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REVIEW ARTICLE

# Atomoxetine for Attention Deficit Hyperactivity Disorder in Children and Adolescents with Autism: A Systematic Review and Meta-Analysis

Suravi Patra, Naresh Nebhinani, Anand Viswanathan, and Richard Kirubakaran

Atomoxetine is prescribed to children with autism spectrum disorder having symptoms of attention deficit hyperactivity disorder. We sought to examine the efficacy and safety of atomoxetine in this population. After screening for inclusion criteria, we identified three randomized placebo controlled trials involving 241 children. We assessed internal validity using standard Cochrane Risk of bias tool for randomized controlled trials (RCTs). We used Revman 5.3 for meta-analysis and GRADE approach to create summary of findings with grading of the quality of evidence. Atomoxetine had a benefit on improving parent-rated hyperactivity (standardized mean difference [SMD] = −0.73, 95% Confidence Interval, CI = −1.15 to −0.34) and parent-rated inattention (SMD = −0.53, 95% CI = −0.93 to −0.12) but the magnitude of effects is uncertain. However, atomoxetine was also associated with increased risk of non-serious adverse effects like nausea and vomiting, decreased sleep, and decreased appetite. Atomoxetine may be effective in improving hyperactivity and inattention in children with autism spectrum disorder and attention deficit hyperactivity disorder. However, we are uncertain about the true effect of this intervention and need more RCTs trials designed to evaluate this. ***Autism Research*** *2018.* © 2018 International Society for Autism Research, Wiley Periodicals, Inc.

**Lay Summary:** Atomoxetine is prescribed for Attention Deficit Hyperactivity Disorder (ADHD). About a third of children and adolescents with autism also suffer from ADHD. We carried out an analysis of data reported from a specific kind of medication trials which had examined the effectiveness and side effects of atomoxetine in this patient population. We could find only three such trials and analyzed the reported data. Our analysis revealed that atomoxetine is effective in improving symptoms of ADHD like hyperactivity and inattention and also causes side effects like nausea, vomiting, decreased sleep, and decreased appetite. However, the existing data are insufficient to provide a conclusive statement with certainty and more trials are needed for this.

**Keywords:** autism; pervasive developmental disorder; attention deficit/hyperactivity disorder; meta-analysis; atomoxetine

## Introduction

Autism Spectrum Disorder (ASD) is an early onset neurodevelopmental disorder marked by impaired capacity of socialization, communication, and restricted stereotyped range of behavior. A large number of children with ASD exhibit symptoms of Attention Deficit Hyperactivity Disorder (ADHD). DSM5 has allowed comorbid diagnosis of ADHD with ASD hence changing the existing nosological convention wherein ADHD symptoms were assumed secondary to underlying ASD [American Psychiatric Association, APA; 2013]. ADHD is the third common co-morbidity and is diagnosed in 37–85% of children with ASD [Gadow, DeVincent, & Pomeroy, 2006; Leyfer et al., 2006]. Co-morbid ADHD often results in lower cognitive, adaptive, and social functioning [Rao, 2014; Yerys et al., 2009]. Also, about 20–60% of children with ADHD have social difficulties similar to autism higher than typically developing (TD) children [Grzadzinski, Dick, Lord, & Bishop, 2016]. There still remains confusion regarding ADHD or autism as the cause of these social difficulties. Impulsivity which is a core symptom of ADHD might contribute to inappropriate intrusiveness; however, even after treatment of ADHD social difficulties in getting along with friends and siblings and expressing affection persist [Grzadzinski et al., 2011]. In addition to symptom overlap; ADHD and ASD share biological and neuropsychological risk factors [Taurines et al., 2012]. Causal and mediational analyses have identified multiple pathways between ASD and ADHD with specific targets for interventions [Sokolova et al., 2017].

Children having co-morbid ADHD and ASD are understood as a distinct phenotype needing special intervention strategies [Craig, 2015]. As in TD children, medications are effective in treatment of symptoms of ADHD. Stimulants are among the most commonly prescribed medications;

From the Department of Psychiatry, All India Institute of Medical Sciences, Bhubaneswar, India (S.P., N.N.); Princess Royal Spinal Injuries Centre, Northern General Hospital, Sheffield, S5 7AU, United Kingdom (A.V.); Cochrane South Asia, Christian Medical College, Vellore, India (R.K.)

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Address for correspondence and reprints: Suravi Patra, Department of Psychiatry, All India Institute of Medical Sciences, Bhubaneswar, India. E-mail: patrasuravi@gmail.com

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however, treatment response is lower and is often associated with more adverse effects [Bachmann, Manthey, Kamp-Becker, Glaeske, & Hoffmann, 2013; Kim et al., 2017; RUPP., 2005]. Stimulants can exacerbate stereotypies, tics, self-injury, and anxiety in children with ASD [Aman et al., 2008; Arnold et al., 2006; Gadow et al., 2005].

Atomoxetine, a non-stimulant medication, is considered second-line alternative in managing ADHD in children with ASD. Atomoxetine acts as a highly specific presynaptic noradrenaline reuptake inhibitor in the prefrontal cortex, the region for attention and other higher cognition processes. It increases the availability of dopamine in prefrontal cortex but does not have any direct activity on dopamine. It does not have action on striatum or midbrain hence is free from addictive potential, stereotypies, and tics [Barton, 2005]. It can be used in case of stimulant failure or intolerance and in presence of comorbidities like tic and anxiety disorders because of better tolerability and safety [Kohn, Tsang, & Clarke, 2012]. The long half-life of atomoxetine makes it effective throughout the day with a single daily dose. Standard dose range recommended for atomoxetine is 0.5–1.8 mg/kg/day. Four to six weeks of treatment is needed for optimal of efficacy with atomoxetine [Clemow, 2014].

Stimulants are the second most commonly prescribed medications in children with ASD and ADHD across the world except in the UK. In UK methylphenidate is the most commonly prescribed medication [Hsia et al., 2014]. In a four continent study involving 10 countries, prescription rates of ADHD medications have risen in the United States and European countries like Denmark, Netherlands, and Spain. Initiation of ADHD medication in ADHD with ASD is much earlier than in ADHD children. Of the children and adolescents with ASD, 16% are prescribed with stimulants and atomoxetine [Dalsgaard, Nielsen, & Simonsen, 2013]. In the United States, 56% children with ASD are prescribed with ADHD medications of which stimulants are the third most common medications. With 8% prescription rates, atomoxetine was the second most common medication among ADHD medications [Williams et al., 2012].

The variation in prescription practices is due to inconsistent treatment guidelines, differences in healthcare systems, and inadequate evidence base of psychopharmacological agents. Systematic reviews conducted by rigorous Cochrane methodology are instrumental in shaping treatment guidelines; hence it is imperative to estimate the efficacy and safety of these psychopharmacological agents.

Many clinical trials have demonstrated that atomoxetine is effective and safe in children with ASD [Aman, 2014; Reichow, 2013]. To our knowledge only three randomized controlled trials have been published demonstrating effectiveness and safety of atomoxetine in ASD [Arnold, 2006; Harfterkamp et al., 2012; Handen et al., 2015]. First of these randomized controlled trials (RCTs) was a double-blind placebo controlled cross over trial of 6 weeks involving 16 subjects which failed to show clinically significant benefit with atomoxetine [Arnold, 2006]. In the second trial of 8 weeks duration involving 97 participants, 20.9% participants on atomoxetine improved much or very much on Clinical Global Improvement (CGI-I) scale as compared to 8.7% on placebo [Harfterkamp, 2012]. The third parallel group four arm RCT involving atomoxetine, placebo, and parent training was of 10 weeks duration in which 46.9% of participants on atomoxetine showed 30% improvement in Swanson, Nolan and Pelham (SNAP) scores as compared to 19.4% on placebo. Two trials reported of serious side effects whereas all three trials reported non-serious side effects.

Two reviews have examined usefulness of Atomoxetine in ADHD co-morbid with ASD [Reichow, 2013; Aman, 2014]. These reviews have not reported inattention and hyperactivity/impulsivity as separate outcomes. The magnitude of side effects was also not reported. The reviews were not carried out using Cochrane methodology or Preferred Reporting Items for Systematic reviews and Metaanalysis (PRISMA) guidelines. Risk of bias and quality of trials were also not addressed by these reviews.

To address these flaws, we carried out a systematic review and meta-analysis using Cochrane guidelines for estimation of risk of bias and GRADE approach for evaluation of quality of trials and report on efficacy and safety of atomoxetine in children with ASD.

## Methods

### *Search Strategy for Identification of Studies*

Three reviewers independently searched Pubmed, Cochrane central register of controlled trials, Cochrane library, Embase, and ClinicalTrials.gov upto April 2018. For Pubmed we used the search strategy: "attention deficit disorder with hyperactivity" (Mesh) AND "autistic disorder" (Mesh) AND "atomoxetine hydrochloride" (Mesh). We adapted the search terms and modified according to the different databases. The search terms used for Cochrane library were: "autistic disorder," "attention deficit disorder with hyperactivity," and "atomoxetine hydrochloride." For Embase we used: "attention deficit disorder with hyperactivity," "autism," and "atomoxetine." For ongoing studies, we searched in ClincialTrials.gov with the terms "autism or pervasive developmental disorder" and an intervention filter for "Atomoxetine hydrochloride OR atomoxetine." We also searched the reference lists of included studies, reviews, and meta-analyses for more citations.

### *Study Selection*

We used the following criteria for selecting studies for inclusion in this review.

1. Randomized placebo controlled trials comparing atomoxetine with placebo.
2. Patient population of children and adolescents of ≤18 years age with diagnosis of ASD as per DSM5 or Pervasive Developmental Disorder as per DSMIV or ICD 10.
3. Trials using atomoxetine at standard dose (0.5–1.8 mg/kg/day) and duration 4 weeks.
4. Trials reporting ADHD symptoms as outcome measures.

We did not include trials involving children with epilepsy or traumatic brain injury.

*Outcome Measures*

Primary outcomes were parent-rated symptoms of ADHD (inattention, hyperactivity, or impulsivity) both short-term (≤6 months) and long-term (≥6 months), social behavior, and serious adverse events. Parent-rated symptoms of ADHD were chosen as primary outcome as parent-rating of ADHD symptoms is more sensitive than teacher-rating in children with ASD [RUPP, 2005]. ADHD symptoms rated on standard scales like SNAP, DSM-IV rating scale, and ADHD rating scale were included in the analysis [Swanson, 1983; DuPaul et al., 1998]. Any event of death, life threatening side effects, prolongation of hospital stay, or disability was defined as serious adverse event.

*Secondary outcomes* were clinician and teacher-rated ADHD symptoms; overall improvement of ADHD symptoms rated on standard scales like CGI-I; parent stress; quality of life; and non-serious adverse events. Non-serious adverse events included nausea and vomiting, decreased appetite, and decreased sleep.

*Data Collection and Analysis*

***Selection of studies.*** Two review authors SP and NN independently read the titles and abstracts of the articles for suitability decision as per the inclusion criteria and used PRISMA flowchart to present the selection of studies. SP and NN extracted data from each included study using standard data extraction forms. We resolved disagreements with discussions and in case of any persisting disagreement, AV acted as arbiter.

***Data extraction and management.*** We extracted data on details of study design (methods), participants, intervention, and outcomes. Disagreements were resolved by discussion and in case of any difficulty we took the third reviewer's help. We contacted study authors for missing data. SP entered the data into Review Manager 5.3 after cross verifying the extracted data against the included studies.

We extracted the 2 × 2 table values for dichotomous outcomes like serious adverse events, non-serious adverse events, and CGI scores. For continuous outcomes like hyperactivity and inattention, we extracted mean, standard deviation, and the total number of participants randomized in the group.

***Assessment of risk of bias in included studies.*** SP and NN independently assessed for internal validity of each included study using the Cochrane risk of bias tool for RCT. There were six domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants (performance bias), blinding of outcomes assessor (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias) and other biases. We assigned risk of bias as high, low, or unclear as per the guidelines provided in Cochrane Handbook of systematic reviews [Higgins, 2011]. We contacted the trial authors in case of any discrepancy or lack of clarity in reporting and also held discussions among the reviewers to clarify any disagreements.

We created risk of bias graph to explain each domain individually and summary figure for the overall domains.

***Measures of treatment effect.*** We combined results of studies reporting effect on symptoms of ADHD using random-effects model. We chose this model due to its nature of assuming both within and between-study variations while pooling the data. Continuous data were either pooled by calculating mean difference between groups with 95% CI or SMD along with 95% CI when same outcomes were measured using different tools.

For dichotomous data we calculated Risk Ratio as proportion of patients experiencing events in the treatment group divided by proportion of patients experiencing events in control group.

We analyzed all the homogenous data using Revman5.3 and also calculated the pooled estimates with 95% CI.

***Unit of analysis issues.*** Crossover trials are more prone to bias owing to carry-over effects, period effects, and errors in unit of analysis. Our original intent was to adjust the effect estimates for the unit of analysis error in crossover trials by conducting a paired analysis. Due to insufficient data we contacted the trial authors for the adjusted data or the first period data. However, we did not get any reply from them; therefore we conducted a stratified analysis based on the study design.

*Assessment of heterogeneity*. We examined forest plots for over lapping confidence interval and using the Chi square test for heterogeneity keeping significance at 10% level to detect heterogeneity in studies, and $I^2$ statistic to detect inconsistency in results which exceeded probability due to chance. $I^2$ value of >50% was understood to denote either moderate or substantial heterogeneity.

*Subgroup analysis and investigation of heterogeneity*. As $I^2$ = 0% and chi square < df, we infer that heterogeneity among included trials was low which could be explained by chance. So, we did not carry out a subgroup analysis.

*Sensitivity Analysis*. Since, we have included only two studies for meta-analysis and the direction of effect estimates are in one side in favor of intervention, we did not perform the sensitivity analysis.

*Assessment of publication bias*. We could not do funnel plot for any analysis to assess publication bias as the number of studies was too small.

*Certainty of evidence and summary of findings (SOF) tables*. We have used the GRADEpro software following the guideline stated in the handbook of GRADE assessment for creating SOF table. The quality of evidence has four levels ranging from High, Moderate, Low, to Very Low. There were five domains to be assessed to arrive at the quality of evidence: (a) risk of bias, (b) inconsistency, (c) indirectness, (d) Imprecision, and (e) publication bias. We judged each domain and assigned the Quality of Evidence for each outcome. We have presented only the important and critical outcomes in the SOF tables.

## Results

*Included Studies*

We identified 104 records after electronic database searching and removed duplicates, 93 records were left which we tested for eligibility. Out of these, we excluded 89 because the trials were either not RCTs, or, population, intervention or outcomes were not relevant to our review (Fig. 1). We included three randomized controlled studies [Arnold et al., 2006; Handen et al., 2015 and Harfterkamp et al., 2012]. We contacted Arnold et al. and authors of clinical trials reported in Clinical Trials.gov twice through email but failed to acquire the raw data.

In the three RCTs, total participants were 241 with $n$ = 16 in first trial, $n$ = 97 in second trial and ($n$ = 128) in third trial [Arnold et al., 2006; Handen et al., 2015; Harfterkamp et al., 2012]. Girls and boys in the age range 5–17 years were included in the trials. Two of the trials were carried out in the United States and one in the Netherlands. The trial duration ranged from 6 to 10 weeks. Handen et al. [2015] was a four-group study in which participants were randomized into Atomoxetine, Placebo, Atomoxetine + Parent Training, and Placebo + Parent Training groups. We included the first two groups on atomoxetine ($n$ = 32) and placebo ($n$ = 32). We did not include the groups with Parent Training in our analysis as our aim was to estimate the effect of atomoxetine. Characteristics of included studies are shown in Table 1.

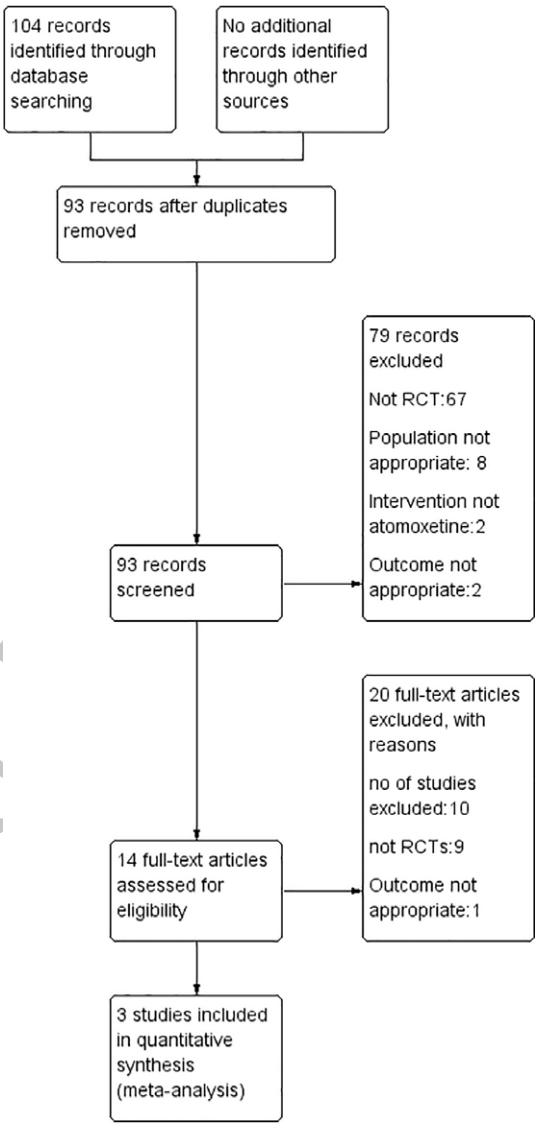


**Figure 1.** Study flow using PRISMA flow diagram.

*Risk of Bias Assessment*

For all the included studies we used adequate method to rule out selection bias, performance bias, attrition bias, and selective outcome reporting bias. However, Arnold et al. had to be judged as high risk of detection bias due to the cross over design of the study and lack of blinding of outcome assessment. Handen et al. was the only study which was federally sponsored but was provided atomoxetine by pharmaceuticals hence was rated having low risk of bias. The other two trials were sponsored by pharmaceuticals manufacturing atomoxetine hence were rated with unclear risk of bias in "other risk of bias" category. Pharmaceutical sponsored trials are known to show higher effect sizes than independent studies and have industry bias that are beyond standard risk assessment tools as recently demonstrated in a Cochrane review [Lundh, 2017]. (Figs. 2 and 3).

**Table 1. Characteristics of Included Studies**

| Study | *N* | Mean age (range) (years) | Gender (%M) | Design | Length of treatment (weeks) | Atomoxetine (mean dose) |
|---|---|---|---|---|---|---|
| Arnold et al. [2006] | 16 | 9.3 (5–15) | 75 | Crossover | 6 | 44.2 mg/day |
| Harfterkamp et al. [2012] | 97 | 10.0 (6–17) | 86 | Parallel | 10 | 1.2 mg/kg/day |
| Handen et al. [2015][a] | 64 | 9.5 (5–14) | 80 | Parallel, four arm | 10 | 1.8 mg/kg/day |

[a]Only two study arms which met inclusion criteria were included in our meta-analysis.

*Symptoms of ADHD*

Only two trials [Arnold et al., 2006; Handen et al., 2015] involving 96 participants provided data on parent rated symptoms of ADHD (inattention and hyperactivity). Results show beneficial effect of atomoxetine as compared to placebo on parent-rated hyperactivity (SMD −0.73, 95% CI = −1.15 to −0.34, low quality evidence (Fig. 4), and parent-rated inattention (SMD −0.53; 95% CI = −0.93 to −0.12, very low-quality evidence (Fig. 5). Based on an accepted rule of thumb for interpretation of effect sizes [Cohen, 1988], SMD of 0.5 and above is generally suggestive of a moderate effect of intervention. There was no statistically significant improvement in parent-rated oppositional behavior or social behavior. There was no statistically significant improvement in clinician-rated and teacher-rated ADHD symptoms. Therefore, we are unclear about the effects of atomoxetine on these outcomes.

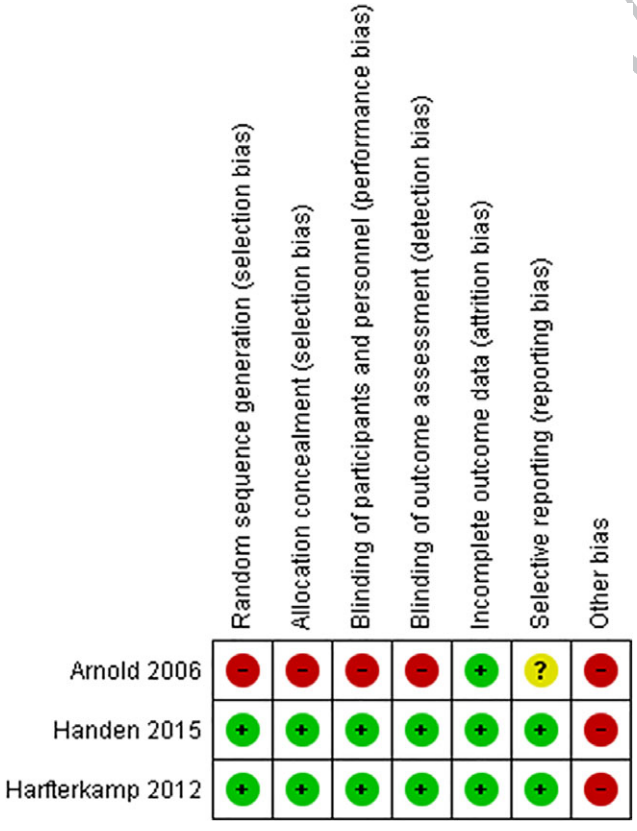


**Figure 2.** Risk of bias summary: Review authors' judgments about each risk of bias item for each included study.

*Long Term Symptoms of ADHD*

Smith et al. carried out 24-week extension of Handen et al. trial; open label prescription of atomoxetine. Complex nature of the trial and absence of any other RCT on long-term efficacy of atomoxetine in ASD with ADHD precluded meta-analysis.

*Serious Adverse Events*

Out of three trials involving 193 participants, one serious adverse event was reported by the cross over RCT [Arnold et al.] and another by parallel group RCT [Handen et al.]. Arnold et al. reported re-hospitalization of one trial participant due to aggressive behavior which they ascribe to lowering of antipsychotic dose. In the RCT carried out by Handen et al. one trial participant needed hospitalization due to seizure caused by suboptimal antiepileptic concentrations. Overall risk of serious adverse events was increased in atomoxetine group (RR 3, 95% CI 0.32 to 27.76, 193 participants low quality evidence); however, the increase is not statistically significant (Fig. 6).

***3.5.1.1.1.. Social behavior.*** Deficits in social communication are the hallmark of ASD. Children with ASD have deficits in social skills and peer interaction. We wished to see if atomoxetine had any effect on social skills. As none of the studies reported on social behavior, no analysis was possible.

*Secondary Outcomes*

***Clinician and teacher-rated symptoms of ADHD.*** Harfterkamp et al. used Clinician-rated symptoms on ADHD RS as the primary outcome variable and Teacher-rated CTRS was the secondary outcome variable. Handen et al. used Parent-rated DSMIV (SNAP) as the primary outcome variable whereas Teacher-rated (SNAP) as the secondary outcome variable. As only Harfterkamp et al. had provided clinician-rated scores, pooling of data was not possible hence meta-analysis could not be done. Harfterkamp et al. had presented data as least square means, hence pooling of data of Handen et al. and Harfterkamp et al. was not possible.

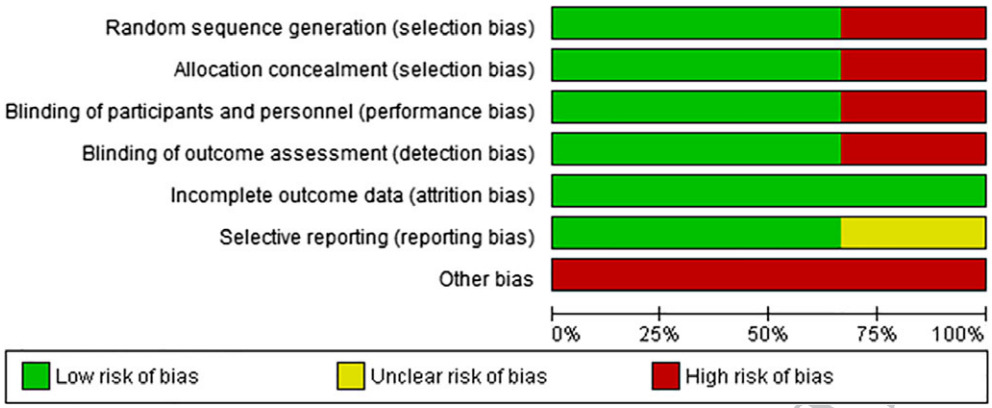


**Figure 3.** Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.

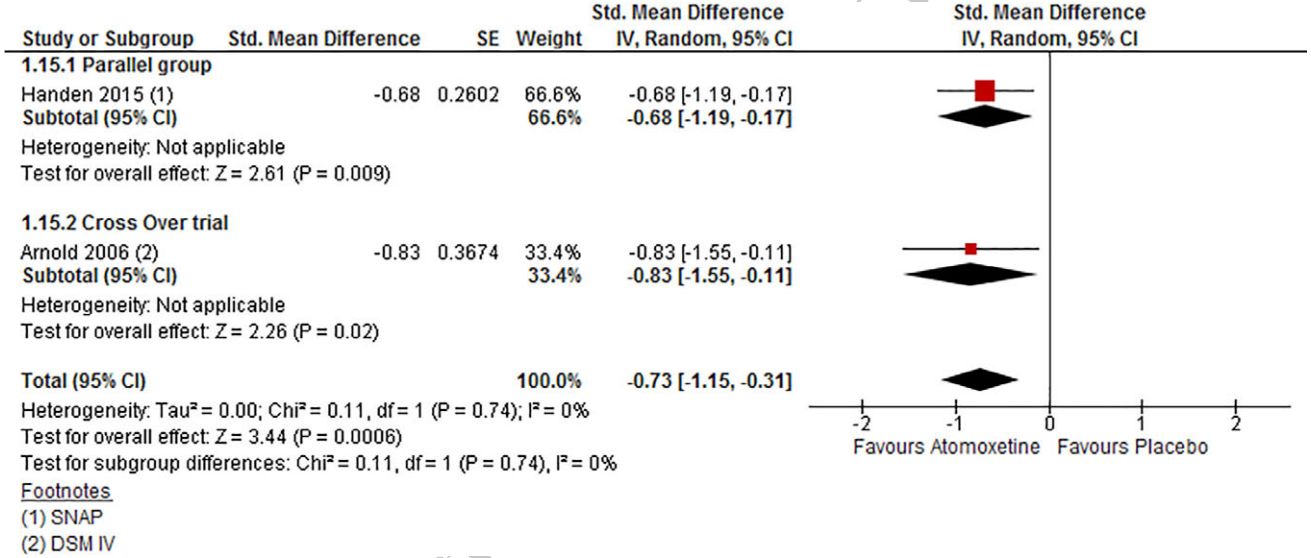


**Figure 4.** Forest plot, outcome estimate: hyperactivity-parent rated.

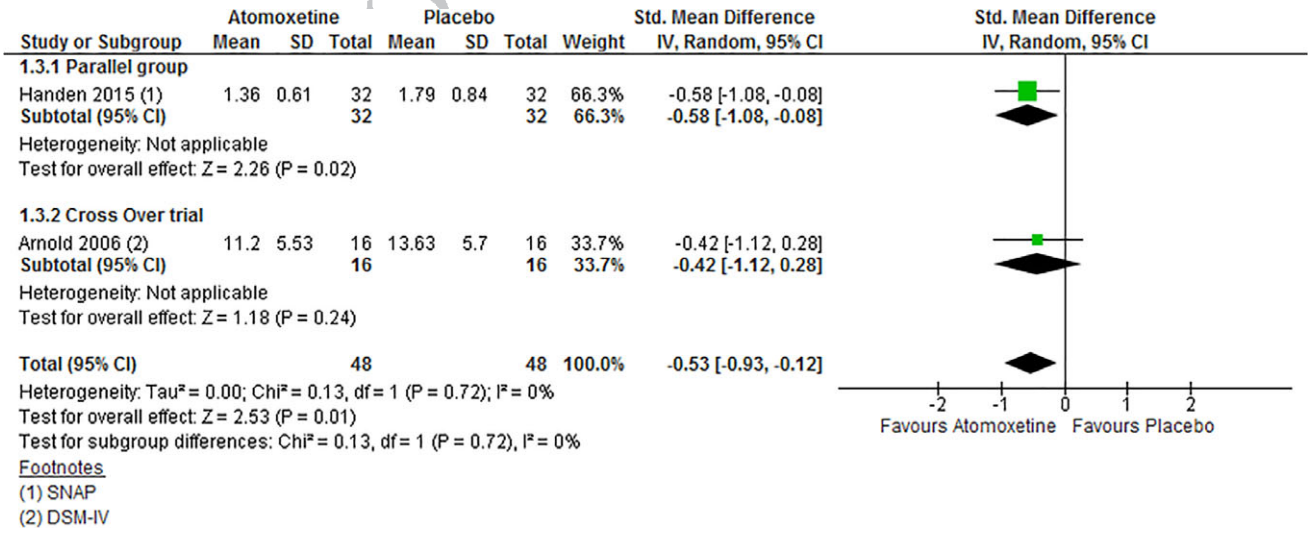


**Figure 5.** Forest plot, outcome estimate: Inattention-parent rated.

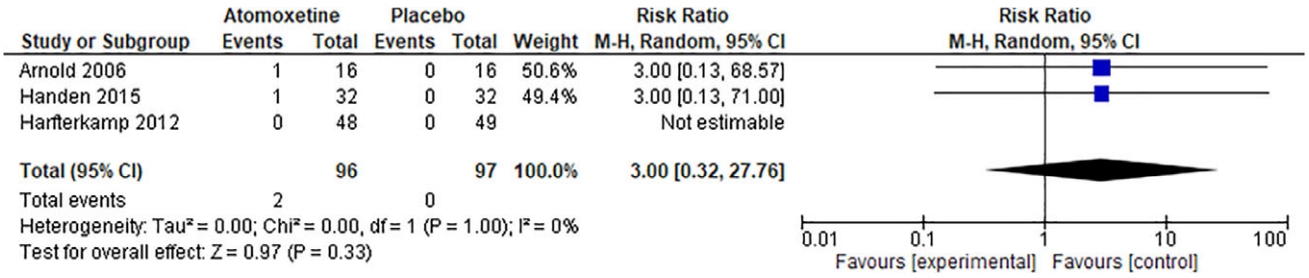


**Figure 6.** Forest plot: Serious adverse events.

***Overall improvement of ADHD symptoms.*** All the three trials involving 193 participants provided data for effect of atomoxetine on overall symptoms of ADHD rated on CGI-I (RR 2.37, 95% CI 1.38, 4.06). There was beneficial effect of atomoxetine as compared to placebo but quality of evidence was low (Fig. 7).

***Non-serious adverse events.*** All the three trials reported significantly higher rates of non-serious adverse effects like nausea/vomiting, stomach pain, decreased appetite, and decreased sleep in atomoxetine group. In addition, symptoms of fatigue, irritability, tiredness, mood swings, headache, and restlessness were also reported. Arnold et al. reported significantly higher rates of fatigue and racing heart rate in atomoxetine group. Significantly higher rates of fatigue and early morning awakening were reported by Harfterkamp et al. in the atomoxetine group.

Data for non-serious side effects were provided by all the three included trials involving 193 participants. As compared to placebo, atomoxetine had a higher risk of non-serious side effects. Risk of nausea and vomiting was: RR 1.91, 95% CI 1.24–2.94, 3 trials, 193 participants, $I^2$ = 0%, decreased sleep: RR 1.79, 95% CI 1.19–2.70, 3 trials, 193 participants, $I^2$ = 0%, and decreased appetite: RR 1.79, 95% CI 1.17 to 2.73, 3 trials, 193participants, $I^2$ = 39%, with atomoxetine; the quality of evidence for all of these outcomes were graded as low (Fig. 8).

Higher rates of non-serious side effects might be due to higher dose of atomoxetine used in the trials. Arnold et al. used atomoxetine at 1.4 mg/kg/day which is almost the highest permissible dose; at >1.2 mg/kg/day the efficacy as well as event of non-serious adverse effects increase [Kohn, 2012].

***Parent stress and quality of life.*** Lecavalier et al. [2017] described the beneficial effect of atomoxetine or parent training on parent stress using Parent Stress Index-Short Form at 10 weeks end point. The authors have described the change in parent stress evaluated during the RCT conducted by Handen et al. Although all parents showed improvement in stress scores, improvement was not related to atomoxetine or parent training; instead it was related to treatment response. Authors conclude that reduction in parent stress levels are more due to placebo response of regular meeting with research staff than either medication or parent training. They have also pointed at need for larger sample size and longer duration of study to increase the power of the study to detect small effect size of parent stress. Data from a single RCT precluded meta-analysis of impact of atomoxetine on parent stress.

None of the included trials reported about quality of life, hence we could not carry out any analysis. Future RCTs should consider measuring these outcomes.

## Discussion

The results of this meta-analysis demonstrate the beneficial effect of atomoxetine on ADHD symptoms in children with co-morbid ASD. Atomoxetine is effective in improving parent rated hyperactivity (SMD −0.73), inattention (SMD −0.53), and overall symptoms of ADHD (RR 2.37). The effect size for hyperactivity (SMD −0.73) in our meta-anaylsis is higher than (SMD = 0.67) reported in TD children with ADHD. However, the effect size for inattention (SMD = 0.53) is lower than (SMD = 0.59) that in TD children [Schwartz, 2014]. Atomoxetine is more effective in reducing symptoms of hyperactivity in children with ASD. Children with ASD show less response to atomoxetine; degree of response is inversely proportional to the degree of severity of autism [Fernandez, 2011, Charnsil, 2011].

Atomoxetine is usually a well-tolerated medicine with mild adverse effects like headache, pain abdomen, nausea, decreased appetite, and weight loss similar to placebo. There are only rare incidents of serious adverse events with atomoxetine. Children with ASD have a higher risk of developing irritability, decrease in appetite and nausea as reported in RCTs involving atomoxetine.

Tumuluru et al. reported in detail about the adverse effects seen during RCT conducted by Handen et al. The authors report increased incidence of non-serious adverse events like decreased appetite and fatigue associated with atomoxetine in children with ASD as compared to TD children. However, there was no incidence of any serious adverse events and authors conclude that atomoxetine is as safe in children with ASD as it is in TD children [Tumuluru et al., 2017]. As reported by authors of the

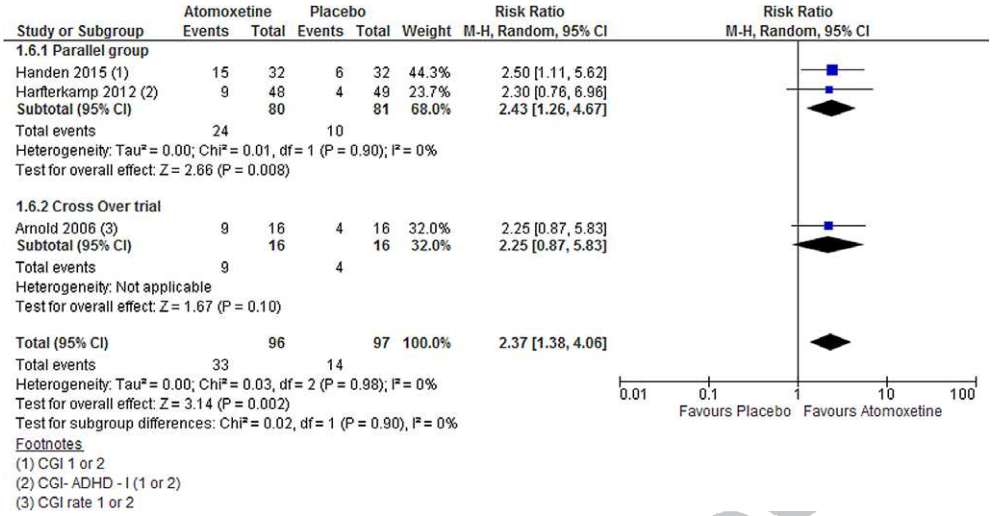


**Figure 7.** Forest plot outcome: Overall symptoms of ADHD (Clinical Global Improvement).

RCT, our meta-analysis also did not find significant difference of serious adverse events in atomoxetine as compared to placebo [Tumuluru et al., 2017]. However, the rate of non-serious side effects is higher in terms of higher risk of gastrointestinal side effects; more than two-third of trial participants experienced decreased appetite and about 50% patients complained of nausea/vomiting. About one-third of patients had impaired sleep. Our findings synthesized the available results of RCTs carried out till date in this patient population and hence gave an estimate of higher risk of non-serious side effects as compared to placebo.

Smith et al. allowed continuation of treatment with atomoxetine for 6 months in patients who were responders (defined as CGI score = 1 or 2 and >30% decrease in ADHD or non-compliance behavior scores). Initial responders

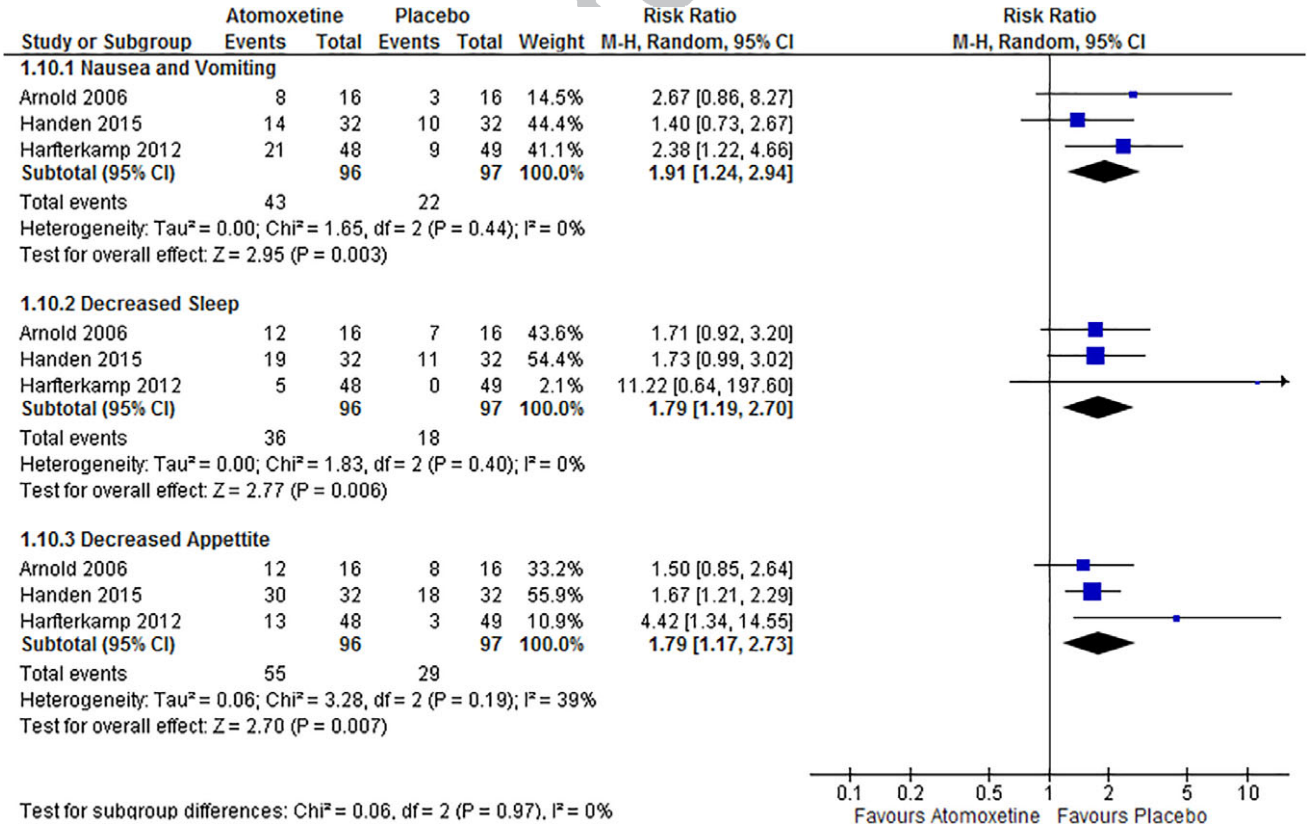


**Figure 8.** Forest plot: Non-serious adverse events.

**Table 2. Summary of Findings: Atomoxetine Compared to Placebo for Attention Deficit Hyperactivity Disorder in Children with Autism**

| Outcomes | No. of participants (studies) follow-up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with placebo | Risk difference with atomoxetine |
| Parent rated hyperactivity<br>DSM-IV ADHD rating scale<br>Follow-up mean: 8 weeks | 96 (2 RCTs) | ⨁⨁◯◯<br>LOW[a,b,c] | – | – | SMD 0.73 SD lower (1.15 lower to 0.34 lower) |
| Parent rated inattention<br>DSM-IV ADHD rating scale<br>Follow-up mean: 8 weeks | 96 (2 RCTs) | ⨁◯◯◯<br>VERY LOW[a,b] | – | – | SMD 0.53 lower (0.93 lower to 0.12 lower) |
| Parent rated oppositional behavior<br>DSM-IV ADHD rating scale<br>Follow up-mean: 8 weeks | 96 (2 RCTs) | ⨁◯◯◯<br>VERY LOW[a,b,d] | – | – | SMD 0.09 lower (0.49 lower to 0.31 higher) |
| Serious adverse events | 193(3 RCTs) | ⨁⨁◯◯ LOW[a,b] | RR 3 (0.32–27.76) | Atomoxetine was not associated with higher risk of serious side effects as compared to placebo | |
| Overall improvement in ADHD<br>Follow-up mean: 10 weeks | 193 (3 RCTs) | ⨁⨁◯◯<br>LOW[a,b] | RR 2.37 (1.38–4.06) | 144 per 1,000 | 198 more per 1,000 (55 more to 442 more) |
| Parent stress and quality of life | No studies have reported this outcome | | | | |
| Non-serious adverse events: nausea and vomiting, decreased appetite, and decreased sleep. | 193 (3 RCTs) | ⨁⨁◯◯<br>LOW[a,b] | The risk ratio for all outcomes ranges from 1.79 to 1.91. with the 95% CI of minimum (1.17 to maximum of 2.94) | Atomoxetine had a significantly higher risk of non-serious side effects in all of the listed outcomes compared to placebo | |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; SMD, standardized mean difference; RR: risk ratio.

GRADE Working Group grades of evidence: High quality—we are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality—we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality—our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality—we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

continued to show sustained improvement in ADHD symptoms. Also, about a third of patients who were non-responders to placebo responded to atomoxetine in the open label extension study period of 6 months [Smith et al., 2016]. This extension study aimed at the combined effect of Parent Training and Atomoxetine on Non-compliant behavior of children with ASD and ADHD. Authors conclude that atomoxetine continues to show beneficial effect when continued for 6 months with similar non-serious adverse effects (gastrointestinal symptoms and sleep problems) as seen in short-term treatment. Complicated design of the trial and absence of any other RCT of 6 months duration precludes pooling of data for meta-analysis.

Out of the three included trials, one was a cross over trial with the limitation of outcome assessor blinding hence having high risk of bias. Two trials were sponsored by pharmaceuticals hence there remains likely sources of risk of bias which is unclear. In most outcomes we found limitation of imprecision with the overall effect estimates which lead us to judge the evidence to be low to very low-quality hence future studies are likely to have an impact on the effect estimates. Our findings based on GRADE assessment are shown in detail in SOF (Table 2).

*Strengths and Limitations of this Study*

We developed the protocol during a workshop conducted by Cochrane South Asia and it was registered in PROSPERO with registration no. CRD42016041395. We assessed risk of bias of the trials as per the recommendations of Cochrane Handbook of Systematic Reviews of Interventions. We could not include unpublished trials in the review which may be considered weakness of the review.

## Conclusions

Atomoxetine may be effective in causing improvement in hyperactivity and inattention as also overall symptoms of ADHD in children with ASD. There are higher reports of gastrointestinal side effects and decreased sleep in atomoxetine group as compared to placebo which require monitoring. However, the analysis did not find any significant difference between atomoxetine and placebo in causing serious side effects.

## Compliance with Ethical Standards

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.


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None.

## Conflict of Interest

The authors declare that none of them have received any grants or funding from any source for this research.

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