

A Double-Blind, Placebo-Controlled Study of Atomoxetine in Young Children with ADHD

BACKGROUND:

- Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with symptoms that usually present as early as preschool age.
- Atomoxetine has been demonstrated to be safe and effective for the treatment of ADHD in children 6 years of age and older, but no controlled data is available for children under the age of 6 years old.

OBJECTIVE

- To evaluate the efficacy and tolerability of atomoxetine for the treatment of ADHD in 5 and 6 year old children

METHODS

- **Design:** Multiple site, double-blinded, randomized parallel trial; Duration: 8 weeks
- **Inclusion criteria:** Informed consent by legal guardian, verbal assent from child, age 5 to 6 years at time of consent; criteria met for any subtype of ADHD on the Diagnostic Interview Schedule for Children, clinical interview, and on review by a clinical consensus conference of all 3 sites; ADHD is primary disorder with symptoms present for ≥ 9 months; a T score of ≥ 65 on the ADHD-RS (ADHD-RS is linked to DSM-IV diagnostic criteria and can be used to both diagnose ADHD and to assess response to therapy.); a Children's Global Assessment Scale score of ≤ 55 ; a CGI-S score of ≥ 4 (at least moderate severity); a Peabody Picture vocabulary Test-III SS score of ≥ 70 ; attending day care, preschool, kindergarten, or elementary school for ≥ 2 half-days per week with a peer group of 8 or more; living with the same parent or guardian for ≥ 6 months; and having a teacher who is able to provide assessments.
- **Exclusion criteria:** Concurrent use of psychotropic or other medications with significant central nervous system effects; current effective treatment with atomoxetine; medical contraindication to atomoxetine; current diagnosis of adjustment disorder, autism, psychosis, bipolar disorder, or significant suicidality; history of abuse that may confound symptoms of ADHD; and failure to respond to an adequate previous trial of atomoxetine.
- **Primary outcome measure:** Change from baseline to end point in parent and teacher ADHD-IV Rating Scale total score.
- **Secondary outcome measures:** Change from baseline to end point in ADHD-specific Clinical Global Impression – Improvement Scale (CGI-I), Clinical Global Impression – Severity (CGI-S), and Children's Global Assessment Scale, and occurrence of adverse events.
- 93 patients (49 placebo and 44 atomoxetine) received either
 - Atomoxetine 0.5mg/kg/day as a single or divided doses
 - OR
 - Placebo 0.5mg/kg/day as a single dose
- Power 80% with an alpha level of 0.05 to detect an 8 point difference in the change between the 2 groups (assuming a SD of 12). This was calculated to be sufficient for 38 people per group, or 76 total patients.
- Data handling method was intent-to-treat.

RESULTS

- 18 patients were lost-to-follow up, but their data was included for a total of 93 patients.
- **Primary outcome measure:** There was a statistically significant difference in change in ADHD-RS parent total score from baseline between groups: Mean change between groups = -7.3. (95% CI -13.7 to -.09; $p=0.009$). The mean change on the ADHD-RS teacher total score was also statistically significant: -12.5 for atomoxetine and -5.0 for placebo ($p=0.02$).

- **Secondary outcome measures:** There was no significant difference in change in CGI-I or CGI-S from baseline between groups: $p=0.1$ for both measures. Results were not reported for Children's Global Assessment Scale. The following adverse events were statistically significant: change in weight ($p=0.006$; but not clinically significant), decreased appetite ($p=0.008$), gastrointestinal upset ($p=0.02$), and sedation ($p=0.02$).
- **Author's conclusion:** Atomoxetine appeared to have statistically significant efficacy in reducing ADHD-RS scores for 5- and 6-year old children, but clinically significant symptoms remained for the majority of children treated with it.

STRENGTHS

- Double-blind, placebo-controlled, randomized design
- Unstudied population
- Standardized training of pharmacotherapists
- Compared intent-to-treat data with per protocol and obtained similar results

LIMITATIONS

- Short study duration
- Potential unblinding
- Subjective titration
- No data provided to account for compliance

CONCLUSION

- Although the study showed that atomoxetine showed a statistically significant decrease in ADHD-RS score, it was not clinically significant.
 - Only 40% of the patients taking atomoxetine were rated as much or very much improved at study end.
 - Atomoxetine, brand name Strattera, is currently available only as a brand name drug. With other medications for ADHD available as generic, it would not be the most cost effective option for patients.
- Future research:
 - Since a significant benefit was not seen until week 6 in the atomoxetine group, a longer trial should be performed to determine if atomoxetine's benefits increase and if its effects are sustainable.

Reference: Kratochvil CJ, Vaughan BS, Stoner JA, Daughton JM, Lubberstedt BD, Murray DW, et al. A double-blind, placebo-controlled study of atomoxetine in young children with ADHD. *Pediatrics*. 2011 Apr;127(4):e862-8. Epub 2011 Mar 21.

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