Atomoxetine is a second-line medication treatment option for ADHD

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WHAT IS ALREADY KNOWN ON THIS TOPIC?

Atomoxetine is a non-stimulant that has no abusive potential and a presynaptic inhibitor of the norepinephrine transporter, and has been found to be a safe and effective treatment for attention deficit/hyperactivity disorder (ADHD) in children, adolescents and adults.[1]

WHAT THIS PAPER ADDS?

- This is the largest meta-analysis of randomised controlled trials of atomoxetine for ADHD.
- The effect size for atomoxetine versus placebo was higher for medication-naïve youth while factors such as demographic factors, mean dose, etc, did not moderate the treatment response.

LIMITATIONS

- Even though atomoxetine improved both inattentive and hyperactive symptoms, response was lower than for stimulants and 40% of participants taking atomoxetine had significant residual ADHD symptoms. Compared with placebo, a higher proportion of those taking atomoxetine had at least one adverse effect, experienced more weight loss and discontinued study participation.
- Important treatment response moderators were not examined. For instance, it has been shown that presence of no or one comorbid disorder predicted a large treatment response while presence of three or more comorbid disorders predicted poor treatment response to methylphenidate.[2] Similarly, comorbid anxiety disorder moderated treatment response across treatment conditions.[3]
- Translation to clinical practice is limited, as the participants received short-term atomoxetine treatment under controlled conditions.
- No statistical correction was made to avoid false-positive or type I error, which may result from multiple comparisons conducted.

WHAT IS NEXT IN RESEARCH?

To be useful clinically, future investigations should: (1) study atomoxetine outcomes in stimulant non-responders, (2) identify responder and non-responder characteristics, (3) compare stimulant and atomoxetine treatment response and (4) study longer term atomoxetine effectiveness and tolerability under naturalistic conditions.

DO THESE RESULTS CHANGE YOUR PRACTICES AND WHY?

No, although not all children and families respond to, tolerate or prefer first-line ADHD stimulant medications, we would emphasise caution in the use of alternative treatment options, such as atomoxetine, until further research. Contrary to everyday clinical practice and professional guidelines, approximately half of the children in this meta-analysis were prescribed atomoxetine as first-line medication. More research is needed to understand factors that may affect the treatment efficacy in ADHD medication-naïve and experienced patients.

Competing interests None. doi:10.1136/eb-2014-101805

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Commentary on

ABSTRACT FROM: Schwartz S, Correll CU. Efficacy and safety of atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder: results from a comprehensive meta-analysis and metaregression. *J Am Acad Child Adolesc Psychiatry* 2014;53:174–87.

Data sources MEDLINE/PubMed, clinicaltrialresults.com, clinicaltrials.gov, lillytrials.com were searched up to August 2012.

Study types included Double-blind randomised controlled trials (RCTs).

Patients/participants Diagnosed with primary ADHD of any type, <18 years of age and IQ >75. Comorbid oppositional defiant disorder (ODD), conduct disorder (CD), anxiety and/or depression were allowed.

Intervention Atomoxetine monotherapy vs placebo.

OUTCOMES

Included studies Twenty-five RCTs including 3928 participants (2449 atomoxetine and 1479 placebo). Trials lasted for mean 8.6 weeks (range 4–18 weeks), and the average atomoxetine dose was 1.17 mg/kg/day. Mean participant age was 10.3 years, 51.3% were naïve to anti-ADHD medication and 44.6% had comorbid ODD or CD.

ADHD symptoms (parent-rated 18-item ADHD scale (ADHD-RS IV P/I)) Atomoxetine significantly reduced total ADHD symptoms from baseline to study end-point compared with placebo (Hedges' g effect size (ES)=−0.64, 95% CI −0.71 to −0.56). Atomoxetine also had significant effect on subscores for inattention (ES=−0.59, 95% CI −0.51 to 0.67) and hyperactivity/impulsivity (ES=−0.67, 95% CI −0.53 to −0.81). Overall, 44.4% of participants taking atomoxetine improved by ≥40%, vs 21.4% taking placebo, with a number needed to treat (NNT) of 4. In meta-regression analyses, reduction in ADHD symptoms was significantly less in studies including a lower proportion of treatment-naïve participants.

ODD symptoms and quality of life-related outcome Atomoxetine had a small effect on ODD symptoms (ES=−0.33, 95% CI −0.43 to −0.24). Atomoxetine also had a significant effect on quality of life, with the greatest effect on the Psychosocial Summary Score (ES=0.48, 95% CI 0.33 to 0.62).

Safety and tolerability Discontinuation due to adverse effects was significantly higher with atomoxetine (RR=1.89, 95% CI 1.08 to 3.31), though low in both groups (3.0% vs 1.4%). Treatment-emergent adverse effects were significantly higher with atomoxetine (RR=1.27, 95% CI 1.18 to 1.36; 70.4% vs 56.1%; NNH=6). Rates of severe adverse effects were not significantly different between groups. Gastrointestinal and neurological adverse effects, anorexia, and fatigue were significantly more common with atomoxetine, although most effects were mild to moderate and did not lead to discontinuation.