MARK W. WILSON, MD
330 WEST 58TH STREET, SUITE 313
NEW YORK, NEW YORK 10019

Strattera

- **General**
  - Generic name is atomoxetine
  - Released 1/10/03
  - FDA-approved for ADHD in folks aged 6 and up
  - Norepinephrine reuptake inhibitor (which indirectly leads to increased dopamine in the prefrontal cortex but not in the nucleus accumbens)
  - May take 6 weeks for full effects to kick in
  - Response rate ~50%
- Data
  - Evidence in youth
    - Wietecha et al, 2013: Strattera in youth (10-16) with ADHD vs. dyslexia vs. both; 16 weeks and then open-label extension for 16 more weeks
      - Effective in all groups, including dyslexia only
    - Harfterkamp et al, 2012: Strattera in youth with ADHD+autism spectrum disorder, 97 subjects; 8 wks
      - Benefits in hyperactivity > inattention in folks with ASD, less effective than in ADHD
      - Common side effects
        - Nausea 29% vs. 8% placebo
        - Decreased appetite 27% vs. 6% placebo
        - Fatigue 22% vs. 8% placebo
        - Early morning awakening 10% vs. 0% placebo
      - No treatment limiting side effects
      - No exacerbation of stereotypies or other repetitive behaviors
    - De Jong et al, 2009: helpful in ADHD plus dyslexia
    - Summer et al, 2009: helpful in ADHD plus dyslexia
    - AJP, 2008: Strattera vs. Concerta vs. placebo
      - Strattera: 44% response rate
      - Concerta: 56% response rate
      - Placebo: 23% response rate
    - 1996-2005:
      - 3,500 children and adolescents have been treated with Strattera in over 30 double-blind and open label clinical trials
        - Of these, 323 have been 6 or 7 year olds
        - Appears to reasonably demonstrate safety and efficacy in children and adolescents
    - Kratochvil et al, 2006: 8-week, open-label, pilot study of 22 young children aged 5-6 yo with ADHD
      - Effective
      - Side effects
        - Decreased appetite in 50%; average weight loss of 2.2+ pounds
    - Wilens, 2006: study on the augmentation of partial responders to Strattera treatment of youths with ADHD with Concerta, ongoing study, two-phase, 7-week open study, ages 6-17, phase 1 is 4 weeks of Strattera treatment, phase 2 is the augmentation of partial responders to Strattera with Concerta
      - 60% overall decrease in symptoms over the 7 weeks
      - 28% of which occurred prior to the introduction of Concerta
      - 32% of which occurred during the period on the combination of Strattera and Concerta
    - Carlson et al, 2006: study on the augmentation of partial responses to Strattera treatment of youths with ADHD with Ritalin LA (or Metadate CD)
      - Safe
      - Evidence not clear for increased efficacy
  - ADHD in adults
    - Effective
    - Side effects (and see below too)
      - Dry mouth 21% vs. 6% placebo
      - Insomnia 13% vs. 6% placebo
      - Nausea 12% vs. 5% placebo
      - Constipation 10% vs. 4% placebo
      - Decreased appetite 10% vs. 3% placebo

- Dizziness 6% vs. 2% placebo
- Decreased libido 6% vs. 2% placebo
- Erectile dysfunction 7% vs. 1% placebo
- Menstruation abnormalities 7% vs. 3% placebo
- Urinary retention 3% vs. 0% placebo

◦ Strattera tolerability in pediatric and adults patients from 22 pediatric and 3 adults trials (Wietecha et al, 2013)
- Pediatric patients; most commonly reported adverse effects
  ◦ Decreased appetite 20.4% vs. 5.1% placebo
  ◦ Abdominal pain 12.1% vs. 7.7% placebo
  ◦ Nausea 11.3% vs. 4.6% placebo
  ◦ Vomiting 10.8% vs. 5.6% placebo
  ◦ Somnolence 9.3% vs. 3.1% placebo
  ◦ Fatigue 8.8% vs. 3.8% placebo
  ◦ Irritability 5% vs. 2.9% placebo
    ▪ AACAP, 2016: 0.037% vs. 0.0% placebo
- Adult patients; most commonly reported adverse effects
  ◦ Nausea 31.9% vs. 8.1% placebo
  ◦ Insomnia 14.7% vs. 7.3% placebo
  ◦ Decreased appetite 12% vs. 3.5% placebo
  ◦ Urinary hesitation/urinary retention 5.4% vs. 0.8% placebo
  ◦ Fatigue 12.9% vs. 8.3% placebo

◦ ADHD and tic/Tourette's syndrome
- Some evidence that Strattera is effective and well-tolerated in children with co-morbid tic disorders
- Spencer et al, 2006: 18 week study of Strattera vs. placebo for youth with ADHD and Tourette syndrome
  - ADHD was well treated with no exacerbation in tic severity
  - Some evidence of a reduction in tic severity

◦ ADHD and Anxiety
- D. Geller et al, 2006: double-blind, acute phase of a multi-center study, 176 youth aged 8-17 with ADHD and generalized or social or separation anxiety disorder; randomized to Strattera or placebo
  - Efficacious
  - Improved functioning
  - Well tolerated
  - Response rate:
    ◦ 59-64% (defined as 30% or more reduction in symptoms)
    ◦ Average time to onset of benefit is 13 days (range of average is 10-15 days)
      ▪ 35% response by day 7
      ▪ 60% by days 15-18
      ▪ 80% by day 45
      ▪ 85% by day 60

◦ ADHD and Autism Spectrum Disorder
- Harfterkamp et al, 2012: beneficial and well-tolerated over 8 weeks
  - Side effects
    ◦ Nausea or vomiting 43.8% vs. 18.3% placebo
    ◦ Abdominal pain 27.1% vs. 12.2% placebo
    ◦ Decreased appetite 27.1% vs. 6.1% placebo
    ◦ Headache 25% vs. 18.4% placebo
    ◦ Fatigue 22.9% vs. 8.2% placebo
    ◦ Early morning awakening 10.4% vs. 0% placebo
    ◦ Dizziness 6.3% vs. 2% placebo

◦ Long-term benefits and functioning in ADHD
- A recent study have demonstrated continued safety and efficacy over 12 months in children, over 2 years in adolescents aged 12-18, and over 97 weeks in adults
- Effective and well-tolerated for up to 2 years in youth with ADHD (Kratochvil, Wilen, et al, 2006)
- Demonstrates improvements in family activities, self-esteem, parent-child relationships and, in adults, global functioning at home and work

◦ Other conditions
- Arnold et al, 2006: 16 youth with autism spectrum disorders and hyperactivity; safe and effective with fewer side effects than Ritalin

◦ Evidence in adults
- FDA-approved for adults with ADHD based on 2 double-blind, placebo controlled trials in 536 adults (max dose 120 mg)

- 56% response rate (defined as 30% or more reduction in symptoms)
- Durell et al, 2006: efficacy in younger adults (aged 18-25; mean 22 years) vs. older adults (aged 26 or more; mean 43), twice-daily dosing, 10 weeks, 536 patients
  - Effective in both groups
  - Response rate defined as 25% reduction in symptoms or more
    - 56.4% in younger adults
    - 47.8% in older adults
  - Tolerability the same, except older adults reported more sexual side effects
- McElroy et al, 2007: safe and effective in binge-eating disorder

◦ In clinical research, does not appear to worsen anxiety or irritability.

◦ Some evidence that Strattera is not as effective as stimulants

- Pharmacodynamics
  - Recommended dose range:
    - 0.5-1.4 mg/kg/d (not to exceed 100 mg/d) given once or twice-a-day
    - 1.8 mg/kg/day appears to have been safe and more effective in treating clients with ADHD and co-morbid oppositional-defiant disorder
  - Peak is 1-2 hours after dose
  - Half-life 3-5 hours (20+ hours in poor metabolizers)
  - Metabolized through liver enzymes 2D6. Prozac and Paxil can inhibit metabolism of Strattera.
    - Poor 2D6 metabolizers can have a 5-fold higher peak concentration to a given dose; use less and use caution
  - Strattera does not appear to affect the metabolism of medications
  - Caps—10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80, 100
- Side Effects, Risks
  - Dry mouth 21-55% vs. 7-20% placebo
  - Nausea/abdominal pain or upset/vomiting 12-50% vs. 5-32% placebo
    - Vomiting 7.8-15.6% vs. 1.1% placebo in youth ages 6-12
    - Abdominal pain 11.1-14.6% vs. 4.4% placebo in youth ages 6-12
    - Nausea 4.4-7.3% vs. 0% placebo in youth ages 6-12
    - Stomach discomfort 4.4-6.3% vs. 0% placebo in youth ages 6-12
  - Headache 21-30% vs. 17-32% placebo
    - 5.6-12.5% vs. 4.4% placebo in youth ages 6-12
  - Decreased appetite7.8-14.6% vs. 3.3% placebo in youth ages 6-12
    - Strattera used in youth ADHD for 5 years (from age ~10 through ~age 15) demonstrated a slowing of growth for the first 1-2 years followed in years 3-5 by a period of catch-up (Spencer, 2007)
    - Transient slow growth with later catch up was seen in a younger group (ages 6-9) given Strattera for 2 years (AACAP, 2006)
  - Sexual side effects:
    - Decreased libido 7% vs. 2% placebo
    - Erectile dysfunction in men 10-16% vs. 1% placebo
    - Priapism (prolonged, painful erection)
    - Decreased appetite 11-18% vs. 3-7% placebo
    - Sedation/fatigue 10-18% vs. 5-13% placebo
      - 4.4-11.5% vs. 1.1% placebo in youth ages 6-12
    - Dizziness 6-15% vs. 0-2% placebo
    - Height and weight
      - Can cause reduced appetite and nausea (which can lower food intake)
      - Spencer et al, 2007: 61 kids treated for 5 years with Strattera for ADHD (from an average of 10 yo → 15 yo)
        - slowing of growth for the first 1-2 years followed by a period of catch up in the years 3-5
        - (not sure if this is connected to the 2006 study below)
      - Spencer et al, 2006: 5 year, open label study on the treatment of ADHD, 1312 subjects
        - weight loss was noted by 6 months, maximal by 12 months, normalized by 36 months, and with more than expected weight (by 2 pounds) by 60 months
        - height slightly lower than expected by 12 months, maximal by 18 months, normalized by 24 months, and with 0.3 cm less than expected height by 60 months.
      - Spence et al, 2005, demonstrated minimal impact on weight and height after two years of use
        - 2.7% less weight gain than expected
        - 2.2% less height gain than expected
  - Insomnia 2-21% vs. 2-9% placebo
  - Constipation 20% vs. 10% placebo
  - Urinary retention, hesitancy (usually in older men)

- Increased heart rate and blood pressure
  - 6-9 bpm increase in heart rate
  - 2-4 mm Hg increase in blood pressure
- Increased sweating 20% vs. 0% in placebo
- Agitation/anxiety/irritability/activation/mania/suicidality rare
  - AACAP, 2016
    - 0.037% with irritability on Strattera, 0% on placebo
    - 1 suicide attempt/1357 patients on Strattera vs. 0 attempts on placebo
  - Manic activation in 50% of bipolar youth but 2.9% overall in one study (versus 3% overall for placebo)
  - Nervousness 35% vs. 15% in placebo
  - Agitation/hostility on 1.2-1.6% (vs. 1.1% on placebo vs. 0.8% on methylphenidate)
  - Suicidal thoughts/behaviors: rare despite black box warning
    - Meta-analysis of suicide-related behavior or ideation in child, adolescent, and adult patients treated with atomoxetine
      - Mark E Bangs, Linda A Wietecha, Shufang Wang, Andrew S Buchanan, Douglas K Kelsey
      - *Journal of Child and Adolescent Psychopharmacology 2014, 24 (8): 426-34*
      - **OBJECTIVE:** This meta-analysis examined suicide-related events in the acute phases of double-blind, placebo-controlled atomoxetine trials in pediatric and adult patients with attention-deficit/hyperactivity disorder (ADHD).
      - **METHODS:** A total of 3883 pediatric and 3365 adult patients were included. Potential events were identified from the adverse events database using a text-string search. Mantel-Haenszel risk ratios (MHRR) were calculated for potential suicide-related events categorized according to United States Food and Drug Administration defined codes.
      - **RESULTS:** In this data set, no completed suicides were reported in the pediatric or adult populations. One pediatric (attempted suicide) (and no adult patient events) was categorized as suicidal behavior in the atomoxetine group. The frequency of combined suicidal behavior or ideation with atomoxetine treatment was 0.37% in pediatric patients (vs. 0.07% with placebo) and 0.11% in adults (vs. 0.12% with placebo) and the risk compared with placebo was not statistically significant (MHRR=1.57; p=0.42 and MHRR=0.96; p=0.96, respectively). In pediatric patients, suicidal ideation only was reported more frequently compared with placebo (MHRR=1.63; p=0.41).
      - **CONCLUSIONS:** Overall in this data set, no completed suicides and 1 pediatric patient suicidal behavior event were reported in atomoxetine-treated pediatric and adult patients. Suicidal ideation was uncommon among atomoxetine-treated pediatric and adult patients, although it was reported more frequently in atomoxetine-treated pediatric patients compared with placebo; the reporting rate difference was not statistically significant. The MHRR of suicidal ideation was consistent with a previous meta-analysis of similar design. There was no evidence of increased risk for suicidal behavior in atomoxetine-treated pediatric or adult patients.
    - **Suicidal ideation:**
      - **0.37% (5/1357) youths on Strattera versus 0% (0/851) youths on placebo (presence or absence of plan or intent not clear).**
      - **Note: the incidence of suicidal thoughts in depressed children on placebo is 2%.**
    - **Self-harm:**
      - **1 of the 5 youths with suicidal thoughts exhibited self-harm.**
      - **There were no incidents requiring medical attention and no completed suicides.**
- **Cardiovascular**
  - **Data from 5 industry-sponsored controlled trials of Strattera in ADHD (involving 342 children and adolescents and 270 adults) showed mild, reversible, clinically insignificant increases in blood pressure and heart rate; no cardiovascular adverse events or arrhythmias were noted.**
  - **Reports of QTc prolongation**
  - **Reports of arrhytmias, fainting, cardiac arrest, myocardial infarction, and stroke in youth and adult patients—not clear if connected to Strattera—being further evaluated by the FDA.**
  - **Reports of sudden deaths in 3 children and 4 adults between 1992 and 2004—being further evaluated by the FDA.**
- **Liver**
  - **Strattera was recently reported to be associated with liver damage in one 14 yo and one 31 yo client; in both cases it was reversible upon discontinuation of Strattera. This is out of an estimated 2 million patients on Strattera.**
  - **There were no reports of liver damage in the 6000 people studied in clinical trials.**
  - **Signs of liver damage include but are not limited to nausea, vomiting, abdominal pain or swelling, tiredness/fatigue, yellow discoloration of skin, and poor concentration**
  - **if you experience any of these signs or symptoms, or any other new or unexplained sign or symptom, please contact me immediately.**
- Seizure risk
  - Wernicke et al, 2007 (funded by Lilly): one seizure occurred among over 1600 young patients (0.06%) in clinical trials and 12 seizures occurred among the more than 5000 patients in the Lilly database (0.2%); in 69% of the seizures, definite or possible confounding factors (e.g., history of seizures, concomitant medications) that contributed to the seizure; in 2% of the events, there was no identified contributing factor other than Strattera
  - Clinical studies: 2/1000 (same as placebo), but see above
  - Post-marketing: 8.2/100,000; no risk in 34,727 pediatric patients with ADHD over one year of use

- Should not be given to clients with narrow angle glaucoma; should be used with caution if given with albuterol (heart rate and blood pressure may increase too much).
- Case report of seizures and EKG abnormalies consequent to overdose in an adolescent (AJP, April, 2004).

Effect of Atomoxetine Treatment on Reading and Phonological Skills in Children with Dyslexia or Attention-Deficit/Hyperactivity Disorder and Comorbid Dyslexia in a Randomized, Placebo-Controlled Trial

Sally Shaywitz, Bennett Shaywitz, Linda Wietecha, Sharon Wigal, Keith McBurnett, David Williams, William G Kronenberger, Stephen R Hooper

Journal of Child and Adolescent Psychopharmacology 2016 July 13

OBJECTIVES: Evaluated the effects of atomoxetine on the reading abilities of children with dyslexia only or attention-deficit/hyperactivity disorder (ADHD) and comorbid dyslexia.

METHODS: Children aged 10-16 years (N=209) met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria for dyslexia only (n=58), ADHD and comorbid dyslexia (n=124), or ADHD only (n=27) and were of normal intelligence. Patients were treated with atomoxetine (1.0-1.4mg/kg/day) or placebo in a 16-week, randomized, placebo-controlled, double-blind trial. The dyslexia-only and ADHD and comorbid dyslexia groups were randomized 1:1; the ADHD-only group received atomoxetine in a blinded manner. Reading abilities were measured with the Woodcock Johnson III (WJIII), Comprehensive Test of Phonological Processing (CTOPP), Gray Oral Reading Tests-4, and Test of Word Reading Efficiency.

RESULTS: Atomoxetine-treated dyslexia-only patients compared with placebo patients had significantly greater improvement ($p<0.02$) with moderate to approaching high effect sizes (ES) on WJIII Word Attack (ES=0.72), Basic Reading Skills (ES=0.48), and Reading Vocabulary (ES=0.73). In the atomoxetine-treated ADHD and comorbid dyslexia group, improvement on the CTOPP Elision measure (ES=0.50) was significantly greater compared with placebo ($p<0.02$). Total, inattentive, and hyperactive/impulsive ADHD symptom reductions were significant in the atomoxetine-treated ADHD and comorbid dyslexia group compared with placebo, and from baseline in the ADHD-only group ($p\leq0.02$). ADHD symptom improvements in the ADHD and comorbid dyslexia group were not correlated with improvements in reading.

CONCLUSIONS: Atomoxetine treatment improved reading scores in patients with dyslexia only and ADHD and comorbid dyslexia. Improvements for patients with dyslexia only were in critical components of reading, including decoding and reading vocabulary. For patients with ADHD and comorbid dyslexia, improvements in reading scores were distinct from improvement in ADHD inattention symptoms alone. These data represent the first report of improvements in reading measures following pharmacotherapy treatment in patients with dyslexia only evaluated in a randomized, double-blind trial.

Effects of Atomoxetine in Individuals with Attention-Deficit/Hyperactivity Disorder and Low-Functioning Autism Spectrum Disorder

Ayse Kilincaslan, Tuba Duzman Mutluer, Basak Pasabeyoglu, Mustafa Deniz Tutkunkardas, Nahit Motavalli Mukaddes

Journal of Child and Adolescent Psychopharmacology 2016 May 26

OBJECTIVES: This naturalistic, retrospective study investigated the effects of atomoxetine (ATX) on attention-deficit/hyperactivity disorder (ADHD) symptoms and autistic features in children with autism spectrum disorders (ASDs) and intellectual disability (ID).

METHODS: Participants (n=37, age range 6-17 years, mean: 10.16±3.60) were assessed at baseline, 4th and 12th weeks using Clinical Global Impressions (CGI) scales, DSM-IV-based ADHD-rating scale (ADHD-RS), and amended Turkish version of Aberrant Behavior Checklist (ABC). The primary outcome measure was a treatment response defined by a CGI-improvement score of 1 or 2 together with a decrease of at least 25% in the parent-rated ADHD-RS total score at the end of 12th week.

RESULTS: Five patients (13.5%) stopped medication at 4 weeks due to ineffectivity (2) and intolerable side effects (increased motor activity and talkativeness [n=1], irritability [n=2], temper outbursts [n=2], and increased blood pressure [n=1]). Sixteen patients (43.2%) were judged to be responders according to primary outcome measure. Improvement rate on CGI scale was 48.8%. On ADHD-RS, there were significant reductions between baseline and 4th week and between baseline and 12th week in both hyperactivity and inattention, and between baseline and 12th week in impulsivity scores. Decrease was significant in hyperactivity and social withdrawal subscales of the parent-reported ABC. Responders based on primary outcome measure were not significantly different from nonresponders in terms of sociodemographic features or clinical parameters, including intellectual, language, autism symptom, and ADHD symptom levels.

CONCLUSION: In this chart review, ATX appears to be safe and effective for social withdrawal and ADHD symptoms in children with ASD and ID.

Efficacy and Safety Extrapolation Analyses for Atomoxetine in Young Children with Attention-Deficit/Hyperactivity Disorder

Himanshu Upadhyaya, Christopher Kratochvil, Jaswinder Ghuman, Angelo Camporeale, Sarah Lipsius, Deborah D'Souza, Yoko Tanaka

Journal of Child and Adolescent Psychopharmacology 2015, 25 (10): 799-809

OBJECTIVES: This extrapolation analysis qualitatively compared the efficacy and safety profile of atomoxetine from Lilly clinical trial data in 6-7-year-old patients with attention-deficit/hyperactivity disorder (ADHD) with that of published literature in 4-5-year-old patients with ADHD (two open-label [4-5-year-old patients] and one placebo-controlled study [5-year-old patients]).

METHODS: The main efficacy analyses included placebo-controlled Lilly data and the placebo-controlled external study (5-year-old patients) data. The primary efficacy variables used in these studies were the ADHD Rating Scale-IV Parent Version, Investigator Administered (ADHD-RS-IV-Parent:Inv) total score, or the Swanson, Nolan and Pelham (SNAP-IV) scale score. Safety analyses included treatment-emergent adverse events (TEAEs) and vital signs. Descriptive statistics (means, percentages) are presented.

RESULTS: Acute atomoxetine treatment improved core ADHD symptoms in both 6-7-year-old patients (n=565) and 5-year-old patients (n=37) (treatment effect: -10.16 and -7.42). In an analysis of placebo-controlled groups, the mean duration of exposure to atomoxetine was ~ 7 weeks for 6-7-year-old patients and 9 weeks for 5-year-old patients. Decreased appetite was the most common TEAE in atomoxetine-treated patients. The TEAEs observed at a higher rate in 5-year-old versus 6-7-year-old patients were irritability (36.8% vs. 3.6%) and other mood-related events (6.9% each vs. <3.0%). Blood pressure and pulse increased in both 4-5-year-old patients and 6-7-year-old patients, whereas a weight increase was seen only in the 6-7-year-old patients.

CONCLUSIONS: Although limited by the small sample size of the external studies, these analyses suggest that in 5-year-old patients with ADHD, atomoxetine may improve ADHD symptoms, but possibly to a lesser extent than in older children, with some adverse events occurring at a higher rate in 5-year-old patients.

Atomoxetine in autism spectrum disorder: no effects on social functioning; some beneficial effects on stereotyped behaviors, inappropriate speech, and fear of change

Myriam Harfterkamp, Jan K Buitelaar, Ruud B Minderaa, Gigi van de Loo-Neus, Rutger-Jan van der Gaag, Pieter J Hoekstra

Journal of Child and Adolescent Psychopharmacology 2014, 24 (9): 481-5

UNLABELLED: Abstract Objective: The objective of this study was to investigate the short-term treatment effects of atomoxetine on autism spectrum disorder (ASD) symptoms in children and adolescents with both ASD and attention-deficit/hyperactivity disorder (ADHD).

METHODS: A total of 97 patients 6-17 years of age, with ASD and ADHD, were treated with 1.2mg/kg/day of atomoxetine during an 8 week double-blind placebo-controlled period. Here, we investigated effects on two parent-based secondary outcome measures, the Aberrant Behavior Checklist (ABC) and the Children's Social Behavior Questionnaire (CSBQ).

RESULTS: After 8 weeks of double-blind treatment, atomoxetine administration was associated with significant treatment effects on the ABC subscales Hyperactivity, Inappropriate Speech, and Stereotypic Behavior, and on the CSBQ subscale Fear for Changes.
CONCLUSIONS: Our study results indicate no beneficial effects of atomoxetine on social functioning. However, atomoxetine may ameliorate restricted and stereotyped behaviors and communication. This study has been registered in ClinicalTrials.gov (www.clinicaltrials.gov) under registration number NCT00380692.

Effect of Atomoxetine Treatment on Reading and Phonological Skills in Children with Dyslexia or Attention-Deficit/Hyperactivity Disorder and Comorbid Dyslexia in a Randomized, Placebo-Controlled Trial

Sally Shaywitz, Bennett Shaywitz, Linda Wietecha, Sharon Wigal, Keith McBurnett, David Williams, William G Kronenberger, Stephen R Hooper

Journal of Child and Adolescent Psychopharmacology 2016 July 13

OBJECTIVES: Evaluated the effects of atomoxetine on the reading abilities of children with dyslexia only or attention-deficit/hyperactivity disorder (ADHD) and comorbid dyslexia.
METHODS: Children aged 10-16 years (N=209) met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria for dyslexia only (n=58), ADHD and comorbid dyslexia (n=124), or ADHD only (n=27) and were of normal intelligence. Patients were treated with atomoxetine (1.0-1.4mg/kg/day) or placebo in a 16-week, randomized, placebo-controlled, double-blind trial. The dyslexia-only and ADHD and comorbid dyslexia groups were randomized 1:1; the ADHD-only group received atomoxetine in a blinded manner. Reading abilities were measured with the Woodcock Johnson III (WJIII), Comprehensive Test of Phonological Processing (CTOPP), Gray Oral Reading Tests-4, and Test of Word Reading Efficiency.
RESULTS: Atomoxetine-treated dyslexia-only patients compared with placebo patients had significantly greater improvement ($p<0.02$) with moderate to approaching high effect sizes (ES) on WJIII Word Attack (ES=0.72), Basic Reading Skills (ES=0.48), and Reading Vocabulary (ES=0.73). In the atomoxetine-treated ADHD and comorbid dyslexia group, improvement on the CTOPP Elision measure (ES=0.50) was significantly greater compared with placebo ($p<0.02$). Total, inattentive, and hyperactive/impulsive ADHD symptom reductions were significant in the atomoxetine-treated ADHD and comorbid dyslexia group compared with placebo, and from baseline in the ADHD-only group ($p\leq0.02$). ADHD symptom improvements in the ADHD and comorbid dyslexia group were not correlated with improvements in reading.
CONCLUSIONS: Atomoxetine treatment improved reading scores in patients with dyslexia only and ADHD and comorbid dyslexia. Improvements for patients with dyslexia only were in critical components of reading, including decoding and reading vocabulary. For patients with ADHD and comorbid dyslexia, improvements in reading scores were distinct from improvement in ADHD inattention symptoms alone. These data represent the first report of improvements in reading measures following pharmacotherapy treatment in patients with dyslexia only evaluated in a randomized, double-blind trial.

Atomoxetine-Related Change in Sluggish Cognitive Tempo Is Partially Independent of Change in Attention-Deficit/Hyperactivity Disorder Inattentive Symptoms

Keith McBurnett, David Clemow, David Williams, Miguel Villodas, Linda Wietecha, Russell Barkley

Journal of Child and Adolescent Psychopharmacology 2016 November 15

OBJECTIVES: To evaluate effects of atomoxetine versus placebo on sluggish cognitive tempo (SCT) and determine factors affecting improvement of SCT in children with attention-deficit/hyperactivity disorder (ADHD) with dyslexia (ADHD+D) or dyslexia only.
METHODS: This is a post hoc analysis of a 16-week placebo-controlled, double-blind randomized phase of a previously reported atomoxetine study in children aged 10-16 years with ADHD+D, Dyslexia-only, or ADHD-only (no placebo arm). Least squares mean changes from baseline to endpoint for atomoxetine versus placebo on the Kiddie-Sluggish Cognitive Tempo Interview (K-SCT) (Parent, Teacher, and Youth) were analyzed using analysis of covariance and multiple regression (partial R(2)) analyses to test contributions of ADHD and dyslexia to improvements in K-SCT scores.
RESULTS: Results were examined for the three informants within the three diagnostic groups (nine outcomes). Atomoxetine treatment was associated with significant reductions from baseline in seven of the nine outcomes using the $p=0.05$ significance level, appropriate for exploratory analysis. When change in ADHD symptom severity was controlled, all of the seven SCT outcomes remained significant; changes in effect sizes were minimal. Regression analyses using SCT change as the criterion found a significant contribution by inattention change only for parent report, whereas, baseline SCT severity was a significant predictor in the randomized groups with the exception of teacher report in the Dyslexia-only group.
CONCLUSION: Given that controlling for change in ADHD symptoms had little effect on change in SCT scores, findings suggest that change in SCT is substantially independent of change in ADHD. By inference, SCT and its response to treatment is a partially distinct phenomenon from ADHD response. Regression analyses did not reveal global effects of inattention change on SCT change; instead, baseline SCT severity was the strongest predictor of placebo-controlled treatment effect on SCT. Atomoxetine effects on SCT appear to be best predicted by how much room for improvement exists for SCT rather than by severity or improvement in inattention.

Adverse Events of Atomoxetine in a Double-Blind Placebo-Controlled Study in Children with Autism

Rameshwari V Tumuluru, Patricia Corbett-Dick, Michael G Aman, Tristram Smith, L Eugene Arnold, Xueliang Pan, Kristin A Buchan-Page, Nicole V Brown, Melissa M Ryan, Susan L Hyman, Jessica Hellings, Craig Williams, Jill A Hollway, Luc Lecavalier, Robert R Rice, Sarah McAuliffe-Bellin, Benjamin L Handen

Journal of Child and Adolescent Psychopharmacology 2017 May 16

OBJECTIVE: Attention-deficit/hyperactivity disorder (ADHD) symptoms, including inattention and over activity, occur in approximately one-third of children with autism spectrum disorder (ASD). We describe the rate and duration of adverse events in a randomized controlled trial of atomoxetine (ATX) and parent training (PT) for ADHD symptoms and noncompliance in children with ASD.
METHODS: We conducted a 10-week, double-blind, 2×2 trial of ATX and PT with 128 children (ages 5-14) randomized to ATX alone, ATX+PT, placebo+PT, or placebo alone. For 6 weeks, ATX (or placebo) doses were clinically adjusted to a maximum of 1.8mg/(kg·day) and maintained for an additional 4 weeks. An average of seven PT sessions were conducted in the two PT arms. Adverse events (AEs) were assessed through parent ratings of common symptoms on a seven-point Likert severity scale and through direct interviews with study medical staff.
RESULTS: ATX was associated with decreased appetite and fatigue, but was otherwise well tolerated. Most reported AEs lasted 4 weeks or less. Unlike reports with typically developing (TD) children, there were no concerns with QTc changes or suicidal ideation.
CONCLUSIONS: This study extends the findings of previous studies of ATX in ASD by documenting that the type of AEs was similar to that of TD children, with no significant safety concerns.