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Efficacy and Tolerability of Atomoxetine Use for Patients with Autism Spectrum Disorders and Attention-Deficit/Hyperactivity Disorder (ADHD) Symptoms: A Systematic Review and Meta-Analysis

Angie El-Said
University of Central Florida

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EFFICACY AND TOLERABILITY OF ATOMOXETINE USE FOR PATIENTS WITH
AUTISM SPECTRUM DISORDERS AND ATTENTION-DEFICIT/HYPERACTIVITY
DISORDER (ADHD) SYMPTOMS: A SYSTEMATIC REVIEW AND META-ANALYSIS

by

ANGIE EL-SAID

A thesis submitted in partial fulfillment of the requirements
for the Honors in the Major Program in Biomedical Sciences
in the College of Medicine
and in the Burnett Honors College
at the University of Central Florida
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Thesis Chair: Zixi Cheng, PhD

Abstract

Introduction: Patients with autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD) show more symptoms of ADHD. Since there are more adverse events caused by psychostimulants compared to non-psychostimulants, the use of a non-psychostimulant such as atomoxetine might prove more beneficial for younger patients and/or those with comorbid ADHD.

Objective: The aim of this thesis is to determine the efficacy and tolerability of atomoxetine in ASD patients presenting with ADHD, by examining (a) differences in ADHD symptoms for participants receiving atomoxetine versus those receiving placebos, and (b) risk differences in adverse events between these participants.

Methods: An electronic search of both PubMed.gov and ClinicalTrials.gov were conducted. To be deemed eligible, studies had to (a) be randomized, double-blind, placebo-controlled trials comparing atomoxetine with a placebo, (b) administer atomoxetine for at least 1 week, and (c) include data on either ADHD outcomes or adverse events. Effect sizes for ADHD outcomes were calculated using Cohen's d, whereas risk differences were calculated for adverse events. For each of these two meta-analyses, effect sizes were aggregated across studies using a random effects method.

Results: Overall ADHD outcomes were better for participants who received atomoxetine than for participants who received placebo, $\bar{d}$=0.297. Participants who received atomoxetine also demonstrated better outcomes in terms of attention and hyperactivity-impulsivity symptoms,

$\bar{d}$=0.345 and 0.393, respectively. Though there were more adverse events for patients taking atomoxetine than placebo, the results were not statistically significant.

Discussion: This thesis extends the findings of previous meta-analyses of pharmacological treatments for ASD and ADHD, while addressing the concerns raised in the critique of existing meta-analyses presented in this thesis, e.g., limited studies, length of treatment weeks, and dichotomization of data. It provides evidence that atomoxetine improves ADHD symptoms, with an overall frequency of adverse events that did not sufficiently differ from placebo beyond chance.

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Introduction

Autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD) are both neuropsychiatric disorders that have a high frequency of comorbidity with each other (Lyall, Schweitzer, Schmidt, Hertz-picciotto, & Solomon, 2018). Whereas approximately 9.4% of children (Danielson et al., 2018) (6.1 million) have been diagnosed with ADHD, ~1.7% percent children (more than 3.5 million) have been diagnosed with ASD (Baio et al., 2018). Among individuals diagnosed with ASD, research has demonstrated that about 30-50% of these patients have comorbid ADHD (Leitner, 2014).

The dual diagnosis of ASD and ADHD was prevented in the fourth edition *Diagnostic and statistical manual of mental disorders* (DSM; American Psychiatric Association [APA], 1994). As more studies have emerged examining the relation between ASD and ADHD, researchers are becoming increasingly aware of the comorbidity between ASD and ADHD. Therefore, the dual diagnosis between ASD and ADHD has been added into the fifth edition of the *Diagnostic and statistical manual of mental disorders* (American Psychatric Association, 2013)**.** The DSM-5 justifies the dual diagnosis of ASD and ADHD, explaining that 70% of individuals with ASD have one other comorbid diagnosis. Addition of a dual diagnosis between ASD and ADHD will, therefore, allow improvement of data collection and aid in identifying trends that were not readily available with the prevention of the dual diagnosis in the DSM-4 (Korioth, 2013). Researchers, such as James Harris, have stressed the significance of a dual diagnosis far before the release of the DSM-5 and have speculated that the prevention of the dual diagnosis stemmed from concerns that clinicians would underdiagnose autism (Johnson, 2012).

More specifically, there was fear that individuals with autism would not be treated due to their autism-related inattentiveness being mistaken for symptoms of ADHD.

The characteristics that manifest in ASD patients include impaired skills in social communication and interaction (American Psychatric Association, 2013). More specifically, these include impaired social reciprocity, nonverbal communication, and maintenance of relationships. Other symptoms include repetitive behavior, interests, or activities, insistence on maintaining routine, and hyper- or hypo-activity to sensory input. Individuals who had been previously diagnosed with autistic disorder, Asperger's disorder, or pervasive developmental disorder in DSM-IV are diagnosed with the broader DSM-5 category of autism spectrum disorders. Attention abnormalities, such as hypo-focus can be common among individuals with ASD. If attention abnormalities exceed what is commonly seen among peers of the same age, an ADHD diagnosis will be considered. Though an ADHD diagnosis is encouraged, a differential diagnosis between ASD and ADHD is not listed in the ASD section of DSM-5.

Individuals with ADHD present with inattention and/or hyperactivity/impulsivity that interfere with their normal activities (Leitner, 2014). Some similarities that both ASD and ADHD have, include inattention, language difficulties, and impaired emotional recognition. Both are characterized as manifesting early in young children (more often seen in males), and they are associated with impairments in academic, social, and emotional life and well-being. Individuals with either ASD or ADHD both display symptoms of inability to focus, communicate socially, and manage behavior. However, under ADHD in the DSM-5, a key differential diagnosis centers on prevalence of tantrums among individuals with ASD due to their inability to tolerate change

(APA, 2013). Individuals with ADHD, in contrast, might have tantrums during major life events/transitions, or impulsivity as result of low self-control.

The cause of the co-occurrence of ASD and ADHD is unknown (Leitner, 2014). Researchers widely speculate that the co-occurrence may be rooted in a shared genetic basis, as both ASD and ADHD are disorders that oftentimes have underlying genetic causes (Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010). 50-72% of the genetic factors that contribute to either disorder have overlap, strengthening the theory of a shared genetic basis. Twin studies have focused on genetic correlations by using parent and teacher ratings. Genetic correlations refer to abnormal functioning genes such as a dopamine transporter gene (DAT1) in both ASD and ADHD, or a shared genetic defect present in a genome-wide linkage analysis. Phenotypic correlations were around 51-54%, among teacher and parent ratings respectively, while genetic correlations were all above 50% (Reiersen, Constantino, Volk, & Todd, 2007). A second twin study used self-reported measures of ADHD (Ronald, Edelson, Asherson, & Saudino, 2010). With a bivariate model as well, the genetic correlation (abnormalities in genes and defect in genes detected in genome-wide linkage analyses) between both ASD and ADHD was once again above 50%, at 72%.

Reports by parents, teachers, and physicians (through rating scales such as SNAP-IV and the Conners' Teachers Rating Scale), suggest that the co-occurrence of ADHD and ASD leads to more difficulty in daily life (Mulligan, Anney, O'Regan, Chen, & Butler, 2009). Difficulty in daily life (e.g., motor, social communication, and reading) is exhibited through higher mean

scores on the Social Communication Questionnaire (SCQ) of ASD individuals compared to siblings with or without ADHD.

Children with comorbid autism and ADHD ultimately show more symptoms of autism (Leitner, 2014). Studies have also shown that children with ASD and ADHD have a higher frequency of cognitive delays compared to individuals who have a single diagnosis of ASD or ADHD (Rao & Landa, 2014; Sinzig, Morsch, & Lehmkuhl, 2008). In Rao et al. (2014), participants were placed in two categories (high functioning or low functioning) based on their non-verbal communication IQ after completion of the Stanford-Binet Intelligent Scales, Fifth Edition (SB-5). Participants who had a comorbidity of ASD and ADHD were classified as low functioning compared to individuals who only had ASD (61% versus 25%). Low functioning does not only relate to non-verbal communication, but also cognitive delays. Cognitive delays were defined as impaired facial and eye-pair recognition in Sinzig et al. (2008). Participants with only ASD had higher scores than participants with both ASD and ADHD indicating more impairment.

Research on the dual diagnosis of ADHD and ASD has shifted from a sole focus on etiology to an increased focus on treatment. ADHD is one of the few neuropsychiatric disorders in which the use of pharmacological treatment in ADHD outperforms behavioral treatment (MTA Groups, 1999). Analysis of parent and teachers reports compared community care, behavioral management, medication management, and combined management among four symptoms domains as rated by parents and teachers. These symptoms include hyperactivity/impulsivity, internalizing, social skills, and parent-child arguing. While combined management consistently had the lowest mean score across all four areas, medication

management had the second lowest mean score for hyperactivity and internalizing symptoms. Within social skills and parent arguing, the mean score of medication management had overlap with the mean score of community care and behavioral treatment. The mean overlap was depicted by similar overall scores on a graph at specific time intervals during prolonged treatment. Therefore, 1 in 4 patients with comorbid ASD and ADHD are treated with psychostimulants (Donald P. Oswald, 2007). Earlier studies focused on a psychostimulant, methylphenidate, in the use of treatment of ADHD symptoms in patients with comorbid ASD and ADHD. Only recently have more randomized, placebo-controlled clinical trials been carried out on a non-psychostimulant, i.e., atomoxetine. As more studies emerge on the reduction of symptoms (efficacy), as well as the magnitude and frequency of adverse effects (tolerability), it is becoming increasingly important clinically to understand the impact treatments have on a patient's wellbeing.

Atomoxetine is a non-psychostimulant drug that was FDA approved in 2002 (Food and Drug Administration, 2002). It is defined as a selective norepinephrine reuptake inhibitor that operates in the prefrontal cortex (Garnock-Jones & Keating, 2009). The exact mechanism of action is not clear, but it is thought that atomoxetine acts on the presynaptic reuptake of norepinephrine. By binding to the presynaptic norepinephrine transporter with high affinity, it induces the release of more catecholamines and dopamine in the *prefrontal cortex* (Bymaster et al., 2002). The most common adverse events for atomoxetine include but are not limited to decreased appetite, headache, and somnolence, (Garnock-Jones & Keating, 2009). Though methylphenidate appears to have a better effect in reducing symptoms in ADHD patients than

nonstimulants, this may not hold true for patients with a dual diagnosis, especially in terms of whether adverse effects of psychostimulants outweigh reduction of ADHD symptoms.

Ghanizadeh et. al (2012) published a review that focused on the short-term effects of atomoxetine in patients with ADHD and autism (Ghanizadeh, 2012). A solid conclusion could not be drawn on the positive effects of atomoxetine in reducing ADHD symptoms, as the studies included were both controlled and uncontrolled, and the studies were short term (no more than ten weeks). The authors recommended that more controlled clinical trials should be performed in the future.

Reichow et al. (2013) published a meta-analysis on the efficacy and tolerability of methylphenidate, clonidine, and atomoxetine in patients with autism and ADHD (Brian Reichow, Fred R. Volkmar, & Michael H. Bloch, M.D., 2013). With 6 included studies, the authors' conclusion focused on the improvement of symptoms in patients treated with methylphenidate. At the time, clonidine and atomoxetine results were preliminary but promising because there were significant improvements in ADHD symptoms in patients taking atomoxetine within Harfterkamp et al. (2012).

Patra et al. (2019) published a meta-analysis that also focused on the efficacy and tolerability of atomoxetine for children with adolescents that have comorbid ADHD (Patra, Nebhinani, Viswanathan, & Kirubakaran, 2019). Though the study was more recently published, it has several limitations. Patra et al. (2019) justified excluding studies that overlap with one of their included studies (i.e., Harfterkamp et al., 2012) due to a lack of parent and teacher rated

surveys (Harfterkamp et al., 2012). Patra et al. (2019) also stated that the data from Harfterkamp

et al. (2012) could not be pooled with data from another included study (i.e., Handen et al., 2015)

because Harfterkamp et al. (2012) presented data as least mean squares (Handen et al., 2015).

Data available in 2010 in clinicaltrials.gov (NCT00380692) for the same participants published

by Harfterkamp et al. (2012), however, provided the relevant data in the form of raw means,

standard deviations, and sample sizes. When coding Harfterkamp et al. (2012), Patra et al. (2019)

also artificially dichotomized a variable that is continuous, specifically data from the Clinical

Global Impressions-ADHD-I, collapsing continuous data into only two categories. This is

problematic since it lowers the statistical power of the data analysis. Data presented in

Harfterkamp et al. (2012) could, in fact, be converted into individual patient raw data (since the

frequencies of each category are presented in this study), so there is no need to collapse and

dichotomize CGI-ADHD-I scores. Patra et al. (2019) also excluded SNAP-IV teacher data from

Handen et al. (2015) due to wrongfully assuming there was no data to pool. Additionally, Patra

et al. (2019) did not include a study conducted by McDougle et al. (2017), despite the fact that it

met their eligibility criteria and was available in the clinicaltrials.gov database that Patra et al.

(2019) indicated that they searched. By excluding McDougle et al. (2017), 60 patients were not

considered in the meta-analysis, so the total number of patients in Patra et al. (2019) was only

177 patients, decreasing the potential sample size by 1/3. Patra et al. (2019) also excluded

Tumuluru et al. (2017) from quantitative analysis but discussed its results in the text.

Given the limitations of these three aforementioned reviews/meta-analyses, an updated

meta-analysis and systematic review would help clinicians and researchers derive stronger

conclusions on the positive impact atomoxetine might have in treating patients with ASD and

ADHD. Specifically, a more rigorous and larger meta-analysis examining the efficacy and tolerability of atomoxetine is needed.

The aim of this thesis is to carry out a systematic review and two meta-analyses to determine the efficacy and tolerability of atomoxetine in patients with ASD and ADHD. This thesis contains two components: 1) analysis of the efficacy of atomoxetine, and (2) analysis of the tolerability of atomoxetine in patients with comorbid ASD and ADHD. This thesis, therefore, includes (1) conduction of an electronic search based on specific eligibility criteria, (2) extraction of raw data from relevant studies, and (3) quantitative synthesis of efficacy data using standardized mean difference scores (specifically Cohen's d) as the relevant metric for ADHD post-test outcomes, and risk differences as the relevant metric for tolerability (i.e., differences in frequency of adverse events between participants taking atomoxetine versus those taking placebo).

It was hypothesized that if patients with ASD and ADHD are treated with atomoxetine for at least one week, they will demonstrate less ADHD symptoms, relative to the control group. Although there was not a specific a priori hypothesis regarding tolerability, the differences in frequencies of adverse events were examined between patients who took atomoxetine versus those who took placebo.

Methods

The following methods are adapted from Reichow et al. (2013) and adhere closely to the PRISMA checklist for systematic reviews and meta-analyses.

Search Strategy for Identification of Studies and Data Source

On January 24, 2019, a search for relevant studies, was conducted on PubMed.gov using "https://www.ncbi.nlm.nih.gov/PubMed/". The following search terms were used: ("autism spectrum disorder"[All Fields] OR "ASD"[All Fields] OR "autism"[All Fields] OR "autistic"[All Fields] OR "Asperger*"[All Fields] OR "PDD"[All Fields] OR "pervasive developmental disorder"[All Fields]) AND ("atomoxetine hydrochloride"[MeSH Terms] OR ("atomoxetine"[All Fields] AND "hydrochloride"[All Fields]) OR "atomoxetine hydrochloride"[All Fields] OR "atomoxetine"[All Fields]). All studies had to be published in English, the population was limited to humans, and the article types were limited to "randomized clinical trials," and "clinical trial."

A second search was conducted on January 24, 2019 on "clinicaltrials.gov, using the search terms: "autism spectrum disorder" OR "ASD" OR "autism" OR "autistic" OR "Asperger*" OR "PDD" OR "pervasive developmental disorder" | "atomoxetine hydrochloride" OR (atomoxetine AND hydrochloride) OR atomoxetine. The limiter of "interventional" was used for study type.

Selection of Studies

Studies qualified for inclusion in the meta-analyses if they met the following eligibility criteria. Participants had to have a diagnosis of at least one of the following: Autism spectrum disorder, Asperger's disorder, Autistic disorder, or Pervasive Developmental Disorder, not otherwise specified. Studies could have investigated participants who had a comorbid diagnosis of ADHD, but they were still eligible as long as the participants met the diagnostic criteria for ASD. Studies had to be randomized, double-blind, placebo-controlled trials comparing atomoxetine with a placebo. The atomoxetine had to be administered for at least 1 week. Finally, studies had to include data on either an ADHD outcome or adverse event(s).

Outcome Measures

The outcomes for the meta-analysis of efficacy of atomoxetine on ADHD symptoms were posttest, between-groups differences (i.e., differences between atomoxetine and placebo) in hyperactivity-impulsivity, attention, or overall ADHD symptoms. For the meta-analysis of atomoxetine tolerability, the outcomes were between-groups differences in presence or absence of adverse events, either during the acute phase of the study or post-test.

Acceptable ADHD symptom measures included common surveys and checklists filled out by parents, teachers, and clinicians, as well as ADHD-relevant, performance-based motor and neuropsychological tasks. More specifically, the studies included in the present thesis measured ADHD symptomology using the following: Conners' Parent and Teacher Rating Scales (Conners, 2001), SNAP-IV Rating Scale (Swanson, 1992), ADHD Rating Scale (DuPaul & Anastopoulos, 1998), generic DSM-IV ADHD symptom scales, Clinical Global Impressions

scale for improvement of symptoms and ADHD (Busner & Targum, 2007), and a variety of

ADHD-relevant, performance-based motor and neuropsychological tasks. An example of a

neuropsychological score/measure would be response inhibition, which is the ability to delay

responses, to interrupt ongoing responses and inhibit responses (Barkley, 1999).

Data Extraction

Data was extracted and inputted into a Microsoft excel spreadsheet using a structured

coding scheme. The following study information and raw data for calculation of effect sizes were

extracted: full study citation, description of ADHD outcomes or adverse events, types of ADHD

outcomes, e.g., inattention and hyperactivity/impulsivity, and types of adverse events. Adverse

events include gastrointestinal, general, vascular, neurological, psychological, etc. Means,

standard deviations, sample sizes, and raw frequency of dichotomous events were also extracted

for ADHD outcomes and/or adverse events. In some cases, Excel-based calculators were used to

transform raw data from a given study into data necessary for calculation of effect sizes, e.g.,

when a study provided the 95% confidence interval for a group mean score rather than the

standard deviation.

For the ADHD outcome meta-analysis, when participants in the atomoxetine group had

less post-test ADHD symptoms than participants in the placebo group, effect sizes were coded in

the positive direction. Effect sizes were coded in the negative direction when participants in the

atomoxetine group had greater post-test ADHD symptoms than participants in the placebo group.

For the adverse events meta-analysis, effect sizes were coded in the positive direction when

participants in the atomoxetine group had fewer adverse events than those in the placebo

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condition, and effect sizes were coded in the negative direction when participants in the atomoxetine group had more adverse events than participants in the placebo group.

Adverse events were coded as falling into one of three potential categories: (a) all-cause mortality, (b) serious adverse events, or (c) other (not including serious) adverse events. These categories and their operational definitions were adapted from the criteria used in clinicaltrials.gov. In addition, all adverse events that were initially coded as "other (not including serious) adverse events," were then coded into one of the following categories: gastrointestinal disorders, general disorders, infections, and infestations, nervous system disorders, psychiatric disorders, renal and urinary disorders, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders, and vascular disorders. Finally, all adverse events that were initially coded as "other (not including serious) adverse events," were then even further subdivided by coding them into the more specific type of adverse events, e.g., coded "Diarrhea" after it had been initially coded as "other (not including serious) adverse events," and then coded as "gastrointestinal" in the aforementioned previous two coding steps.

Quantitative Data Analysis

A fixed-effect model assumes there is only one true effect size shared by all relevant studies, irrespective of potential differences in their methodological characteristics (Salkind, 2010). For this thesis, a random effects model was used instead, since the assumptions of this model are considered more representative of real-world data (National Research Council, 1992).

Heterogeneity tests for both meta-analyses were conducted to determine *whether* the degree of observed variance across studies could be attributed to chance or not. The Q statistic and its associated p-value was used to conduct this test.

In addition, the I^2 statistic, as seen in equation 1, was utilized to determine the *magnitude* of the variance that could be attributed to true between-study differences rather than chance.

$$I^2 = 100\% * \frac{Q - df}{Q}$$

Equation 1

ADHD Outcome, Cohen's *d*

In the meta-analysis of ADHD outcomes, the relevant effect size metric is Cohen's *d* (1988), since it provides a standardized between-groups mean difference score. Cohen's *d* was utilized to determine the effect sizes of ADHD symptomology in this thesis. To calculate Cohen's *d*, the means, standard deviations, and sample sizes from the experimental (atomoxetine) and control (placebo) groups were used, as seen in equation 2.

$$d = \frac{|\overline{x}_{experimental} - \overline{x}_{control}|}{SD_{pooled}}$$

Equation 2

where d denotes Cohen's d, $\overline{x}$ denotes the mean, and SD_{pooled} denotes the standard deviation

pooled across the two groups. The pooled standard deviation is calculated using the formula

below in Equation 3 (Ponton & Rovai, 2018),

$$SD_{pooled} = \sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{n_1 + n_2 - 2}}$$

Equation 3

where n_1 and SD_1 denote the sample size and standard deviation, respectively for the

experimental group, and n_2 and SD_2 denote the sample size and standard deviation, respectively,

for the control group.

Cohen's (1988) benchmarks for d were used to interpret results. Specifically, Cohen

(1988) suggested that a d of 0.20 is considered small, 0.50 is considered medium, and 0.80 is

considered large. In one instance, ADHD outcome data were presented as raw dichotomous

frequency data, and these data were transformed into Cohen's d.

Absolute Risk Difference for Adverse events

In the context of this thesis, a risk difference is defined as the difference in risk of a

particular adverse event between two groups. Risk difference scores were used to compare the

two groups.

Adverse events are dichotomous/binary, meaning they are either present or absent. A common 2x2 used in research was considered for presence or absence of an event. The total number of patients in treatment and control groups, and the total number of patients who experienced an adverse event in the treatment and control groups were considered in this table and when determining the risk difference.

By using equation 4, the risk difference can be determined across several different studies to determine if atomoxetine or placebo carries a greater risk in leading to an adverse event

$$Risk\ difference = \frac{a}{a+b} - \frac{c}{c+d}$$

Equation 4

Where $\frac{a}{a+b}$ denotes the proportion of adverse events occurring for the treatment group, and $\frac{c}{c+d}$ denotes the proportion of adverse events occurring for control group.

Publication Bias

Studies that have findings that are statistically significant are more likely to be published rather than studies with nonsignificant results, leading to potential publication bias (Joober, Schmitz, Annable, & Boksa, 2012). Potential publication bias was, therefore, assessed using (a) Begg and Mazumdar's (1994) rank correlation, (b) Egger's regression intercept (Egger, Davey Smith, Schneider, & Minder, 1997) and (c) Duval and Tweedie's trim and fill procedure (Duval & Tweedie, 2000; Weinhandl & Duval, 2012). If publication bias is present, Duval and Tweedie's trim and fill procedure provides for statistical correction of such bias.

A visual representation used to examine potential publication bias is a funnel plot (Sterne et al., 2011). A funnel plot, in this thesis, is a scatter plot of the standard errors of the effect size from each study on the vertical axis and the effect size itself (i.e., either atomoxetine's effect on ADHD symptoms or the risk difference in presence of adverse events) on the horizontal axis. An inverted funnel with effect sizes that are distributed asymmetrically in the quadrants (specifically void in the lower left quadrant) suggests potential publication bias.

Meta-Analytic Procedure

All analyses for ADHD outcomes and risk differences in adverse events were conducted using Comprehensive Meta-Analysis, Version 2 software (Borenstein, 2005). These meta-analyses included calculation of overall effect sizes, tests of heterogeneity, and publication bias analyses. When more than one effect size was present in a single study, these effect sizes were averaged, in order to maintain the statistical assumption of the independent effects.

Results

Included studies

      The initial search on clinicaltrials.gov and PubMed.gov resulted in the identification of fourteen studies. During the first phase, the abstracts and titles were initially screened and two studies that did not match the inclusion criteria were excluded. Two additional studies were considered ineligible when the full manuscript was reviewed using the inclusion and exclusion criteria.

      During extraction of data, two additional studies were removed. Harfterkamp et al. (2014) was excluded since the hyperactivity data was drawn from a measure on the Aberrant Behavior Checklist (ABC), which is used for children with ASD. Harfterkamp et al. (2013) was excluded because ADHD outcomes for atomoxetine were not compared to a placebo, rather the effects were compared at different time points.
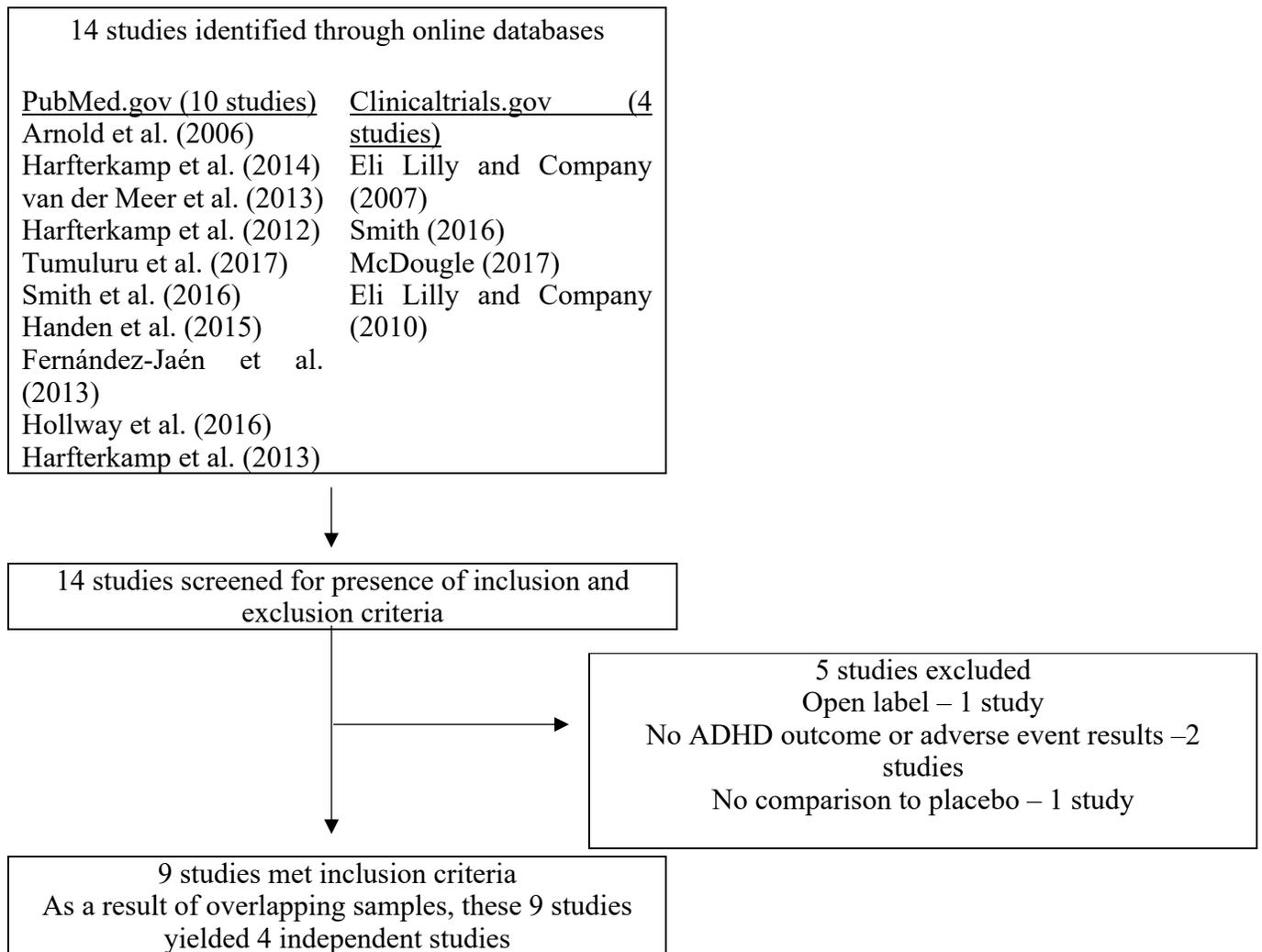
```
┌─────────────────────────────────────────────────────────────────┐
│          14 studies identified through online databases           │
│                                                                   │
│  PubMed.gov (10 studies)    Clinicaltrials.gov        (4          │
│  Arnold et al. (2006)       studies)                              │
│  Harfterkamp et al. (2014)  Eli  Lilly  and  Company              │
│  van der Meer et al. (2013) (2007)                                │
│  Harfterkamp et al. (2012)  Smith (2016)                          │
│  Tumuluru et al. (2017)     McDougle (2017)                       │
│  Smith et al. (2016)        Eli  Lilly  and  Company              │
│  Handen et al. (2015)       (2010)                                │
│  Fernández-Jaén   et   al.                                        │
│  (2013)                                                           │
│  Hollway et al. (2016)                                            │
│  Harfterkamp et al. (2013)                                        │
└─────────────────────────────────────────────────────────────────┘
                              │
                              ▼
┌─────────────────────────────────────────┐
│  14 studies screened for presence of     │
│  inclusion and exclusion criteria         │
└─────────────────────────────────────────┘
                              │            ┌──────────────────────────────────────┐
                              │──────────▶ │         5 studies excluded            │
                              │            │       Open label – 1 study            │
                              │            │  No ADHD outcome or adverse event     │
                              │            │      results –2 studies               │
                              ▼            │  No comparison to placebo – 1 study   │
┌─────────────────────────────────────────┐└──────────────────────────────────────┘
│      9 studies met inclusion criteria     │
│  As a result of overlapping samples,      │
│  these 9 studies yielded 4 independent    │
│  studies                                  │
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Figure 1. Workflow of included studies

Study Characteristics

The 9 included studies consisted of 301 participants. The age range of subjects was 5-17 years of age. The average length of treatment, in weeks, was 8.5 weeks. The majority of studies reported both presence of adverse events and ADHD outcomes. ADHD outcomes included presence/absence of meeting DSM-IV ADHD criteria at post-test, ADHD-R:S, CTRS-R:S, and SNAP-IV. One study included performance-based, ADHD-relevant neuropsychological test data.

Table 1: Characteristics of Included Studies

Study	Patients (n)	Mean age, (range in years)	Outcome measures	Length of treatment (weeks)
Arnold et al., 2009	16, n versus n	9.3 (5-15)	DSM-IV, CGI-S, and CGI-I, Motor Tasks, adverse events	6
Eli and Company, 2010**	97, 48 versus 49	9.9 (6-17)	CGI-ADHD-I, DSM-IV, CTRS-R:S, ABC, neuropsychological and motor tasks, adverse events	28
Harfterkamp et al., 2012	97, 48 versus 49	10.0 (6-17)	ADHD-RS, CGI-ADHD-I, CTRS-R:S, adverse events	10
van der Meer, et al., 2013**	97, 48 versus 49	10.0 (6-17)	Neuropsychological and motor tasks, ADHD-RS, CTRS-R:S	8
Handen et al., 2015***	64, 32 versus 32	9.5 (5-14)	SNAP-IV, CGI-I, adverse events	10
Smith, 2016***	64, 32 versus 32	8.4 (5-14)	SNAP-IV, adverse events	10
Smith et al., 2016***	22, 16 versus 6	8.4 (5-14)	SNAP-IV	34
McDougle, 2017	60, 29 versus 31	8.8 (5-15)	ADHD-RS, CGI-I, adverse events	8
Tumuluru et al., 2017	128, 64 versus 64*	8.1 (5-14)	Adverse events	10

Note: All studies were double-blind placebo controlled, Arnold et al. (2005) is a cross over trial, patient number is determined by patients enrolled.
* ATX and PBO were both collapsed with parent training for adverse events
** Overlap with Harfterkamp et al. (2012)
***Overlap with Tumuluru et al. (2017)

Quantitative Data Synthesis

Effect sizes of ADHD outcomes

Aggregated across all included studies, results indicated that participants in the

atomoxetine groups had better ADHD outcomes than participants in the placebo groups, and that

this difference was statistically significant ($\bar{d}$=0.297, 95% confidence interval [CI]= 0.034-0.560,

p<0.05; see table 2). Results also indicated no demonstrable heterogeneity across effect sizes

(p=0.843 I^2=0, and Q-value=0.826, $\tau^2 = 0$). When specifically examining effect sizes for

ADHD outcomes based on measures of overall ADHD symptoms (rather than specific measures

of either hyperactivity or inattention), the effect size was 0.411 (95% CI= 0.119-0.703), see table

3. Here, too, there was no demonstrable heterogeneity, (p=0.953, I^2=0, and Q-value=0.097, $\tau^2 =$

0).

Table 2: Random Effects Meta-Analysis of Overall ADHD Outcomes

Study Name	*Statistics for Each Study*			
	$\bar{d}$	*95% CI*	*Z-value*	*p*
Arnold et al. (2016)	0.219	-0.478-0.916	0.617	0.537
Harfterkamp et al. (2012)	0.183	-0.232-0.597	0.864	0.388
McDougle (2017)	0.475	-0.052-1.003	1.768	0.077
Tumuluru et al. (2017)	0.361	-0.219-0.940	1.220	0.222
	0.297	0.034-0.560	2.217	0.027

Note. [a] Positive effect sizes indicate better ADHD outcomes for the atomoxetine group than the placebo group. *
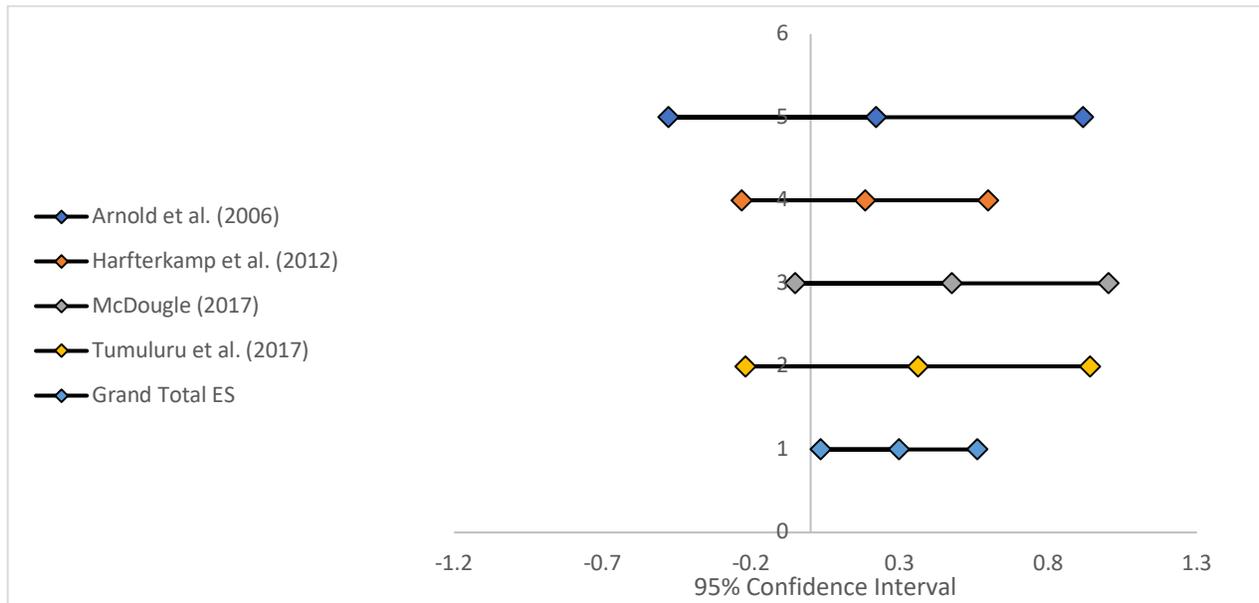*p<.05*

Figure 2. Forest plot of overall ADHD outcomes

Table 3: Random Effects Meta-Analysis of Outcomes Based on Overall ADHD Measures Only

Study Name	Statistics for Each Study			
	$\bar{d}$	95% CI	Z-value	p
Harfterkamp et al. (2012)	0.369	-0.051-0.788	1.721	0.085
McDougle (2017)	0.475	-0.052-1.003	1.768	0.077
Tumuluru et al. (2017)	0.416	-0.222-1.054	1.277	0.201
	0.411	0.119-0.703	2.760	0.006

Note. [a] Positive effect sizes indicate better ADHD outcomes for the atomoxetine group than the placebo group. [*] *p<.05*
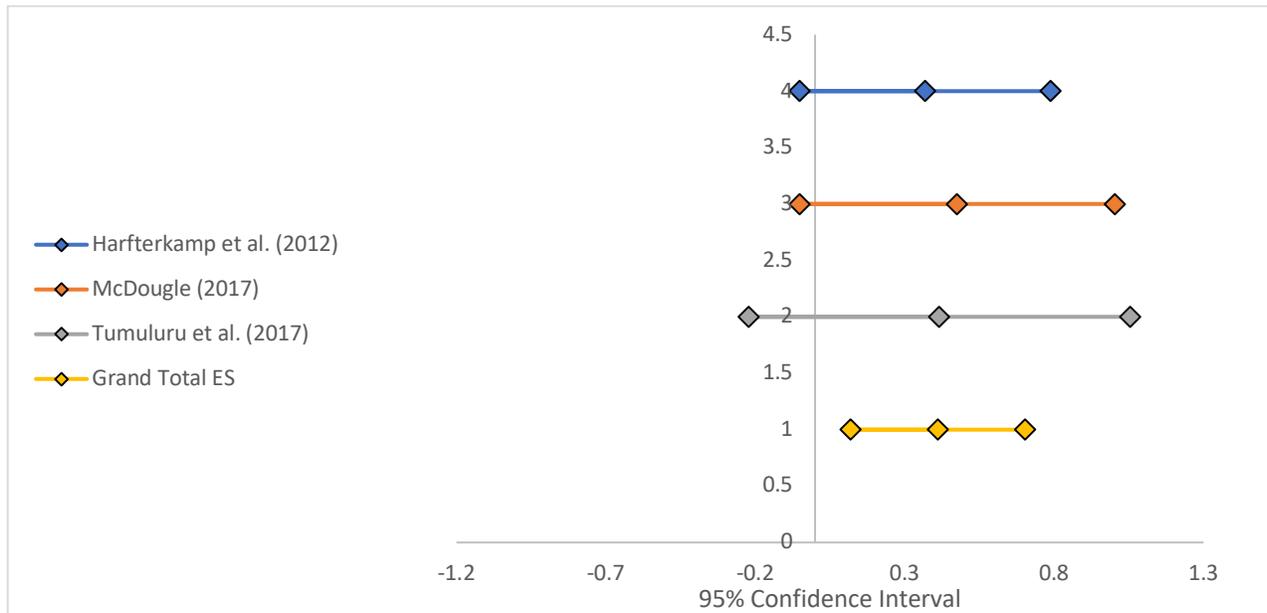
Figure 3. Forest plot of overall ADHD outcomes only

The effect of the treatment also extended to the specific ADHD outcome measures of attention and hyperactivity-impulsivity. The effect size for attention was 0.345 and was statistically significant (95% CI= 0.092-0.598, p=008). There was no demonstrable heterogeneity, p=0.26, I^2=0, and Q-value=0.469, $\tau^2 = 0$. The effect size for hyperactivity-impulsivity was 0.393 and was statistically significant (95% CI= -0.190-0.805, p=0.002). There was no demonstrable heterogeneity, p=0.931, I^2=0, and Q-value=0.46, $\tau^2 = 0$. The effect size for ADHD-relevant, performance-based neuropsychological measures was -0.044 and was not statistically significant (95% CI= -0.451-0.362, p=0.831). Heterogeneity was not examined for this outcome type, since only one study provided data.

Table 4: Random Effects Meta-Analysis of Attention outcome in ADHD

Study Name	Statistics for Each Study			
	$\bar{d}$	95% CI	Z-value	p
Arnold et al. (2006)	0.181	-0.516-0.877	0.509	0.611
Harfterkamp et al. (2012)	0.391	-0.022-0.804	1.854	0.064
McDougle (2017)	0.443	-0.083-0.969	1.650	0.099
Tumuluru et al. (2017)	0.276	-0.219-0.771	1.092	0.275
	0.345	0.092-0.598	2.672	0.008

Note. [a] Positive effect sizes indicate better ADHD outcomes for the atomoxetine group than the placebo group. [*] *p<.05*
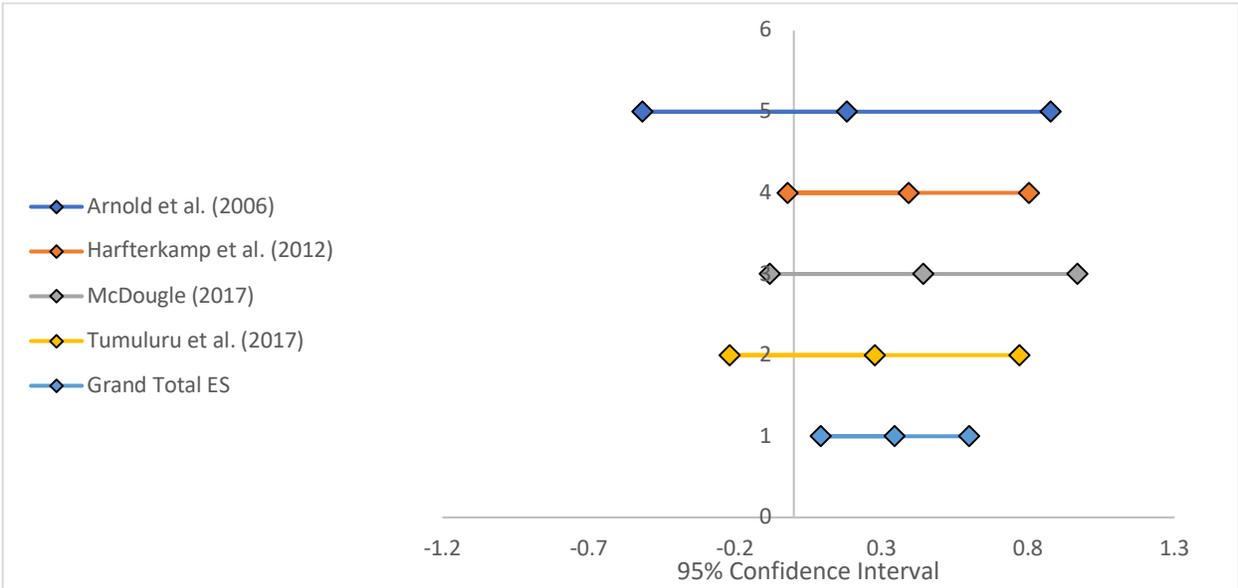

Figure 4. Forest plot of attention outcome in ADHD

Table 5: Random Effects Meta-Analysis of ADHD Hyperactivity-Impulsivity

Study Name	Statistics for Each Study			
	$\bar{d}$	95% CI	Z-value	p
Arnold et al. (2006)	0.284	-0.414-0.982	0.797	0.426
Harfterkamp et al. (2012)	0.412	-0.004-0.828	1.941	0.052
McDougle (2017)	0.523	-0.006-1.052	1.938	0.053
Tumuluru et al. (2017)	0.308	-0.190-0.805	1.213	0.225
	0.393	0.139-0.648	3.030	0.002

Note. [a] Positive effect sizes indicate better ADHD outcomes for the atomoxetine group than the placebo group. [*] *p<.05*
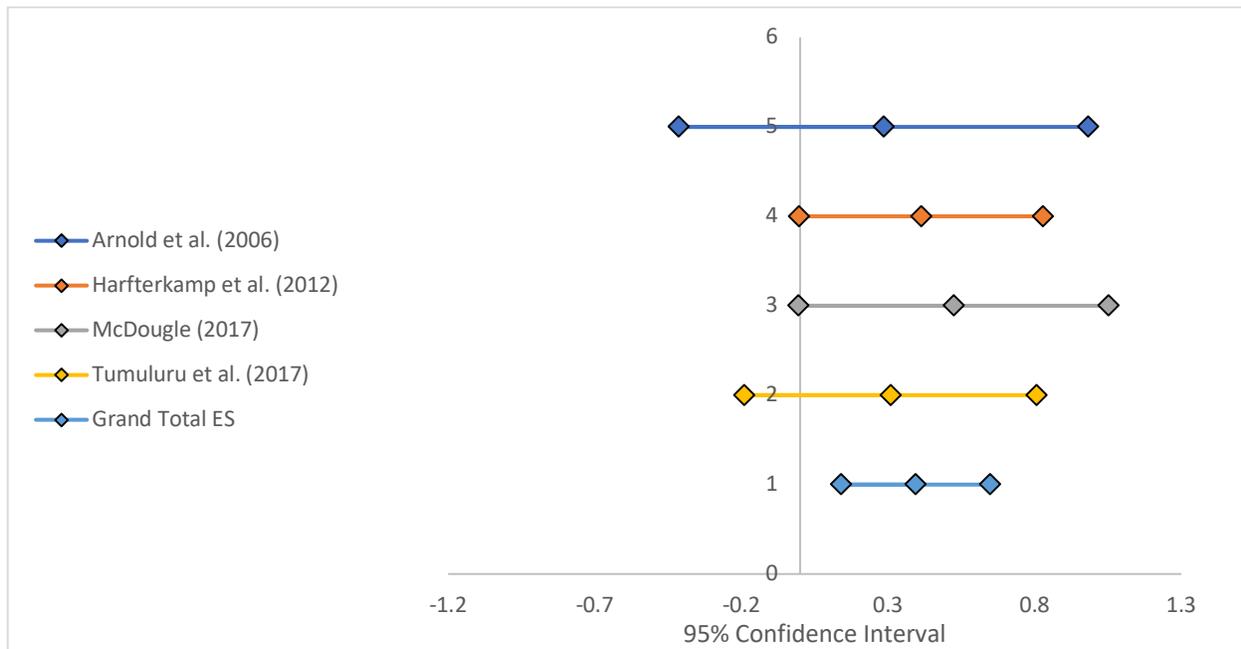

Figure 5. Forest plot of ADHD hyperactivity-impulsivity

Table 6: Random Effects Meta-Analysis of Neuropsychological Performance

Study Name	Statistics for Each Study			
	$\bar{d}$	*95% CI*	*Z-value*	*p*
van der Meer et al. (2013)	-0.044	-0.451-0.362	1-0.213	0.831
	-0.044	-0.451-0.362	1-0.213	0.831

Note. a Positive effect sizes indicate better ADHD outcomes for the atomoxetine group than the placebo group. *
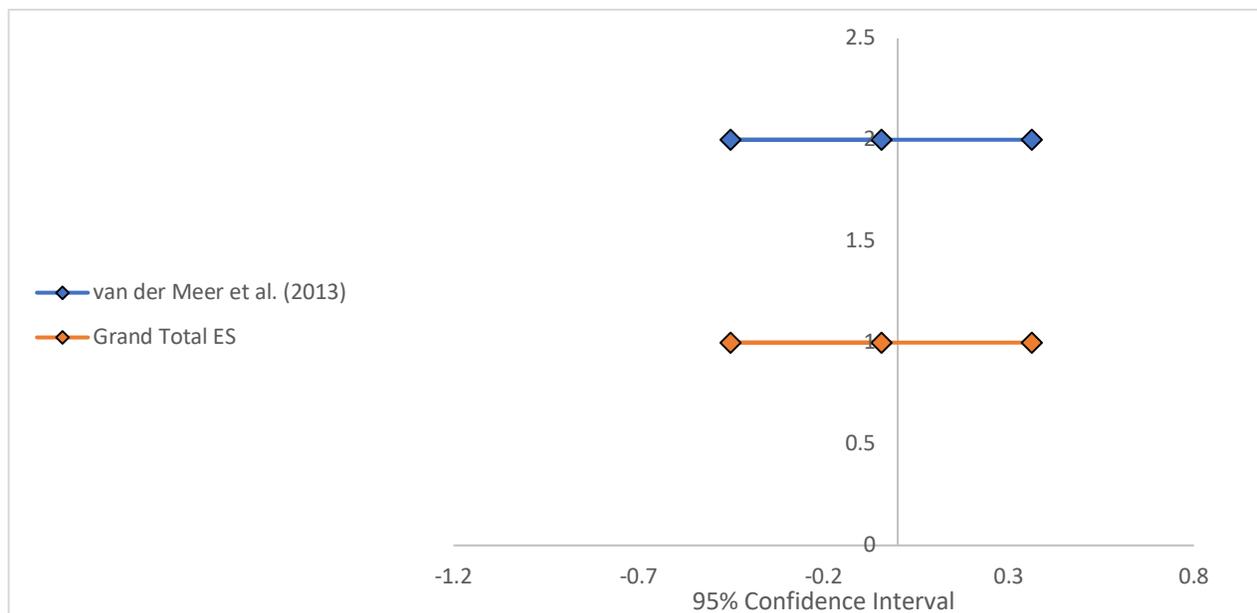*p*<.05

Figure 6. Forest plot of neuropsychological performance

Effect sizes of adverse events

The risk difference for adverse events was -0.042, as detailed in table 7, indicating that the atomoxetine group had about 4% greater frequency of adverse events. Nevertheless, this aggregated risk difference was not statistically significant. Results indicated that there was no demonstrable heterogeneity, p=0.953, I^2=0, and Q-value=0.097, $\tau^2 = 0$.

Table 7: Random Effects Meta-Analysis of Overall Adverse Events Only

Study Name	Statistics for Each Study			
	Risk difference	*95% CI*	*Z-value*	*p*
Arnold et al. (2006)	-0.092	-0.367-0.184	-0.654	0.513
Harfterkamp et al. (2012)	-0.078	-0.191-0.035	-1.348	0.178
McDougle (2017)	-0.014	-0.006-1.052	-0.195	0.845
Tumuluru et al. (2017)	-0.013	-0.158-0.130	-0.219	0.827
	-0.042	-0.132-0.026	-1.206	0.228

Note. [a] Negative effect sizes indicate greater frequency of adverse events in the atomoxetine group than in the placebo group.
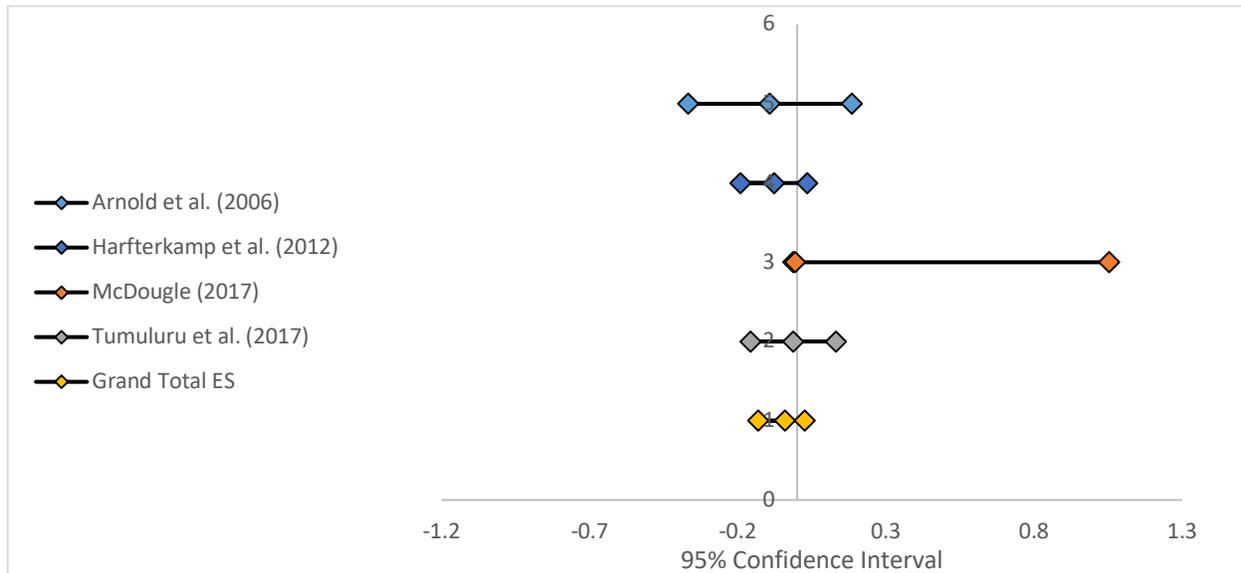
Figure 7. Forest plot of overall adverse events

Publication Bias for overall effect sizes

For overall ADHD outcomes, the Duval and Tweedie trim and fill method indicated that no studies needed to be imputed to correct for potential publication bias. Using Begg and Mazumdar's rank correlation (and kendall's tau with continuity correction), the tau was 0.00, and the p-value (1-tailed) was 0.50, indicating that there was no demonstrable publication bias. Egger's regression intercept was 0.80 and had a p-value of 0.333, again indicating the lack of demonstrable publication bias.

For overall adverse events, the Duval and Tweedie trim and fill method indicated that no studies needed to be imputed to correct for potential publication bias. Using Begg and Mazumdar's rank correlation (and Kendall's tau with continuity correction), the tau was 0.00, and the p-value (1-tailed) was 0.50, indicating that there was no demonstrable publication bias.

Egger's regression intercept was -0.32 and had a p-value of .403 as it is greater than 0.05, again indicating the lack of demonstrable publication bias.

A graphic representation of potential publication bias can be seen in figures 8 and 9. Although there were only four independent studies, visual inspection of the symmetry of the funnel plots does not indicate any clear cause for concern regarding potential publication bias.
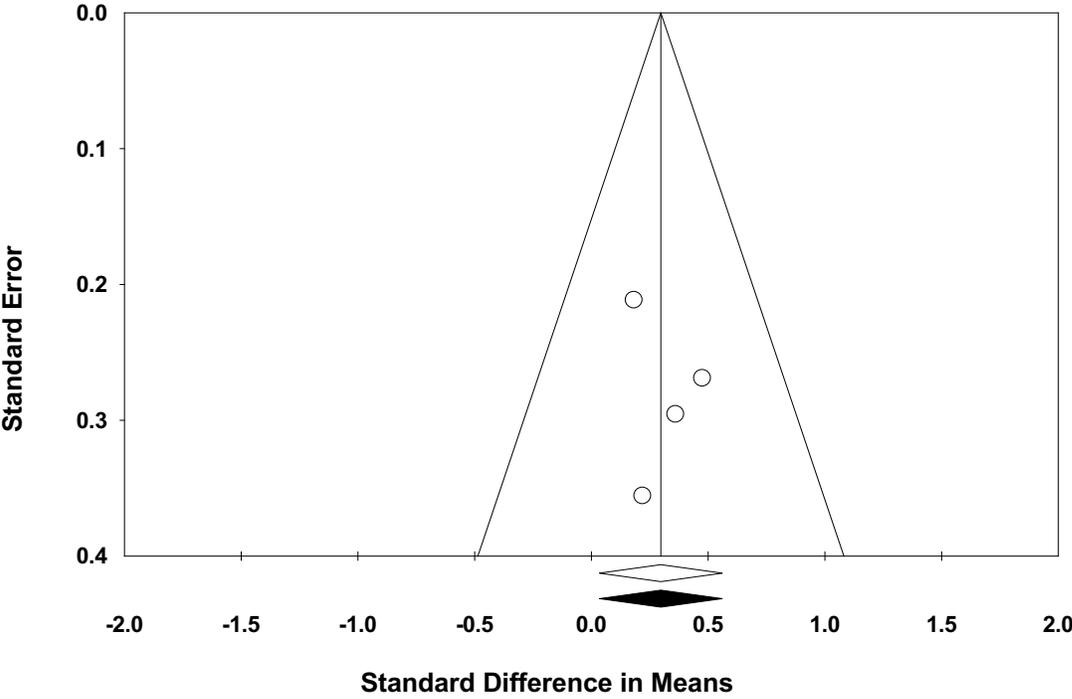

Figure 8. Funnel plot for potential publication bias in ADHD outcomes
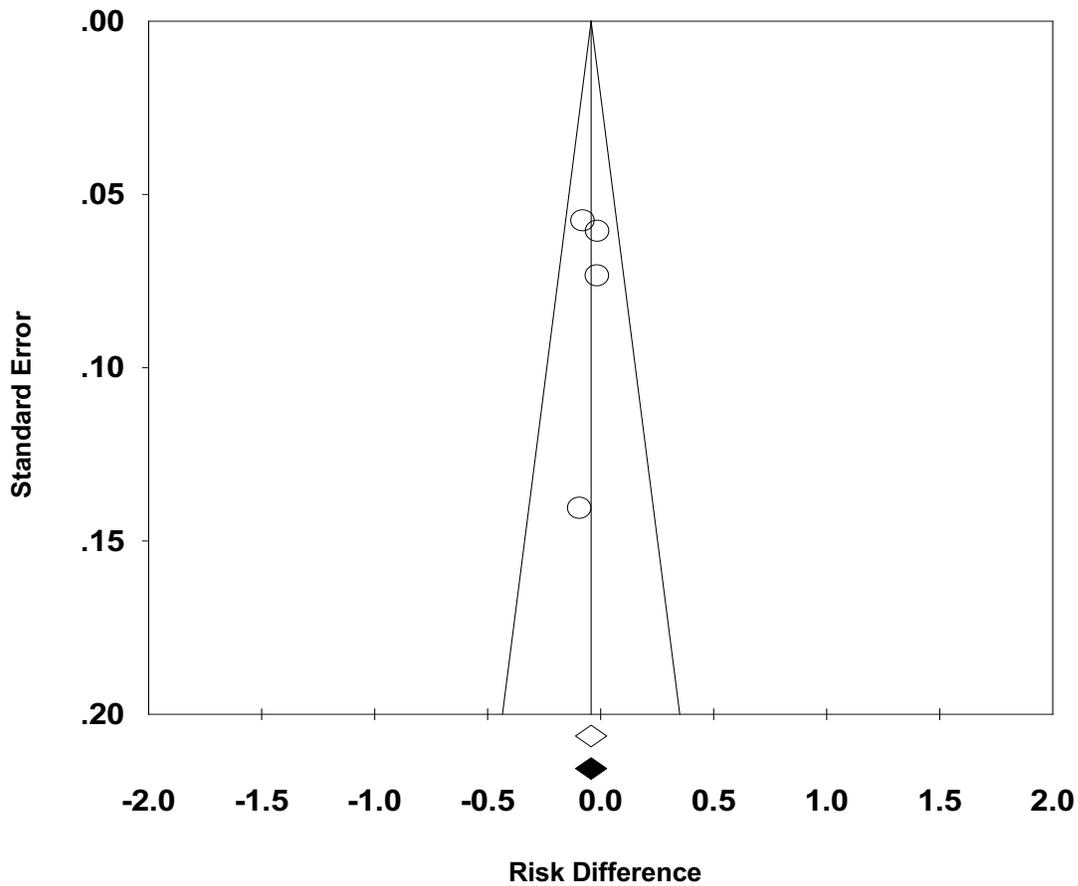
Figure 9. Funnel plot for potential publication bias in presence of adverse events

Limitations

In addition to the several conclusions made, there are some limitations that should be considered. There were only four independent studies, given that two of these four studies had overlapping samples with other included studies. Although the total number of participants in the present meta-analysis was larger than the one conducted by Patra et al. (2019), the overall sample size of the present study still remained somewhat small, suggesting that caution is warranted in generalizing conclusions towards the population of ASD patients with ADHD symptoms. Second, neuropsychological tests were only present in one study, which appears to

have lowered the overall ADHD outcomes effect size, as seen in table 2. It is possible that ADHD outcomes may be better measured using ADHD symptom-specific measures, rather than performance-based neuropsychological tasks whose underlying constructs may differ from that of ADHD symptomatology. Third, the quality of included studies was also variable, given that Arnold et al. (2006) was a cross over study and Tumuluru et al. (2017), Smith et al. (2016), Handen et al. (2015), and Smith (2016) included parent training in addition to the use of atomoxetine and placebo.

Future Research

Given the limited literature on atomoxetine in patients with ASD and ADHD symptoms, a backwards reference search of primary studies included in meta-analyses in this area, as well as searches of additional electronic databases and contacting the authors of published primary studies to solicit references to additional studies, might increase the sample size for a future meta-analysis. Additionally, a search for relevant theses and dissertations could also be conducted. In addition to the analyses carried out for publication bias and heterogeneity, a "leave-one-out" sensitivity analysis could be conducted to ensure that no single study disproportionately impacts the findings. As more studies are published on other non-psychostimulants such as clonidine ER, and guanfacine ER, an additional meta-analysis on the aforementioned medications might allow clinicians and researchers to expand their understanding of non-psychostimulants.

Conclusion

The findings of this study support the hypothesis that the non-psychostimulant atomoxetine is efficacious in terms of overall ADHD, attention, and hyperactivity-impulsivity symptoms in ASD patients who had ADHD symptoms. Although the frequency of adverse events was larger for atomoxetine than for placebo, this difference was not statistically significant. Finally, results indicated a lack of demonstrable heterogeneity or publication bias.

Discussion

Since previous meta-analyses have been carried out in determining the efficacy and tolerability of pharmacological treatments, this thesis extends this literature in a number of ways. Specifically, this thesis included the gathering of more recent articles, including data otherwise excluded from other analyses, and use of raw data to calculate more accurate effect sizes that avoided artificial dichotomization of variables that are continuous in their nature (this artificial dichotomization occurred in several instances in previous meta-analytic work).

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