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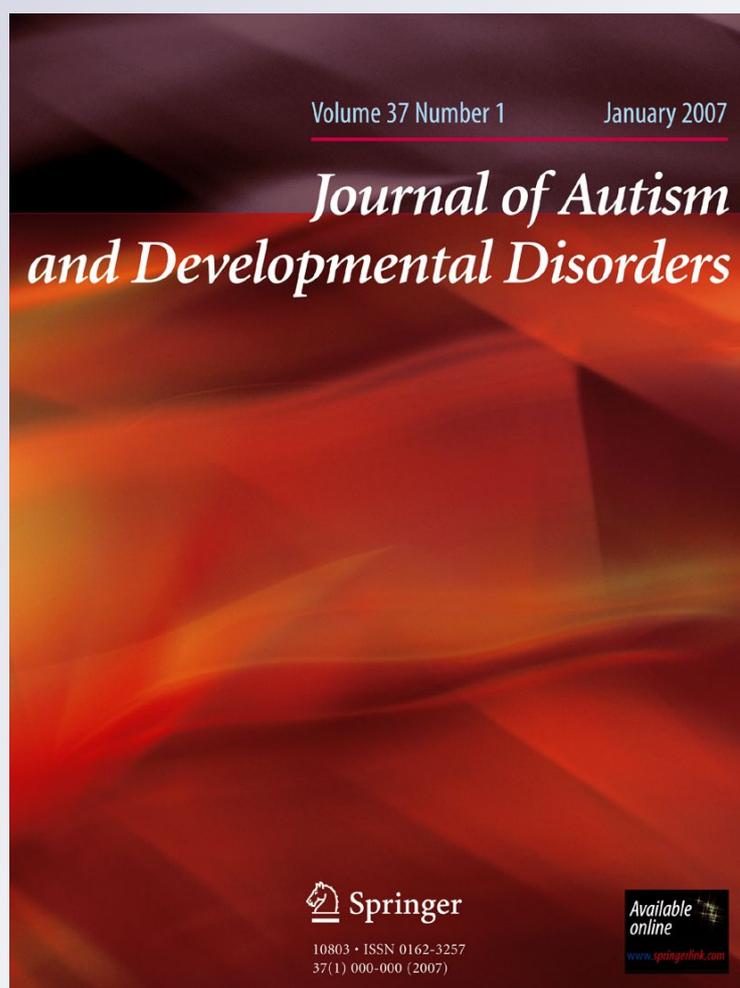
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Psychotropic Medications in Children with Autism Spectrum Disorders: A Systematic Review and Synthesis for Evidence-Based Practice

Matthew Siegel · Amy A. Beaulieu

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Abstract This paper presents a systematic review, rating and synthesis of the empirical evidence for the use of psychotropic medications in children with autism spectrum disorders (ASD). Thirty-three randomized controlled trials (RCTs) published in peer-reviewed journals qualified for inclusion and were coded and analyzed using a systematic evaluative method specific to autism research (Reichow et al. in *Journal of Autism and Developmental Disorders* 38:1311–1319, 2008). Results are presented by agent and primary target symptom(s). The findings suggest established evidence for relatively few agents, with preliminary and promising evidence for a larger group. Challenges and opportunities in the developing field of ASD psychopharmacology are identified, and recommendations for further research are provided.

Keywords Autism · Evidence base · Pharmacology · Review · Trials

Introduction

The population of children with autism spectrum disorders (ASD) has increased significantly over the past decade with

the prevalence of ASD now estimated at a rate as high as 6 cases per 1,000 (Johnson and Myers 2007). The desire for children with ASD to function in the least restrictive settings and achieve their full potential has increased the demand for effective treatments, including psychotropic medications.

Approximately 45% of children with ASD are prescribed psychotropic medication (Aman et al. 2003) with a global market-value for autism therapeutics ranging between \$2.2 and \$3.5 billion (King and Bostic 2006). Children with ASD also have high rates of non-prescribed or unregulated use of chemical compounds (Wong and Smith 2006), sometimes known as complementary and alternative medicines (CAM).

Randomized controlled trials (RCTs) targeting the ASD population have accelerated over the past three decades (see Fig. 1), including a recent increase in the number of studies examining CAM compounds.

Despite this expanding research base, the process of applying this information to therapeutic practices employed by treating clinicians has been hampered by at least six factors: (a) Absence of an accepted diagnostic system for detecting and rating co-morbid psychopathology in individuals with ASD, particularly for anxiety and psychosis; (b) Divergence on whether to study treatment of identifiable co-morbid psychiatric syndromes in ASD, such as depression, or to evaluate treatment of symptom domains, such as aggression; (c) Debate as to whether certain behaviors in ASD are symptomatic of psychopathology found in the neurotypical population. For example, targeting repetitive behavior in ASD with medications that are efficacious for obsessive compulsive symptoms in the neurotypical population; (d) The scarcity of widely used outcome measures normed and validated for the ASD population; (e) A focus on patented prescription medications to the relative

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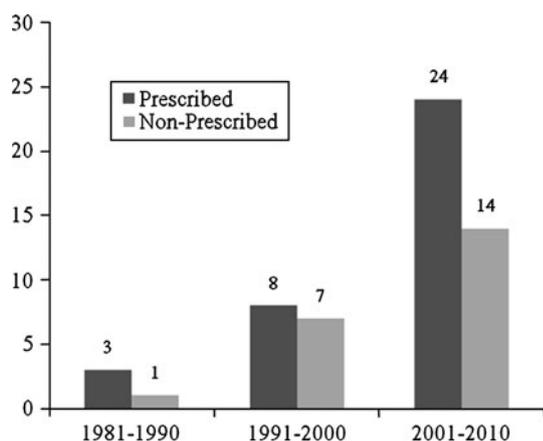


Fig. 1 Randomized controlled trials of psychotropics in children with ASD 1981–2010

exclusion of other possibly efficacious agents; and (f) Lack of a standardized and validated rating system for establishing evidence-based practice for the ASD population.

To address the final issue, Reichow and colleagues developed a system for evaluating the quality of research in autism: the *Evaluative Method for Determining Evidence-Based Practice in Autism* (Reichow et al. 2008). This system provides quality indicators to determine the relative strength of an individual study, and then assigns a level of evidence rating by aggregating the amount and quality of studies performed on a particular intervention.

To assist translation of the psychotropic literature into recommendations for evidence-based practice, we undertook a systematic review of all published randomized controlled trials of typically prescribed medications in ASD, utilizing the Reichow et al. (2008) methodology. A recent review of medical interventions for children with autism included 18 studies, 10 of which were randomized controlled trials, and found sufficient evidence for the use of risperidone and aripiprazole for irritability and challenging behavior (McPheeters et al. 2011). The study included controlled and uncontrolled evidence for treatment of children with ASD 12 years old and under, and evaluated antipsychotics, SRIs, and stimulants. The current review includes all typically prescribed psychotropic agents which have undergone randomized controlled trial in individuals with ASD ≤ 18 years old. This approach yielded studies on additional drug classes such as alpha-2 agonists, mood stabilizers, norepinephrine reuptake inhibitors, and other miscellaneous agents, and allowed for the detection of areas with preliminary or promising evidence. To our knowledge this article presents the first systematic review and rating of the controlled evidence base for all typically prescribed psychotropic medications in children and adolescents with ASD.

Methods

Search Procedure

A two-phase literature search was conducted, with the first phase performed in 2008–2009 for an earlier unpublished systematic review (Beaulieu et al. 2009). The second phase was executed in 2010 to update and expand on the earlier findings using the same search procedures and review protocols.

The keywords autism, asperger's, PDD, medication, psychotropic, and specific names of psychotropic agents (see Table 1) were searched in the electronic databases PubMed, MEDLINE, PsychInfo, CINAHL, and the Cochrane Database of Systematic Reviews. Publication year was

Table 1 Search terms by psychotropic agent

Class	Generic name	Brand name
Alpha-2 agonist	Clonidine	Catapres
	Guanfacine	Tenex
Antipsychotic	Aripiprazole	Abilify
	Chlorpromazine	Thorazine
	Clozapine	Clozaril
	Haloperidol	Haldol
	Olanzapine	Zyprexa
	Perphenazine	Trilafon
	Risperidone	Risperdal
Mood stabilizer	Ziprasidone	Geodon
	Carbamazepine	Tegretol
	Divalproex	Depakote
	Lamotrigine	Lamictal
	Levetiracetam	Keppra
	Lithium	n/a
Selective norepinephrine reuptake inhibitor	Oxcarbamazepine	Trileptal
	Atomoxetine HCl	Strattera
Serotonin reuptake inhibitor	Citalopram	Celexa
	Clomipramine	Anafranil
	Desipramine	Norpramin
	Fluoxetine	Prozac
	Fluvoxamine	Luvox
	Paroxetine	Paxil
	Sertraline	Zoloft
	Methylphenidate	Ritalin
Stimulant	Amphetamine	Adderall
	Amantadine	Symmetrel
	Cyproheptadine	Periactin
	Donepezil	Aricept
	Naltrexone	ReVia
Miscellaneous	Pentoxifylline	Trental

not restricted. References from relevant reviews and qualifying studies were also examined to identify additional studies.

Results of the initial search were winnowed using four inclusion criteria: (a) Studies must be published in a peer-reviewed academic journal; (b) The majority of study participants must be 0–18 years old and possess a diagnosis of Autistic Disorder, Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), or Asperger's Syndrome. Studies that included participants with a diagnosis of intellectual disability, Fragile X Syndrome, or other conditions without a concurrent ASD diagnosis were excluded. Only studies where the majority of participants were 0–18 years old were included to provide a more homogenous evidence base; (c) The intervention focused on the core symptoms of ASD or associated symptoms, such as aggression; and (d) Studies were randomized controlled trials (RCTs).

Open-label trials, case series, retrospective case reviews and sub-group analyses of RCTs published as a separate paper were excluded. One study was excluded based upon the retraction of a paper by the investigator. Thirty-three

studies qualified for inclusion and were coded and analyzed.

Coding and Analysis

We used a standardized, empirically-validated, and structured process to discern the strength of research and level of evidence for psychotropic interventions in ASD (Reichow et al. 2008). Studies were categorized by class (e.g., antipsychotics). Each study was independently coded by at least two reviewers, including a child psychiatrist, on its primary and secondary quality indicators (see Table 2).

Studies were assigned a research strength rating of “strong,” “adequate,” or “weak” according to the number of primary and secondary quality indicators (see Table 3).

Inter-rater reliability (IR) was assessed on 60% of studies coded. IR was calculated for the 14 quality indicators as a percentage of total initial agreements on items coded. Inter-rater agreement ranged from 94 to 100% on individual indicators, with 97% agreement across all quality indicators. There was 88% initial agreement on overall research rigor ratings. IR was $k = 0.80$

Table 2 Study quality indicators

Primary quality indicators	Secondary quality indicators
1. Participant characteristics: Age and gender for all participants, specific diagnostic information for autism, standardized test scores provided as applicable, and interventionist characteristics provided	1. Random assignment: Participant assigned by a random assignment procedure
2. Independent variable (intervention): Information about the treatment was provided with replicable precision	2. Interobserver agreement: Interobserver agreement measures collected across all conditions, raters, and participants with inter-rater agreement at or above .80, and a minimum of .60. Psychometric properties of standardized tests were reported and were $k \geq .40-.70$
3. Comparison condition (control group): Defined with replicable precision, including a description of any other interventions received	3. Blind raters: Raters blind to the participant's treatment condition
4. Dependent variable (outcome): Described with replicable precision, showed a clear link to the treatment outcome, and collected at appropriate times	4. Fidelity: Procedural fidelity assessed across participants, conditions, and implementers, and if applicable, had measurement statistics $\geq .80$
5. Link between research question and data analysis: Data analyses strongly linked to research question(s) and analysis used correct units of measure	5. Attrition: Attrition rate did not differ by more than 25% across conditions and $<30\%$ at the final outcome measure
6. Use of statistical tests: Proper statistical analyses were conducted for each measure with an adequate power and a sample size of ≥ 10 in each group	6. Generalization/treatment maintenance: Outcome measures were collected after the final data collection to assess generalization and/or maintenance

Note: Adapted from Reichow et al. (2008). Used with kind permission from Springer Science + Business Media B.V

Table 3 Research strength ratings for individual studies

Rating	Requirements
Strong	High quality ratings on all primary quality indicators and showed evidence of four or more secondary quality indicators
Adequate	High quality ratings on four or more primary quality indicators and showed evidence of at least two secondary quality indicators. No unacceptable ratings on primary quality indicators.
Weak	Less than four high quality ratings on primary quality indicators or showed evidence of less than two secondary quality indicators.

Note: Adapted from Reichow et al. (2008). Used with kind permission from Springer Science + Business Media B.V

Table 4 Level of evidence criteria for ASD treatments

Level of evidence	Criteria
Established evidence	≥ 2 strong studies conducted in separate settings by research teams OR ≥ 4 adequate studies conducted in at least two separate settings by separate research teams
Promising evidence	≥ 2 adequate studies
Preliminary evidence	≥ 1 adequate study
Studied and no evidence of effect	≥ 2 adequate studies showed no significant positive effect
Insufficient evidence	Conclusions cannot be drawn due to lack of quality research and/or mixed outcomes across several studies
Evidence of harm	Studies or published case reports indicate that the intervention can involve significant harm or risk of harm, including injury and/or death

Note: Adapted from Reichow et al. (2008). Used with kind permission from Springer Science + Business Media B.V

($p < 0.001$), indicating substantial agreement among raters (Landis and Koch 1977).

Based upon the research strength of individual studies, each compound was assigned a level of evidence by primary outcome(s) according to an adapted version of the Reichow et al. (2008) rating scale. Several levels of evidence were added to the original rating scale in order to capture the full spectrum of evidence in ASD psychopharmacologic research (see Table 4).

Results

Alpha-2 Agonists

Clonidine

Clonidine is a nonselective agonist at central post-synaptic alpha 2a, 2b and 2c receptors. One RCT met review criteria and received a weak research rating due to the use of non-standardized diagnostic measures and a sample size of 8 subjects (Jaselskis et al. 1992). Clonidine produced a statistically significant and clinically relevant (as defined by a $> 25\%$ reduction in subscale score) change in the Aberrant Behavior Checklist (ABC) Hyperactivity subscale (Aman et al. 1985), but there is currently insufficient evidence for this agent due to the weak research rating and lack of replication (Tables 5).

Guanfacine

Guanfacine is a selective agonist of central postsynaptic alpha 2a receptors, with a longer half-life than clonidine. One RCT of guanfacine met review criteria (Handen et al. 2008). The study included seven children with ASD and showed a statistically significant and clinically relevant

impact on the ABC Hyperactivity subscale. The study received a weak research rating due to the small sample size and use of non-standardized ASD diagnostic measures. Further study is warranted.

Antipsychotics

Risperidone

Risperidone is an antagonist of both dopamine and serotonin receptors and is the most well researched psychotropic treatment for children with ASD. There have been multiple RCTs performed on the effects of risperidone in this population, the largest being a federally-funded study of 101 children by the Research Units for Pediatric Psychopharmacology (RUPP 2002; McDougle et al. 2005). Based upon the studies reviewed, there is established evidence for risperidone's efficacy in the treatment of irritability and hyperactivity in children with autism, and preliminary evidence for efficacy in reducing repetitive behavior and stereotypy. The term "irritability" in these studies was defined by use of the Aberrant Behavior Checklist (ABC)—Irritability subscale, which primarily consists of frequency and intensity of aggression, self injury and tantrums. Many studies also showed positive results for other outcome measures, such as the Hyperactivity and Stereotypy subscales of the ABC, and the compulsions score of the Children's Yale Brown Obsessive Compulsive Scale (C-YBOCS) (used to measure repetitive behavior)(Scahill et al. 1997). A study by Shea et al. (2004) received a strong research rating but used less rigorous diagnostic criteria for ASD, utilizing the CARS screening tool to establish ASD, which resulted in a more diagnostically heterogeneous group of children than the RUPP sample. This study found a statistically significant response to risperidone on all five subscales of the ABC, though only the Irritability (0.7) and

Table 5 Randomized controlled trials of psychotropic medications in ASD

Agent	Study (Rating of strength)	Target symptoms	Dose	Demographics	Significant side effects	Primary outcome(s)
Alpha-2 agonists						
Clonidine	Jaselskis et al. (1992) (Weak)	Hyperactivity, irritability, inappropriate speech, stereotypy	0.15–0.20 mg divided TID	8 children 5–13 years old	Hypotension, drowsiness	Statistically and clinically relevant decrease in ABC <i>Irritability</i> subscale
Guanfacine	*** Handen et al. (2008) (Weak)	Hyperactivity, inattention	1–3 mg divided TID	7 children with ASD, 5–9 years old	Drowsiness, irritability	45% with a > 50% decrease in ABC <i>Hyperactivity</i> subscale
Antipsychotics						
Aripiprazole	** Marcus et al. (2009) (Strong)	Irritability, hyperactivity, stereotypy, social withdrawal inappropriate speech	5, 10 or 15 mg per day, fixed dose	218 children 6–17 years old	Somnolence, weight gain, drooling, tremor, fatigue, vomiting	56% positive response* for 5 mg aripiprazole versus 35% on placebo. Significant improvement in <i>Irritability, Hyperactivity and Stereotypy</i> subscales
	** Owen et al. (2009) (Strong)	Irritability, hyperactivity, stereotypy, social withdrawal inappropriate speech	5–15 mg per day, flexibly dosed	98 children 6–17 years old	Somnolence, weight gain, drooling, tremor, fatigue, vomiting	52% positive response* for aripiprazole versus 14% on placebo. Significant improvement in <i>Irritability, Hyperactivity and Stereotypy</i> subscales
Haloperidol	Anderson et al. (1989) (Strong)	Multiple behavioral symptoms, global functioning	0.25–4 mg per day	45 children 2–7 years old	Sedation, extrapyramidal symptoms	<i>Behavioral symptoms</i> improved with significant decrease in 7 of 14 items of the CPRS
Olanzapine	** Hollander et al. (2006) (Weak)	Global functioning, aggression, compulsions, irritability	7.5–12.5 mg per day	11 children 6–14 years old	Weight gain, sedation	50% of those on olanzapine much or very much improved in <i>global functioning</i> versus 20% on placebo
Risperidone	RUPP (2002) (Strong)	Irritability, hyperactivity, stereotypy, social withdrawal, inappropriate speech	0.5–3.5 mg per day	101 children 5–17 years old	Weight gain, increased appetite, fatigue, drowsiness, drooling, dizziness	69% had a positive response* on risperidone vs. 12% positive response* on placebo. Significant positive findings for <i>hyperactivity</i> and <i>stereotypy</i>
	** Shea et al. (2004) (Strong)	Irritability, hyperactivity, stereotypy, social withdrawal inappropriate speech	0.02–0.06 mg/kg/day	79 children 5–12 years old	Weight gain, somnolence,	64% improvement in ABC <i>Irritability</i> on risperidone vs. 31% improvement on placebo. Significant positive finding for <i>hyperactivity</i>
	McDougle et al. (2005) (Strong)	Social and communication impairment, repetitive behavior and stereotypy	0.5–3.5 mg per day	101 children 5–17 years old	Weight gain, increased appetite, fatigue, drowsiness, drooling, dizziness	Significant response**** for <i>repetitive behavior and stereotypy</i> on risperidone

Table 5 continued

Agent	Study(Rating of strength)	Target symptoms	Dose	Demographics	Significant side effects	Primary outcome(s)
Risperidone vs. Haloperidol	** Miral et al. (2008) (Weak)	Behavior, social, sensory, language	0.01–0.08 mg/kg/day	30 children 8–18 years old	EPS, weight gain, gynecomastia	Risperidone reported superior to haloperidol only on ABC Total score, no sub-scales reported
Mood stabilizers						
Valproic acid	Hellings et al. (2005) (Strong)	Irritability	20 mg/kg/day Mean VPA level 75–78	30 subjects 6–20 years old	Increased appetite, skin rash	No significant difference for ABC Irritability sub-scale
	** Hollander et al. (2005a, b) (Weak)	Repetitive behavior	500–1,500 mg per day	12 children 5–17 years, and 1 adult, 40 years old	Irritability, aggression	Statistically, but not clinically, significant decrease in <i>repetitive behavior</i> on C-YBOCS
	Hollander et al. (2010) (Strong)	Global irritability	Dosed to a mean level of 89.8 mcg per ml	27 children 5–17 years old	Skin rash, irritability	62.5% positive response for <i>irritability</i> on the CGI on divalproex vs. 9.09% on placebo
Lamotrigine	** Belsito et al. (2001) (Strong)	Irritability, social behavior	5 mg per kg per day	28 children 3–11 years old	Insomnia, hyperactivity	No significant difference in <i>irritability or social behavior</i> on multiple instruments
Levetiracetam	** Wasserman et al. 2006 (Strong)	Irritability Global functioning	20–30 mg per kg per day	20 children 5–17 years old	Aggression	No significant difference in <i>global functioning or irritability</i>
Norepinephrine reuptake inhibitors						
Atomoxetine HCl	** Arnold et al. 2006 (Adequate)	Hyperactivity inattention	20–100 mg divided bid (mean 44 mg/day)	16 children 5–15 years old	Upper gastrointestinal symptoms, fatigue, racing heart	57% positive response* for parent-rated ABC <i>Hyperactivity</i> subscale vs. 25% on placebo
Serotonin reuptake inhibitors						
Citalopram	King et al. (2009) (Strong)	Repetitive behavior	2.5–20 mg per day (mean 16 mg/day)	149 children 5–17 years old	Hyperactivity, insomnia, inattention, impulsivity, diarrhea, stereotypy and dry skin	No significant difference in <i>repetitive behavior</i> on CGI-I and CY-BOCS PDD
Fluoxetine	Hollander et al. (2005a, b) (Weak)	Repetitive behavior	2.4–20 mg per day (mean 9.9 mg/day)	39 children 5–17 years old	None significant	Statistically but not clinically significant decrease in <i>repetitive behavior</i> on CY-BOCS compulsions scale
Clomipramine	Gordon et al. 1993 (Weak)	Stereotypy, repetitive behavior, compulsions	25–250 mg/day (Mean 152)	12 children 6–18 years old	Insomnia, constipation, twitching, tremors	Decrease in <i>repetitive behavior</i> by CPRS
	Remington et al. 2001 (Adequate)	Stereotypy, irritability, hyperactivity	100–150 mg per day (mean 128.4 mg/day)	31 subjects less than 20 years old	Lethargy, tremors, tachycardia, insomnia, diaphoresis, nausea	No significant difference in <i>stereotypy, irritability, or hyperactivity</i> for clomipramine on the ABC

Table 5 continued

Agent	Study(Rating of strength)	Target symptoms	Dose	Demographics	Significant side effects	Primary outcome(s)
Stimulants						
Methylphenidate	RUPP 2005 (Strong)	Hyperactivity	7.5–50 mg per day divided tid	58 children 5–14 years old	Decreased appetite, insomnia, irritability, emotionality	49% positive responders* for <i>hyperactivity</i> versus 15.5% on placebo
	Handen et al. (2000) (Adequate)	Hyperactivity	0.3–0.6 mg per kg per dose, bid-tid	13 children 5–11 years old	Social withdrawal, irritability	8 of 13 children with a >50% decrease in <i>hyperactivity</i> on the Teacher Conners Hyperactivity Index
	*** Quintana et al. (1995) (Adequate)	Hyperactivity	10–20 mg bid	10 children 7–11 years old	Irritability, decreased appetite, insomnia	Decrease in ABC <i>Hyperactivity</i> subscale by 8 points > placebo
Miscellaneous						
Amantadine	** King et al. (2001) (Adequate)	Hyperactivity, Irritability	2.5–5.0 mg per kg per day	39 children 5–19 years old	Insomnia	No statistical difference by parent ABC <i>Hyperactivity</i> or <i>Irritability</i> sub scales, statistical improvement in clinician-rated <i>Hyperactivity</i> and <i>Inappropriate Speech</i> subscales.
Cyproheptadine (In combination with haloperidol)	*** Akhondzadeh et al. (2004) (Weak)	ABC total score CARS	Titrated up to 0.2 mg/kg per day	40 children 3–11 years old	None significant, trend toward increased appetite	Statistically significant difference in <i>ABC—Total score</i> and <i>CARS</i> diagnostic screening tool, with unknown clinical significance
Donepezil	*** Chez et al. (2003) (Weak)	“Autistic behavior” Expressive-receptive communication	1.25–2.5 mg per day	43 children 2–10 years old	Diarrhea, stomach cramping, irritability	“ <i>Autistic behavior</i> ” statistically, but not clinically, improved on <i>CARS</i> diagnostic screening tool
Naltrexone	Willemsen-Swinkels, et al. (1995) (Weak)	“Social behavior” irritability	Single 40 mg dose	20 children 3–7 years old	Sedation, Increased stereotypy	No effect on <i>social behavior</i> Significant reduction in <i>ABC Irritability</i> compared to placebo
	** Kolmen et al. (1995) (Weak)	Hyperactivity communication initiation	1 mg/kg per day	13 children 3–8 years old	Transient sedation	No significant difference in <i>communication initiation</i>
	** Feldman et al. (1999) (Adequate)	Communication	1 mg/kg per day	24 children, 3–8 years old	Transient sedation	No significant difference in <i>communication</i> across multiple measures.
	Campbell et al. (1990) (Adequate)	CGI CPRS Discriminant learning Hyperactivity	0.5-1 mg/kg per day	18 children 3–8 years old	Increased aggression and stereotypy	No significant difference in the <i>CGI</i> or <i>CPRS</i> or in <i>discriminant learning</i> . Positive trend seen for <i>hyperactivity</i>
	Campbell et al. (1993) (Adequate)	Hyperactivity Discriminant learning Self injurious behavior	0.5–1 mg/kg per day	41 children 3–8 years old	None significant	Significantly reduced <i>hyperactivity</i> ; no effect on <i>discriminant learning</i> . Positive trend for <i>self injurious behavior</i>

Table 5 continued

Agent	Study(Rating of strength)	Target symptoms	Dose	Demographics	Significant side effects	Primary outcome(s)
Pentoxifylline (In combination with risperidone)	Akhondzadeh et al. (2010) (Strong)	Irritability, Hyperactivity, stereotypy, social withdrawal Inappropriate speech	200–600 mg per day	40 children/ 4–12 years old	Sedation, GI effects, increased appetite	Statistically and clinically significant improvement on the ABC <i>Irritability and Social Withdrawal</i> subscales

* A positive response in this study was defined as a > 25% reduction in the ABC subscale and a much improved or very much improved rating on the CGI-I

** Study funded by pharmaceutical industry

*** Study funding source not identified

**** A positive response in this study was defined as a >25% reduction in the C-YBOCS compulsions score and a much improved or very much improved rating on the CGI-I

Hyperactivity (0.9) subscales achieved an effect size of >0.4. The effect of risperidone in this study was reduced by a placebo response of 31% on the primary outcome measure, compared to a 12% placebo response in the RUPP study, which may be attributable to both reduced entry criteria and lower mean risperidone dose.

Aripiprazole

Aripiprazole is a partial agonist at dopamine 2 and serotonergic receptors. Two pharmaceutical industry-funded RCTs of aripiprazole in more than 98 children met review criteria and each obtained a strong research strength rating (Marcus et al. 2009; Owen et al. 2009). The studies provide established evidence for the efficacy of aripiprazole in reducing irritability, hyperactivity and stereotypy in children with autistic disorder. Both RCTs of aripiprazole were performed by groups composed of a number of the same researchers within the same time period.

Haloperidol

Haloperidol is a first generation antipsychotic with antagonist activity at dopamine 2 receptors. Two RCTs on haloperidol, which enrolled forty to forty-five children, were reviewed (Anderson et al. 1984, 1989). The studies used DSM-III diagnostic criteria for what was then termed Infantile Autism. Both studies received strong research ratings and showed significant positive effects on multiple behavioral factors and global functioning, as represented on the Children's Psychiatric Rating Scale (CPRS) and the CGI score. These strong studies suggest there may be a role for haloperidol in cases of severe, refractory negative behaviors. Miral et al. (2008) compared haloperidol to risperidone in a head-to-head investigation. This study

obtained only adequate research strength due, in part, to use of a non-systematic diagnostic system for ASD. Risperidone was found superior to haloperidol only for the ABC Total score, which has unclear clinical meaning as the ABC is a factor analyzed scale, with the total score calculated as the sum of multiple carrying sub-scales.

Olanzapine

Olanzapine is a dopamine and serotonin receptor antagonist with one small RCT in eleven children with ASD (Hollander et al. 2006). The study found no significant change in target symptoms of aggression, irritability or compulsions. Global functioning, however, was deemed to be improved in three of six subjects by clinician rating. Due primarily to the very small sample size, the study received a weak research strength rating. Given the high frequency of weight gain in this and other studies of olanzapine (Beduin and de Haan 2010), and the evidence for the efficacy of other atypical antipsychotics, olanzapine should not be considered a first-line agent at this time.

Mood Stabilizers

Divalproex Sodium/Valproic Acid

Divalproex sodium is a mood stabilizer with a mechanism of action that is not well understood. It has been the subject of three RCTs in the ASD population, enrolling 12–30 subjects (Hellings et al. 2005; Hollander et al. 2006, 2010). The use of divalproex sodium to target global clinical irritability, or ABC subscale-defined irritability, has produced conflicting results. Hellings et al. found no significant difference on the ABC—Irritability sub-scale, but also described high inter-subject variability and a large placebo

effect. Hollander et al. used greater symptomatic entry criteria to reduce inter-subject variability, and showed a significant difference between divalproex sodium and placebo in favor of divalproex, particularly for those who obtained serum levels of 87–110 mcg/ml.

Additionally, Hollander et al. (2005a, b) reported positive results for the use of divalproex sodium to treat repetitive behavior in a small study of 12 children. This result, however, was based upon a decrease in the C-YBOCS score of 0.9 points on a 20 point scale. This likely reflects a clinically insignificant change, as a decrease of >25% in the C-YBOCS total score is typically used as the definition of positive response in studies utilizing this measure (Freeman et al. 2009). A potential positive signal was detected in the very small ($n < 7$) subgroup of children who showed high-order compulsive behaviors on the baseline Autism Diagnostic Interview (ADI) measure.

Based upon these conflicting results, there is insufficient evidence for the use of divalproex sodium to treat irritability in children with ASD. Further research that targets irritability may be considered.

Lamotrigine

Lamotrigine is an anticonvulsant with an unknown mechanism of action. One RCT of lamotrigine in 28 children with ASD was identified (Belsito et al. 2001), and obtained a strong research strength rating. The study showed no evidence of effect on irritability or social behavior on multiple measures. The study did not utilize a diagnosis of a mood disorder in the inclusion criteria, possibly limiting generalizability of the results.

Levetiracetam

Levetiracetam is an anticonvulsant whose mechanism of action is not well understood. One RCT of 20 children met review criteria (Wasserman et al. 2006), showed strong research strength and found no significant difference between levetiracetam and placebo on the ABC subscales and the CGI for global functioning.

Norepinephrine Reuptake Inhibitors

Atomoxetine HCl

Atomoxetine selectively inhibits the presynaptic norepinephrine transporter. One small RCT on the effects of atomoxetine in 16 children with ASD was identified (Arnold et al. 2006). This study obtained adequate research strength with positive findings for hyperactivity. Based

upon this rating, there is preliminary evidence for the efficacy of atomoxetine for hyperactivity.

Serotonin Reuptake Inhibitors

Citalopram

Citalopram is a selective serotonin reuptake inhibitor (SSRI), with one identified RCT in children with ASD (King et al. 2009). This large study of 149 children obtained a strong research strength rating and found no significant effect on repetitive behavior. The study targeted repetitive behaviors in part due to the evidence that SSRI's are efficacious for reducing ritualistic behavior in obsessive compulsive disorder.

Fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI). An RCT examining the effect of fluoxetine on repetitive behaviors in 39 children with ASD obtained a weak research strength rating due to the use of a cross-over design for an ultra-long acting medication, non-reproducible statistical analyses, and a positive but likely clinically insignificant result (Hollander et al. 2005a, b). This study produced a mean decrease of 1.3 points on the 20-point C-YBOCS compulsions scale.

Clomipramine

Clomipramine is a tricyclic antidepressant with non-selective serotonin reuptake blockade and prominent anticholinergic effects. Two RCTs on clomipramine met review criteria (Gordon et al. 1993; Remington et al. 2001). A small study of 13 children by Gordon et al. reported positive effects on repetitive behaviors but received a weak research strength rating. Remington et al.'s study of 31 children obtained an adequate research strength rating and compared clomipramine, haloperidol and placebo, finding no significant difference between clomipramine and placebo on the ABC, including the Stereotypy subscale. Twice as many participants receiving clomipramine stopped the study medication due to side effects or lack of efficacy.

Stimulants

Methylphenidate

Methylphenidate is a psychostimulant medication which acts on the dopaminergic and norepinephrine systems. We identified three published RCTs investigating the effects of methylphenidate in children with ASD (Quintana et al. 1995; Handen et al. 2000; RUPP 2005). The RUPP trial

included 66 participants with PDD and hyperactivity in a crossover design using three doses of active medication and placebo. This study received a strong research strength rating. The two other small studies of 10–13 children received an adequate rating, leading to a determination of a promising level of evidence for methylphenidate treatment of hyperactivity in children with ASD.

Miscellaneous Agents

Amantadine

Amantadine is a non-competitive NMDA antagonist. One RCT of this agent in 39 children met review criteria (King et al. 2001). This study obtained an adequate research strength rating, but produced conflicting results based upon the reporter. The parent-rated ABC, the primary outcome measure, showed no statistically significant difference in Hyperactivity and Irritability subscales while the clinician-rated ABC showed a statistically significant difference in the Hyperactivity and Inappropriate Speech subscales. The improvement, however, fell below the typically used clinical threshold of a >25% decrease in ABC subscale score.

Cyproheptadine

Cyproheptadine is an antagonist of 5-HT₂ receptors and one RCT of 40 children met review criteria (Akhondzadeh et al. 2004). This study used the ABC—Total score and the Childhood Autism Rating Scale (CARS) to measure the effect of cyproheptadine + haloperidol versus haloperidol + placebo. Both the ABC Total score and CARS score improved with cyproheptadine. However, the study obtained a weak research strength rating because it lacked specific diagnostic measures for ASD and did not fully report results. Furthermore, the study reported primary outcomes with the CARS, which was designed as a diagnostic screening tool, and the ABC-Total score, which is of unknown clinical relevance.

Donepezil

Donepezil is an acetylcholinesterase inhibitor, with one RCT in 40 children identified (Chez et al. 2003). Although the study had overall positive results, it received a weak research strength rating due to the use of outcome measures not validated for the ASD population, nor designed to measure treatment effects. Of the three outcome measures that were used in the study, two (Gardner's Expressive One-Word Picture Vocabulary Test and Receptive One-Word Picture Vocabulary Test) are intended for the general population rather than for children with ASD. The third outcome measure was designed as a diagnostic screening

tool. A mixed sample also complicated the study, as it included three children with Landau-Kleffner Syndrome. The minimally positive findings would need to be replicated in a better-defined population with different outcome measures.

Naltrexone Hydrochloride

Five RCTs have been performed using naltrexone, an opioid antagonist, in children with ASD (Campbell et al. 1990, 1993; Feldman et al. 1999; Kolmen et al. 1995; Willemsen-Swinkels et al. 1995). The largest study was performed by Campbell et al. (1993) with 41 children and obtained an adequate research strength rating. The investigators found a significant improvement in hyperactivity across three measures. Findings in the other studies were scattered and conflicting, though some reported impressive effects in a number of subjects and noted that the selected populations were quite heterogeneous. Inclusion criteria were generally not based upon co-morbidity in addition to the primary ASD diagnosis. Further study of the effect of naltrexone on hyperactivity in a well-defined ASD sub-population is indicated.

Pentoxifylline

Pentoxifylline is a methylxanthine that has been found to have immunologic and serotonergic effects. One RCT compared the effects of risperidone versus risperidone plus pentoxifylline in 40 children and achieved an adequate research strength rating (Akhondzadeh et al. 2010). Children were enrolled in the study based upon ASD diagnostic characterization that was less rigorous than in studies that achieved a strong research strength rating. Clinician-rated ABC scores showed reductions in Irritability and Social Withdrawal subscales that were statistically significant and of marginal clinical significance. This study provides preliminary evidence that pentoxifylline in combination with risperidone may be mildly efficacious for reducing some aspects of aberrant behavior in children with ASD. More research would need to be done to validate and extend these findings.

Discussion

This systematic review identified a large number of RCTs of psychotropic medications in children with ASD. The pace, quality and distribution of studies has increased over the past decade. The period of 1981–1999 was characterized by a few scattered, single-site studies of haloperidol, clomipramine and clonidine, and utilized heterogeneous populations of children with ASD. In contrast, the period of

2000–2010 was marked by a number of large scale, multi-site RCTs of different compounds on more homogenous ASD populations.

Despite this progress, by our rubric only a few psychotropic interventions have emerged with strong enough research data to obtain a rating of “Established Evidence,” all within the antipsychotic class (see Table 6). In children with ASD, risperidone and aripiprazole have established evidence for treatment of irritability and hyperactivity, haloperidol has established evidence for the treatment of negative behavioral symptoms, and aripiprazole also has established evidence for treatment of stereotypy.

Encouragingly, a number of other compounds have acquired promising or preliminary evidence ratings. Methylphenidate has a promising level of evidence for treatment of hyperactivity in ASD. Medications with preliminary evidence include naltrexone and atomoxetine for hyperactivity, risperidone for repetitive behavior and stereotypy, and pentoxifylline in combination with risperidone for irritability and social withdrawal.

Our analysis reveals several challenges in the developing field of pharmacotherapy for ASD. In general, the established genetic, environmental, cognitive and social heterogeneity in the autism phenotype produced some

highly variable study samples and may have reduced the potential effect size for a given intervention. A placebo response of 30–40% was seen in a number of trials, such as those of aripiprazole, creating the potential for floor effects and reduction of effect sizes. Some studies also lacked a significantly impaired study population, risking false negative trial results. Of the 33 studies reviewed, 70% reported positive results, suggesting a positive result publication bias. Only 39% of the studies utilized an $N \geq 40$ of study subjects, perhaps reflecting the challenges of recruitment paired with the expense of running large, multi-site trials (see Table 7).

Most trials were hampered by the lack of widely accepted diagnostic tools to establish co-occurring psychopathology in the ASD population. This knowledge gap severely limits the ability to rationally extend the relatively large evidence base available from the neurotypical treatment literature, contributing to a speculative investigative approach across a range of substance classes. For example, the efficacy of SSRI's in the treatment of anxiety in ASD, as distinct from repetitive behavior, is untested, perhaps because there is no validated means of measuring anxiety in children with ASD. A number of studies, such as the lamotrigine trial, attempted to treat “autism” with

Table 6 Level of evidence for primary target symptom(s)

Class	Agent	Primary target symptom(s)	Level of evidence
Alpha 2 Agonist	Clonidine	Hyperactivity	Insufficient evidence
	Guanfacine	Hyperactivity	Insufficient evidence
Antipsychotics	Aripiprazole	Irritability, hyperactivity, stereotypy	Established evidence
	Haloperidol	Behavioral symptoms	Established evidence
	Risperidone	Irritability, hyperactivity	Established evidence
	Risperidone	Repetitive behavior, stereotypy	Preliminary evidence
	Olanzapine	Global functioning	Insufficient evidence
Mood Stabilizers	Divalproex sodium/ valproic acid	Irritability	Insufficient evidence (conflicting results)
	Divalproex sodium/ valproic acid	Repetitive behavior	Insufficient evidence
	Lamotrigine	Irritability, social behavior	Insufficient evidence
	Levitiracetam	Irritability	Insufficient evidence
Norepinephrine reuptake inhibitor	Atomoxetine HCl	Hyperactivity	Preliminary evidence
Serotonin reuptake inhibitor	Citalopram	Repetitive behavior	Insufficient evidence
	Fluoxetine	Repetitive behavior	Insufficient evidence
	Clomipramine	Repetitive behavior, stereotypy, irritability, hyperactivity	Insufficient evidence
Stimulants	Methylphenidate	Hyperactivity	Promising evidence
Miscellaneous	Amantadine	Hyperactivity, irritability	Insufficient evidence
	Naltrexone	Social behavior, communication, indiscriminant learning, SIB	Insufficient evidence
	Naltrexone	Hyperactivity	Preliminary evidence
	Pentoxifylline	Irritability, social withdrawal	Preliminary evidence

Table 7 Demographics of studies reviewed

Characteristic	Number of studies
Study funded by pharmaceutical industry	12 (36%)
Study funding source not identified	3 (9%)
Study funded by government, institution, or foundation	18 (54%)
Study reporting positive findings for target symptom/outcome	23 (70%)
Study reporting negative or equivocal findings for target symptom/outcome	10 (30%)
Studies with sample size $N \geq 40$	13 (39%)

psychotropic medications that have shown efficacy for well defined psychopathology in neurotypical populations. This was done without determining if such psychopathology was present in the ASD study population.

The use of outcome measures that are normed and validated for the ASD population, such as the Aberrant Behavior Checklist (ABC), are becoming more common but are not uniformly adopted or used as intended. In the case of the ABC, several studies attempted to suggest positive findings by utilizing the ABC Total score, which is not clearly interpretable since the instrument is a factorial analysis that produces multiple sub-scales. Existing measures also present challenges for mapping results onto current diagnostic schema and functional domains, as the ABC and others have no correlates for depression, anxiety or other relatively common conditions. Some outcome measures specifically designed for the ASD population, such as the Social Responsiveness Scale (Constantino et al. 2003), are not yet widely employed by investigators. In a few cases, measures designed for other purposes, such as the CARS autism diagnostic screening tool, are being used to measure treatment outcomes, with unknown validity.

Even when preferred outcome measures such as the ABC-Irritability subscale are utilized, potential problems emerge. Use of this subscale supported the finding of established evidence and FDA indication for use of risperidone and aripiprazole in the treatment of *irritability* in children with autism. The subscale items primarily detect the frequency and intensity of aggression, self injury and tantrums. The term “irritability” as so used does not correspond to the colloquial use of the word, and clinicians should be cautious in applying it to the broader ASD population. For example, one study showed that only 20% of individuals with ASD show moderate to severe irritability on the ABC-I (LeCavalier 2006).

Significant effort has been expended investigating some agents based upon loose theoretical connections between suspected pathophysiology, purported agent mechanism, and presumed clinical results, as is the case with

cyproheptadine. These studies have produced primarily unrevealing results. This and many other agents have undergone controlled study following publication of a positive case report or case series. It is possible that greater success would be obtained if agents were initially investigated with single subject design methodology, as a large number of behavioral treatments in ASD have been, before the significant effort and expense of controlled trials are undertaken.

Our analysis also revealed several encouraging trends in ASD psychopharmacology research. There is increasing study of sub-populations of the general ASD population, defined by symptom, diagnosis or functional domain. This is likely to increase effect sizes and produce more targeted treatments. For example, after five essentially unrevealing RCTs of naltrexone, a positive finding was appreciated for the subset of children with hyperactivity. This secondary finding has yet to be replicated in a targeted study of children with ASD and well defined hyperactivity.

Lessons, Limitations and Areas of Future Research

The results of this systematic review identify both the increasing speed with which research into pharmacotherapy in ASD is proceeding, as well as the sizable challenges that stand before the goal of providing the right treatment to the right child at the right time. Hampered by the unknowns presented by a heterogeneous ASD population, inadequate diagnostic tools for psychiatric co-morbidity, a scarcity of validated outcome measures, and the relative lack of an organized effort to undertake step-wise multi-center research into promising treatment, the short history of ASD pharmacotherapy is rife with dead ends. Despite these challenges, several groups of investigators have been able to compile a foundational evidence base for rational use of psychotropics in the ASD population. In this paper we have used a published rubric to systematically grade and synthesize the literature to encourage evidence-based practice.

Limitations for this study include the possible inadvertent exclusion of studies that would change our ratings, possible subjectivity in our coding of quality indicators despite the use of a multi-rater consensus process, and the narrowly-defined inclusion criteria of published randomized controlled trials - excluding a possibly informative body of less rigorously controlled research. This review suggests multiple areas of future research, including the development of a rigorous psychiatric co-morbidity assessment tool for the ASD population, increasingly sophisticated outcome measures specific to the population, and the identification and targeting of promising sub-populations of youth with ASD that may have a greater response to individual agents.

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References

- Akhondzadeh, S., Erfani, S., Mohammadi, M. R., Tehrani-Doost, M., Amini, H., Gudarzi, S. S., et al. (2004). Cyproheptadine in the treatment of autistic disorder: A double-blind placebo-controlled trial. *Journal of Clinical Pharmacy & Therapeutics*, 29(2), 145–150.
- Akhondzadeh, S., Fallah, J., Mohammadi, M. R., Imani, R., Mohammadi, M., Salehi, B., et al. (2010). Double-blind placebo-controlled trial of pentoxifylline added to risperidone: Effects on aberrant behavior in children with autism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 34, 32–36.
- Aman, M. G., Singh, N. N., & Stewart, A. W. (1985). The aberrant behavior checklist: A behavior rating scale for the assessment of treatment effects. *American Journal of Mental Deficiencies*, 89, 485–491.
- Aman, M. G., Lam, K. S., & Collier-Crespin, A. (2003). Prevalence and patterns of use of psychoactive medicines among individuals with autism in the Autism Society of Ohio. *Journal of Autism and Developmental Disorders*, 33, 527–534.
- Anderson, L. T., Campbell, M., Grega, D. M., Perry, R., Small, A. M., & Green, W. H. (1984). Haloperidol in infantile autism: Effects on learning and behavioral symptoms. *American Journal of Psychiatry*, 141(10), 195–202.
- Anderson, L. T., Campbell, M., Adams, P., Small, A. M., Perry, R., & Shell, J. (1989). The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. *Journal of Autism and Developmental Disorders*, 19(2), 227–239.
- Arnold, L. E., Aman, M. G., Cook, A. M., Witwer, A. N., Hall, K. L., Thompson, S., et al. (2006). Atomoxetine for hyperactivity in autism spectrum disorders: Placebo-controlled crossover pilot trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, 45(10), 1196–1205.
- Beaulieu, A., Tweed, L., & Connolly, N. (2009). *Interventions for autism spectrum disorders: State of the evidence*. Augusta, Maine: Muskie School of Public Service and Maine Department of Health and Human Services.
- Beduin, A. S., & de Haan, L. (2010). Off-label second generation antipsychotics for impulse regulation disorders: A review. *Psychopharmacology Bulletin*, 43(3), 45–81.
- Belsito, L., Law, P., Kirk, K., Landa, R. J., & Zimmerman, A. W. (2001). Lamotrigine therapy for autistic disorder: A randomized double-blind placebo-controlled trial. *Journal of Autism and Developmental Disorders*, 31(2), 175–181.
- Campbell, M., Anderson, L. T., Small, A. M., Locascio, J. J., Lynch, N. S., & Choroco, M. C. (1990). Naltrexone in autistic children: A double-blind and placebo-controlled study. *Psychopharmacology Bulletin*, 26(1), 130–135.
- Campbell, M., Anderson, L. T., Small, A. M., Adams, P., Gonzalez, N. M., & Ernst, M. (1993). Naltrexone in autistic children: Behavioral symptoms and attentional learning. *Journal of the American Academy of Child and Adolescent Psychiatry*, 32(6), 1283–1291.
- Chez, M. G., Buchanan, T. M., Becker, M., Kessler, J., Aimonovitch, M. C., & Mrazek, S. R. (2003). Donepezil hydrochloride: A double-blind study in autistic children. *Journal of Pediatric Neurology*, 1(2), 83–88.
- Constantino, J. N., Davis, S. A., Todd, R. D., Schindler, M. K., Gross, M. M., Brophy, S. L., et al. (2003). Validation of a brief quantitative measure of autistic traits: Comparison of the Social Responsiveness Scale with the Autism Diagnostic Interview-Revised. *Journal of Autism and Developmental Disorders*, 33(4), 427–433.
- Feldman, H. M., Kolmen, B. K., & Gonzaga, A. M. (1999). Naltrexone and communication skills in young children with autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, 38(5), 587–593.
- Freeman, J. B., Choate-Summers, M. L., Garcia, A. M., Moore, P. S., Sapyta, J. J., Khanna, M. S., et al. (2009). The pediatric obsessive-compulsive disorder treatment study II: Rationale, design and methods. *Child and Adolescent Psychiatry and Mental Health*, 3(1), 4.
- Gordon, C. T., State, R. C., Nelson, J. F., Hamburger, S. D., & Rapoport, J. L. (1993). A double-blind comparison of clomipramine, deipramine, and placebo in the treatment of autistic disorder. *Archives of General Psychiatry*, 50, 441–447.
- Handen, B. L., Johnson, C. R., & Lubetsky, M. (2000). Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. *Journal of Autism and Developmental Disorders*, 30(3), 245–255.
- Handen, B., Sahl, R., & Harden, A. (2008). Guanfacine in children with autism and/or intellectual disabilities. *Journal of Developmental and Behavioral Pediatrics*, 29(4), 303–308.
- Hellings, J. A., Weckbaugh, M., Nickel, E. J., Cain, S. E., Zarcone, J. R., Reese, R. M., et al. (2005). A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. *Journal of Child and Adolescent Psychopharmacology*, 15(4), 682–692.
- Hollander, E., Phillips, A., Chaplin, W., Zagursky, K., Novotny, S., Wasserman, S., et al. (2005a). A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. *Neuropsychopharmacology: Official Publication of The American College of Neuropsychopharmacology*, 30(3), 582–589.
- Hollander, E., Soorya, L., Wasserman, S., Esposito, K., Chaplin, W., & Anagnostou, E. (2005b). Divalproex sodium vs. placebo in the treatment of repetitive behaviours in autism spectrum disorder. *The International Journal of Neuropsychopharmacology: Official Scientific Journal of The Collegium Internationale Neuropsychopharmacologicum (CINP)*, 9(2), 209–213.
- Hollander, E., Wasserman, S., Swanson, E. N., Chaplin, W., Schapiro, M. L., Zagursky, K., et al. (2006). A double-blind placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. *Journal of Child & Adolescent Psychopharmacology*, 16, 541–548.
- Hollander, E., Chaplin, W., Soorya, L., Wasserman, S., Novotny, S., Russoff, J., et al. (2010). Divalproex sodium vs. placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology*, 35(4), 990–998.
- Jaselskis, C. A., Cook, E. H., Fletcher, K. E., & Leventhal, B. L. (1992). Clonidine treatment of hyperactive and impulsive children with autistic disorder. *Journal of Clinical Psychopharmacology*, 12(5), 322–327.

- Johnson, C. P., & Myers, S. M. (2007). Identification and evaluation of children with autism spectrum disorders. *Pediatrics*, *120*(5), 1183–1215.
- King, B. H., & Bostic, J. Q. (2006). An update on pharmacologic treatments for autism spectrum disorders. *Child and Adolescent Psychiatry Clinics of North America*, *15*(1), 161–175.
- King, B. H., Wright, D. M., Handen, B. L., Sikich, L., Zimmerman, A. W., McMahon, W., et al. (2001). Double-blind placebo-controlled study of amantadine hydrochloride in the treatment of children with autistic disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*, 658–665.
- King, B. H., Hollander, E., Sikich, L., McCracken, J. T., Scahill, L., Bregman, J. D., et al. (2009). Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior. *Archives of General Psychiatry*, *66*(6), 583–590.
- Kolmen, B. K., Feldman, H. M., Handen, B. L., & Janosky, J. E. (1995). Naltrexone in young autistic children: A double-blind placebo-controlled crossover study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *34*(2), 223–231.
- Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, *33*, 159–174.
- LeCavalier, L. (2006). Behavioral and emotional problems in young people with pervasive developmental disorders: Relative prevalence, effects of subject characteristics, and empirical classification. *Journal of Autism and Developmental Disorders*, *36*, 1101–1114.
- Marcus, R. N., Owen, R., Kamen, L., Manos, G., McQuade, R. D., Carson, W. H., et al. (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 Psychiatry*, *48*(11), 1110–1119.
- McDougle, C. J., Scahill, L., Aman, M. G., McCracken, J. T., Tierney, E., Davies, M., et al. (2005). Risperidone for the core symptom domains of autism: Results from the study by the autism network of the research units on pediatric psychopharmacology. *American Journal of Psychiatry*, *162*(6), 1142–1148.
- Mcpheeters, M. L., Warren, Z., Sathé, N., et al. (2011). A systematic review of medical treatments for children with autism spectrum disorders. *Pediatrics*, *127*, e1312.
- Miral, S., Gencer, O., Inal-Emiroglu, F. N., Baykara, B., Baykara, A., & Dirik, E. (2008). Risperidone versus haloperidol in children and adolescents with AD: A randomized, controlled, double-blind trial. *European Child and Adolescent Psychiatry*, *17*(1), 1–8.
- Owen, R., Sikich, L., Marcus, R. N., Corey-Lisle, P., Manos, G., McQuade, R. D., et al. (2009). Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*, *124*, 1533–1540.
- Quintana, H., Birmaher, B., Stedje, D., Lennon, S., Freed, J., Bridge, J., et al. (1995). Use of methylphenidate in the treatment of children with autistic disorder. *Journal of Autism and Developmental Disorders*, *25*(3), 283–294.
- Reichow, B., Volkmar, F. R., & Cicchetti, D. V. (2008). Development of the evaluative method for evaluating and determining evidence-based practices in autism. *Journal of Autism and Developmental Disorders*, *38*, 1311–1319.
- Remington, G., Sloman, L., Konstantareas, M., Parker, K., & Gow, R. (2001). Clomipramine versus haloperidol in the treatment of autistic disorder: A double-blind, placebo-controlled, crossover study. *Journal of Clinical Psychopharmacology*, *4*, 440–444.
- Research Units on Pediatric Psychopharmacology Autism Network. (2002). Risperidone in children with autism and serious behavioral problems. *New England Journal of Medicine*, *347*(5), 314–321.
- Research Units on Pediatric Psychopharmacology Autism Network. (2005). A randomized, double-blind, placebo-controlled, crossover trial of methylphenidate in children with hyperactivity associated with pervasive developmental disorders. *Archives of General Psychiatry*, *62*, 1266–1274.
- Scahill, L., Riddle, M., & McSwiggin-Hardin, M. (1997). Children's yale-brown obsessive compulsive scale: Reliability and validity. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*, 844–852.
- Shea, S., Turgay, A., Carroll, A., Schulz, M., Orlik, H., Smith, I., et al. (2004). Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*, *114*, e634–e641.
- Wasserman, S., Iyengar, R., Chaplin, W. F., Watner, D., Waldoks, S. E., Anagnostou, E., et al. (2006). Levetiracetam versus placebo in childhood and adolescent autism: A double-blind placebo-controlled study. *International Clinical Psychopharmacology*, *21*(6), 363–367.
- Willemsen-Swinkels, S. H., Buitelaar, J. K., Weijnen, F. G., & van Engeland, H. (1995). Placebo-controlled acute dosage naltrexone study in young autistic children. *Psychiatry Research*, *58*(3), 203–215.
- Wong, H. H. L., & Smith, R. G. (2006). Patterns of complementary and alternative medical therapy use in children diagnosed with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *36*, 901–909.