The efficacy of atomoxetine in treating adult attention deficit hyperactivity disorder (ADHD): A meta-analysis of controlled trials

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ABSTRACT

Atomoxetine, a non-stimulant, is FDA approved drug used in the management of adult ADHD. Since the presentation of adult ADHD is different from the childhood onset condition, there is an urgent need to study the efficacy of atomoxetine on the different symptom domains of adult ADHD. To study the efficacy of atomoxetine in treating adult ADHD compared to placebo, we performed a Medline search for English language publications of Randomized Controlled Trials (RCTs) comparing atomoxetine to placebo for adult ADHD using the keywords “adult ADHD”, ”atomoxetine” and “placebo”. A total of 41 RCTs were returned of which we included 13 relevant RCTs reporting data on 1824 patients with adult ADHD in the analysis. Standardized mean difference between atomoxetine and placebo for the mean baseline-to-endpoint change in total ADHD scores, impulsivity/hyperactivity and inattention scores was calculated, with a 95% confidence limit. Atomoxetine had superior efficacy than placebo on overall adult ADHD scores [-0.45; 95% CI -0.54, -0.35; overall effect p < 0.00001]. Atomoxetine was superior to placebo on the domains of both inattention [-0.42; 95% CI -0.49, -0.35; overall effect p < 0.00001] and impulsivity/hyperactivity [-0.36; 95% CI -0.44, -0.29; overall effect p < 0.00001]. Atomoxetine was significantly more efficacious (p < 0.00001) in treating inattention than hyperactivity/impulsivity. Atomoxetine is efficacious in treating adult ADHD compared to placebo, though the efficacy is significantly superior for inattention than hyperactivity/impulsivity.

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a disorder that is frequently diagnosed in childhood and is characterized by hyperactivity, inattention and impulsivity (DSM-5 American Psychiatric Association, 2013). Prevalence estimates of adult ADHD reported in the World Health Organization (WHO) World Mental Health Survey Initiative averaged 3.4% (range 1.2–7.3%), with lower prevalence in lower income countries (1.9%) compared with higher-income countries (4.2%) (Fayad et al., 2007).

There is evidence to suggest that there is persistence of ADHD symptoms from childhood into adulthood with a wide variation ranging from 8% to 30%. Such discrepancy is likely to be due to variation in definitions of remission. Co-morbid disorders from childhood tend to persist and new co-morbidities develop with increasing age in these individuals, including anxiety and mood disorders and substance use disorders (Biederman, 2004). This has been acknowledged in DSM V, wherein 5 out of 9 symptoms from the inattention and hyperactivity domains are required to make a diagnosis of ADHD in individuals 17 years or older (DSM-5 American Psychiatric Association, 2013).

ADHD is reportedly under diagnosed in the adult population owing to its subtle presentation including poor time management, difficulties in relationships, poor motor vehicle driving skills, psychiatric co-morbidities including substance abuse disorders and is frequently undertreated (Upadhyaya et al., 2013). Further, impulsivity and inattention are more prominent in adult ADHD than hyperactivity. This is significant as reportedly while other symptoms decrease with age, inattention tends to persist, with a self-reported increase in inattention (Bramham et al., 2012). Impulsivity has been shown to be associated with more emotional distress, interpersonal problems and disruptive behavior while inattention is associated with deficits in focus-oriented constructs (McKinney et al., 2013).

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Aberrations in functional brain connectivity of the frontal cortex with the amygdala-occipital and temporal-occipital networks (Cocchi et al., 2012) are reported to underlie the inattentive and hyperactivity/impulsivity symptom dimensions of adult ADHD. Further, deficits in cognitive functioning in the domains of working memory, particularly spatial working memory (Alderson et al., 2013) and executive functions affecting inhibition response and capacity for planning (Rodriguez-Jiménez et al., 2006) are being increasingly documented and could underlie the inattention domain of ADHD symptoms. Hence there is an urgent need to identify pharmacological treatments that not only effectively treat ADHD persisting into adulthood but is also effective against the different symptom domains of adult ADHD.

While stimulants have traditionally been employed to treat ADHD, atomoxetine, a non-stimulant, has been received considerable attention in the treatment of adult ADHD for over a decade now. Atomoxetine is a norepinephrine reuptake inhibitor that has shown efficacy in trials on adult ADHD compared to placebo. Atomoxetine has been shown to improve total ADHD symptom scores (Simpson and Posker, 2004), executive function (Ni et al., 2013), driving performance (Sobanski et al., 2013), outcomes in patients with alcohol use disorders (Benegal et al., 2013), co-morbid social anxiety disorder (Adler et al., 2009b), quality of life (Agarwal et al., 2012) and also functional outcomes in patients with adult ADHD (Durell et al., 2013). However, variability in study designs and the populations studied makes it difficult to generalize the findings of these studies.

Given the paucity of data and the variable nature of evidence, the objective of this paper was to conduct a meta-analysis of the available evidence to examine the efficacy of atomoxetine in treating adult ADHD and the symptom domains of adult ADHD compared to placebo.

2. Methods

2.1. Data source and search methods

We conducted a MEDLINE search for English-language publications of randomized controlled trials that compared oral atomoxetine to placebo in the treatment of adult ADHD until September 30, 2015. The search terms used were ‘adult attention deficit hyperactivity disorder’, ‘Adult ADHD’, ‘Atomoxetine’, ‘treatment of adult ADHD’, and ‘Pharmacological treatment of adult ADHD’. We obtained additional references from the bibliography of published studies and review articles.

We included in our analysis randomized, double-blind, placebo-controlled clinical trials that have assessed the efficacy of atomoxetine in the treatment of adult ADHD. All studies have measured response to treatment on the CAARS-INV (Conners’ Adult Attention Rating Scale – INV; Investigator rated) on the domains of inattention and hyperactivity/impulsivity and total ADHD scores in adults with ADHD as primary outcome. We also included those studies which included co-morbidities like alcohol dependence, social anxiety etc. We excluded those trials where atomoxetine was not compared to placebo and those without investigator rated adult ADHD scores, as the assessments would be subjective. We did not access conference proceedings.

The criteria for inclusion in the meta-analysis were:

1. English language publications of randomized controlled trials
2. Atomoxetine compared to placebo
3. Primary outcome measures were rated on investigator-rated scales of adult ADHD.

2.2. Data analysis

We employed a random effects model to analyse the data as it incorporates both within-study and between-study variance into the estimate of average treatment effects in studies with different methodologies.

Our primary efficacy measure was the mean change in total ADHD symptoms score and secondary measure was the mean change in hyperactivity/impulsivity and inattention sub-scores from baseline to the endpoint (10–24 weeks) as defined in each of the included studies. The Standardised Mean Difference (SMD) was calculated with 95% confidence interval. We first analysed the efficacy of atomoxetine versus placebo on total ADHD scores as the primary outcome measure. We then conducted a secondary analysis comparing the efficacy of atomoxetine to placebo on hyperactivity/impulsivity and inattention sub-scores independently and the efficacy of atomoxetine for inattention versus hyperactivity/impulsivity.

We conducted our analysis using the software Review Manager 5.2 (Cochrane collaboration, 2012), which is available for free download and use from the Cochrane website http://ims.cochrane.org/revman/download. One study presented their results in the mean ± standard error of the mean (SE) format (Durell et al., 2013). The SE was converted to standard deviation (SD) using the review manager software.

All studies were reviewed and the data included in the analysis was verified independently by two authors (VR and SVC).

3. Results

3.1. Trials included in the analysis

Our initial MEDLINEs search yielded 41 studies of atomoxetine in adult ADHD of which 23 were excluded as they were not relevant to our current analysis. We further excluded studies in which there was no investigator rated ADHD scores (Spencer et al., 1998, 2006; Wilens et al., 2011). We also excluded additional 2 studies (Sutherland et al., 2012) and (Lee et al., 2014). Sutherland et al. study had not mentioned the data separately for the atomoxetine arm and placebo arm which was relevant for our analysis and full text for Lee et al. study could not be obtained. The methodology has been depicted in PRISMA flow diagram below.

13 double-blind placebo-controlled trials were included in our final meta-analysis (Adler et al., 2009a,b; Farone et al., 2005; Wilens et al., 2008; Michelson et al., 2003; Durell et al., 2013; Reimherr et al., 2005; Young et al., 2011; Wietecha et al., 2012; Sobanski et al., 2012; Goto et al., 2013). The data extracted from each study was as follows: author, date, dose of atomoxetine, duration of treatment, number of participants in the atomoxetine and placebo arms, mean change in ADHD total scores and subscores from baseline to treatment endpoint for both atomoxetine and placebo. The details of these studies are provided in Table 1.

3.2. Efficacy

CAARS scores: The Standardized Mean Difference (SMD) of the mean change in total ADHD scores in all trials combined was superior with atomoxetine compared to placebo [−0.45; 95% CI −0.54, −0.35; test for overall effect Z = 9.18; p < 0.000001]. There was significant heterogeneity in the SMD between the studies was noted to be significant when all studies were included [Chi² = 23.29, df = 12 (P = 0.03); I² = 48%]. When the analysis was done without inclusion of an outlier (Sobanski et al., 2012), the heterogeneity was no longer significant [Chi² = 7.47, df = 11 (P = 0.76); I² = 0%]. However, the test for overall effect Z was still
significant even after excluding this study from the analysis \( Z = 12.79, \ p < 0.00001 \).

The results are presented in Fig. 1.

We further analysed the efficacy of atomoxetine on the domains of hyperactivity/impulsivity and inattention. Atomoxetine was superior to placebo on both the domains of inattention \([-0.42; 95\% \ CI \ -0.49, -0.35\); test overall effect \( Z = 11.56; p < 0.00001 \] and impulsivity/hyperactivity \([-0.36; 95\% \ CI \ -0.44, -0.29\); test for overall effect \( Z = 10.10; p < 0.000001 \]. There was no heterogeneity in the SMD between the two groups on the impulsivity/hyperactivity domain \( p = 0.69 \). However heterogeneity was noted between the groups for the domain of inattention \( p = 0.03 \). The results are presented in Figs. 2 and 3.

In order to compare if atomoxetine is equally efficacious on the hyperactivity/impulsivity and the inattention domains, we compared the SMD of atomoxetine in inattention to impulsivity/hyperactivity. Atomoxetine was significantly more efficacious in treating inattention than impulsivity/hyperactivity \([-0.21; 95\% \ CI \ -0.28, -0.14\); test for overall effect \( Z = 5.97; p < 0.00001 \]. The result is presented in Fig. 4.

### 4. Discussion

Given the paucity of data on this difficult to treat condition, our meta analysis helps to highlight the efficacy of atomoxetine on investigator-rated overall ADHD scores and the domains of hyperactivity/impulsivity and inattention.

### Table 1

Characteristics of included randomized placebo-controlled trials of atomoxetine for adult ADHD.

<table>
<thead>
<tr>
<th>SL No.</th>
<th>Study</th>
<th>Dose of Atomoxetine (mg/d)</th>
<th>Duration of the study (weeks)</th>
<th>Atomoxetine group N Mean change in total ADHD score (Std Deviation)</th>
<th>Placebo group N Mean change in total ADHD score (Std Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adler et al. (2009b)</td>
<td>40–100</td>
<td>14</td>
<td>127 ( -8.7 ) ( (10.0) )</td>
<td>137 ( -5.6 ) ( (10.2) )</td>
</tr>
<tr>
<td>2</td>
<td>Adler et al. (2009a)</td>
<td>25–100</td>
<td>24</td>
<td>94 ( -14.1 ) ( (13.3) )</td>
<td>112 ( -10.5 ) ( (12.7) )</td>
</tr>
<tr>
<td>3</td>
<td>Faraone et al. (2005)</td>
<td>60–120</td>
<td>10</td>
<td>133 ( -9.5 ) ( (10.1) )</td>
<td>134 ( -6 ) ( (9.3) )</td>
</tr>
<tr>
<td>4</td>
<td>Faraone et al. (2005)</td>
<td>60–120</td>
<td>10</td>
<td>124 ( -10.5 ) ( (10.9) )</td>
<td>124 ( -6.7 ) ( (9.3) )</td>
</tr>
<tr>
<td>5</td>
<td>Wilens et al. (2008)</td>
<td>25–100</td>
<td>12</td>
<td>72 ( -13.6 ) ( (11.4) )</td>
<td>75 ( -8.3 ) ( (11.4) )</td>
</tr>
<tr>
<td>6</td>
<td>Michelson et al. (2003)</td>
<td>60–120</td>
<td>10</td>
<td>133 ( -9.5 ) ( (10.1) )</td>
<td>134 ( -6 ) ( (9.3) )</td>
</tr>
<tr>
<td>7</td>
<td>Michelson et al. (2003)</td>
<td>60–120</td>
<td>10</td>
<td>129 ( -10.5 ) ( (10.9) )</td>
<td>127 ( -6.7 ) ( (9.3) )</td>
</tr>
<tr>
<td>8</td>
<td>Durell et al. (2013)</td>
<td>40–100</td>
<td>12</td>
<td>192 ( -13.6 ) ( (8.1) )</td>
<td>199 ( -9.3 ) ( (9.1) )</td>
</tr>
<tr>
<td>9</td>
<td>Reimherr et al. (2005)</td>
<td>60–120</td>
<td>10</td>
<td>75 ( -14.3 ) ( (13.5) )</td>
<td>69 ( -7.7 ) ( (9.4) )</td>
</tr>
<tr>
<td>10</td>
<td>Young et al. (2011)</td>
<td>60–100</td>
<td>12</td>
<td>268 ( -14.3 ) ( (11.8) )</td>
<td>234 ( -8.3 ) ( (11.0) )</td>
</tr>
<tr>
<td>11</td>
<td>Witecka et al. (2012)</td>
<td>40–100</td>
<td>24</td>
<td>264 ( -14.3 ) ( (11.8) )</td>
<td>232 ( -8.3 ) ( (11.0) )</td>
</tr>
<tr>
<td>12</td>
<td>Sobanski et al. (2012)</td>
<td>18–80</td>
<td>12</td>
<td>22 ( -13.1 ) ( (7.7) )</td>
<td>21 ( -0.4 ) ( (4.8) )</td>
</tr>
<tr>
<td>13</td>
<td>Goto et al. (2013)</td>
<td>40–120</td>
<td>10</td>
<td>191 ( -14.3 ) ( (10.4) )</td>
<td>195 ( -8.8 ) ( (9.6) )</td>
</tr>
</tbody>
</table>

*Fig. 1. Comparison between atomoxetine and placebo: Total ADHD SCORES.*

CAARS scores: The Standardized Mean Difference (SMD) of the mean change in total ADHD scores in all trials combined was superior with atomoxetine compared to placebo \([-0.45; 95\% CI \ -0.54, -0.35\); test for overall effect \( Z = 9.18; p < 0.00001 \]. There was significant heterogeneity in the SMD between the studies was noted to be significant when all studies were included \( \chi^2 = 23.29, df = 12 \) \( p = 0.03 \); \( I^2 = 48\% \). When the analysis was done without inclusion of an outlier \( [ \text{Sobanski et al., 2012} ] \), the heterogeneity was no longer significant \( \chi^2 = 7.47, df = 11 \) \( p = 0.76 \); \( I^2 = 0\% \). However the test for overall effect \( Z \) was still significant even after excluding this study from the analysis \( Z = 12.79, p < 0.00001 \).
inattention and hyperactivity/impulsivity in comparison to placebo. The results indicate that atomoxetine is far superior to placebo in treating adult ADHD and significantly more efficacious in treating inattention than impulsivity/hyperactivity.

Our study basically reflects that atomoxetine has modest efficacy in treating adult ADHD (Effect size = 0.43). The findings of our analysis are consistent with the findings reported independently in the included studies. Further, the effect size for improvement in domain of inattention is 0.42 and for hyperactivity/impulsivity is 0.36. This effect size is considered to be in “modest” range.
While the first line treatment for ADHD is stimulant drug therapy such as Methylphenidate, it is not widely used because of the abuse potential (Bruggisser et al., 2012). A comparison of 5 head to head trials of atomoxetine versus stimulants in treating ADHD, showed atomoxetine to have equal efficacy as stimulants while both groups of medications were equally well tolerated (Gibson et al., 2006). Another study reported that while both stimulants and atomoxetine improved executive function, atomoxetine was superior to methylphenidate in improving spatial planning (Ni et al., 2013).

A recent study by Bédard et al. (2015) measuring the differential impact of methylphenidate and atomoxetine on sustained attention in youth with ADHD showed methylphenidate to improve means scores on cognitive performance test (CPT) measures of sustained attention better than atomoxetine. However the authors have mentioned in their limitations that the changes in the CPT indices did not correlate with the overall ADHD symptom change suggesting the titration approaches to be used differentially to avoid the dissociation between cognitive and behavioral effects of ADHD medications and obtain optimal benefit (Bédard et al., 2015). Nevertheless, non stimulant medications such as atomoxetine serve as an important option for treatment of this functionally disabling condition.

The efficacy of atomoxetine in treating inattentiveness is an important finding of our analysis. A retrospective chart review reported that in children, atomoxetine was more efficacious in treating overall ADHD than inattention symptoms alone (Ercan et al., 2013), while other studies have shown that long term treatment with atomoxetine improves both inattention and hyperactivity in children with autistic spectrum disorders (Harf- terkamp et al., 2013). Since inattention is one of the most important features of adult ADHD, our finding that atomoxetine is significantly more efficacious in improving inattention vis-a-vis hyperactivity shows that atomoxetine may have differential action on ADHD symptoms in adults compared to children.

A recent fMRI study in adult ADHD has shown that atomoxetine causes increased activation of the dorsolateral prefrontal cortex, parietal cortex, caudate, and cerebellum-brain regions implicated in attention, motor control and the pathophysiology of ADHD (Bush et al., 2013). Further, while the activation patterns were similar with atomoxetine and methylphenidate, unlike methylphenidate, atomoxetine did not activate the dorsal anterior midcingulate region. So while there may be an overlap, there are also considerable differences in the neurobiological actions of these two medications, which could determine their differential efficacy on the symptoms domains of adult ADHD. It has been suggested that atomoxetine could block the norepinephrine transporter in brain areas like locus coeruleus, thalamus, midbrain, cingulate cortex and supplementary motor area, increasing synaptic availability of norepinephrine, which may boost “downstream” signal-to-noise in fronto-parietal and cerebellar regions. This could improve attention, filtering of distracting information, and possibly regulate motor inhibition (Bush et al., 2013) thereby enhancing its efficacy on the inattention domain of adult ADHD.

Strengths of this study include that since the entire RCTs included investigator rated ADHD scores and heterogeneity was accounted for, conclusions drawn regarding the efficacy of atomoxetine being superior to placebo for adult ADHD could be generalizable. There is a well established evidence base for efficacy of atomoxetine for treatment of ADHD in children and adolescents. The data for treatment of adult ADHD is sparse and hence this study was essential to support the use of atomoxetine.

One of the limitations of this meta-analysis is to have included studies with “pure” adult ADHD, without significant co morbidity, which is unlike what is seen in routine clinical practice. And also it does not provide us the comparable efficacy of atomoxetine with other stimulant medications in adult ADHD. Further, only investigator rated CAARS scores was used in the efficacy analysis and improvements on other assessments cannot be commented upon, like for example, executive functions. Most of the studies are industry sponsored studies and would have had overlap of subjects which is also a potential source of bias in our study. Excluding some relevant studies where data was not available to us is also a limitation. Also, we were not able to analyse response rates in these studies as exact numbers of responders were not available and most studies have reported this information as percentage of responders.

Further studies are required to understand the impact of atomoxetine on adult ADHD in individuals with significant psychosocial co-morbidity. Some investigations are being made in this direction with the reports of successful use of atomoxetine for adult ADHD with comorbid alcohol dependence (Benegal et al., 2013), social anxiety (Adler et al., 2009b) and partially responsive generalized anxiety (Gabriel and Violato, 2011), while no benefits were seen in co-morbid marijuana dependence (McKae-Clark et al., 2010). Determinants of response to atomoxetine would also be helpful in understanding which groups of patients with adult ADHD are likely to respond well to treatment.

To conclude, meta-analysis of data from thirteen randomized double blind placebo controlled trials shows that atomoxetine is superior to placebo in adult ADHD and is significantly more efficacious on the domain of inattention than on hyperactivity/ impulsivity.

References


