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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 comorbidity 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;

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1 however, treatment response is lower and is often associ- 56
2 ated with more adverse effects [Bachmann, Manthey, 57
3 Kamp-Becker, Glaeske, & Hoffmann, 2013; Kim et al., 2017; 58
4 RUPP., 2005]. Stimulants can exacerbate stereotypies, tics, 59
5 self-injury, and anxiety in children with ASD [Aman et al., 60
6 2008; Arnold et al., 2006; Gadow et al., 2005].

7 Atomoxetine, a non-stimulant medication, is consid- 61
8 ered second-line alternative in managing ADHD in chil- 62
9 dren with ASD. Atomoxetine acts as a highly specific 63
10 presynaptic noradrenaline reuptake inhibitor in the pre- 64
11 frontal cortex, the region for attention and other higher 65
12 cognition processes. It increases the availability of dopa- 66
13 mine in prefrontal cortex but does not have any direct 67
14 activity on dopamine. It does not have action on striatum 68
15 or midbrain hence is free from addictive potential, stereo- 69
16 typies, and tics [Barton, 2005]. It can be used in case of 70
17 stimulant failure or intolerance and in presence of co- 71
18 morbidities like tic and anxiety disorders because of bet- 72
19 ter tolerability and safety [Kohn, Tsang, & Clarke, 73
20 2012]. The long half-life of atomoxetine makes it effec- 74
21 tive throughout the day with a single daily dose. Standard 75
22 dose range recommended for atomoxetine is 0.5– 76
23 1.8 mg/kg/day. Four to six weeks of treatment is needed 77
24 for optimal of efficacy with atomoxetine [Clemow, 2014]. 78

25 Stimulants are the second most commonly prescribed 79
26 medications in children with ASD and ADHD across the 80
27 world except in the UK. In UK methylphenidate is the 81
28 most commonly prescribed medication [Hsia et al., 82
29 2014]. In a four continent study involving 10 countries, 83
30 prescription rates of ADHD medications have risen in the 84
31 United States and European countries like Denmark, 85
32 Netherlands, and Spain. Initiation of ADHD medication 86
33 in ADHD with ASD is much earlier than in ADHD chil- 87
34 dren. Of the children and adolescents with ASD, 16% are 88
35 prescribed with stimulants and atomoxetine [Dalsgaard, 89
36 Nielsen, & Simonsen, 2013]. In the United States, 56% 90
37 children with ASD are prescribed with ADHD medica- 91
38 tions of which stimulants are the third most common 92
39 medications. With 8% prescription rates, atomoxetine 93
40 was the second most common medication among ADHD 94
41 medications [Williams et al., 2012]. 95

42 The variation in prescription practices is due to inconsis- 96
43 tent treatment guidelines, differences in healthcare systems, 97
44 and inadequate evidence base of psychopharmacological 98
45 agents. Systematic reviews conducted by rigorous Cochrane 99
46 methodology are instrumental in shaping treatment guide- 100
47 lines; hence it is imperative to estimate the efficacy and 101
48 safety of these psychopharmacological agents. 102

49 Many clinical trials have demonstrated that atomoxe- 103
50 tine is effective and safe in children with ASD [Aman, 104
51 2014; Reichow, 2013]. To our knowledge only three ran- 105
52 domized controlled trials have been published demon- 106
53 strating effectiveness and safety of atomoxetine in ASD 107
54 [Arnold, 2006; Harfterkamp et al., 2012; Handen et al., 108
55 2015]. First of these randomized controlled trials (RCTs)

was a double-blind placebo controlled cross over trial of 56
6 weeks involving 16 subjects which failed to show clini- 57
cally significant benefit with atomoxetine [Arnold, 2006]. 58
In the second trial of 8 weeks duration involving 97 par- 59
ticipants, 20.9% participants on atomoxetine improved 60
much or very much on Clinical Global Improvement 61
(CGI-I) scale as compared to 8.7% on placebo [Harfter- 62
kamp, 2012]. The third parallel group four arm RCT 63
involving atomoxetine, placebo, and parent training was 64
of 10 weeks duration in which 46.9% of participants on 65
atomoxetine showed 30% improvement in Swanson, 66
Nolan and Pelham (SNAP) scores as compared to 19.4% 67
on placebo. Two trials reported of serious side effects 68
whereas all three trials reported non-serious side effects. 69

70 Two reviews have examined usefulness of Atomoxetine in 70
71 ADHD co-morbid with ASD [Reichow, 2013; Aman, 2014]. 71
72 These reviews have not reported inattention and hyperactiv- 72
73 ity/impulsivity as separate outcomes. The magnitude of side 73
74 effects was also not reported. The reviews were not carried 74
75 out using Cochrane methodology or Preferred Reporting 75
76 Items for Systematic reviews and Metaanalysis (PRISMA) 76
77 guidelines. Risk of bias and quality of trials were also not 77
78 addressed by these reviews. 78

79 To address these flaws, we carried out a systematic 79
80 review and meta-analysis using Cochrane guidelines for 80
81 estimation of risk of bias and GRADE approach for evalu- 81
82 ation of quality of trials and report on efficacy and safety 82
83 of atomoxetine in children with ASD. 83
84

85 **Methods** 86

87 *Search Strategy for Identification of Studies* 88

89 Three reviewers independently searched Pubmed, 89
90 Cochrane central register of controlled trials, Cochrane 90
91 library, Embase, and ClinicalTrials.gov upto April 2018. For 91
92 Pubmed we used the search strategy: “attention deficit dis- 92
93 order with hyperactivity” (Mesh) AND “autistic disorder” 93
94 (Mesh) AND “atomoxetine hydrochloride” (Mesh). We 94
95 adapted the search terms and modified according to the dif- 95
96 ferent databases. The search terms used for Cochrane library 96
97 were: “autistic disorder,” “attention deficit disorder with 97
98 hyperactivity,” and “atomoxetine hydrochloride.” For 98
99 Embase we used: “attention deficit disorder with 99
100 hyperactivity,” “autism,” and “atomoxetine.” For ongoing 100
101 studies, we searched in ClincialTrials.gov with the terms 101
102 “autism or pervasive developmental disorder” and an inter- 102
103 vention filter for “Atomoxetine hydrochloride OR atomox- 103
104 etine.” We also searched the reference lists of included 104
105 studies, reviews, and meta-analyses for more citations. 105
106

107 *Study Selection* 108

109 We used the following criteria for selecting studies for 109
110 inclusion in this review. 110

1	1. Randomized placebo controlled trials comparing atomoxetine with placebo.	56
2		57
3	2. Patient population of children and adolescents of	58
4	≤18 years age with diagnosis of ASD as per DSM5 or	59
5	Pervasive Developmental Disorder as per DSMIV or	60
6	ICD 10.	
7	3. Trials using atomoxetine at standard dose (0.5–1.8 mg/kg/	
8	day) and duration 4 weeks.	
9	4. Trials reporting ADHD symptoms as outcome measures.	
10		
11	We did not include trials involving children with epi-	
12	lepsy or traumatic brain injury.	
13		
14	<i>Outcome Measures</i>	
15	Primary outcomes were parent-rated symptoms of ADHD	
16	(inattention, hyperactivity, or impulsivity) both short-	
17	term (≤6 months) and long-term (≥6 months), social	
18	behavior, and serious adverse events. Parent-rated symp-	
19	toms of ADHD were chosen as primary outcome as	
20	parent-rating of ADHD symptoms is more sensitive than	
21	teacher-rating in children with ASD [RUPP, 2005]. ADHD	
22	symptoms rated on standard scales like SNAP, DSM-IV	
23	rating scale, and ADHD rating scale were included in the	
24	analysis [Swanson, 1983; DuPaul et al., 1998]. Any event	
25	of death, life threatening side effects, prolongation of	
26	hospital stay, or disability was defined as serious adverse	
27	event.	
28	<i>Secondary outcomes</i> were clinician and teacher-rated	
29	ADHD symptoms; overall improvement of ADHD symp-	
30	toms rated on standard scales like CGI-I; parent stress;	
31	quality of life; and non-serious adverse events. Non-	
32	serious adverse events included nausea and vomiting,	
33	decreased appetite, and decreased sleep.	
34		
35	<i>Data Collection and Analysis</i>	
36		
37	Selection of studies. Two review authors SP and NN	
38	independently read the titles and abstracts of the articles	
39	for suitability decision as per the inclusion criteria and	
40	used PRISMA flowchart to present the selection of studies.	
41	SP and NN extracted data from each included study using	
42	standard data extraction forms. We resolved disagree-	
43	ments with discussions and in case of any persisting dis-	
44	agreement, AV acted as arbiter.	
45		
46	Data extraction and management. We extracted	
47	data on details of study design (methods), participants,	
48	intervention, and outcomes. Disagreements were resolved	
49	by discussion and in case of any difficulty we took the	
50	third reviewer's help. We contacted study authors for	
51	missing data. SP entered the data into Review Manager	
52	5.3 after cross verifying the extracted data against the	
53	included studies.	
54	We extracted the 2 × 2 table values for dichotomous	
55	outcomes like serious adverse events, non-serious adverse	
	events, and CGI scores. For continuous outcomes	56
	like hyperactivity and inattention, we extracted mean,	57
	standard deviation, and the total number of participants	58
	randomized in the group.	59
		60
	Assessment of risk of bias in included studies. SP	61
	and NN independently assessed for internal validity of	62
	each included study using the Cochrane risk of bias tool	63
	for RCT. There were six domains: random sequence gen-	64
	eration (selection bias), allocation concealment (selection	65
	bias), blinding of participants (performance bias), blind-	66
	ing of outcomes assessor (detection bias), incomplete out-	67
	come data (attrition bias), and selective outcome	68
	reporting (reporting bias) and other biases. We assigned	69
	risk of bias as high, low, or unclear as per the guidelines	70
	provided in Cochrane Handbook of systematic reviews	71
	[Higgins, 2011]. We contacted the trial authors in case of	72
	any discrepancy or lack of clarity in reporting and also	73
	held discussions among the reviewers to clarify any	74
	disagreements.	75
	We created risk of bias graph to explain each domain	76
	individually and summary figure for the overall domains.	77
		78
	Measures of treatment effect. We combined results of	79
	studies reporting effect on symptoms of ADHD using	80
	random-effects model. We chose this model due to its	81
	nature of assuming both within and between-study varia-	82
	tions while pooling the data. Continuous data were	83
	either pooled by calculating mean difference between	84
	groups with 95% CI or SMD along with 95% CI when	85
	same outcomes were measured using different tools.	86
	For dichotomous data we calculated Risk Ratio as pro-	87
	portion of patients experiencing events in the treatment	88
	group divided by proportion of patients experiencing	89
	events in control group.	90
	We analyzed all the homogenous data using Revman5.3	91
	and also calculated the pooled estimates with 95% CI.	92
		93
	Unit of analysis issues. Crossover trials are more prone	94
	to bias owing to carry-over effects, period effects, and	95
	errors in unit of analysis. Our original intent was to	96
	adjust the effect estimates for the unit of analysis error in	97
	crossover trials by conducting a paired analysis. Due to	98
	insufficient data we contacted the trial authors for the	99
	adjusted data or the first period data. However, we did	100
	not get any reply from them; therefore we conducted a	101
	stratified analysis based on the study design.	102
		103
	Assessment of heterogeneity. We examined forest plots for	104
	overlapping confidence interval and using the Chi	105
	square test for heterogeneity keeping significance at 10%	106
	level to detect heterogeneity in studies, and I^2 statistic to	107
	detect inconsistency in results which exceeded probabil-	108
	ity due to chance. I^2 value of >50% was understood to	109
	denote either moderate or substantial heterogeneity.	110

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

5
 6 *Sensitivity Analysis.* Since, we have included only two
 7 studies for meta-analysis and the direction of effect esti-
 8 mates are in one side in favor of intervention, we did not
 9 perform the sensitivity analysis.

10
 11 *Assessment of publication bias.* We could not do funnel
 12 plot for any analysis to assess publication bias as the
 13 number of studies was too small.

14
 15 *Certainty of evidence and summary of findings (SOF) tables.*
 16 We have used the GRADEpro software following the
 17 guideline stated in the handbook of GRADE assessment
 18 for creating SOF table. The quality of evidence has four
 19 levels ranging from High, Moderate, Low, to Very Low.
 20 There were five domains to be assessed to arrive at the
 21 quality of evidence: (a) risk of bias, (b) inconsistency,
 22 (c) indirectness, (d) Imprecision, and (e) publication bias.
 23 We judged each domain and assigned the Quality of Evi-
 24 dence for each outcome. We have presented only the
 25 important and critical outcomes in the SOF tables.

26 Results

27 Included Studies

28
 29 We identified 104 records after electronic database
 30 searching and removed duplicates, 93 records were left
 31 which we tested for eligibility. Out of these, we excluded
 32 89 because the trials were either not RCTs, or, population,
 33 intervention or outcomes were not relevant to our review
 34 (Fig. 1). We included three randomized controlled studies
 35 [Arnold et al., 2006; Handen et al., 2015 and Harfterkamp
 36 et al., 2012]. We contacted Arnold et al. and authors of
 37 clinical trials reported in Clinical Trials.gov twice through
 38 email but failed to acquire the raw data.

39
 40 In the three RCTs, total participants were 241 with
 41 $n = 16$ in first trial, $n = 97$ in second trial and ($n = 128$) in
 42 third trial [Arnold et al., 2006; Handen et al., 2015; Har-
 43 fterkamp et al., 2012]. Girls and boys in the age range
 44 5–17 years were included in the trials. Two of the trials
 45 were carried out in the United States and one in the Neth-
 46 erlands. The trial duration ranged from 6 to 10 weeks.
 47 Handen et al. [2015] was a four-group study in which par-
 48 ticipants were randomized into Atomoxetine, Placebo,
 49 Atomoxetine + Parent Training, and Placebo + Parent
 50 Training groups. We included the first two groups on ato-
 51 moxetine ($n = 32$) and placebo ($n = 32$). We did not
 52 include the groups with Parent Training in our analysis
 53 as our aim was to estimate the effect of atomoxetine.
 54 Characteristics of included studies are shown in Table 1.

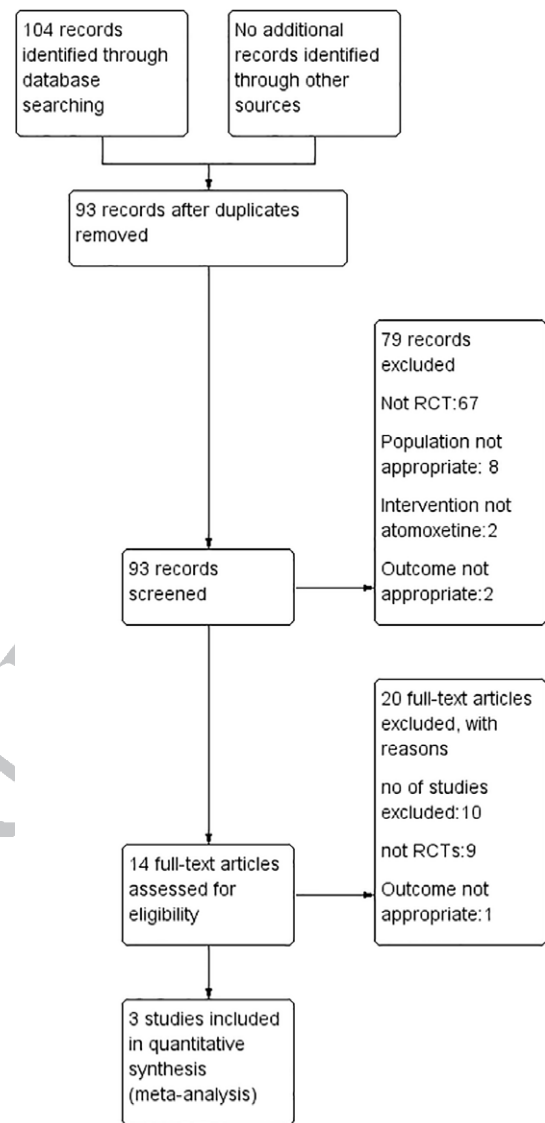


Figure 1. Study flow using PRISMA flow diagram.

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

^aOnly 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.

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.

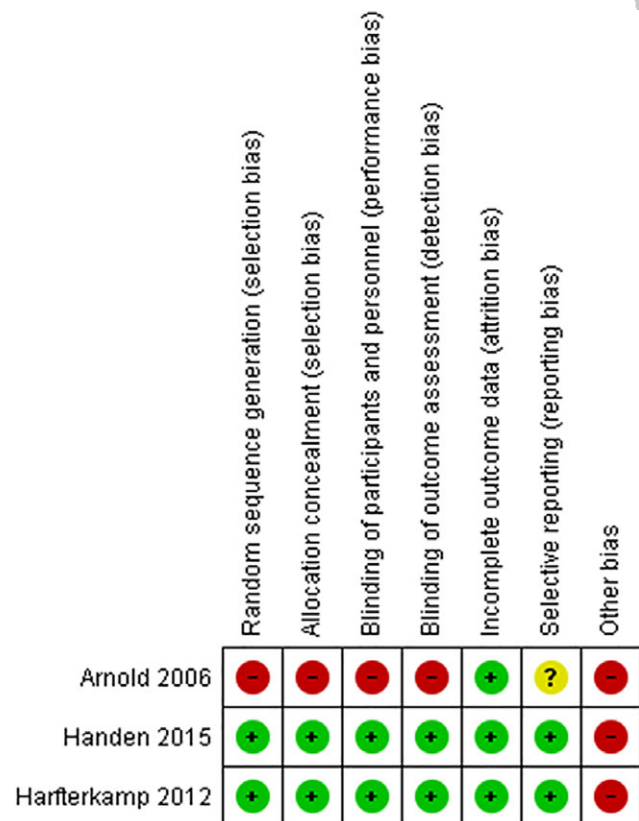


Figure 2. Risk of bias summary: Review authors’ judgments about each risk of bias item for each included study.

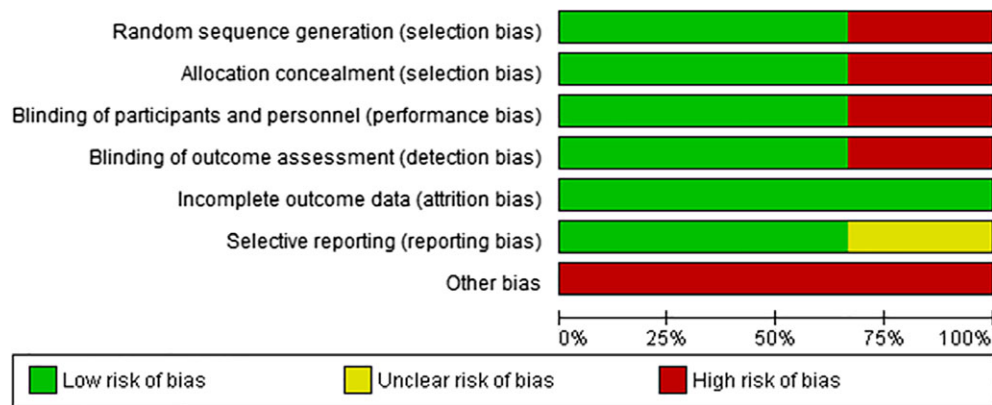


Figure 3. Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.

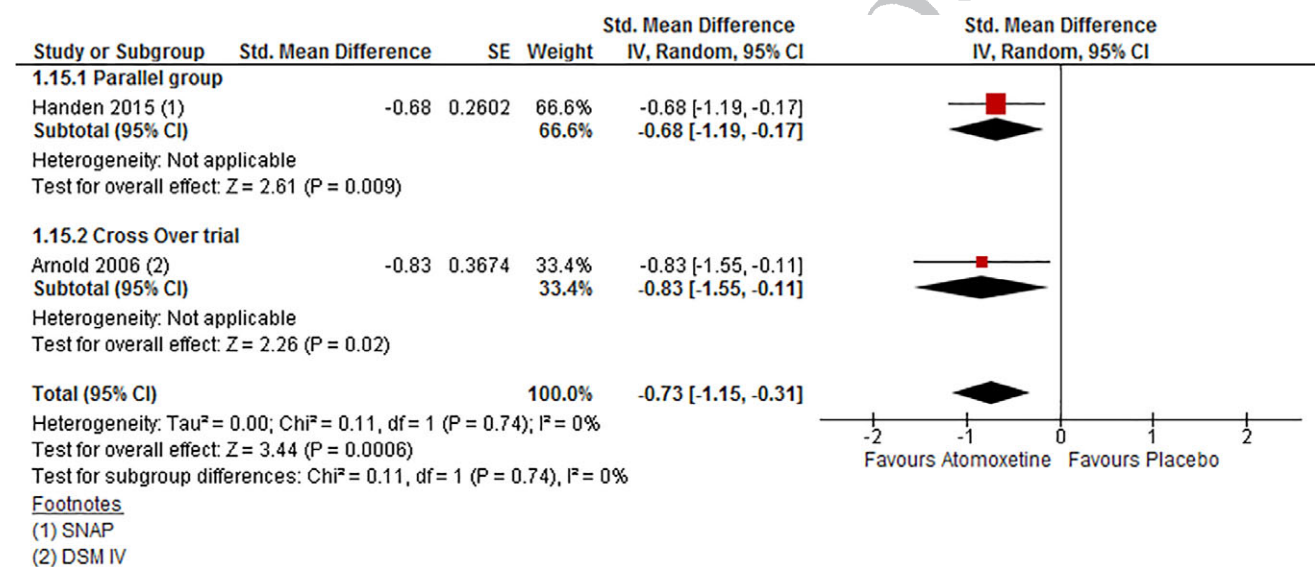


Figure 4. Forest plot, outcome estimate: hyperactivity-parent rated.

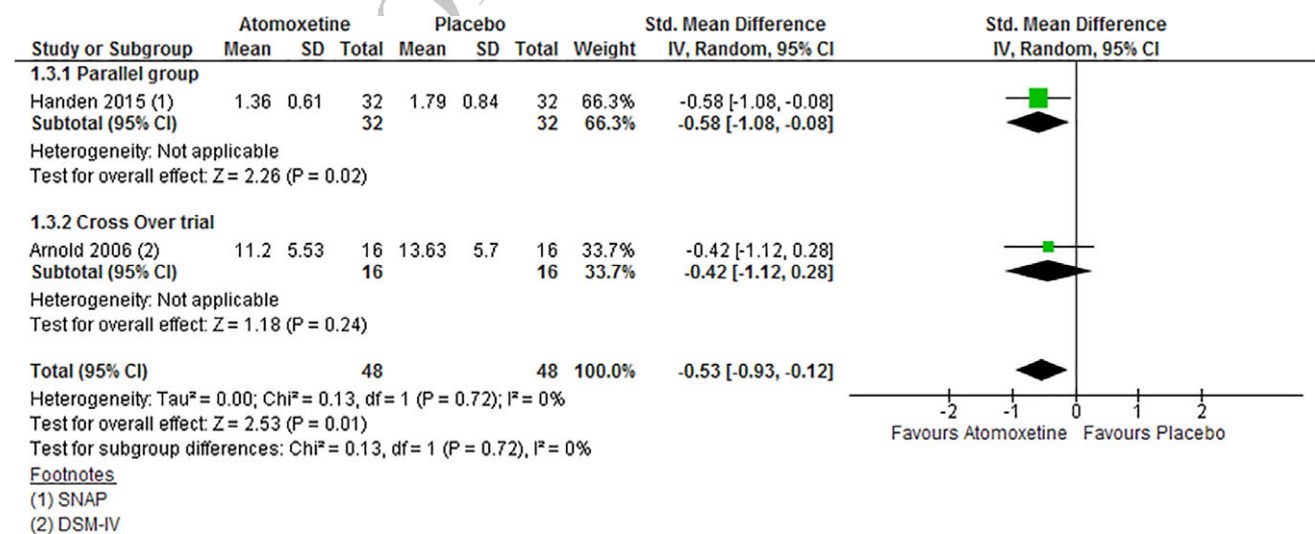


Figure 5. Forest plot, outcome estimate: Inattention-parent rated.

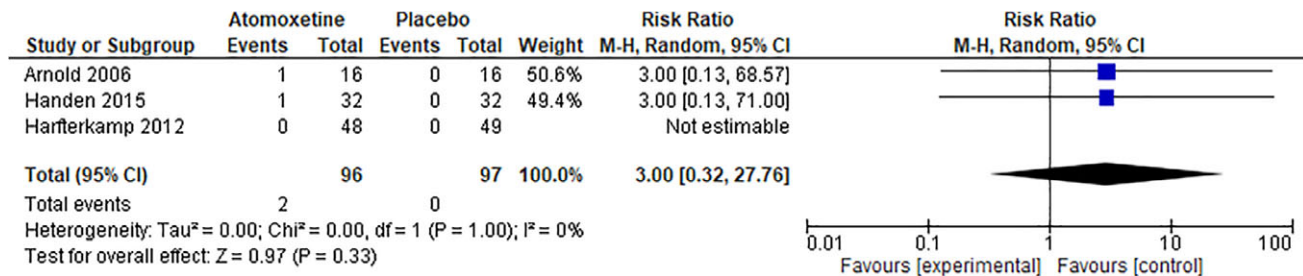


Figure 6. Forest plot: Serious adverse events.

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 Harterkamp 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, 193 participants, $I^2 = 39\%$, 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 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-analysis 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

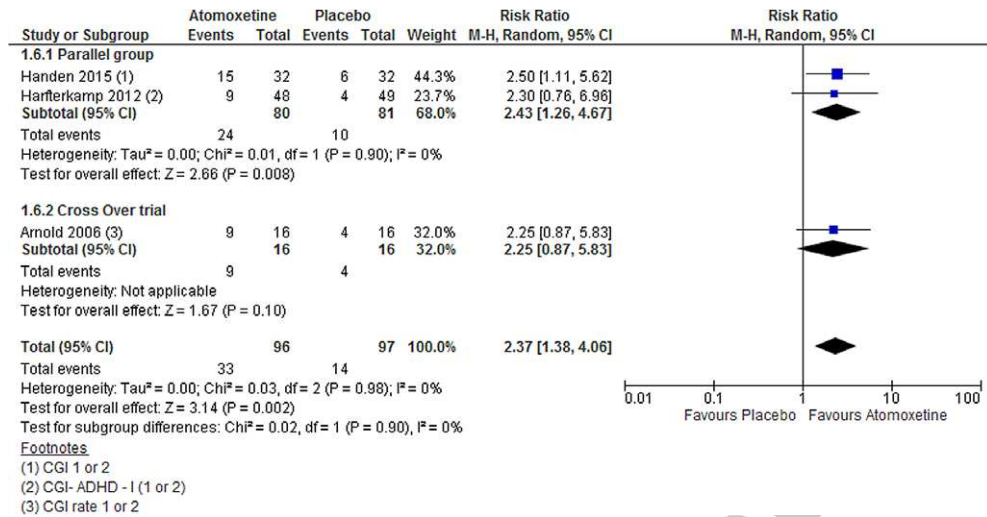


Figure 7. Forest plot outcome: Overall symptoms of ADHD (Clinical Global Improvement).

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

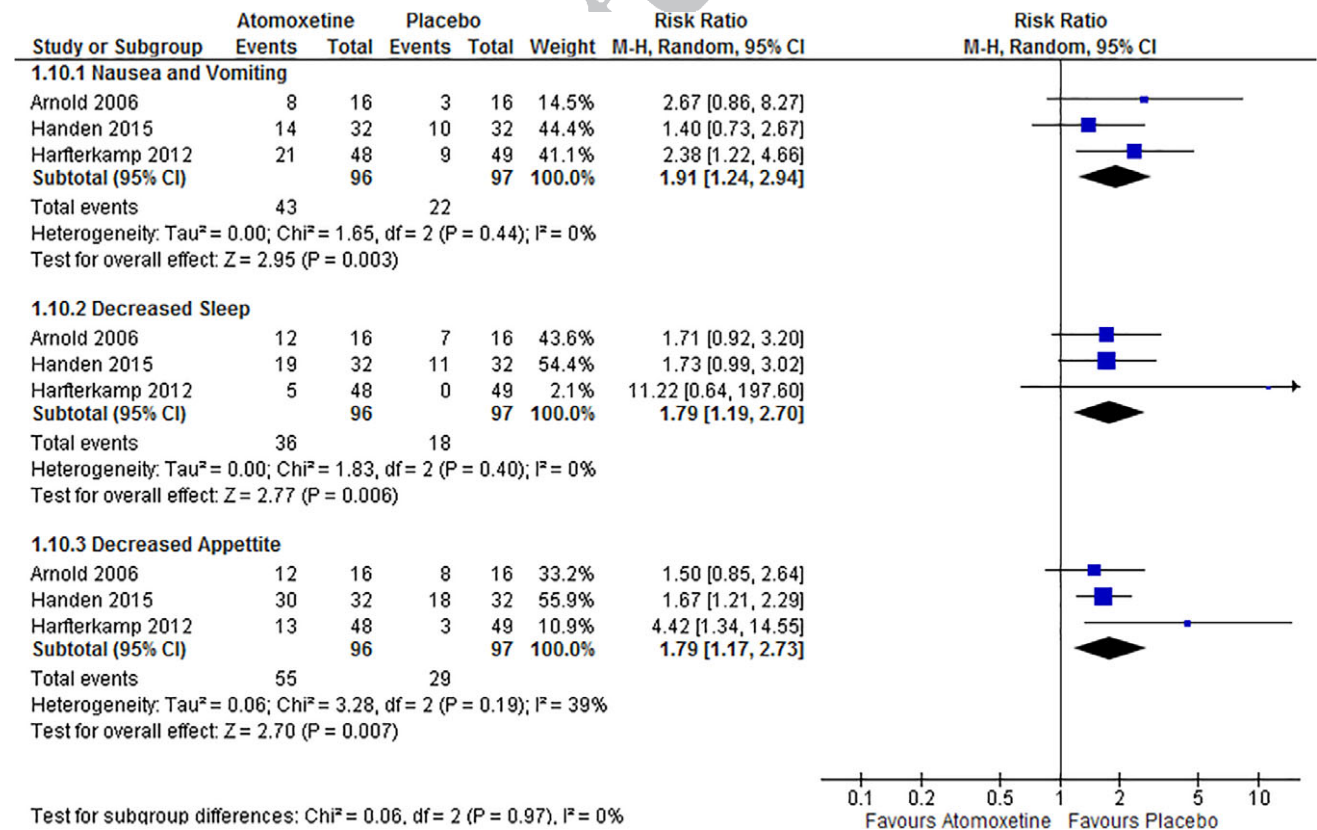


Figure 8. Forest plot: Non-serious adverse events.

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 DSM-IV ADHD rating scale Follow-up mean: 8 weeks	96 (2 RCTs)	⊕⊕○○ LOW ^{a,b,c}	-	-	SMD 0.73 SD lower (1.15 lower to 0.34 lower)
Parent rated inattention DSM-IV ADHD rating scale Follow-up mean: 8 weeks	96 (2 RCTs)	⊕○○○ VERY LOW ^{a,b}	-	-	SMD 0.53 lower (0.93 lower to 0.12 lower)
Parent rated oppositional behavior DSM-IV ADHD rating scale Follow up-mean: 8 weeks	96 (2 RCTs)	⊕○○○ 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 Follow-up mean: 10 weeks	193 (3 RCTs)	⊕⊕○○ 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)	⊕⊕○○ 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.

Sources of Funding

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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Uncorrected Proofs