) by dividing the dose further. The dose titration was continued until either the optimal dose or the maximum dose of 0.6 mg/day was reached.

Investigators were allowed to deviate from the above guidelines for methylphenidate and clonidine dosing and adjust the dose to minimize side effects or to optimize efficacy. Subject enrollment was scheduled to avoid dose titration occurring during school vacations. There was also regular telephone contact with parents using the Conners ASQ-Parent and the Side Effects Rating Scale.

An 8-week maintenance dose period followed the dose titration phases, during which subjects received methylphenidate (or matching placebo) and/or clonidine (or matching placebo) at the doses found to be optimal in the dose titration phases. However, dose changes to optimize efficacy were not permitted during the final 2 weeks of the dose maintenance period so that the final evaluation would be an accurate assessment of a treatment regimen that had been in place for at least 14 days.

The same clinical evaluations performed at the baseline (week 0) visit (with the exception of classroom observations) were repeated after the clonidine dose titration period (week 4), after the methylphenidate dose titration period (week 8), at the halfway point of the maintenance dose period (week 12), and at the end of the study (week 16). Classroom observations were repeated only at the time of the final evaluation visit (week 16). Postbaseline assessments at each visit also included the following: a rating of clinical change (NIMH Clinical Global Impression Improvement Scale17,18) completed independently by the parent, teacher, and site investigator; a systematic review of adverse events and checks of weight, blood pressures and pulses, and ECGs. ECG tracings were obtained at study sites and faxed to the CTCC for reading by a pediatric cardiologist. The reading and interpretation of abnormal tracings were sent to a pediatric cardiologist (Dr. Peter Harris) at the CTCC for final determination. Compliance was monitored at each visit using pill counts. Each subject received a small gift, each parent received $75, and each teacher received $100 when the protocol was completed and all of the necessary rating forms were received.

When the final evaluation was completed, subjects received instructions on how to discontinue study medications, including a gradual tapering schedule over 7 days for clonidine to avoid possible withdrawal effects. After completion of the study, routine clinical care was provided at the participating site by an individual with expertise in treating ADHD. Alternatively, subjects had the option of participating in a 1-year extension phase of the study that will be reported in a separate research report.

An independent safety monitoring committee, consisting of a pediatric cardiologist, pediatrician, and statistician, reviewed data regarding adverse events throughout the study. A National Institutes of Health–appointed Data and Safety Monitoring Board similarly reviewed safety data in overseeing the trial. No interim analyses were performed for examination of efficacy results.

Statistical Methods

Outcome Variables. The primary outcome variable was the change from baseline to week 16 in the ASQ-Teacher score. Changes from baseline to weeks 4, 8, 12, and 16 (when applicable) in other measures of ADHD and global functioning (CGAS) were examined as secondary outcome variables. Medication dose (clonidine and methylphenidate) was also considered as an outcome variable. Measures included safety the frequency and severity of individual adverse events and abnormal ECG results, as well as changes from baseline to each visit in vital signs.

Sample Size. The trial was originally planned to examine two primary comparisons: CLON versus PBO and COMB versus MPH; these comparisons represent the effects of clonidine in settings with
and without concurrent methylphenidate, respectively. A sample size of 140 subjects (35 per treatment group) was determined to provide between 80% and 90% power to detect a group difference of 4 to 5 points in the mean change from baseline to week 16 in the ASQ-Teacher score for either of the two primary comparisons, using a t test and two-tailed Bonferroni-adjusted significance level of 2.5%, accounting for an anticipated 10% rate of subject withdrawal. The SD of this outcome variable was assumed to be 5.0 points based on previous trials.3,19-21 Before unblinding, due primarily to the finding of no evidence of interaction between clonidine and methylphenidate in the TACT Trial, the strategy for the primary statistical analyses was changed to emphasize estimation of the main effects of clonidine (i.e., those in the CLON and COMB groups versus those in the MPH and PBO groups) and methylphenidate (i.e., those in the MPH and COMB groups versus those in the CLON and PBO groups) rather than the comparisons among the individual treatment combinations.

Statistical Analysis. The analysis of the primary outcome variable used an analysis of covariance model that included methylphenidate treatment and clonidine treatment as the factors of interest, center as a stratification factor, and baseline ASQ-Teacher score as a covariate. Two-tailed t tests for the main effects of methylphenidate and clonidine, adjusted for center and baseline ASQ-Teacher score, were performed, and 95% confidence intervals (CIs) were computed for these effects using the analysis of covariance model.

The assumption of no statistical interaction between methylphenidate and clonidine was examined by including the appropriate interaction term in the above analysis of covariance model and testing for its significance. This expanded model also was used to estimate pairwise contrasts between each of the active treatment groups and the PBO group using a Bonferroni-adjusted significance level of 1.7%. Effect sizes for the main effects of methylphenidate and clonidine, as well as for the comparisons of each of the three active treatment groups with the PBO group, were computed as the differences between the adjusted group means at week 16 divided by the pooled SD computed from the analysis of covariance model.

The above analyses were repeated for the secondary outcome variables for efficacy, as well as for vital signs. Fisher exact tests were used to compare treatment groups with regard to the frequencies of adverse events and ECG abnormalities.

The primary statistical analyses were performed according to the intention-to-treat principle and included data from all of the randomized subjects, as randomized. For the analyses of the outcome variables for efficacy, if a subject was missing a response at a particular visit, then the last available observation for that subject was carried forward and imputed for that visit, even if this was a baseline observation.

RESULTS

Clinical Characteristics

Of 201 eligible patients, 122 were enrolled and randomized between October 2000 and April 2004. Four subjects who were screened were ineligible. Subjects who were eligible did not enroll due to several factors, including school denied participation, subjects and parents decided to pursue community clinical care, subjects and parents did not want to adhere to all of the protocol requirements, and they chose to enroll in competing clinical trials. Participant flow in the trial is shown in Figure 1. The distribution of ADHD subtype by treatment group was as follows: PBO, 76.7% Combined; 13.3% Inattentive; 10% Hyperactive/Impulsive; MPH, 75% Combined; 25% Inattentive; 0% Hyperactive/Impulsive; CLON, 77.4% Combined; 22.6% Inattentive; 0% Hyperactive/Impulsive; and COMB,
75% Combined, 18.8% Inattentive, 6.2% Hyperactive/Impulsive. Comparable with other ADHD studies, the majority of participants were male; 98 boys and 24 girls enrolled with a mean age of 9.5 ± 1.6 years. Ethnic groups were white (n = 95), black (n = 13), Hispanic (n = 8), and other (n = 6). Relevant demographic and clinical characteristics of the subjects at baseline in each of the four treatment groups are summarized in Table 1.

The subject groups were similar except for a higher percentage of whites in the CLON group, and there were some minor differences with regard to family histories of ADHD and tics.

**Dosing**

Mean end-of-study doses in groups on active treatment were as follows: CLON, 0.24 ± 0.11 mg/day; MPH, 30.2 ± 18.9 mg/day; COMB clonidine, 0.23 ± 0.13 mg/day; and methylphenidate, 25.4 ± 18.2 mg/day. At the end of the study, the average methylphenidate daily dose was 0.76 ± 0.54 mg/kg for subjects taking methylphenidate (MPH or COMB).

**Subject Disposition**

Forty-four subjects withdrew before completing the study, with the greatest number of withdrawals in the PBO group. Of the MPH group, 38% (11) withdrew, and four of these withdrew during the first 4 weeks (i.e., before actually receiving methylphenidate). “Parent request” for withdrawal was usually unspecified. There was one serious adverse event in the MPH group that

### TABLE 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>PBO (n = 30)</th>
<th>MPH (n = 29)</th>
<th>CLON (n = 31)</th>
<th>COMB (n = 32)</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>9.0 (1.5)</td>
<td>9.4 (1.6)</td>
<td>9.4 (1.2)</td>
<td>10.0 (2.0)</td>
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<td>Males, %</td>
<td>76.7</td>
<td>82.8</td>
<td>87.1</td>
<td>75.0</td>
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<td>White, %</td>
<td>70.0</td>
<td>82.8</td>
<td>93.6</td>
<td>65.6</td>
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<td>Pubertal, %</td>
<td>0.0</td>
<td>6.9</td>
<td>3.2</td>
<td>15.6</td>
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<td>Family history, %</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>ADHD</td>
<td>36.7</td>
<td>24.1</td>
<td>48.4</td>
<td>40.6</td>
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<td>Tics</td>
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<td>0.0</td>
<td>0.0</td>
<td>12.5</td>
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<tr>
<td>Treatment history, %</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulant</td>
<td>40.0</td>
<td>41.4</td>
<td>58.1</td>
<td>46.9</td>
</tr>
<tr>
<td>Clonidine</td>
<td>3.3</td>
<td>7.1</td>
<td>6.5</td>
<td>9.4</td>
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<tr>
<td>Comorbid ODD, %</td>
<td>50.0</td>
<td>44.8</td>
<td>43.3</td>
<td>50.0</td>
</tr>
<tr>
<td>Comorbid conduct disorder, %</td>
<td>10.0</td>
<td>3.5</td>
<td>16.7</td>
<td>6.3</td>
</tr>
<tr>
<td>Conners ASQ-Teacher</td>
<td>14.5 (7.2)</td>
<td>13.3 (7.3)</td>
<td>12.8 (7.0)</td>
<td>13.8 (6.7)</td>
</tr>
<tr>
<td>Conners ASQ-Parent</td>
<td>19.3 (7.0)</td>
<td>17.5 (6.0)</td>
<td>19.2 (7.3)</td>
<td>17.8 (7.2)</td>
</tr>
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<td>Iowa Conners</td>
<td></td>
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</tr>
<tr>
<td>I/O</td>
<td>8.4 (3.6)</td>
<td>8.1 (3.6)</td>
<td>8.0 (3.8)</td>
<td>8.3 (3.7)</td>
</tr>
<tr>
<td>O/D</td>
<td>4.2 (4.3)</td>
<td>3.6 (3.9)</td>
<td>3.4 (3.5)</td>
<td>3.8 (4.2)</td>
</tr>
<tr>
<td>Total</td>
<td>12.6 (7.4)</td>
<td>11.6 (7.1)</td>
<td>11.5 (6.6)</td>
<td>12.1 (7.2)</td>
</tr>
<tr>
<td>WIAT</td>
<td>98.3 (12.9)</td>
<td>93.7 (13.6)</td>
<td>95.6 (14.3)</td>
<td>95.2 (18.4)</td>
</tr>
</tbody>
</table>

**Note:** Values are mean (SD) unless otherwise indicated. PBO = placebo; MPH = methylphenidate alone; CLON = clonidine alone; COMB = combination of methylphenidate and clonidine; ADHD = attention-deficit/hyperactivity disorder; ODD = oppositional defiant disorder; ASQ = Abbreviated Symptom Questionnaire; I/O = impulsive/oppositional; O/D = oppositional/defiant; WIAT = Wechsler Individual Achievement Test.

### TABLE 2

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Treatment Effect</th>
<th>CI</th>
<th>p</th>
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<tbody>
<tr>
<td>Methylphenidate vs. no methylphenidate</td>
<td>-2.9</td>
<td>-5.1 to -0.8</td>
<td>.008</td>
</tr>
<tr>
<td>Clonidine vs. no clonidine</td>
<td>-1.4</td>
<td>-3.6 to 0.7</td>
<td>.19</td>
</tr>
<tr>
<td>Methylphenidate × clonidine</td>
<td></td>
<td></td>
<td>.69</td>
</tr>
<tr>
<td>interaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPH vs. PBO</td>
<td>-2.5</td>
<td>-6.3 to 1.3</td>
<td>.12</td>
</tr>
<tr>
<td>CLON vs. PBO</td>
<td>-1.0</td>
<td>-4.7 to 2.7</td>
<td>.52</td>
</tr>
<tr>
<td>COMB vs. PBO</td>
<td>-4.4</td>
<td>-8.0 to -0.7</td>
<td>.005</td>
</tr>
<tr>
<td>MPH vs. CLON</td>
<td>-1.5</td>
<td>-4.6 to 1.6</td>
<td>.34</td>
</tr>
<tr>
<td>COMB vs. MPH</td>
<td>-1.9</td>
<td>-4.9 to 1.2</td>
<td>.23</td>
</tr>
<tr>
<td>COMB vs. CLON</td>
<td>-3.4</td>
<td>-6.4 to -0.4</td>
<td>.03</td>
</tr>
</tbody>
</table>

**Note:** Treatment effect is the group difference in mean change from baseline to week 16 in the outcome variable, adjusted for center and the baseline value of the outcome variable in an analysis of covariance model. Conners ASQ-Teacher = Conners Abbreviated Symptom Questionnaire for Teachers; CI, confidence interval; MPH = methylphenidate; CLON = clonidine; COMB = combination of clonidine and methylphenidate; PBO = placebo.
CLONIDINE EFFICACY AND TOLERABILITY OUTCOMES

Primary Efficacy Outcome Measure (ASQ-T)

The mean, SD changes from baseline to week 16 on the Conners ASQ-Teacher for the four treatment groups were $-3.20, 6.38$ (PBO), $-3.35, 5.78$ (CLON), $-5.07, 6.79$ (MPH), $-7.28, 7.91$ (COMB). Analyses of treatment efficacy using the Conners ASQ-Teacher are shown in Table 2 and Figure 2. On the ASQ-Teacher, subjects receiving methylphenidate (COMB or MPH) performed better than those not receiving methylphenidate (CLON or PBO); difference in adjusted group means $-2.9$, $95\%$ CI $-5.1$ to $-0.8$; $p = .008$. Subjects receiving clonidine (COMB or CLON) performed better than those not receiving clonidine (MPH or PBO), but this effect ($-1.4$ points, $95\%$ CI $-4.6$ to $0.7$) was not statistically significant ($p = .19$). No significant interaction effect between clonidine and methylphenidate was evident ($p = .69$). The effect sizes (based on the results in Table 2 and the estimated pooled SD of 5.98) were as follows: methylphenidate versus no methylphenidate, $-0.49$; clonidine versus no clonidine, $-0.24$; MPH versus PBO, $-0.41$; CLON versus PBO, $-0.17$; COMB treatment versus PBO, $-0.73$.

Secondary Efficacy Outcome Measures

A different pattern of treatment effects was found when analyzing some of our other secondary outcome measures. A different pattern of treatment effects was found when analyzing some of our other secondary outcome.
measures for ADHD. On the ASQ-Parent, subjects receiving clonidine (COMB or CLON) performed better than those not receiving clonidine (MPH or PBO) (difference in adjusted group means 3.7, 95% CI −6.1 to −1.7; p = .003). In contrast, the effect of methylphenidate was not significant (1.2 points, 95% CI −3.7 to 1.2; p = .31; Table 3). On the CGAS, subjects receiving clonidine performed better than those not receiving clonidine (difference in adjusted group means 7.5, 95% CI −3.6 to 11.4; p = .0002); the effect of methylphenidate on the CGAS was slightly less (3.7 points, 95% CI −0.2 to 7.5; p = .06). There was a suggestion of an interaction between clonidine and methylphenidate on the CGAS (p = .02), reflecting the pattern that the effect of combined treatment was less than the sum of the effects of the individual treatments (CLON versus PBO 12.2 points, 98.3% CI 5.7–18.8; p < .0001; MPH versus PBO 8.6 points, 98.3% CI 1.9–15.3; p = .002; COMB versus PBO 11.3 points, 98.3% CI 4.8–17.8; p < .0001; Table 4).

The Iowa Conners Scale demonstrated significant benefits of methylphenidate on the total score (p = .003) and on the inattention/overactivity (p = .003) and oppositional/defiant (p = .02) subscores (Table 5). In addition, direct classroom observation measures revealed a benefit of methylphenidate on on-task behaviors (p = .02). No treatment effects were found for the Wechsler Individual Achievement Test (Table 5).

**DISCUSSION**

This is the largest prospective, controlled study to date of clonidine, alone and in combination with methylphenidate, for primary pediatric ADHD. As expected, we found methylphenidate to be a safe and effective treatment for ADHD based on the primary outcome measure using teacher ratings (ASQ-Teacher). This finding was replicated on several other outcome variables (Iowa Conners subscales, direct classroom observation of on-task behavior, CGAS). Clonidine was not found to be as effective as methylphenidate in reducing ADHD symptoms based on the ASQ-Teacher. However, secondary outcome measures using parent (ASQ-Parent) ratings of ADHD symptoms and clinician ratings of global functioning (CGAS) suggested a benefit of clonidine.

Overall, findings should be viewed cautiously in light of the differential rates of attrition across groups. Although the attrition rate was high in the PBO group, almost all of this was due to lack of perceived efficacy/parent request/loss to follow-up, so our strategy for imputing missing data (last observation carried forward) is reasonable in this short-term trial for this nonprogressive condition. This strategy was likely conservative, however, particularly for the active treatment groups; hence, it may have led to attenuation of the treatment effects. Findings are also limited by the exclusion of children with certain comorbid disorders such as mood and anxiety disorders, which are not uncommon in clinical practice. Also, given that all of the subjects participated in psychoeducational and behavioral interventions as part of the protocol, these results may be limited to settings in which these behavioral interventions are applied.

Suggestions of benefit on certain ratings with clonidine came at the expense of a higher adverse event profile; thus, the risk–benefit of using clonidine must be
carefully weighed when considering treatment options. Sedation was the most problematic side effect, but the frequency of this decreased after week 8, suggesting that this is an acute more than a long-term problem with clonidine. Sedation did not lead to subject withdrawal from the trial except in one case. Guanfacine, another commonly used α-agonist, has advantages over clonidine in that it can be dosed less frequently and is reportedly less sedating.

Further studies of the efficacy and safety of guanfacine in combination with methylphenidate may be warranted given these findings. No consistent treatment effects were noted in terms of ECG findings or vital signs. However, because children with known cardiac problems or abnormal ECGs at baseline were excluded from the study, the safety of clonidine, methylphenidate, and combination treatment in children with cardiac risks cannot be inferred from these data. Clinically, physicians prescribing clonidine should continue to monitor side effects and changes in cardiovascular outcomes.

This study supports previous findings from the TACT Trial that clonidine, used alone or with methylphenidate, is relatively safe and well tolerated. The methylphenidate dose ranges in the MPH and COMB groups were comparable to those achieved in the TACT trial. Yet, these results differ from the TACT Trial findings in that more robust treatment effects of clonidine were found in the TACT Trial. This may be a result of inherent neurobiological differences between children with tics and ADHD and children with primary ADHD. The TACT Trial sample had a preponderance of Inattentive subtype ADHD (71%) and a smaller proportion of Combined subtype ADHD (26%) than expected in the primary ADHD population. In this study, 76% of subjects met Diagnostic Interview Schedule for Children criteria for Combined subtype ADHD and 20% for Inattentive subtype ADHD. Thus, this significant difference in ADHD symptom profiles between the two study groups may have affected treatment response.

In addition, in the TACT Trial, subjects in all active treatment groups had a significant reduction of tics. Therefore, perhaps teachers and parents place a premium on different behaviors. Additional analyses of our clinical trial databases are planned to further examine these issues.

Future Research Directions

Long-term monitoring of children on these treatments is a future research issue that is important to address. Additional analyses of our clinical trials databases may be helpful in discerning differential effects of each treatment on specific symptoms. In addition, combining the database with that from the TACT Trial to examine both similarities and differences between the samples may be important in helping us to understand the psychobiology of ADHD with and without comorbid tics. Last, studies using long-acting methylphenidate treatments in combination with clonidine or guanfacine are needed given current prescribing.

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REFERENCES


