Pharmacologic Treatment of Repetitive Behaviors in Autism Spectrum Disorders: Evidence of Publication Bias

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KEY WORDS

antidepressive agents, autism, meta-analysis, pervasive child development disorders, publication bias

ABBREVIATIONS

ASD—autism spectrum disorders
CI—confidence interval
OCD—obsessive-compulsive disorder
RRB—restricted and repetitive behavior
SMD—standardized mean difference
SRI—serotonin receptor inhibitor
SSRI—selective serotonin reuptake inhibitor

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WHAT'S KNOWN ON THIS SUBJECT: Although several randomized trials have examined the efficacy of serotonin receptor inhibitors in the treatment of repetitive behaviors, there still remains clinical uncertainty as to whether these agents are effective in treating such behaviors in children and adults with autism spectrum disorders.

WHAT THIS STUDY ADDS: The goal of this meta-analysis was to examine randomized trials of serotonin receptor inhibitors for treating repetitive behaviors in autism spectrum disorders. Although a small but significant effect of these agents was observed, this effect is likely due to the selective publication of trial results.

abstract

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OBJECTIVE: The goal of this study was to examine the efficacy of serotonin receptor inhibitors (SRIs) for the treatment of repetitive behaviors in autism spectrum disorders (ASD).

METHODS: Two reviewers searched PubMed and Clinicaltrials.gov for randomized, double-blind, placebo-controlled trials evaluating the efficacy of SRIs for repetitive behaviors in ASD. Our primary outcome was mean improvement in ratings scales of repetitive behavior. Publication bias was assessed by using a funnel plot, the Egger's test, and a meta-regression of sample size and effect size.

RESULTS: Our search identified 5 published and 5 unpublished but completed trials eligible for meta-analysis. Meta-analysis of 5 published and 1 unpublished trial (which provided data) demonstrated a small but significant effect of SRI for the treatment of repetitive behaviors in ASD (standardized mean difference: 0.22 [95% confidence interval: 0.07–0.37], z score = 2.87, $P < .005$). There was significant evidence of publication bias in all analyses. When Duval and Tweedie's trim and fill method was used to adjust for the effect of publication bias, there was no longer a significant benefit of SRI for the treatment of repetitive behaviors in ASD (standardized mean difference: 0.12 [95% confidence interval: −0.02 to 0.27]). Secondary analyses demonstrated no significant effect of type of medication, patient age, method of analysis, trial design, or trial duration on reported SRI efficacy.

CONCLUSIONS: Meta-analysis of the published literature suggests a small but significant effect of SRI in the treatment of repetitive behaviors in ASD. This effect may be attributable to selective publication of trial results. Without timely, transparent, and complete disclosure of trial results, it remains difficult to determine the efficacy of available medications. *Pediatrics* 2012;129:e1301–e1310

As many as 1 in 100 children are diagnosed with an autism spectrum disorder (ASD),[1] and recent epidemiologic findings suggest that autism is 3 times more prevalent than previously thought.[2–4] Autism is characterized by disturbances in social function and communication, and the presence of repetitive behaviors.[5] Restricted and repetitive behaviors (RRBs) include stereotyped motor mannerisms, restricted patterns of interest, atypical sensory interests, and the insistence for things to remain exactly the same.[6] Repetitive sensorimotor behaviors tend to be present over the years and rarely disappear altogether; meanwhile, behaviors associated with the "insistence on sameness" seem to worsen with age.[7] Repetitive behaviors can cause significant difficulties for the individual with autism at school, and they may interfere with the ability to learn and partake in daily activities.[8] In addition, these symptoms produce stress among caregivers.[9]

Repetitive behaviors in autism share some overlap with characteristic symptoms of obsessive-compulsive disorder (OCD).[10] When compared on a series of repetitive behaviors, children with ASD engage in similar levels of "sameness" behaviors and repetitive movements as children with OCD, as reported by their parents.[11] Patients with ASD and OCD share, to varying degrees, a number of features, including compulsive behavior that is often focused around routines and rituals. In ASD, there is a higher prevalence of "compulsive-like behaviors," including hoarding, touching, tapping or rubbing rituals, and self-damaging or self-mutilating behaviors.[12–14] Interestingly, relatives of individuals with autism are more likely to have OCD, or to display obsessive-compulsive behaviors, compared with the rest of the population, thus suggesting familiality in both disorders.[15,16] Current evidence suggests an overlap in affected neural and monoamine systems that may bring about repetitive behavior in both OCD and ASD, including an affected SLC6A/serotonin system and the presence of cortico-striatal-thalamic circuitry dysfunction in both disorders.[17] Given the similarities between some of the repetitive behaviors of ASD and OCD,[18] many have speculated whether overlapping symptoms will respond to the same medications, including selective serotonin reuptake inhibitor (SSRIs).[19]

SSRIs displayed greater efficacy in the treatment of OCD compared with placebos in 17 separate placebo-controlled trials.[20] Meta-analysis demonstrated that patients with OCD were nearly twice as likely to respond to treatment with serotonin receptor inhibitor (SRI) pharmacotherapy than to placebo. For SSRIs, the number needed to treat (ie, the required number of patients who must be treated with an SSRI for 1 to respond who would not have responded with placebo[21]) was estimated at 5 (95% confidence interval [CI]: 4–8).[20] Furthermore, meta-analysis results suggest that higher doses of SSRIs are more effective than low doses in treating adults with OCD, perhaps signifying that many of these trials may have underestimated treatment effects.[22] Meta-analysis also suggests that SSRIs may be equally effective in treating children with OCD as adults.[23]

Several randomized trials have examined the efficacy of SRIs in the treatment of repetitive behaviors in children with ASD. However, clinical uncertainty remains as to whether SRIs are effective in treating repetitive behavior in children and adults with ASD.[24] Several large-scale studies have reported the use of SRIs among a substantial minority of children with ASD.[25–27] The goal of this meta-analysis was to examine the randomized, placebo-controlled trials of SRIs in ASD to determine the efficacy of these medications in treating repetitive behaviors. We examined possible moderators of SRI efficacy in the ASD population by means of stratified analyses and meta-regression. We sought to examine whether dose or type of SRI medication, age of ASD population, or measure of repetitive behaviors affected measures of SRI efficacy. Finally, we explored a number of indicators of publication bias as part of our standard procedure for pursuing a meta-analysis.

METHODS

Search Strategy for Identification of Studies

Two reviewers searched PubMed for all relevant clinical trials. The PubMed search was conducted by using the search strategy ("Serotonin Uptake Inhibitors"[MeSH] OR "Antidepressive Agents"[MeSH]) AND "Child Development Disorders, Pervasive"[MeSH]). PubMed filters were activated to further limit the search to meta-analyses or randomized controlled trials. In addition, ClinicalTrials.gov was searched for completed, unpublished trials of relevance to this analysis. The ClincialTrials.gov search was conducted by using a targeted search of the term "autism" and limited to completed trials. There were no language limitations on these searches.

Study Selection

Two reviewers evaluated all articles obtained by using this search strategy to determine if the articles were potentially eligible for inclusion in this meta-analysis. Studies were included if they met the following inclusion criteria: (1) randomized, double-blind, placebo-controlled trials comparing an SRI medication (fluoxetine, citalopram, fluvoxamine, sertraline, escitalopram, paroxetine, or clomipramine) with placebo; (2) duration of medication use lasted at least 4 weeks; (3) the trial measured the effect of medication on repetitive behaviors and obsession

and compulsion severity; and (4) participants had a diagnosis of a pervasive developmental disorder (autism, Asperger's syndrome, pervasive developmental disorder not otherwise specified, or Rett syndrome). Trials were considered randomized when investigators explicitly stated them to be so in the methods section of their publication. Trials in which other psychoactive substances were required to be taken in parallel with the targeted medication were also excluded.

Outcome Measures

Our primary outcome measures were mean improvement in repetitive behavior (including obsessions and compulsions), as captured by using rating scales. Acceptable clinical measures, in order of preference, included the Children's Yale-Brown Obsessive-Compulsive Scale modified for pervasive developmental disorders,[28] the Yale-Brown Obsessive-Compulsive Scale[29] or the Children's Yale-Brown Obsessive-Compulsive Scale[30] (based on subject age), and additional measures assessing repetitive behaviors, including the Aberrant Behavior Checklist (stereotypic behavior dimension).[31] A hierarchy of selected RRB and/or obsessive-compulsive rating scales for testing outcome measures was determined a priori to avoid any treatment effect inflation (which would have otherwise occurred by selecting studies for inclusion in the meta-analysis whose measures provided evidence for the greatest treatment effect).

Meta-Analytic Procedure

Excel spreadsheets were used to extract data from included articles. Data extracted included type of medication, average and maximum dose of medication, duration of trial, age range and average age in trials, method of analysis (intention-to-treat versus completers), sample size, and adverse effect frequency. In addition, ratings of trial quality were determined by using the scale developed by Jadad et al[32] (a measure on the appropriateness of each study's randomization and double-blinding procedure, and also the degree to which patient withdrawals and dropouts were reported in the study). Missing information was requested from study investigators. Information from completed, unpublished trials of relevance was also requested from the study investigators, as listed in ClinicalTrials.gov.

We examined the difference between treatment and placebo for the desired outcome by calculating the standardized mean difference by using Comprehensive Meta-Analysis, a comprehensive software program for the analysis and display of meta-analytic data (http://www.meta-analysis.com/). The use of the standardized mean difference as a measure was favored over weighted mean difference because rating scales differed between the included studies.

Publication bias was first explored by plotting the effect size against SE for each trial (funnel plot). Larger studies with greater sample sizes are more precise; they therefore tend to be plotted toward the top of the funnel plot (ie, they have a lower SE) and cluster near the mean effect size. Meanwhile, smaller studies (with higher SEs) appear toward the bottom of the graph and do not cluster around the mean effect size, given that that their results are more widely variable. In the presence of publication bias, missing unfavorable or nonsignificant trials with smaller effects will contribute to the asymmetry of the funnel plot by failing to evenly distribute about the mean effect size, thus producing an asymmetric plot; meanwhile, in the absence of publication bias, studies included in the meta-analysis will be symmetrically scattered about the mean effect size, given the randomness of the sampling error.[33] A fixed (as opposed to random) effects model was used for the meta-analysis because there was considerable evidence of publication bias in the literature.

In addition, publication bias was statistically tested by using the Egger test (a linear regression method that specifies the level of asymmetry evidenced in a funnel plot)[34] and by determining the association between adjusted sample size and effect size in meta-regression. Adjusted sample size was calculated by adding together the sample size from parallel-group trials and the sample size (multiplied by 2) from crossover trials (given that, in crossover trials, the same subjects received both the placebo and the SRI under study in sequence, and thus were included in the calculation of the adjusted sample size twice). For the analyses of publication bias, the one unpublished trial with data we were able to obtain was excluded.[35]

Heterogeneity of treatment response was determined by means of 2 separate statistical estimates using Comprehensive Meta-Analysis. First, a Q statistic was used to provide a test of statistical significance indicating whether the differences in effect sizes are due to subject-level sampling error alone or other sources. In addition, we estimated heterogeneity by using the I^2 statistic, which estimates the proportion of between-studies variance.

For secondary analyses, several subgroup analyses and meta-regression were performed. Stratified subgroup analysis in Comprehensive Meta-Analysis was used to assess the effects of the following: (1) the SRI agent used; (2) the type of trial (crossover versus parallel group); and (3) the method of analysis (completers versus intention-to-treat). We used the test for subgroup differences in Comprehensive Meta-Analysis to determine whether subgroups reduced overall heterogeneity.[36] We initially intended to also examine the effects of age group (child versus adult) and rating scale used on measured SRI

efficacy. However, there were not enough trials in several of the subgroups to conduct these analyses.

Meta-regression was performed in Comprehensive Meta-Analysis. To examine the association between SRI efficacy and continuous variables such as dose of SRI (in clomipramine equivalents), trial duration, trial methodologic quality (as measured by using the Jadad scale), and adjusted sample size, we used a meta-regression technique. For meta-regression, the standardized mean difference (SMD) in repetitive behaviors improvement with SRI treatment was the dependent variable, and our variable of interest was the independent variable. Studies were weighted by using the generic inverse variance method, a meta-analytic procedure that makes use of treatment outcome estimates and their SE for the purpose of calculating an overall estimate of effect (eg, whether SRIs are effective for the treatment of RRBs in ASD). Our *P* value of significance threshold was selected to be $<.05$ for the primary analysis, as well as for all subgroup analyses and meta-regression. Any significant findings should be regarded as exploratory because we did not adjust for inflation of false-positive error from our 6 secondary analyses.

RESULTS

Included Studies

Our initial PubMed and Clinicaltrials.gov search identified 15 studies that were potentially eligible for inclusion in this meta-analysis. Four of the studies found by means of this original search were excluded, including 1 meta-analysis, 2 nonrandomized controlled trials, and 1 randomized controlled trial of fluvoxamine for autism that was a duplicate of a similar study published in Japanese.[37–40] An additional study initially considered to be eligible for meta-analysis was also dropped given that it did not provide quantitative information on baseline and outcome measures of repetitive behavior, thus making it impossible to assess improvement within this behavioral domain.[41] The Clinicaltrials.gov search also identified 5 completed and unpublished studies that were potentially eligible for inclusion in this meta-analysis.[35,42–45] We sent requests to the principal investigators by e-mail for data associated with each of these trials. We received trial data in response to our requests for only 1 trial.[35] The available information for these unavailable, unpublished trials is presented along with the demographic characteristics for included trials in Table 1. Figure 1 depicts our selection strategy for inclusion of trials.

Six eligible trials were identified for inclusion in this meta-analysis. Table 1 presents the characteristics of the 5 published trials[46–50] and the 1 unpublished trial included in this meta-analysis.[35] Three of these 5 published trials reported a statistically significant benefit of SRI treatment in ASD.[46–47,49] Two published trials and the 1 available unpublished trial reported some or no benefit of antidepressant treatment.[35,48,50]

Efficacy of SRI Treatment of Autism

Overall, meta-analysis of 6 trials involving 365 participants demonstrated a small effect of SRIs for the treatment of repetitive behaviors, including obsessions and compulsions, in autism (SMD: 0.22 [95% CI: 0.07–0.37], *z* score = 2.87, $P < .005$). Figure 2 provides a Forest plot depicting the benefit of SRI use in the treatment of autism. There was evidence of significant heterogeneity (heterogeneity Q value: 15.95; df = 5 [$P = .007$], $I^2 = 69\%$). When the 1 unpublished trial was excluded from the meta-analysis, these results did not change appreciably (SMD: 0.22 [95% CI: 0.07–0.37], *z* score = 2.84, $P = .005$; heterogeneity Q value: 15.93, df = 4 [$P = .003$], $I^2 = 75\%$). A random effects model showed a greater effect of SRI treatment than the fixed effects model (SMD: 0.37 [95% CI: 0.06–0.68], *z* score = 2.37, $P = .018$).

Our literature search first alerted us to the presence of 5 completed studies that were possibly eligible for inclusion in this meta-analysis but remained unpublished at the time the manuscript was put together, thus suggesting the presence of publication bias in the field. Both the Egger regression test (intercept = 4.5 [95% CI: 2.3–6.7], $t = 6.6$, $P = .007$) and a regression of adjusted sample size versus trial effect size demonstrated significant evidence of publication bias ($\beta = -.005$ [95% CI: −0.008 to −0.001], *z* score = −2.8, $P = .004$). Figure 3 depicts a funnel plot of the 5 published trials demonstrating significant evidence of publication bias in the literature. Duval and Tweedie's trim and fill method was used to provide an adjusted estimate of the effect of SRI treatment in ASD by taking into account the role of unpublished studies within the field.[33,51] This nonparametric method revealed that there was no longer a significant benefit of SRI for the treatment of repetitive behaviors in ASD when taking into account publication bias (SMD: 0.12 [95% CI: −0.02 to 0.27]).

Type of SRI Medication

Subgroup analysis demonstrated no significant effect of type of medication (test for subgroup difference Q value = 0.25, df = 1, $P = .62$). The 4 trials using SSRIs (SMD: 0.20 [95% CI: 0.02–0.37], $t = 2.23$, $P = .03$) and 2 trials using clomipramine (SMD: 0.29 [95% CI: −0.01 to 0.58], $t = 1.87$, $P = .06$) showed similar results when testing the effects on repetitive behavior symptoms.

For the sake of completeness, a meta-analysis of the individual SRI medications is presented. The 2 trials using citalopram (SMD: 0.04 [95% CI: −0.18 to 0.26]), $t = 0.37$, $P = .72$), and the 1 trial using fluoxetine (SMD: 0.32 [95% CI: −0.00 to 0.64], $t = 1.94$, $P = .05$) showed

TABLE 1 Characteristics of Included Studies

Study	Year	Medication	Sample Size	Design	Length of Treatment	Mean Age	Gender (% Male)	JADAD Score	Mean Dose (mg/d)
Gordon et al[46]	1993	Clomipramine (TCA)	12	Crossover	5 wk	10.4 y	57	3	152
McDougle et al[47]	1996	Fluvoxamine (SSRI)	30	Parallel	12 wk	30.1 y	90	4	277
Remington et al[48]	2001	Clomipramine (TCA)	36	Crossover	7 wk	16.4 y	83	3	128
Hollander et al[49]	2005	Fluoxetine (SSRI)	39	Crossover	8 wk	8.2 y	77	3	10.6
King et al[50]	2009	Citalopram (SSRI)	149	Parallel	12 wk	9.4 y	86	5	16.5
Functional MRI Evaluation of the Effect of Citalopram in Autism Spectrum Disorders,[a] NCT00609531[35]	Active, not recruiting	Citalopram (SSRI)	13	Parallel	12 wk	22 y	Information not provided	3	18.3
McDougle et al,[b] unpublished[52]	Completed	Fluvoxamine (SSRI)	34	Parallel	12 wk	5–18	85	UK	106.9
Study of Fluoxetine in Autism (SOFIA),[b] NCT00515320[43]	Completed 1/09	Fluoxetine (SSRI)	158	Parallel	14 wk	5–17 y	UK	UK	UK
Study of Fluoxetine in Adults With Autistic Disorder,[b] NCT00027404[44]	Completed 10/05	Fluoxetine (SSRI)	48	Parallel	12 wk	18–65 y	UK	UK	UK
Fluvoxamine and Sertraline in Childhood Autism – Does SSRI Therapy Improve Behaviour and/or Mood?[b] NCT00655174[45]	Completed 1/07	Fluvoxamine (SSRI)	108	Parallel	Children were started on 12.5 mg. If no therapeutic effectiveness was observed after 8 wks, then the child's dosage could be increased for an additional 8 wk	3–10 y	UK	UK	12.5
Effectiveness of Early Intervention With Fluoxetine in Enhancing Developmental Processes in Children With Autism,[b] NCT00183359[46]	Completed 2/08	Fluoxetine (SSRI)	19	Parallel	12 mo	30–58 mo	UK	UK	2–20

SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; UK, unknown.

[a] We received trial data in response to our request for relevant data for this trial only.

[b] Studies completed but unpublished. Requests were sent to the principal investigators for data associated with each of these trials.

modest effects on repetitive behaviors, whereas the 1 trial using fluvoxamine (SMD: 1.04 [5% CI: 0.41–1.67], $t = 3.25$, $P = .00$) reported a greater effect.

Dosing of SRI Medication

Meta-regression demonstrated a significant effect of SRI dose on medication efficacy for repetitive behaviors in ASD. Increased dose was significantly associated with greater efficacy in treating repetitive behaviors in ASD ($\beta = .0038$ [95% CI: 0.0012–0.0064], $t = 2.84$, $P < .005$).

Patient Age

Meta-regression did not demonstrate a significant effect of SRI treatment with age ($\beta = .03$ [95% CI: −0.0008 to 0.0530], $t = 1.90$, $P = .05761$). However, at trend levels, increased average patient age in trials was associated with a greater treatment effect.

Trial Characteristics

We found a significant effect of trial methodologic quality (as measured by using the Jadad scale) on the measured efficacy of SRI medications ($\beta = -.22$ [95% CI: −0.40 to −0.03], $t = -2.30$, $P = .02$). Lower-quality trials reported a greater efficacy of SRI treatment.

Effects of method of analysis (intention-to-treat versus completers) were also assessed. Whereas intention-to-treat analyses include all randomized participants in a trial (regardless of whether they completed the randomized controlled trial), completers' analyses only assess the effect of a given medication in participants that actually completed the randomized controlled trial.[53] Method of analysis did not significantly affect SRI efficacy in trials (test for subgroup difference Q value = 3.21, df = 1, $P = .07$). However, the 2 trials that relied on completers' analysis (SMD: 0.45 [95% CI: 0.16–0.74], $t = 3.00$, $P = .003$) showed greater SRI

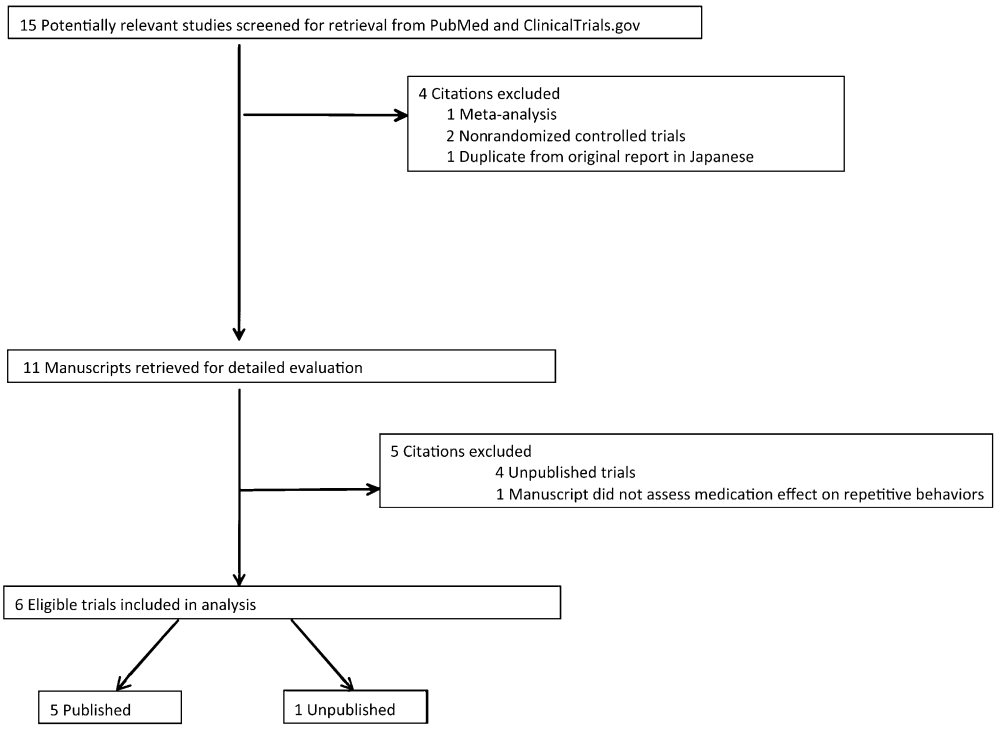

FIGURE 1

Flowchart depicting study selection. Two reviewers evaluated all articles obtained by using this search strategy to determine if they were potentially eligible for inclusion in this meta-analysis. Studies were included in this review if they met the following inclusion criteria: (1) randomized, double-blind, placebo-controlled trials comparing an SRI medication (fluoxetine, citalopram, fluvoxamine, sertraline, escitalopram, paroxetine, or clomipramine) with placebo; (2) duration of medication use lasted at least 4 weeks; (3) the trial measured the effect of medication on repetitive behaviors and obsession and compulsion severity; and (4) participants had a diagnosis of a pervasive developmental disorder (autism, Asperger's syndrome, pervasive developmental disorder not otherwise specified, or Rett syndrome).

efficacy than the 3 trials that used intention-to-treat analysis (SMD: 0.14 [95% CI: −0.04–0.31], $t = 1.50$, $P = .134$) at trend levels.

Stratified subgroup analysis demonstrated no significant difference in SRI efficacy based on trial design (test for subgroup difference Q value = 1.0, df = 1, $P = .32$). Parallel-group (SMD: 0.15 [95% CI: −0.06 to 0.35], $t = 1.41$, $P = .16$) and crossover (SMD: 0.30 [95% CI: 0.08–0.52], $t = 2.69$, $P = .007$) trials reported similar measures of SRI efficacy. Finally, meta-regression demonstrated no significant effect of trial duration on reported SRI efficacy ($\beta = -.042$ [95% CI: −0.103 to 0.020], $t = -1.33$, $P = .18$).

DISCUSSION

RRBs constitute a core feature of ASD. In the past decade, a flurry of research activity has allowed for the better understanding of RRB subtyping and the development of better tools for diagnosing and measuring RRBs. Unfortunately, a gap continues to exist in the literature with regard to the effective pharmacologic treatment of RRBs in children and adults diagnosed with this disorder.[54] Addressing this question remains of utmost importance, given that RRBs continue to be a major barrier toward learning and social adaptation in both children and adults with ASD.

Initial results showed a small effect of SRIs for the treatment of repetitive behaviors in autism, including obsessions and compulsions. However, a closer look at the trials included in this meta-analysis demonstrated significant evidence of heterogeneity and publication bias. It is noteworthy that, after adjusting for publication bias in the literature, the effect of SRI medications in ASD was no longer significant.

As part of this meta-analysis, we also evaluated a number of indicators of publication bias, including funnel plots, adjusted effect sizes after publication had been taken into account using Duval and Tweedie's procedure, and tests for the symmetry of the funnel plots by using Egger's linear regression method. This research made it clear that the effects of SRI treatment in ASD are considerably overrated because of publication bias. In addition, our search strategy uncovered as many completed SRI trials in ASD with unpublished results as have been published, further supporting the influence of potential publication bias on effect estimates.

Publication bias has been demonstrated previously to influence the estimates of

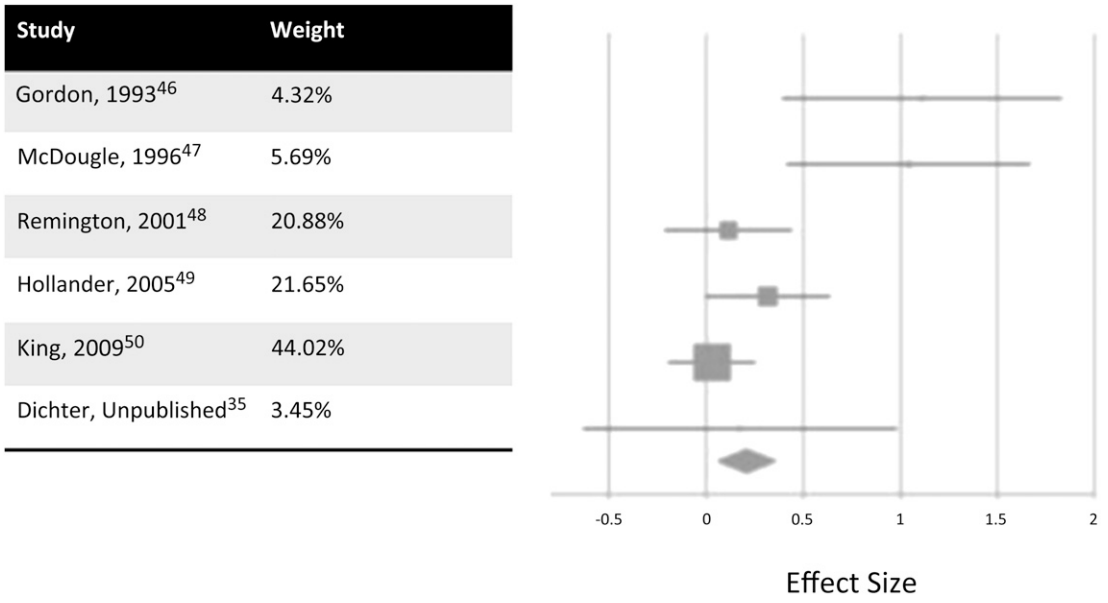

FIGURE 2

Forest plot depicting the benefit of SRI use in the treatment of autism. A meta-analysis involving 6 trials and 365 participants showed that SRIs have a small effect in reducing repetitive behaviors in autism (SMD: 0.22 [95% CI: 0.07–0.37], *z* score = 2.87, *P* = .005). In this figure, solid squares represent each of the studies included in the meta-analysis; increasing square size reflected the increasing weight that a given study was assigned to when computing the summary effect (the latter which was represented by a diamond at the bottom of the graph).

many other interventions in child psychiatry and medicine. The potential efficacy of antidepressant agents has been particularly influenced by this phenomenon. For example, previous research found that only 51% of the antidepressant trials registered with the US Food and Drug Administration reported positive results. By contrast, as many as 94% of trials published in the peer-reviewed literature evaluating antidepressant agents reported positive results.[55]

A particularly influential meta-analysis published in 2004 suggested that published trials of antidepressant agents in children demonstrated greater evidence of efficacy and a more benign risk/benefit profile than those trials that were not published but submitted to regulatory agencies.[56] A time-lag bias in the pediatric antidepressant literature whereby negative trials have a longer time to publication than positive trials has also been demonstrated.[57] Regardless of whether frank publication bias or time-lag bias is the cause of the large unpublished available literature in SRI trials for the treatment of repetitive behaviors in autism, there is a strong possibility that publication has distorted the perception (and evidence) of how effective these medications likely are.

Our meta-analysis is not without limitations. Our analyses were limited by the reduced number of published, randomized, placebo-controlled trials of SRIs in ASD that are currently available and were bound to whichever rating scales the authors used to study RRB outcomes. Unfortunately, in most studies included in this meta-analysis, changes in RRBs were quantified by using a number of scales that were originally written for quantifying obsessions and compulsions in OCD (eg, Children's Yale-Brown Obsessive-Compulsive Scale). The overall lack of specific assessments to better quantify RRBs in autism clinical trials is an ongoing issue in the field and one that complicates meta-analysis research.

When making a decision regarding whether to initiate a medication, it is important to weigh the potential benefits against potential risks. All articles included in this meta-analysis provided data on the adverse events associated with the use of SRIs versus placebo in patients with ASD.[46–50] In general, the adverse event profile of medications was very similar to that observed in the general population. Clomipramine, a tricyclic antidepressant, was poorly tolerated by subjects, with a substantially increased number of dropouts due to adverse effects in the treatment compared with placebo groups. Increased rates of sedation, insomnia, and cardiovascular adverse events were observed with clomipramine compared with placebo. Although SRIs were better tolerated than clomipramine, increased rates of gastrointestinal adverse events were observed compared with placebo. Finally, although perhaps not effective in the treatment of RRBs, there is some evidence to suggest that SRIs may be helpful for the proper management of comorbid anxiety in ASD, and therefore its therapeutic use in ASD should not be completely dismissed.[58]

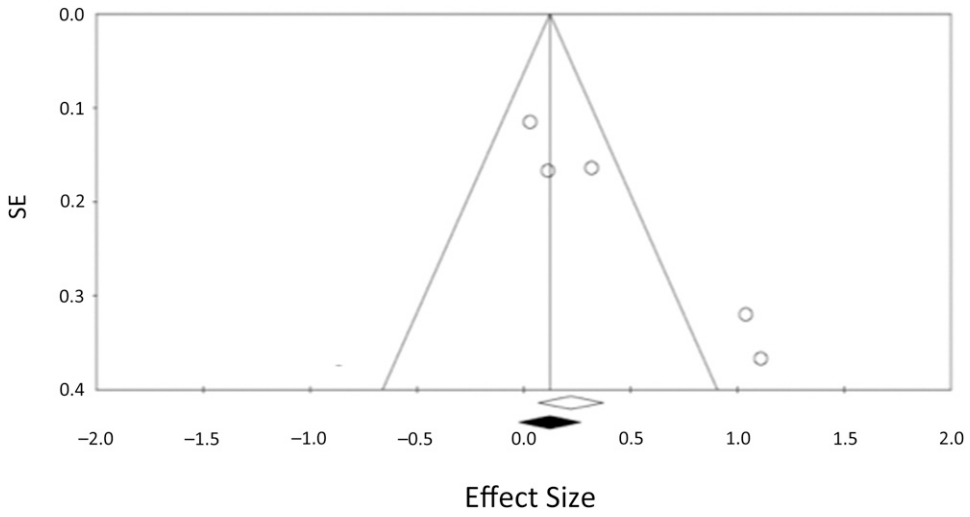

FIGURE 3

Funnel plot analysis as an exploratory tool for assessing publication bias in autism SRI clinical trials. For each trial included in the meta-analysis (represented here by the open circles), the effect size was plotted against the SE. The summary effect size was calculated by using a meta-analysis and is represented by the open diamond at the bottom of the plot; the solid diamond represents the adjusted estimate of the effect of SRI treatment in ASD by taking into account the role of unpublished studies. Additional adjustments were made to make this plot symmetrical. In the absence of publication bias, studies included in the meta-analysis will be symmetrically scattered about the mean effect size, given the randomness of the sampling error. In the presence of publication bias, missing unfavorable or nonsignificant trials with smaller effects will contribute to the asymmetry of the plot by failing to evenly distribute about the underlying true mean effect size. Findings here provided qualitative evidence of publication bias in autism SRI trials.

CONCLUSIONS

RRBs are an important barrier to learning and social functioning in children with ASD and have been speculated by clinicians and researchers to be closely related to OCD symptoms. This hypothesis has led to widespread clinical use and to several randomized, placebo-controlled trials evaluating the efficacy of SRIs in the treatment of repetitive behaviors in ASD. Unfortunately, a large number of these trials have not been published. Meta-analysis of trials with available data demonstrated a small but significant effect of SRIs for the treatment of RRBs in ASD. The effect was no longer significant when publication bias was adjusted for. Further research is needed to find effective treatments for children with ASDs. Identifying effective treatments for these patients will be difficult if partial and selective publication of clinical trials persists, an issue that experts indicate is widespread across all fields of medicine, is not specific to industry or academia (but plagues both), and that may be best addressed with greater enforcement of the registration and reporting of all clinical trials and their results.[59]

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