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Does atomoxetine improve inattentiveness in adults with attention-deficit hyperactivity disorder?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review of three composite studies is to determine whether or not atomoxetine improves inattentiveness in adults with attention-deficit hyperactivity disorder (ADHD)?

Study Design: A systematic review of three blinded randomized controlled trials (RCTs) published between 2011 and 2021.

Data Sources: Research was gathered from PubMed and Embase in December 2020-February 2021 for the three RCTs, and supplemental articles were found in September through November 2021 from PubMed. All three RCTs were published in English and found in peer-reviewed journals and were chosen based on their relevance to the topic question.

Outcome Measured: A reduction in inattentiveness while taking atomoxetine vs. placebo. This was measured by the Conners' Adult ADHD Rating Scale Investigator-Rated/Self-Report Screening Version: Inattention Subscale (CAARS-Inv/S:SV IS)[3,5] and Brown Attention-Deficit Disorder Scale (BADDS)[4] for Adults before and after P.O. administration of placebo or atomoxetine. The scales range from 0-27 with lower scores indicating milder symptoms and higher scores suggesting greater severity of inattention.

Results: In all three RCTs, atomoxetine resulted in a significant reduction in inattentiveness compared to placebo evidenced by symptom scales (p value < 0.001 in Durell et al.[3] and Upadhyaya et al.[5], and p value < 0.05 in Brown et al.[4]). Mean changes from baseline inattentiveness scores maintained 4.4 points of difference between atomoxetine and placebo groups in the article by Durell et al.,[3] 2.2 points in Brown et al.[4], and 1.9 points of difference in the RCT by Upadhyaya et al.[5] All p-values were statistically significant and all three RCTs had a moderate treatment effect.

Conclusions: All three reviewed studies show that atomoxetine resulted in significantly reduced inattentiveness in adults with ADHD. The findings suggest atomoxetine is more effective than placebo for improving focus in the mature ADHD brain. Future studies may cover the recommended treatment duration for atomoxetine in adults, the sufficiency of atomoxetine monotherapy for the treatment of ADHD in adults, and long-term side effects of chronic atomoxetine use in people aged ≥ 18 years old.

Key Words: atomoxetine, adults with ADHD, inattention/inattentiveness

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a cognitive affliction that causes difficulty with self-regulation and focus in multiple settings. More than 6 million children in the U.S. have been diagnosed with ADHD, and this does not include disadvantaged people unable to make appointments for evaluation and diagnosis.[1,2] It is the most common neurodevelopmental condition in children[2] and over half of children diagnosed with ADHD have symptoms that persist into adulthood.[3,4] The etiology and pathophysiology of ADHD are not fully understood, but it is proposed that genetic and environmental factors contribute and the neurotransmitter norepinephrine is affected. People with ADHD may be distractible, inattentive, forgetful, hyperactive and impulsive, causing difficulty in academics and employment, alcohol and drug use disorders, and car or work accidents resulting in emergency room visits.[1-5] Per a 2017 NCHS Data Brief, ADHD accounts for roughly 6 million medical visits per year,[2] an amount which does not include adults or visits for ADHD's common comorbidities nor accidents due to ADHD. Commonly comorbid conditions include anxiety disorders, tics, personality disorders, and drug addiction.[1,3] Patients with ADHD may be seen in psychiatric facilities, addiction clinics, primary care offices, emergency departments, and more. Annual costs for ADHD in the U.S. are estimated to be between $38 billion and $72 billion.[1]

Pharmacotherapy is of great importance in the management of ADHD. Treatments for children with ADHD have been thoroughly studied, however the effectiveness of such treatments in adults is not well-known. Stimulants such as amphetamine/dextroamphetamine and methylphenidate are first-line pharmacotherapy for ADHD and are the usual method of treatment for ages > 6 years old. They are effective yet have high addiction potential and unpleasant side effects.[5] Behavioral therapy or educational support are common adjunctive options; they lack side effects but are less effective alone and are usually paired with stimulants. Alternative

medications include alpha 2-agonists guanfacine and clonidine, and the SNRI atomoxetine; these can be used alone or in combination with stimulants. The alpha 2-agonists are more commonly used for children with behavioral problems. Atomoxetine is an FDA-approved non-stimulant ADHD medication that works by selectively inhibiting presynaptic norepinephrine reuptake in the prefrontal cortex. It is vastly more tolerable than stimulants and has no addiction potential. Atomoxetine has been proven to work in pediatric populations,[4] but the extent to which it benefits adults has not been as thoroughly studied. This paper examines the results of three randomized controlled trials (RCTs) that sought to determine the effectiveness of atomoxetine at reducing functional impairment in adults with ADHD.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Does atomoxetine improve inattentiveness in adults with ADHD?"

METHODS

Studies were selected based on reliability, applicability to the patient-oriented outcome in question and having a primary RCT design. All articles needed to be blinded, in English, and published in peer-reviewed journals no earlier than a decade prior to the start of this study's research. Their population, problem and comparison investigated needed to comprise adults meeting DSM-IV-TR criteria for ADHD with inattentiveness symptoms treated with the clinical intervention of either atomoxetine or placebo alone. The outcome of interest was improved executive function, specifically including change in attentiveness after treatment. Chosen studies were found on PubMed and Embase in late 2020 through early 2021 using the following keywords in searches: atomoxetine, adults, ADHD, executive function, and outpatients. All three RCTs were published after 2010 and were in English; Upadhyaya et al.[5] was also published in

Spanish. Any studies only evaluating children or containing the terms "meta-analysis"/ "systematic review" in the title or study design were excluded.

Statistical assays used in the articles included analyses of covariance to calculate the Least Squares mean change from baseline in the CAARS:SV for Durell et al.[3] and Upadhyaya et al.[5], standard deviations, confidence intervals, and mean change from baseline in BADDS scale in Brown et al.[4] P-values were reported. Table 1 depicts each article's participant demographics.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	INT
Durell[3] 2013 (1)	Double blind RCT	445	Adults 18 to 30 years of age	18-30 y/o's who met DSM-IV-TR ADHD criteria w/ CGIADHD-S score ≥4, (+) scores on symptom scales,[a] and functional impairment confirmed by clinical interview	Pts outside of the age range, or who had Symptom Checklist scores that changed by > 25% between Visits 1 & 2, or who carried certain psychiatric diagnoses.[b]	200	40-100 mg atomox-etine PO vs. placebo, x 12 weeks
Brown[4] 2011 (2)	Double blind RCT	501	Adults 18 to 54 years of age	18-54 y/o's who met DSM-IV-TR ADHD criteria w/ CGIADHD-S score ≥4, (+) scores on symptom scales,[c] and resultant functional impairment confirmed by clinical interview	Pts outside the age range, or who had Symptom Checklist scores that changed by > 25% between Visits 1 & 2, non-responders to other ADHD meds, being in a past atomoxetine study, regular use of specific meds or certain psych. diagnoses.[d]	177	25-100 mg atomox-etine PO vs. placebo, x 6 months
Upadhya ya[5] 2013 (3)	Double blind RCT, Withdr awal subtype	524	Adults 18 to 50 years of age	18-50 y/o's who met DSM-IV-TR ADHD criteria w/ CGIADHD-S score ≥4 at Visits 1 & 2, who responded to previous tx w/ atomoxetine, had (+) scores on symptom scales[e] and functional impairment confirmed by clinical interview	Pts outside of the age range, or who were non-responders to atomoxetine in clinical trials, or who met DSM-IV-TR diagnostic criteria for certain psychiatric disorders.[f]	175	40-100 mg atomo-xetine PO vs. placebo, x 25 weeks

[a]CAARS, Adult ADHD Clinician Diagnostic Scale version 1.2. [b]Major depression, panic disorder, PTSD, an eating disorder, substance abuse or dependence, OCD in the past or present, bipolar disorder, or psychosis.[3] [c]Adult ADHD Investigator Symptom Rating Scale. [d]Regular use of antiepileptics for seizures or any psychotropic medication routinely, bipolar disorder or psychosis, and pregnant or breastfeeding women, or people with uncontrolled hypertension.[4] [e]CAARS. [f]Major depression, bipolar disorder, history of psychosis, current panic disorder, current social phobia, or current generalized anxiety disorder, current alcohol consumption, substance abuse or use disorder or substance dependence.[5] Parentheticals with author names denote the study cited.

OUTCOME MEASURED

The outcome in focus was decreased inattentiveness on atomoxetine vs. placebo. This was measured by the Conners' Adult ADHD Rating Scale, Screening Version: Inattention Subscale (CAARS-SV: IS) Self-Report version Upadhyaya et al.[5] and the Investigator-Rated version of the CAARS-SV: IS in Durell et al.,[3] and the "focus" subset of the Brown Attention-Deficit Disorder Scale (BADDS) for Adults in Brown et al.[4] These focus/inattention subscales are completed by the participants and each have 9 symptom questions with answers graded by severity from 0-3 points. Total scores, then, range from 0-27 with lower scores indicating milder symptoms and higher scores suggesting greater severity of inattention. If statistically significant, any change in the difference in points scored for inattention between the atomoxetine and the control group from before and after taking the capsule is evidence that atomoxetine had some effect on inattention that was different from the placebo's effect. Even a score improvement by just 3 points for example could indicate complete eradication of one of the inattention symptoms. The three studies' results show patient-reported consequences of an ADHD treatment which the patients in question experienced in their daily lives and which providers should pay attention to for treatment purposes.

RESULTS

All three studies enrolled adults 18 years and older who met DSM-IV-TR and Adult ADHD Diagnostic criteria for ADHD and evaluated changes in their related symptoms' severity while taking up to 100 mg oral atomoxetine or placebo. The atomoxetine dosage in Brown et al.[4] was 25-100 mg and was 40-100 mg atomoxetine in the articles by Durell et al.[3] and Upadhyaya et al.[5] Outcomes in each of the blinded RCTs were not dichotomous data nor able to be converted to dichotomous form, therefore summary statistics such as "Risk Ratio" and "Number needed to treat/harm" etc. were incalculable.

The study by Durell et al.[3] compared subjects' ADHD symptom scores after taking 40-100 mg atomoxetine or placebo for 12 weeks. Mean score change on the CAARS was the primary efficacy measure and inattention was the primary symptom in question. This study employed a 2 week double blinded "sham placebo lead-in period"[3] wherein all participants were started on placebo unbeknownst to the scientists and participants and then half of the participants were switched to atomoxetine at a time unknown to them nor the investigators. Subjects were randomly assigned to groups in a 1:1 ratio by computer program and were analyzed within these groups. Participants were from the U.S. and were mostly white males with similar education levels, though some females were included; see Table 1. Overall, 220 participants received atomoxetine and 225 received placebo.

Treatment effect was moderate in Durell et al.[3] according to Cohen's *d* score.[8] The participants' average baseline was 21.6 on the CAARS-SV: IS and after intervention the atomoxetine group's score decreased to 14.6, though the placebo's only decreased to 16.8. That is, the atomoxetine groups' inattention symptom scores improved by roughly 7 points on a 0–27-point scale. Mean change from baseline was 4.4 points of difference between groups after 12 weeks, see Table 2; p-value < 0.001. The narrow 95% CI (-3.51-1.19) including zero demonstrates there may be uncertainty regarding treatment effect; however, based on the significant improvement in inattention scores with confidence intervals not crossing zero demonstrated by the other scales in the article with the same treatment effect, it can be deduced this risk is minimal and the results remain clinically meaningful per Durell et al.[3]

Table 2. Comparison of Symptom Score Change between Groups from Baseline to Week 12 Measured on CAARS-Inv-SV: Inattention Subscale (in Durell et al.[3])

Group	Baseline- *Mean (SD)*	Endpoint- *Mean (SD)*	Mean Change from Baseline- *LS Mean ± SE*	P-value
Atomoxetine	21.6 (3.4)	14.6 (6.4)	-7.6 ± 0.5	P < 0.001
Placebo	21.6 (3.6)	16.8 (6.3)	-5.2 ± 0.5	P < 0.001

Treatment-related adverse events, weight and vital signs were monitored at each visit and ECG readings were recorded for patients at the first and last visit in Durell et al.,[3] and any subject who received one or more doses of atomoxetine underwent safety analyses. Discontinuation due to side effects (n = 27) was more common in the atomoxetine group (n = 21, 9.5%) compared to placebo group (n = 6, 2.7%; P = 0.003). Adverse effects included irritability, fatigue, decreased appetite, insomnia, xerostomia, nausea and dyspepsia.[3] Other discontinuations were from loss to follow-up (n = 97) or participant decision (n = 54). Ultimately 52.3% of subjects taking atomoxetine and 57.8% of subjects taking placebo completed the study, and the completion rate disparity between groups was not statistically significant (P = 0.25).[3]

The study by Brown et al.[4] compared subjects' ADHD symptom scores on the BAADS scale after placement on atomoxetine 25-100 mg/day or placebo for 26 weeks. The primary efficacy measure was the AISRS and secondary measure was the BAADS scale; the primary outcome of interest for the review regarded the "focus" component of the BAADS. The patient cohort was from the U.S. and maintained similar demographics such as education level, gender, and age across groups.[4]

In Brown et al.,[4] participants were randomly assigned 1:1 by computer system in a blinded manner to atomoxetine or placebo groups after a washout period from Visit 1-2. Overall, 250 people received atomoxetine and 251 received placebo. A total of 37.6% of patients taking atomoxetine and 44.6% of patients taking the placebo completed the study. Reasons for discontinuation included lack of improvement in the placebo group and treatment-related adverse events from atomoxetine in the intervention group such as xerostomia, nausea, weight loss, anorexia, fatigue, urinary hesitation, sexual dysfunction, and tachycardia. Heart rate increased significantly in the atomoxetine vs. placebo group ($p < 0.001$). There were significantly more

discontinuations due to adverse events in the atomoxetine group (17.2%) compared to placebo (5.6%) ($p < 0.001$).[4]

Treatment effect was moderate and for the BAADS score LS mean difference the 95% confidence interval was -12.67 to -3.25 in Brown et al.[4] The participants' baseline focus score on the BAADS averaged 21.3 and after treatment decreased by 7.49 in the atomoxetine group and 5.33 in the placebo group.[4] Mean change from baseline was 2.2 points of difference between groups, with p-value <0.001 within groups and p-value < 0.002 between groups, see Table 3.

Table 3. Comparison of Symptom Score Change between Groups from Baseline to Week 26 Measured on BAADS Scale's Focus Cluster (in Brown et al.[4])

Groups	Baseline- *Mean* ± *SD*	Endpoint- *Mean* ± *SD*	Mean Change from Baseline- *Mean* ± *SD*	P-value
Atomoxetine	21.27 ± 3.98	13.78 ± 6.71	-7.49 ± 6.84	P < 0.001
Placebo	21.26 ± 4.22	15.92 ± 7.09	-5.33 ± 6.73	P < 0.001

Study period 3b of Upadhyaya et al.'s[5] research was a randomized withdrawal trial which is a type of RCT in which only previous responders to atomoxetine were permitted into the design. This portion compared subjects' ADHD symptom scores after taking up to 80-100 mg atomoxetine or placebo for 25 weeks. The primary efficacy measure was maintenance of response and a secondary measure was the CAARS-Inv/S:SV; the primary outcome of interest regarded the CAARS-SV: IS. Patient demographics were similar across groups as most were white European males, see Table 1.

Atomoxetine responders able to maintain response in trials of 40-100 mg were randomized by undisclosed methods in a 1:1 ratio to atomoxetine or placebo in Upadhyaya et al.[5] The atomoxetine group had 266 participants and a study completion rate of 69.2% while the placebo group had 258 and a completion rate of 64.0%. Reasons for discontinuation in the placebo group were lack of treatment efficacy and failing to meet maintenance criteria. Patients discontinued in the atomoxetine trial due to adverse events (n = 348), and reasons for leaving in both groups included physician or patient decision, loss to follow up, or protocol violations.

Treatment effect size was moderate in Upadhyaya et al.[5] Significantly more patients who received atomoxetine than placebo maintained sufficient treatment response overall (64.3% vs 50.0%, $p < 0.001$) and up to the 25 week endpoint ($p < 0.05$). Lower symptom severity was shown by LS mean in the CAARS-Inv:SV IS scores between atomoxetine and placebo-treated patients ($p < 0.001$). CAARS-S:SV IS is a smaller version and so the ADHD patients' baseline inattention score of 8.6 was still high, and the atomoxetine group's score decreased by 0.7 points while the placebo group's score actually increased by 1.2. Mean change from baseline was 1.9 points of difference between groups (p-value <0.001).[5] See Table 4 below.

Table 4. Comparison of Symptom Score Change between Groups from Start of Withdrawal Period to Week 25 Measured on CAARS-S:SV Inattention subscale (in Upadhyaya et al.[5])

Groups	Baseline- *Mean (SD)*	Endpoint- *Mean (SD)*	Mean Change from Baseline- *LS Mean (SE)*	P-value
Atomoxetine	8.7 (4.6)	7.7 (4.6)	-0.7 (0.4)	P < 0.001
Placebo	8.5 (5.1)	9.3 (6.1)	1.2 (0.4)	P < 0.001

DISCUSSION

Attention-deficit hyperactivity disorder (ADHD) is a condition that affects patients' daily lives and productivity in a detrimental way by disturbing their executive functioning. Executive function includes the brain's ability to maintain attention, concentrate, self-regulate and stay organized.[4,5] Over half of children diagnosed with ADHD have symptoms of impaired executive function that persist into adulthood,[3,4] but treatments for adults have been less thoroughly studied. ADHD has no cure but it is manageable by therapies combined with medications, the primary type of which is stimulants such as methylphenidate and dexamphetamine. These are first-line but have undesirable side effects, supporting the need for alternative pharmacologic agents. One such agent is atomoxetine hydrochloride, a non-stimulant presynaptic selective norepinephrine reuptake inhibitor that is FDA-approved for the treatment of ADHD in people above 6 years old.

Unlike the traditional treatment, atomoxetine has no addiction potential due to its action in the prefrontal cortex as opposed to the nucleus accumbens, so it is preferred for patients at risk for substance abuse.[6] Atomoxetine also treats anxiety disorders, tic disorders, dyslexia, and elimination disorders which may be comorbid.[6] It lowers potential for relapse and also may be useful in treating symptoms of Parkinson's disease and autism spectrum disorders.[5,6] Due to fewer side effects, atomoxetine is reported to promote a greater quality of life.[6] Negative side effects are usually mild and include xerostomia, dizziness, nausea, tachycardia, dyspepsia, fatigue, erectile dysfunction, decreased appetite and weight loss, and urinary hesitation.[3,4] Atomoxetine previously carried a black box warning for increased suicide risk in children, but this has since been debunked.[7]

This review evaluated atomoxetine's effectiveness for decreasing inattention symptoms in adults meeting DSM-IV-TR criteria for ADHD in a primary care setting. This was accomplished through analysis of results from three double-blinded RCTs with moderate effect sizes comparing atomoxetine with placebo treatments in the U.S. and Europe. All three RCTs demonstrated statistically significant improvements in inattention scores through the BAADS or CAARS after several weeks of treatment ($p < 0.001$).[3,4,5] This proved that atomoxetine is more effective than placebo for improving inattention symptoms in adults with ADHD.

Compliance: In Brown et al.[4] compliance was measured at each visit by directly asking the patients and by checking the amount of unused and used drug. Compliance was positive if patients took their prescribed dose ≥70% of the time.[4] It was defined the same way in Upadhyaya et al.,[5] and was measured by maintenance of the patients' initial atomoxetine responses. Compliance was about 82% in both groups in the withdrawal phase by Upadhyaya et al.,[5] a high

number due to the fact that only atomoxetine responders fully compliant with their doses and protocols in previous trials were involved.[5] Compliance was not addressed in Durell et al.[3]

Validity: Sample sizes were adequate. Blinding was achieved and the control and intervention groups were similar at the start in all studies. The randomization allocation was concealed from those enrolling subjects into the trial in Durell et al.[3] and Brown et al.,[4] but it was not so in Upadhyaya et al.[5] This along with the fact that data were analyzed in their assigned groups in Durell et al.[3] but not in Brown et al.[4] or Upadhyaya et al.[5] could impair the validity of the latter two studies. Follow-up was sufficiently long in all three RCTs. At the conclusion of the trials, losses to follow-up were not < 20% in all three articles but a worst-case analysis was performed on all subjects lost to follow-up in each,[3,4,5] decreasing opportunity for bias.

Outliers: Upadhyaya et al.[5] included adults over the age of 30 and up to 50, unlike Durell et al.[3] and Brown et al.[4] It is unclear how this may have affected the results until further studies are completed comparing response to atomoxetine in older vs. younger adults, though previous studies suggest a slightly greater response in young adults to ADHD treatment per Durell et al.[3] It is important to note for treatment purposes that stimulants, though first-line, do not always work for all patients with ADHD. Therefore, more knowledge about atomoxetine use for ADHD is relevant for patient care. Brown et al.[4] excluded patients who had previous nonresponse to stimulant medications, while Durell et al.[3] included such patients; one-third of the participants in Durell et al.[3] had tried stimulants in the past. Upadhyaya et al.[5] only included participants who were previous responders to atomoxetine, which is different from the other two studies.

Limitations: Each study had limitations. Most participants were white in all the studies, which does not accurately represent the overall population of adults with ADHD. Lower completion rate in Durell et al.[3] (~55%) and Brown et al.[4] (~41%) than other related studies reduced the

statistical power of these results. The higher completion rate in Upadhyaya et al.[5] (~67%) can be explained by that study's inclusion of only atomoxetine-responders, whereas not all patients receiving atomoxetine in the other articles were guaranteed to have a clinical response. In addition, the use of a single self-rating scale for patients with ADHD in each of the three studies makes the presence of a self-reporting bias possible. In Upadhyaya et al.,[5] LOCF was only carried forward to visit 18 out of 25, therefore some follow-up data may be missing. Relapse post-atomoxetine might not always be immediate, and therefore some cases of relapse may have been missed in Upadhyaya et al.[5] Furthermore, there was not a washout period between the Double-Blind Maintenance of Response Period and the Randomized Withdrawal Period in the aforementioned study, so patients previously on atomoxetine who were then switched to placebo in the withdrawal period may have had lingering effects of atomoxetine still impacting their symptom scores. This study[5] also did not account for how patients' environmental changes in the trial may have impacted their symptom scores. For example, a patient who previously had improvement in executive function while taking atomoxetine may feel more positively about his or her capacity to overcome symptoms in the withdrawal phase, and thereby may perform better regardless of whether they are receiving atomoxetine or placebo.[5]

Generalizability: In Durell et al.[3] and Brown et al.,[4] the results are generalizable to Caucasian adult patients with ADHD including inattentive-type symptoms, but may not be generalizable to their non-white counterparts. In Upadhyaya et al.,[5] the generalizability is also limited to atomoxetine responders, and in Brown et al.[4] the generalizability is also limited by exclusion of adults who failed previous ADHD medications. Though both the treatment and placebo groups experienced a decrease in problems focusing in Brown et al.,[4] the atomoxetine group experienced a greater decrease that was statistically significant ($p < 0.001$), suggesting

atomoxetine is more effective to improve focus than placebo. Furthermore, Upadhyaya et al.[5] showed that withdrawal of atomoxetine treatment resulted in relapse of inattentiveness symptoms.

CONCLUSION

Each of the three trials[3,4,5] in this review demonstrated statistically significant improvements in inattention symptoms on atomoxetine vs. placebo, making the answer to this paper's clinical question "Does atomoxetine improve inattentiveness in adults with ADHD?" a resounding "yes." Atomoxetine was found to improve quality of life for these adult patients. Future studies are warranted for comparing the results of atomoxetine treatment in adults under vs. over 50 years old, and subsequent studies may be useful for determining the recommended treatment duration of atomoxetine for adults with ADHD, the potential and timeline for relapse in older adults, and long-term side effects of chronic atomoxetine use in people ≥ 18 years old.

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