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THE EFFICACY OF ANTI-PSYCHOTIC MEDICATIONS IN TREATING THE BEHAVIOR, SOCIAL, AND COMMUNICATION DEFICITS ASSOCIATED WITH AUTISM SPECTRUM DISORDERS IN CHILDREN AND ADOLESCENTS: A SYSTEMATIC REVIEW

by

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A thesis submitted in partial fulfillment of the requirements
for the Honors in the Major Program in Interdisciplinary Studies
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and in the Burnett Honors College
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Thesis Chair: Dr. Bernardo Ramirez

ABSTRACT

Background: Autism spectrum disorders (ASD) are a group of complex developmental disabilities which can cause behavior, social, and communication deficits. Anti-psychotic medications are often prescribed when symptoms such as aggression, irritability, hyperactivity, tantrums, and self-injurious behavior occur.

Objective: To determine if anti-psychotic medications improve the behavior, social, and communication symptoms associated with ASD in children and adolescents.

Search Strategy: Electronic literature searches were performed to find relevant studies and utilized the (1) Cochrane Database of Systematic Reviews, (2) Hispanic American Periodicals Index, (3) Medline, (4) PAIS International, (5) ProQuest Dissertations and Theses, (6) PsycInfo, (7) PubMed, (8) Springer LINK, (9) Taylor and Francis Journals, and (10) Sage Premier.

Selection Criteria: Randomized controlled trials (RCTs) or quasi-experimental design (QED) studies of any dose of an anti-psychotic medication compared to a placebo or other prescription drug, in participants with autism spectrum disorder.

Data Collection and Analysis: All studies which met the full-text level criteria were reviewed by a third party to validate the decision of inclusion. Meta-analyses in this review implemented both random and fixed-effects models.

Main Results: Ten RCTs were included. Six studies evaluated a drug versus a placebo and four studies investigated the effects of two separate anti-psychotic medications or the efficacy of an additive medication to a drug and placebo group.

Author's Conclusions: Limited evidence suggests the effectiveness of anti-psychotic medications in treating the behavior, social, and communication symptoms associated with autism; however, further research is needed to determine the implications of long-term use.

ACKNOWLEDGEMENTS

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For my grandparents, Domenick and Doris Manzo, for their unconditional love and encouragement.

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INTRODUCTION

Autism spectrum disorders (ASD) are a group of complex developmental disabilities that result in behavior, social, and communication deficits. Recent data shows that 1 in 88 children have an ASD (CDC, 2012). However, the number of cases of autism appears to be rising. It is not yet clear whether this occurrence is due to improved detection methods and reporting of autism, an actual increase in the amount of cases, or a combination of both (Mayo Foundation for Medical Education and Research, 2010).

There are five different categories of ASDs; autistic disorder (also called "classic" autism), Asperger syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS), Rett syndrome and childhood disintegrative disorder. The American Psychiatric Association's Diagnostic and Statistical Manual-IV, Text Revision (DSM-IV-TR) 1 provides standardized criteria to assist in diagnosing ASD and is summarized as follows:

- Autistic disorder: A person diagnosed with autistic disorder shows clinically significant impairments in social and communication behaviors, as well as restricted, repetitive, or stereotyped patterns of behavior. Beginning prior to 3 years of age, individuals with autistic disorder display deficits or abnormal functioning in a minimum of one of the following areas: (1) social interaction, (2) language as utilized in social communication, or (3) symbolic or imaginative play (American Psychiatric Association [APA], 2000).
- Asperger syndrome: Individuals with Asperger syndrome generally exhibit milder symptoms of autistic disorder. They may have social deficits and display repetitive

behaviors. However, those with Asperger syndrome do not typically display severe language or cognitive deficits (APA, 2000).

- Pervasive developmental disorder not otherwise specified: Those who do not meet all of the criteria for autistic disorder or Asperger syndrome due to atypical or sub-threshold symptomatology or late age of onset may be diagnosed with PDD-NOS. (APA, 2000).
- Rett syndrome: This condition primarily affects girls. It was recently discovered that Rett syndrome is caused by mutations in the methl-CpG-binding protein 2 (MeCP2) gene (Amir & Zoghbi, 2000). Males born with this defective gene do not have a second X chromosome to compensate for the mutation (NINDS, 2011). Consequently, the defect often results in miscarriage, stillbirth, or premature death. Since females have two X chromosomes, the other X chromosome is normal enough for the child to survive. Those with Rett syndrome show typical perinatal and psychomotor development. However, at 5 to 30 months of age individuals experience the loss of previously acquired purposeful hand skills and the onset of severely impaired expressive and receptive language development and clinically significant psychomotor regression (APA, 2000).
- Childhood disintegrative disorder: A condition in which children develop normally before age 10, after which, children may lose language, motor, social, and other skills they previously acquired (APA, 2000).

There is currently no single gene or genetic test that definitively diagnoses autism (El-Fishawy & State, 2010). The diagnosis of autism remains primarily based on clinical observation and assessment of neurological, cognitive, and language abilities. A first step often includes a questionnaire or other screening instrument to collect information about a child's development

and behaviors (NINDS, 2012). Some screening instruments depend entirely on parent observations, while others utilize a combination of parent, physician, and other professional's reports and observations. If the screening shows the possibility of an ASD, a more comprehensive evaluation is recommended including a complete neurological, cognitive, and language assessment (NINDS, 2012).

Social interaction issues are some of the most common deficits associated with ASD. These symptoms often include avoidance or hypersensitivity to eye and physical contact, the presence of neutral or inappropriate facial expressions, difficulty understanding the feelings of others, and not understanding or recognizing personal space boundaries (CDC, 2010).

Communication deficits are frequently seen in individuals with ASD and manifested in their difficulty in using or understanding gestures, and interpreting body language or tone of voice (CDC, 2010). Developmentally, these communication issues can also include delayed speech and language, repetition of words or phrases (echolalia), speaking in an unusual manner, and use of idiosyncratic grammar (CDC, 2010).

Behavior issues can include hyperactivity, impulsivity, aggression, self-injury, and short-attention span. It is quite common for individuals with ASD to display hyper-organized behaviors such as lining up objects or exhibit unusual interests or behaviors that are viewed as obsessive interests or repetitive motions. Individuals with ASD may thrive on routine by following a strict set of rituals. Any change in these types of routines or rituals can lead to severe frustration or tantrums (CDC, 2010).

There is currently no known cure for autism; however, the combination of behavioral therapy, specialized therapies, and medication are commonly used to manage the symptoms of ASD. Medications are frequently implemented when symptoms such as aggression, irritability, hyperactivity, tantrums and self-injurious behavior occur but are not used to treat the core symptoms of ASD. The classes of medications most frequently used to treat the behavioral problems associated with ASD include anti-depressants, stimulants, mood stabilizers, and anti-psychotics. Of these classes, anti-psychotic medications are the most commonly prescribed medication for children with ASD (Cascade, Kalali & Feifel, 2008).

In 2006, the U.S. Food and Drug Administration approved risperidone, an anti-psychotic drug intended for use with adults, for the treatment of irritability in children and adolescents with autism. This general labeling of irritability also included treatment of behaviors such as aggression, self-injury, and tantrums. The effectiveness of risperidone in the treatment of irritability associated with pediatric ASD was examined in two 8-week, placebo-controlled trials monitoring 156 patients aged 5-16 years of age. The results of this study were evaluated and indicated that children treated with risperidone attained significantly improved scores for certain behavioral symptoms associated with autism compared to children being treated with a placebo.

Only one study has been identified that assessed the efficacy of anti-psychotic medications in treating the core features of ASD (Barnard, Young, Pearson, Geddes, & O'Brien, 2002). The study conducted by Barnard and colleagues reviewed 19 trials conducted between 1992 and 1999. Due to the limited number of studies, no restrictions were placed on the study

designs within this review. The majority of studies focused on children between the ages of 4 and 18.

The studies contained a moderately homogenous group of patients who were severely affected by their behaviors that were predominantly aggressive to self-injurious. Two studies implemented a randomized, double blind crossover design with the remaining being prospective, retrospective, or non-randomized. Thirteen studies examined the effects of risperidone, three studies assessed olanzapine, and one study each investigated quetiapine, amisulpride, and clozapine.

Barnard et al (2002) reviewed the effects of these medications on social functioning, repetitive behaviors, language, aggression, hyperactivity, mood, and cognition. The studies analyzed were characterized by a lack of blinding or randomization, an absence of systematic and consistent measures among cases, and the use of small sample sizes, in addition to the use of other medications. Barnard et al (2002) explained that much of the available research was based upon case studies in which researchers may have been biased to only report those patients who responded. The information gathered from these 19 included studies led Barnard and colleagues to conclude that there was inadequate evidence to inform practice reliably and that well designed randomized trials were needed.

Since the report performed by Barnard and colleagues (2002) there have been no systematic reviews or meta-analyses that assess the efficacy of anti-psychotic medications in treating the common behavioral issues associated with ASD in children or adolescents. Thus, the purpose of this study was to conduct a systematic review and meta-analysis to determine the

efficacy of anti-psychotic medications in treating the behavior, social, and communication deficits associated with ASD in children and adolescents and thereby add to the body of knowledge currently available on the topic. This study sought to advance the review performed by Barnard and colleagues by expanding the (1) number of databases accessed in the information retrieval process, (2) the chronological dates used in the information retrieval process, (3) the data analysis to include a quantification of the treatment effects using meta-analytic procedures, and (4) expanding beyond English language only databases.

METHOD

Search Strategy

Electronic literature searches were performed to find relevant studies and utilized the (1) Cochrane Database of Systematic Reviews, (2) Hispanic American Periodicals Index, (3) Medline, (4) PAIS International, (5) ProQuest Dissertations and Theses, (6) PsycInfo, (7) PubMed, (8) Springer LINK, (9) Taylor and Francis Journals, and (10) Sage Premier. To locate pertinent studies the search terms were categorized and combined according to:

Diagnostic: ‘autism’, ‘anti-psychotic’, ‘children’, ‘adolescents’

Symptom: ‘atypical’, ‘behavior’, ‘social’, ‘communication’, ‘speech’, ‘intervention’

Drug Treatment: ‘medication’, ‘trial’, ‘ risperidone’, ‘aripiprazole’, ‘haloperidol’, ‘olanzapine’, ‘thioridazine, ‘quetiapine’, ‘ clozapine’

Study Design: ‘randomized controlled trial’, ‘quasi-experimental design trial’

Inclusion Criteria

Decisions for studies to be included were made at two levels; (1) title and abstract retrieval, and (2) full-text retrieval. Studies included at the title and abstract retrieval level must have met the following criteria in order to advance to the full-text retrieval stage; (1) the use of anti-psychotic medications in treating behavioral outcomes, and (2) participants must have been under 18 years of age. Any title or abstract meeting these conditions advanced to the full text retrieval stage in which a complete manuscript of each study was obtained and evaluated for

inclusion criteria including; (1) the person receiving treatment must have been clinically diagnosed with autism, Asperger syndrome or PDD-NOS, (2) the treatment must have included anti-psychotic medications in treating the behavior, social, or communication issues of children and adolescents, (3) participants must have been between 2 and 18 years of age, (4) there must have been a minimum of three participants included within the clinical trial, and (5) the study must have used a randomized controlled trial or quasi-experimental research design.

Study Coding

All studies which met the full-text level criteria were reviewed by a third party to validate the decision of inclusion. The coding of each included study was performed independently by two coders. Once both coders completed the coding for a study, they compared the coding conclusions. If there were any differences in coding judgments, the differences were discussed to reach a consensus on the coding decision. In the event they were unable to reach a consensus, a third coder evaluated the study and made a final decision. Every article included was coded to determine the reporting of the variables listed below. A codebook was created to provide definitions of each item on the coding form and is located in Appendix B.

Participant Characteristics: The participants for this review must have had a primary clinical diagnosis of autism, Asperger syndrome, or PDD-NOS. Studies involving participants diagnosed with Rett syndrome or childhood disintegrative disorder were not included. Participants must have been between the ages of 2 and 18 years.

Treatment Characteristics: Only psychopharmaceutical interventions to treat the behavior, social, or communication deficits associated with ASD were used as the treatment agent. There were no

restrictions regarding the duration of clinical trial, frequency of medication administration, or dosage of medication(s).

Outcomes Characteristics: The behavior outcomes of interest were those related to aggression, tantrums, self-injurious behaviors, repetitive tendencies, hyperactivity, and irritability. The social outcomes of interest were those related to social withdrawal and social responsiveness. The communication outcomes of interest were those associated with speech, language, and nonverbal communication. Studies that assessed the physiological outcomes of pharmaceutical intervention (e.g., metabolic changes, weight gain, prolactin levels, etc.) were not included.

Design Characteristics: Only randomized controlled trials and quasi-experimental design trials were included in this review. Studies utilizing a single subject, prospective or retrospective research design were excluded.

Data Calculation

Since the outcome data of included studies was presented in varying formats, Comprehensive Meta-Analysis (CMA) (Borenstein, Hedges, Higgins & Rothstein, 2005) software was used to analyze the treatment effect sizes. This software is capable of accepting data in more than 100 different formats in order to convert it to a common effect size and variance.

Effect Size Calculations

The appropriate formula, in CMA (Borenstein et al., 2005) was used to calculate a standardized mean difference with a small sample size correction (Hedges' g). The calculation of

the treatment effect was based on the mean difference between the treated and comparison groups, accounting for the variance of measurement associated with participant performances. The basic formula is as follows:

$$g = \frac{TX_{mean} - CTL_{mean}}{SD_{pooled\ groups}}$$

When means and standard deviations were not provided, treatment effects were calculated using the standard effect size formulae for F-Test, t-test, or p value. All reported values were based on a calculation of Hedges' *g* and were interpreted according to standards provided by Cohen (1988): small effect = 0.0 to .20; medium effect = 0.20 to 0.70; large effect = 0.70 or greater.

Synthesis of Effect Sizes

Using the standardized mean difference (i.e., Hedges' *g*), the effect sizes from each study were weighted by the inverse variance and averaged to create an overall study effect size. If a study reported more than one outcome for the same "treatment vs comparison group" comparison only a single effect size was included in the meta-analysis for any outcome measure. If a study involved more than two groups only the "treatment vs control group" comparison was used to create a single effect size for the study.

Homogeneity Analysis

A homogeneity analysis was applied to examine whether the differences in a set of effect sizes may be considered a result of sampling error and/or a result of other participant and study factors. Data synthesis for this study was conducted using both a random and fixed effects model.

In order to allow for the widest application of the available data, a random effects model was used for all data interpretations and conclusions. In the random effects procedure, the meta-analyses provides effect size estimates that vary across studies as a result of variations among the study population parameters such as age, severity of behavior, as well as errors associated with the sampling of participants within the study populations. Thus, the results from a random effects model provides for an accounting of these variations to allow for a generalization of findings to the population represented by the studies sampled for this review and analysis (Kline, 2004).

Publication Bias

To assess potential publication bias, the trim and fill procedure was applied. The analysis is provided in the resulting funnel plot (Rothstein, Borenstein, and Sutton, 2005).

Sensitivity Analysis

The one study removed analysis examined the impact of a single study effect size on the overall effect size for any outcome with multiple studies measuring the same outcome. The procedures involved the removal of the effect size for a single study, recalculation of the average overall effect for the remaining studies, then removal of the next study effect size while replacing the previous study effect size to calculate the overall treatment effect. This method allowed for a

more precise picture of the contribution of each study to the overall treatment effect results, such that, those studies with larger sample sizes were given proportionately more weight than studies with small samples sizes when estimating the average effect size in any calculation.

Moderator Analyses

Moderator analyses were performed to assess differences in the average effect sizes for the following study-level characteristics; (1) socioeconomic status, (2) sample source, (3) participant severity, and (4) participant ethnicity/race. The moderator analyses were conducted using the fixed effects model.

RESULTS

Search Results

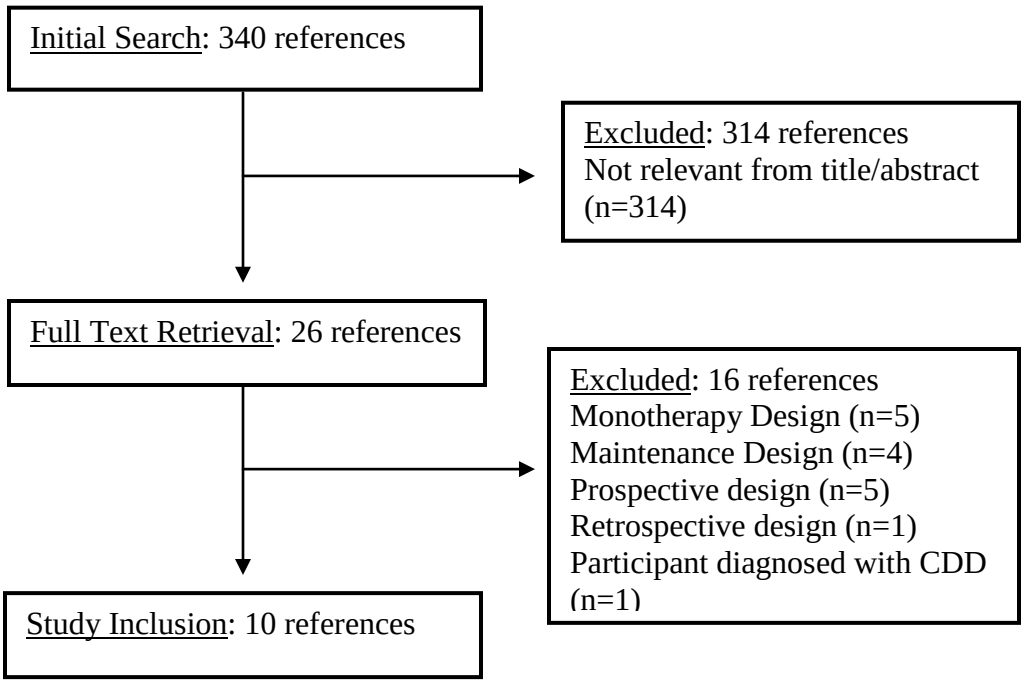


Figure 1: Flowchart of search results

The initial search identified 340 studies. Of these, 314 were excluded as not relevant based on titles or abstracts. The remaining 26 studies were evaluated after retrieval of the full text. Upon review of the 26 studies, 16 studies were excluded for the following reasons. One study; Shea et al. (2004), was excluded in the analysis stage due to the author's inclusion of participants diagnosed with childhood disintegrative disorder. A total of five studies were excluded due to a monotherapy design (Nicholson, Awad, & Sloman, 1998; Findling, Maxwell, & Wiznitzer, 1997; McDougle et al., 1997; Perry et al., 1997; Martin et al., 1999). Four studies were excluded due to utilization of a discontinuation/continuation maintenance study design (Gencer et al., 2007; McCracken et al., 2005; Troost et al., 2005; Marcus et al., 2011). Five

studies were excluded due to the utilization of a prospective case series study design (Fisman & Steele, 1996; Hardan, Johnson, & Hrecznyj, 1996; Malek-Ahmadi & Simonds, 1998; Horrigan, Barnhill, & Courvoise, 1997; Zuddas et al., 1996). Lastly, a study by Posey et al. (1999) was excluded due to a retrospective case series study design. Ten studies met the inclusion criteria to be analyzed in this review. Table 1 shows the characteristics of participants within these studies. While this review allowed for both RCT and QED study designs the ten studies which met inclusion criteria all utilized a RCT design.

Table 1: Characteristics of participants

Study Name	Tx n	Tx Mean Age (yrs)	Tx % Male	Tx Mean Weight (kg)	Com n	Com Mean Age (yrs)	Com % Male	Com Mean Weight (kg)
Dollfus	5	6.9	56%	NR	4	6.9	56%	NR
McCracken	49	8.8	80%	NR	52	8.8	83%	NR
Nagaraj	19	4.8	84%	16.2	20	5.3	90%	18.3
Pandina	20	7.4	70%	30.4	21	7.1	86%	27.3
Luby	11	4.1	81%	19.2	11	4	66%	18.1
Miral	13	10	73%	33.3	15	10.9	87%	42.1
Akhondzadeh	20	7.5	78%	26.2	20	7.1	75%	26
Owen	46	9.7	89%	43.9	49	8.8	86%	40.6
Marcus	47	9.5	89%	43.1	38	10.2	92%	42.2
Rezaei	20	8.2	65%	26.8	20	7.9	70%	27.4

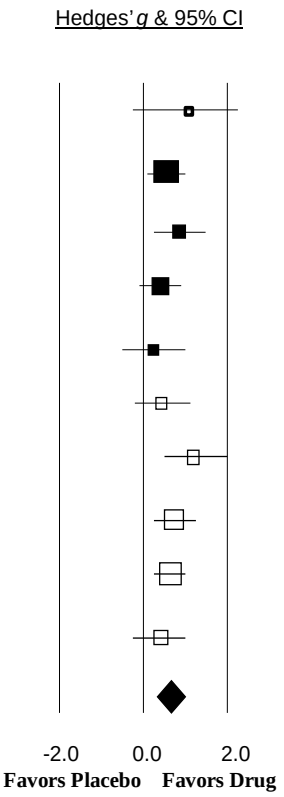
Overall Treatment Effect

An analysis of the general effects of anti-psychotic drug treatment was assessed by first calculating an effect size for all outcomes in all 10 included studies to produce a single study effect size. Next these effect sizes were averaged for each study to produce a meta-analysis of an estimate of the overall treatment impact. Figure 2 displays the average effect of anti-psychotic

medications versus a comparison drug or placebo for all outcomes reported (g = 0.67, p = 0.000, 95% CI = 0.49 to 0.86). This analysis suggested that anti-psychotic medications appear to have a statistically significantly positive effect on children and adolescents diagnosed with ASD to improve the behavior, social, and communication outcomes.

A test of heterogeneity was calculated using a fixed effects model to evaluate the amount of variation in study effect sizes beyond sampling error. The analysis resulted in a non-significant measurement of heterogeneity (Q = 6.516, df = 9, p = 0.719), suggesting that variation in the effect sizes, and thus the treatment effect, can be attributed to factors other than sampling error, namely the drug intervention. To further substantiate this finding the overall analysis was subjected to a random effects model with the resulting g value, lower and upper limits, and p value being identical to the fixed effects result. These findings support the assumption that, in general, the observed effect sizes were drawn from a similar population and generalizations are appropriate to all participants reported in the included studies and potentially to similar studies not included in this review.

Study Name	Year	Comparison	Outcome	Hedges' *g*	Lower Limit	Upper Limit	p-Value	Exp n	Comp n
Dollfus	1992	Amisul v Bromo	Combined	0.925	-0.346	2.215	0.160	5	4
McCracken	2002	Risp v Placebo	Combined	0.576	0.180	0.972	0.004	49	52
Nagaraj	2005	Risp v Placebo	Combined	0.889	0.242	1.536	0.007	19	20
Pandina	2006	Risp v Placebo	Combined	0.637	-0.178	1.453	0.126	20	21
Luby	2006	Risp v Placebo	Combined	0.302	-0.507	1.111	0.465	11	11
Miral	2007	Risp v Halp	Combined	0.549	-0.191	1.288	0.146	13	15
Akhondzadeh	2009	Combined	Combined	1.347	0.281	2.022	0.000	20	20
Owen	2009	Aripip v Placebo	Combined	0.692	0.220	1.103	0.001	46	49
Marcus	2009	Aripip v Placebo	Combined	0.656	0.217	1.092	0.003	47	38
Rezaei	2010	Risp+Topira v Risp+Placebo	Combined	0.421	-0.197	1.039	0.182	20	20
				0.674	0.493	0.856	0.000		



Q= 6.516, df= 9, p=.719

Figure 2: Overall treatment effect

Publication Bias Analysis

Publication bias addresses the possibility that the included studies, which are composed of peer-reviewed publications, may result in an inaccurate measurement of the drug treatment effect. To analyze potential publication bias a funnel plot of standard error by Hedges' *g* was created. Figure 3 shows that the ten studies conform to the shape of the funnel plot suggesting one can be confident that the included studies constitute a representative sample of studies that may have not been identified and included in this review. Furthermore, the trim and fill analysis was then applied to the data, which trims exceptionally large studies and imputes small studies

that are purportedly missing. Under the fixed effect model the point estimate and 95% confidence interval for the combined studies was 0.67 (95% CI = 0.49 to 0.86). Using the trim and fill analysis these values remained unchanged. This symmetry suggests the absence of publication bias.

A second publication bias analysis was also conducted by calculating the number of studies that would have to exist and not be included in this review to significantly alter the obtained treatment effect. This analysis revealed that a total of 123 studies with an average treatment effect size of 0.0 would have to exist in order negate the current overall effect size of 0.67. That is, while it is possible that one or more studies may not have been identified that would have met the inclusion criteria; these data suggest that it is reasonably unlikely additional studies, if identified, would statistically alter the observed treatment effect in this review.

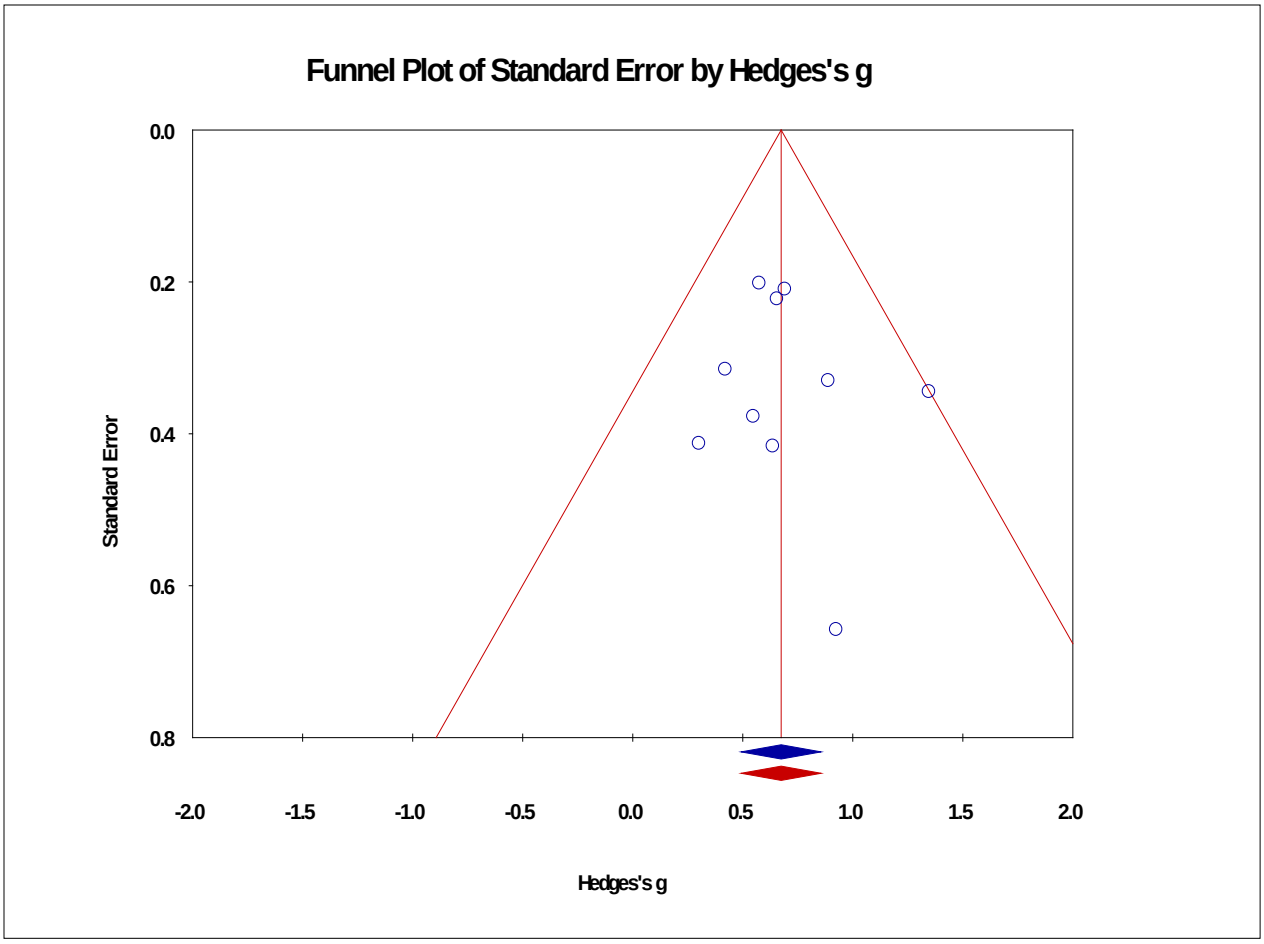


Figure 3: Funnel plot of standard error by Hedges' g

Overall Treatment Effect: Drug versus Placebo

An analysis was performed to evaluate the overall effect size of anti-psychotic medication treatment versus placebo treatment. Four studies were identified that examined the efficacy of risperidone compared to a placebo treatment (McCracken et al., 2002; Nagaraj, Singhi, & Malhi, 2005; Pandina et al., 2006; Luby et al., 2006) while two studies were identified that investigated the efficacy of aripiprazole versus placebo treatment (Owen et al., 2009; Marcus et al., 2009). All dependent variables were categorized into three major types of

outcomes: behavior, social, and communication. The following is a summary of the treatment effects for each outcome category.

Overall Effect for Behavior Outcomes

Several behavior outcomes are represented in the summary data below (e.g., hyperactivity, irritability, stereotypic behavior, etc.). Table 2 provides a summary of both treatment medications. Risperidone exhibited an overall effect of g = 0.67 (p = 0.000, 95% CI= 0.38 to 0.96) and Aripiprazole an overall effect of g = 0.65 (p = 0.000, 95% CI = 0.35 to 0.95). A meta-analysis of all behavior outcomes across both drugs and all studies, resulted in a statistically significant treatment effect of g = 0.66 (p = 0.000, 95% CI = 0.45 to 0.87) in favor of the treated participants for both drug types.

Table 2: Overall effect for behavior outcomes

Study Name	Year	Drug	Hedges' g	Lower Limit	Upper Limit	p-value	Tx n	Ctl n
Luby		Risperidone	0.288	-0.520	1.097	0.484	11	11
McCracken	2002	Risperidone	0.670	0.272	1.068	0.001	49	52
Nagaraj	2005	Risperidone	0.918	0.269	1.567	0.006	19	20
Pandina	2006	Risperidone	0.655	-0.206	1.516	0.136	18	20
Fixed Effects		Risperidone	0.669	0.375	0.963	0.000		
Marcus	2009	Aripiprazole	0.599	0.165	1.034	0.007	47	38
Owen	2009	Aripiprazole	0.692	0.281	1.103	0.001	46	49
Fixed Effects		Aripiprazole	0.648	0.350	0.947	0.000		

Overall Effect for Social Outcomes

The assessment of social outcomes (e.g., social withdrawal, social responsiveness, etc…) was conducted in three studies, all using the anti-psychotic medication risperidone (McCracken et al., 2002; Nagaraj et al., 2005; Pandina et al., 2006). A meta-analytic analysis revealed a statistically significant improvement for the treated participants of $g = 0.55$ (p = 0.000, 95% CI = 0.26 to 0.83). Table 3 presents a summary of the effects associated with each study and an overall aggregate of the treatment effect.

Table 3: Overall effect for social outcomes

Study Name	Year	Drug	Hedges' g	Lower Limit	Upper Limit	p-Value	Tx n	Ctl n
McCracken	2002	Risperidone	0.435	0.043	0.827	0.030	49	52
Nagaraj	2005	Risperidone	0.810	0.169	1.450	0.013	19	20
Pandina	2006	Risperidone	0.566	0.032	1.101	0.038	27	28
			0.545	0.262	0.829	0.000		

Overall Effect for Communication Outcomes

The assessment of the treatment effects on communication outcomes (e.g., inappropriate speech) was also performed in the same three studies as the social outcomes (McCracken et al., 2002; Nagaraj et al., 2005; Pandina et al., 2006) and yielded a statistically significant treatment effect of $g = 0.55$ (p = 0.000, 95% CI = 0.26 to 0.83). Table 4 presents a summary of the effects associated with each study and the meta-analysis of the combined studies for the measurement of social outcome effects.

Table 4: Overall effect for communication outcomes

Study Name	Year	Drug	Hedges' g	Lower Limit	Upper Limit	p-Value	Tx n	Ctl n
McCracken	2002	Risperidone	0.435	0.043	0.827	0.030	49	52
Nagaraj	2005	Risperidone	0.880	0.235	1.525	0.008	19	20
Pandina	2006	Risperidone	0.520	-0.015	1.055	0.057	26	28
			0.545	0.261	0.829	0.000		

Summary of Treatment Effects

Overall, risperidone had a statistically significant effect across studies on behavior (g = 0.66), social (g= 0.55), and communication (g = 0.55) outcome measures, suggesting improved scores for these outcomes were due to the daily treatment intervention of risperidone.

Risperidone vs Placebo Effect as Moderated by SES

In order to assess the potential impact of specified independent variables on the magnitude of the treatment effect, a moderator analysis was conducted for the variables of socioeconomic status (SES), sample source, participant severity, and race/ethnicity. These analyses were conducted under the fixed effects model with a non-significant Q value resulting (p= 0.05). Table 5 illustrates the impact of SES on the effect of risperidone when compared to a placebo. Two studies; McCracken et al. (2002) and Nagaraj et al. (2005), reported participants from an SES group composed of Middle-Upper class participants. One study (Pandina et al., 2006), provided no information regarding the SES of participants and another single study (Luby et al., 2006), had an unclear definition of SES for group participants.

Due to the limited number of studies reporting socioeconomic status, it was not possible to draw a reliable conclusion on the impact this factor had in the measured treatment effect of

risperidone versus placebo. The treatment effect could suggest a potential finding in which studies reporting less information on SES might exhibit smaller treatment effects.

Table 5: Risperidone versus placebo effect as moderated by SES

Moderator	Study Name	Year	Hedges's g	Lower Limit	Upper Limit	p-Value	Tx n	Ctl n
Mid-Up	McCracken	2002	0.576	0.180	0.972	0.004	49	52
Mid-Up	Nagaraj	2005	0.889	0.242	1.536	0.007	19	20
Mid-Up			0.661	0.324	0.999	0		
NR	Pandina	2006	0.637	-0.178	1.453	0.126	20	21
Unclear	Luby	2006	0.302	-0.507	1.111	0.465	11	11
Overall			0.612	0.321	0.903	0		

Risperidone versus Placebo Effect as Moderated by Sample Source

The assessment of the moderator effect of the source from which the study sample was drawn is presented in Table 6. Two studies reported no information as to the sample source (Pandina et al., 2006 & McCracken et al., 2002) while one study indicated that the participants were drawn from a clinic (Nagaraj et al., 2005) and another study where participants were drawn from several different sources (Luby et al., 2006). Due to the small number of studies that reported the source of their samples, an analysis of the overall effect of the sample was not warranted or appropriate.

Table 6: Risperidone versus placebo effect as moderated by sample source

Moderator	Study Name	Year	Hedges's g	Lower Limit	Upper Limit	p-Value	Tx n	Ctl n
Clinic	Nagaraj	2005	0.889	0.242	1.536	0.007	19	20
Mixed	Luby	2006	0.302	-0.507	1.111	0.465	11	11
NR	McCracken	2002	0.576	0.180	0.972	0.004	49	52
NR	Pandina	2006	0.637	-0.178	1.453	0.126	20	21
NR			0.588	0.232	0.944	0.001		
Overall			0.612	0.321	0.903	0		

Risperidone versus Placebo Effect as Moderated by Participant Severity

A summary of the moderating effect of the participant severity reporting is presented in Table 7. Since only a single study was represented for each of four different reporting levels of participant severity, these data can only be understood as descriptive of the individual study. The absence of multiple studies reporting information relative to participant severity when comparing risperidone versus placebo treatment provided no useful information as to the potential impact of participant severity on the magnitude of the treatment effect for any single severity rating.

Table 7: Risperidone versus placebo effect as moderated by participant severity

Moderator	Study Name	Year	Hedges's g	Lower Limit	Upper Limit	p-Value	Tx n	Ctl n
Mix	Luby	2006	0.302	-0.507	1.111	0.465	11	11
Mod-Sev	McCracken	2002	0.576	0.180	0.972	0.004	49	52
NR	Nagaraj	2005	0.889	0.242	1.536	0.007	19	20
Sev	Pandina	2006	0.637	-0.178	1.453	0.126	20	21
Overall			0.612	0.321	0.903	0		

Risperidone versus Placebo Effect as Moderated by Participant Ethnicity/Race

Table 8 displays the effect of participant ethnicity/race in the efficacy of risperidone versus placebo treatment. Three studies; Luby et al. (2006), McCracken et al. (2002), and

Pandina et al. (2006), reported a mixed sample of participant ethnicity/race. The aggregated effect across the studies was g = 0.61 (p = 0.000, 95% CI = 0.32 to 0.90). One study (Nagaraj et al., 2005) did not report participant ethnicity/race and showed an effect size almost twice as large as the other three studies reporting a mixed ethnic/racial representation. While the data are sparse, the results do call into question the credibility of the effect size of the study not reporting information regarding participant ethnicity/race given that the resulting effect is almost twice as large as the other three studies combined.

Table 8: Risperidone versus placebo effect as moderated by participant ethnicity/race

Moderator	Study Name	Year	Hedges' g	Lower Limit	Upper Limit	p-Value	Tx n	Ctl n
Mixed	Luby	2006	0.302	-0.507	1.111	0.465	11	11
Mixed	McCracken	2002	0.576	0.180	0.972	0.004	49	52
Mixed	Pandina	2006	0.637	-0.178	1.453	0.126	20	21
Mixed			0.541	0.216	0.867	0.001		
NR	Nagaraj	2005	0.889	0.242	1.536	0.007	19	20
Overall			0.612	0.321	0.903	0		

CONCLUSION

The purpose of this systematic review and meta-analysis was to evaluate the efficacy of anti-psychotic medications in treating the maladaptive behaviors associated with ASD in children and adolescents. Electronic literature searches were performed to find relevant studies. Ten clinical trials were found that met the inclusion criteria for this review. The meta-analysis in this review implemented both random and fixed-effects models.

Six of the included studies investigated the effects of a drug versus a placebo and four studies examined the effects of two separate anti-psychotic medications or the efficacy of an additive medication to a drug and placebo group. Based on this selection of studies, an analysis was performed to assess the causal effect of the drug treatments and the potential moderating effect of selected independent variables. The following provides a discussion of the results and conclusions to be drawn.

Overall Treatment Effect

Overall, anti-psychotic medications were shown to have a positive and statistically significant effect on the behavior, social, and communication outcomes reported for children and adolescents with ASD. The systematic review performed by Barnard and colleagues (1992) was unable to inform reliably on the use of anti-psychotics due to the lack of RCTs available at the time. However, based on this analysis, the overall effect size suggested that daily use of an anti-psychotic medication for at least eight weeks improved the behavior, social, and communication deficits associated with ASD.

The aggregation of effect sizes across multiple studies using different medications, varying treatment characteristics, and study design characteristics did not provide a clear interpretation of the effects of any particular medication or treatment protocol. A more precise interpretation can only be made when the studies that are combined are similar across one or more important study features.

Risperidone Treatment Effect

Specifically, the results of the studies comparing risperidone to a placebo allowed for a causal statement of the treatment effect and indicated that risperidone produced a positive and statistically significant effect on behavior (g = 0.66), social (g = 0.55), and communication (g = 0.55) symptoms. These results suggest that, when treated daily with risperidone, children and adolescents with ASD displayed an overall improvement on the measured treatment outcomes (e.g., aggressiveness, social withdrawal, speech, and self-injury).

Overall Effect for Behavior Outcomes

An analysis of the overall effect for behavior outcomes also provided for a causal statement of the overall treatment effect. When treated with risperidone compared to a placebo, participants exhibited a positive and statistically significant effect on the behavior measures utilized across studies (g = 0.66). This result suggests that, when treated daily with risperidone, children and adolescents with ASD displayed an overall improvement on the measured behavior outcomes (e.g., irritability, hyperactivity/noncompliance, etc.).

Overall Effect for Social Outcomes

In relation to social outcomes, the data revealed that when treated with risperidone compared to a placebo, participants demonstrated a statistically significant positive but moderate effect on the social measures observed across studies ($g = 0.55$). This finding suggests that social behaviors (e.g., social withdrawal, lethargy, social responsiveness, etc.) improved when children and adolescents with ASD receive treatment daily with risperidone.

Overall Effect for Communication

The analysis of the overall effect for communication outcomes allows for a causal statement of the overall treatment effect. When treated with risperidone compared to a placebo, risperidone produced a statistically significant positive moderate effect on the communication outcomes ($g = 0.55$). This result suggests that, when treated daily with risperidone, children and adolescents with ASD displayed an overall improvement on the reported communication outcomes (such as language skill and inappropriate speech).

Aripiprazole Treatment Effect

Two studies were identified and included in this review that investigated the efficacy of aripiprazole in children and adolescents using a treatment vs placebo design (Owen et al., 2009 & Marcus et al., 2009). A meta-analysis was conducted and revealed an uneven reporting of outcome performances that would allow for a substantial causal conclusion.

Overall Effect for Behavior Outcomes

The meta-analytic analysis for two studies examining the efficacy of aripiprazole in children and adolescents (Owen et al., 2009 & Marcus et al., 2009) also allow for a causal statement of the impact of the drug treatment with an overall treatment effect size of $g = 0.65$. Due to the small number of studies available comparing aripiprazole to a placebo condition, the available data must be interpreted cautiously and is best understood as a descriptive estimate of the treatment effect of the individual studies.

Overall Effect for Social Outcomes

The two studies (Owen et al., 2009 & Marcus et al., 2009) assessing the efficacy of aripiprazole in treating children and adolescents did not report social outcome measures. Therefore, an analysis of data could not be performed.

Overall Effect for Communication Outcomes

Owen et al., (2009) and Marcus et al. (2009) examined the efficacy of aripiprazole in treating children and adolescents but did not report communication outcome measures. Consequently, an interpretation of data could not be made.

Overall Effect of Moderator Variables

An analysis of the overall effect of moderator variables (i.e., SES, sample source, participant severity, and participant race) illustrated that too few studies reported details such as SES or participant race. As a result, an interpretation of the impact of these factors in a risperidone versus placebo comparison could not be made.

Limitations

There are several limitations to this study.

1. Only two studies observed the effects of anti-psychotic treatment for more than twelve weeks, so while a majority of participants had a positive response to treatment, results of this study only assess the short-term efficacy of anti-psychotic medications.

2. This review focuses on the behavior, social, and communication improvement of children and adolescents with ASD and does not thoroughly examine the physiological implications of anti-psychotic medication treatment.

3. This analysis excluded studies with a participant diagnosis of childhood disintegrative disorder and Rett syndrome.

4. There were too few studies represented for any treatment medication other than risperidone to support widespread application for use on children and adolescents with autism.

5. The reporting of potentially moderating variables was limited or absent in many studies making any explanatory interpretation of the nature of the treatment impact limited.

Implications for Future Research

There is a need to enhance the research base through the use of RCT designed studies that analyze the effects of individual anti-psychotic medications on behavior, social, and communication skills through longer term trials and larger sample sizes. While it is apparent at least two anti-psychotic medications have a generally positive impact on maladaptive behaviors,

there is a lack of research investigating either the moderating variables that might contribute to an explanation as to the critical variables impacting the treatment effect or the long-term implications of routine anti-psychotic treatment. Do side effects of anti-psychotics subside over time? Or, does long-term use worsen the potential side effects? Also, does long-term use lead to drug tolerance and a need to increase daily dose over time?

APPENDIX A: CODING SHEET

Coding

Number_____

APA Citation:_____

Publication Source:

1. Journal Article
2. Conference Paper
3. Master Thesis
4. Organization Report
5. Technical Report
6. Doctoral Dissertation
7. Book or Book Chapter
8. Not Reported
9. Other_____

Funding Source (pg. ____):

Subject Characteristics (pg. ____):

	Groups	Pre-treatment (n)	Post-Treatment (n)	Attrition (n)	Follow-up (n)	Age (years)	% male
T (1)							
T (2)							
C (1)							
C (2)							
Com (1)							
Com (2)							

Comments: _____

SES (pg.____)

1. Low
5. Middle-Upper

2. Middle
3. Upper
4. Low-Middle
9. Not Reported
6. Labeled Mixed
7. Unclear
8. Other_____

Sample Source: (pg.____)

1. Public School
2. Private School
3. Univ. Clinic / Outpatient Clinic
4. Not Reported
5. Unclear
6. Other_____

Comments:_____

Setting (pg.____)

1. Urban
2. Suburban
3. Rural
4. Urban-Suburban
5. Urban-Rural
6. Suburban-Rural
7. Unclear
8. Other_____
9. Not Reported

Comments:_____

Geographic Setting: _____

Author's Labeling of Participants:

1. Autism
2. Asperger
3. PDD-NOS
4. Unclear
5. Not Reported
6. Other_____

Severity of Participants Pre-test (pg. ____)

1. Mild
2. Mild-Moderate
3. Moderate
4. Moderate-Severe
5. Severe
6. Unclear
7. Mixed
8. Not Reported

Comments: _____

Education Level of Participants (pg. ____):

1. Pre-School
6. Clinic Only

2. K-5
3. Middle School (6-8)
4. High School (9-12)
5. Homeschool
7. Unclear
8. Other_____
9. Not Reported

Race/Ethnicity (pg. ____):

1. African American
2. American Indian
3. Asian
4. Hispanic /Latino
5. White/Caucasian
6. Unclear
7. Mixed_____
8. Not Reported

Intervention Characteristics: (pg. ____):

1. Drug Name: _____
2. Dose: _____
3. Length of intervention (pg. ____): _____
4. Frequency of treatments: _____
5. Treatment setting: _____
6. Side effects: _____

Outcome Measure(s): (pg. ____)

1. Norm Referenced Test (pg. ____)

_____

Who administered the measure? (pg. ____)

1. Physician/Researcher
2. Parents
3. Teacher Counselor/Clinician
4. Unclear
5. Not Reported
6. Other_____

2. Criterion Referenced Test (pg. ____)

_____

Who administered the measure? (pg. ____)

1. Physician/Research
2. Parents
3. Teacher Counselor/Clinician
4. Unclear
5. Not Reported
6. Other_____

3. Rating Scale (pg. ____)

_____

Who administered the measure? (pg. ____)

1. Physician/Researcher
2. Parents
3. Teacher Counselor/Clinician
   Other_____
4. Unclear
5. Not Reported
6.

Outcome Variables: (pg. ____)

Design Characteristic: (pg. ____)

Recruitment Pool (pg. ____)

1. Referral
2. Criterion_____
3. Scores on Norm Referenced Test _____
4. Existing Group
5. Volunteer
6. Waiting List
4. Unclear
5. Not Reported
6. Other_____

Design Type (pg. ____)

1. RCT
2. Quasi-Experimental

Subject Assignment (pg. ____)

1. Individual Random
2. Whole Group Random
3. Individual Matched-Random
4. Matched Non-Random
6. Non-Matched Non-Random
7. Unclear
8. Not Reported
9. Other_____

Method of Random Assignment (pg. ____)

1. Random Number Generation
2. Simple Random
3. Coin Flip
4. Unclear
4. Not Reported
5. Allocation/Assignment
6. Other_____

Type of Analysis (pg. ____)

1. Intent to Treat
2. Treat Only

Individual Blinding 1 (pg. ____)

1. Researcher (pg. ____)
2. Participants (pg. ____)
3. Intervener (pg. ____)
4. Assessor (pg. ____)
5. No Blinding
6. Unclear
7. Not Reported

Group Blinding 2 (pg. ____)

1. Open
2. Single Blind
3. Double Blind
4. Triple Blind

Two Groups Compared	Group 1:		Group 2:			
Outcomes						
Groups	Exp	Ctl	Exp	Ctl	Exp	Ctl
Mean						
SD						
N at Posttest						
N at Follow-up 1						
N at Follow-up 2						
N at Follow-up 3						
d-index						
F value						
t value						
p value						

APPENDIX B: DEFINITIONS FOR CODING SHEET

Publication Source

Journal article - An article published in a periodical devoted to a particular subject matter; can be peer or non-peer reviewed.

Conference paper - An original paper submitted and/or presented at a formal conference.

Master thesis - A paper on a specific subject of original research by a candidate for a diploma or degree.

Organization report - A paper describing results of a study that was performed for a government agency, private foundation, or corporate group.

Technical report - A paper that explains the progress or results of technical or scientific research; usually not peer reviewed.

Doctoral dissertation - A paper on a specific subject of original research by a candidate for a degree or professional qualification.

Book or book chapter - A printed work of nonfiction.

Not Reported - The format of publication was not reported.

Other - A paper or article of any format other than those presented here.

Subject Characteristics

Control - A group of subjects used for comparison in a scientific experiment.

Experimental - A group of subjects used in an experiment to perform a test and an independent variable is applied (e.g., treatment).

Attrition - A reduction in participants assigned to either experimental or control conditions.

SES (socioeconomic status)

An individual's or group's position within a hierarchical social structure. The author's/authors' designation of one of the following:

Low
Low-middle: includes reference to both low and middle levels of SES
Middle
Middle-upper: includes reference to both middle and upper levels of SES
Upper
Labeled mixed: includes reference to all levels of SES or a non-specific reference to a multi-level SES representation (e.g., "…. participants represented all levels of SES).
Unclear: A statement that does not explicitly indicate the SES of participants obtained.
Other: A SES other than those presented here.
Not reported: The SES of participants was not reported.

Sample Source

The organization from which participants were obtained before group assignment.

School - A public or private institution in which instruction is given.

Clinic - A facility; often affiliated with a hospital, university, or a private practice, that is committed to the diagnosis and treatment of outpatients.

Not reported - The origin of the sample source was not reported.

Unclear - A statement that does not explicitly indicate a specific organization from which participants were obtained.

Other – The sample of participants was obtained from a source other than those presented here

Sample Setting

The geographic location in which participants within a sample were retrieved. The author's/authors' designation of one of the following:

Urban
Suburban
Rural
Urban-Suburban: reference must include both and only these terms
Urban-Rural: reference must include both and only these terms
Suburban-Rural: reference must include both and only these terms
Unclear: A statement that does not explicitly indicate a specific geographic location from which participants were obtained.
Other: The sample of participants was obtained from a geographic location other than those presented here.
Not Reported: The geographic location of participants was not reported.

Author's Labeling of Participants

The diagnosis attributed to an individual participant or group. The author's/authors' designation of one of the following:

Autism
Asperger
PDD-NOS
Unclear
Not Reported
Other

Severity of Participants Pre-Test

The degree of severity associated with an individual participant's or group diagnosis. The author's/authors' designation of one of the following

Mild
Mild-Moderate: reference must include both and only these terms
Moderate
Moderate-Severe: reference must include both and only these terms
Severe
Unclear: A non-specific reference to multi-levels of severity (e.g., all levels of severity were represented)
Mixed: reference to mild, moderate, and severe representation in the same group
Not Reported: The severity of participants was not reported.

Education Level of Participants

The level of education completed by an individual participant or group. The author's/authors' designation of one of the following:

Preschool
K-5
Middle School (6-8)
High School (9-12)
Home School
Clinic Only
Unclear: A statement that does not explicitly indicate the formal level of education of a participant or group.
Other: The education level of a participant or group varied from those presented here.
Not Reported: The education level of participants was not reported.

Race/Ethnicity

The ethnic affiliation of an individual participant or group. The author's/authors' designation of one of the following:

African American
American Indian

Asian
Hispanic/Latino
White/Caucasian
Unclear: non-specific reference to multiple racial/ethnic group representation (e.g., "…several race/ethnic groups were represented in the study.")
Mixed: reference must include at least two specific race/ethnic group labels
Not Reported

Recruitment Pool

The method for identifying potential participants for assignment into groups.

Referral - Recommendation as participant(s) based on existing knowledge of participant characteristics (e.g., physician referred).

Criterion - The participants are chosen based on specific characteristics (e.g., score less than a specified cutoff score on a test administered before assignment).

Scores on norm referenced test- The participants are chosen based on scores reported on a norm referenced test (e.g., Wechsler Intelligence Scale for Children).

Existing group - A group already together based on specific characteristics (e.g., outpatients from a specialty clinic).

Volunteer - The participants offer themselves for inclusion in the study (e.g., respond to media ad).

Waiting list – The recruitment pool is comprised of participants who have been on a waiting list (e.g., waiting list for an intervention or program).

Unclear - A statement that does not explicitly indicate the method of participant recruitment.

Not Reported - The method of participant recruitment was not reported.

Other – The method of participant recruitment varied from than those presented here.

Design Type

Randomized controlled trial (RCT) - Participants are randomly assigned to either experimental or control groups. The researcher manipulates one or more independent variables and measures any changes in the dependent variable(s) (Kerlinger & Lee, 2000, p. 491).

Quasi-experimental - Participants are not randomly assigned to either the experimental or control group.

Subject Assignment

Individual random - "Assignment to experimental treatments of members of a universe in a ways such that, for any given assignment to a treatment, every member of the universe has an equal probability of being chosen for that assignment" (Kerlinger & Lee, 2000, p. 170). In short, participants are randomly assigned to a condition.

Whole group random - Groups are randomly assigned to an experimental or control group. These groups of participants are matched "in terms of overall distribution of the selected variable or variables, rather than on an individual-by-individual basis" (Kerlinger & Lee, 2000, p. 491).

Individual matched-random - Participants are matched on one or more variables and then randomly assigned to an experimental or control group. (Kerlinger & Lee, 2000).

Matched non-random - Participants are matched on one or more variables, but not randomly assigned to conditions.

Non-matched non-random - Participants are not matched on one or more variables and are not randomly assigned to condition.

Unclear - A statement that does not explicitly indicate the method of subject assignment.

Not reported - Method of subject assignment was not reported.

Other - Assignment to condition(s) by any method other than those presented here.

Method of Random Assignment

Random number generation - Random assignment is utilized using a software program or random number table.

Simple random - Random assignment within groups by participant characteristics (CONSORT Statement, 2001).

Coin flip - Random assignment is completed by the flip of a coin.

Allocation/Assignment - The generation of an allocation sequence in which the number of assignments to intervention groups satisfies a specified allocation ratio (such as 1:1 or 2:1) after every "block" of specified size (CONSORT Statement, 2001).

Unclear - A statement that does not explicitly indicate the method of random assignment.

Other - Neither random number generated nor coin flip is used to complete the random assignment.

Not reported – The method of random assignment was not reported.

Type of Analysis

Intent to treat - Analysis of trial results which includes the data of all participants whether they completed the treatment or not.

Treat only - Analysis in which only data from participants who completed the trial is used in the final results.

Individual Blinding

Participants, caregivers, outcome assessors, and analysts are all potential candidates for blinding. However, blinding of certain individuals may not be feasible (i.e., surgeons in surgical trials). The author's/authors' assigned designation to the following:

Researcher
Participants
Intervener
Assessor
No Blinding
Unclear: A statement that does not explicitly indicate which individuals were blinded during the study.
Not reported: Blinding during the study was not reported.

Group Blinding

The procedure of preventing those involved in a trial from knowing which comparison group a participant belongs. The possibility of bias is reduced when as few people as possible know who is receiving the experimental intervention or the control intervention.

Open - In an open label experiment, both the researchers and participants are aware of which treatment is being administered.

Single blinding - In a single blind experiment, the individual subjects do not know whether they are members of a control group or members of an experimental group.

Double blinding - In a double-blind experiment, two parties do not know who belongs to the control group and the experimental group.

Triple blinding – In a triple-blind experiment, three parties do not know which participants belong to the control group and the experimental group.

REFERENCES

Akhondzadeh, S., Fallah, J., Mohammadi, M., Imani, R., Mohammadi, M., Salehi, B., Ghanizaheh, A., Raznahan, M., Mohebbi-Rasa, S., Rezazadeh, S., & Forghani, S. (2010). Double-blind placebo-controlled trial of pentoxifylline added to risperidone: effects on aberrant behavior in children with autism. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *34*(1), 32-36. doi: 10.1016/j.pnpbp.2009.09.012

Akhondzadeh, S., Tajdar, H., Mohammadi, M., Mohammadi, M., Nouroozinejad, G., Shabstari, O., & Ghelichnia, H. (2008). A double-blind placebo controlled trial of piracetam added to risperidone in patients with autistic disorder. *Child Psychiatry and Human Development*, 39, 237-245. doi: 10.1007/s10578-007-0084-3.

Alarcon, M., Cantor, R., Liu, J., Gilliam, T., the Autism Genetic Resource Exchange Consortium, & Geschwind, D. (2002). Evidence for a language quantitative trait locus on chromosome 7q in multiplex autism families. *The American Journal of Human Genetics*, (70), 60-71. Retrieved from http://www.ncbi.nlm.nih.gov.ezproxy.lib.ucf.edu/pmc/article\s/PMC38 4904/?tool=pubmed

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders text revision*. (4 ed., pp. 60-70). Washington, D.C.

Amir, R., & Zoghbi, H. (2000). Rett syndrome: Methyl-cpg-binding protein 2 mutations and phenotype-genotype correlations. *American Journal of Medical Genetics*, *97*(2), 147-152. doi: 10.1002/1096-8628(200022)97:2<147::AID-AJMG6>3.0.CO;2-O

Arking, D., Cutler, D., Brune, C., Teslovich, T., West, K., Ikeda, M., Rea, A., & Guy, M., Lin, S. , Cook, E., & Chakravarti, A. (2008). A common genetic variant in the neurexin

superfamily member CNTNAP2 increases familial risk of autism. *The American Journal of Human Genetics*, (82), 160-164. doi: 10.1016/j.ajhg.2007.09.015

Barnard, L., Young , A., Pearson, J., Geddes, J., & O'Brien, G. (2002). A systematic review of the use of atypical antipsychotics in autism. *Journal of Psychopharmacology*, *16*(1), 93-101. doi: 10.1177/026988110201600113

Borenstein M, Hedges L, Higgins J, & Rothstein H. (2005). Comprehensive Meta-analysis Version 2, Biostat, Englewood NJ

Cascade, E., Kalali, A., & Feifel, D. (2008). Treatment of autistic children. *Psychiatry (Edgmont)*, *5*(2), 35-37. Retrieved from http://www.ncbi.nlm.nih.gov.ezproxy.lib.ucf.edu/pmc/articles/PMC2708111/?tool=pubmed

Centers for Disease Control and Prevention. (2012). *Data and statistics*. Retrieved from http://www.cdc.gov/ncbddd/autism/data.html

Centers for Disease Control and Prevention. (2010). *Signs and symptoms*. Retrieved from http://www.cdc.gov/ncbddd/autism/signs.html

Centers for Disease Control and Prevention. (2010). *Treatment*. Retrieved from http://www.cdc.gov/ncbddd/autism/treatment.html

Cohen, J. (1988). *Statistical power analysis for behavioral sciences*. (2 ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

Dollfus, S., Petit, M., Menard, J., & Lesieur, P. (1992). Amisulpride versus Bromocriptine in infantile autism: a controlled crossover comparative study of two drugs with opposite effects on dopaminergic function. *Journal of Autism and Developmental Disorders*, *22*(1), 47-60. doi: 10.1007/BF01046402.

Douglas G., Altman, G., Schulz, F., Moher, D., Egger, M., Davidoff, F., Elbourne, D., Gøtzsche, C., & Lang, T. (2001). The Revised CONSORT Statement for Reporting Randomized Trials: Explanation and Elaboration", *Annals of Internal Medicine, 134,* 553-694.

El-Fishawy, P., & State, M. (2010). The genetics of autism: Key issues, recent findings, and clinical implications. *Psychiatric Clinics of North America, 33*(1), 83-105. doi: 10.1016/j.psc. 2009.12.002.

Findling, R., Maxwell, K., & Wiznitzer, M. (1997). An open clinical trial of risperidone monotherapy in young children with autistic disorder. *Psychopharmacology Bulletin, 33,*155-159.

Fisman, S., & Steele, M. (1996). Use of risperidone in pervasive developmental disorders: a case series. *Journal of Child and Adolescent Psychopharmacology, 6,* 177-190.

Gencer, O., Neslihan Inal Emiroglu, F., Miral, S., Baykara, B., Baykara, A., & Dirik, E. (2008). Comparison of long-term efficacy and safety of risperidone and haloperidol in children and adolescents with autistic disorder. *European Child and Adolescent Psychiatry, 17,* 217-225.doi: 10.1007/s00787-007-0656-6.

Harden, A., Johnson, K., & Hrecznyj, B. (1996). Risperidone treatment of children and adolescents with developmental disorders. *Journal of the American Academy of Child and Adolescent Psychiatry,35,* 1551-1556.

Horrigan, P., Barnhill, J., & Courvoise, E. (1997). Olanzapine in PDD. *Journal of the American Academy of Child and Adolescent Psychiatry, 36,* 1166-1167.

Kerlinger, F., & Lee, H. (2000). *Foundations of behavioral research* (4th ed.). United States: Wadsworth Thomson Learning

Kinney, D., Barch, D., Chayka, B., Napoleon, S., & Munir, K. (2010). Environmental risk factors for autism: Do they help cause de novo genetic mutations that contribute to the disorder? *Medical Hypotheses, 74*(1), 102-106. doi: 10.1016/j.mehy.2009.07.052.

Kline, R. (2004). *Beyond significance testing: Reforming data analysis methods in behavioral research*. Washington, D.C.: American Psychiatric Association.

Luby, J., Mrakotsky, C., Meade-Stalets, M., Belden, A., Heffelfinger, A., Williams, M., & Spitznagel, E. (2006). Risperidone in preschool children with autism spectrum disorders: an investigation of safety and efficacy. *Journal of Child and Adolescent Psychopharmacology, 16*, 575-587.

Malek-Ahmadi, P., & Simonds, J. (1998). Olanzapine for autistic disorder with hyperactivity. *Journal of the American Academy of Child and Adolescent Psychiatry,37,* 902.

Marcus, R., Owen, R., Kamen, L., Manos, G., McQuade, R., Carson, W., & Aman, M.(2009). A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *Journal of the American Academy of Child and Adolescent Psychiatr, 48*(11), 1110-1119. doi: 10.1097/CHI.0b013e3181b76658

Marcus, R., Owen, R., Manos, G., Mankoski,R., Kamen, L., McQuade, R., Carson, W., & Findling, R. (2011). Safety and tolerability of aripiprazole for irritability in pediatric patients with autistic disorder: a 52-week, open-label, multicenter study. *The Journal of Clinical Psychiatry, 72*(9), 1270-1276.

Martin, A., Koenig, K., Scahill, L., & Bregman, J. (1999). Open-label quetiapine in the treatment of children and adolescents with autistic disorder. *Journal of Child and Adolescent Psychopharmacology, 9,* 99-107.

Mayo Foundation for Medical Education and Research. (2010). *Autism*. Retrieved from http://www.mayoclinic.com/health/autism/DS00348/DSECTION=risk-factors

McDougle, C., Holmes, J., Bronson, M., Anderson, G., Volkmar, F., Price, L., & Cohen, D. (1997). Risperidone treatment of children and adolescents with pervasive developmental disorders: a prospective open-label study. *Journal of the American Academy of Child and Adolescent Psychiatry, 36,* 685-693.

Miral, S., Gencer, O., Neslihan Inal-Emiroglu, F., Baykara, B., Baykara, A., & Dirik, E. (2008). Risperidone versus haloperidol in children and adolescents with AD. *European Child and Adolescent Psychiatry*, *17*, 1-8. doi: 10.1007/s00787-007-0620-5.

Nagaraj, R., Singhi, P., & Malhi, P. (2006). Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *Journal of Child Neurology*, *21*(6), 450-455. doi: 10.1177/08830738060210060801.

National Institute of Neurological Disorders and Stroke. (2012). *Autism fact sheet*. Retrieved from http://www.ninds.nih.gov/disorders/autism/detail_autism.htm

National Institute for Neurological Disorders and Stroke. (2011). *Rett syndrome fact sheet*. Retrieved from http://www.ninds.nih.gov/disorders/rett/detail_rett.htm

Nicholson, R., Awad, G., & Sloman, L. (1998). An open trial of risperidone in young autistic children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *37*, 372-37 6

Owen, R., Sikich, L., Marcus, R., Corey-Lisle, P., Manos, G., McQuade, R., Carson, W., & Findling, R. (2009). Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Journal of the American Academy of Pediatrics, 124*(6), 1533-1540. doi: 10.1542/peds.2008-3782

Pandina, G., Bossie, C., Youssef, E., Zhu, Y., & Dunbar, F. (2006). Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. *Journal of Autism and Developmental Disorders, 37*, 367-373. doi: 10.1007/s10803-006-0234-7

Perry, R., Pataki, C., Munoz-Silva, D., Armenteros, J., & Silva, R. (1997). Risperidone in children and adolescents with pervasive developmental disorder: pilot trial and follow-up. *Journal of Child and Adolescent Psychopharmacology, 7*, 167-179.

Posey, J., Walsh, H., Wilson, A., & McDougle, J. (1999). Risperidone in the treatment of two very young children with autism. *Journal of Child and Adolescent Psychopharmacology, 9*, 273-276.

Rezaei, V., Mohammadi, M., Ghanizadeh, A., Sahraian, A., Tabrizi, M., Rezazadeh, S., & Akhondzadeh, S. (2010). Double-blind, placebo-controlled trial of risperidone plus topiramate in children with autistic disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 34*(7), 1269-1272. Retrieved from http://www.sciencedirect.com.ezproxy.lib.ucf.edu science/article/pii/S0278584610002538

Research Units on Pediatric Psychopharmacology Autism Network. (2002). Risperidone in children with autism and serious behavioral problems. *The New England Journal of*

Medicine, *347*(5), 314-321. Retrieved from http://www.nejm.org.ezproxy.lib.ucf.ed u/doi/full/10.1056/NE JMoa013171

Research Units on Pediatric Psychopharmacology Autism Network. (2005). Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. *American Journal of Psychiatry*, *126*(7), 1361-1369. Retrieved from http://ajp.psychiatryo nline.org.ezproxy.lib.ucf.edu/article.aspx?volume=162&page=1361

Roak, B., & State, M. (2008). Autism genetics: Strategies, challenges, and opportunities. *Autism Research*, (1), 4-17. doi: 10.1002/aur.3

Rothstein, H., Borenstein, M., & Sutton, A. J. (2005). *Publication bias in meta-analysis: prevention, assessment, and adjustments*. New York: John Wiley & Sons.

Shea, S., Turgay, A., Carroll, A., Schulz, M., Orlik, H., Smith, I., & Dunbar, F. (2004). risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *American Academy of Pediatrics*, *114*(5),634-641.doi: 10.1542/peds.2003-0264-F

Troost, P., Lahuis, B., Steenhuis, M., Ketelaars, C., Buitelaar, J., Engeland, H., Scahill, L., Minderaa, R., & Hoekstra, P. (2005). Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *44*(11), 1137-1144. Retrieved from http://www.sciencedirect.com.ez proxy.lib.ucf.edu/science/article/pii/S0890856709 622164

U.S. Food and Drug Administration. (2006). *FDA approves the first drug to treat irritability associated with autism, risperdal*. Retrieved from http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108759.htm

Zuddas, A., Ledda, G., Fratta, A., Muglia, P., & Cianchetti, C. (1996). Clinical effects of clozapine on autistic disorder. *American Journal of Psychiatry*, *153*, 738.