Published in final edited form as:

Drugs. 2013 March ; 73(4): 303–314. doi:10.1007/s40265-013-0021-7.

Pharmacotherapy for the Core Symptoms in Autistic Disorder: Current Status of the Research

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Abstract

The current review covers extant literature on pharmacotherapy for core symptoms of autism. The core symptoms of autism include impairments in social interaction and communication, as well as the presence of restricted and repetitive behaviors. There are no known efficacious treatments for the core social symptoms, although effects on repetitive behaviors are indicated with some data. While studies of fenfluramine, secretin, opiates, and mood stabilizers generally find no effect, mixed results suggest more research is needed on antidepressants and atypical antipsychotics. Newer lines of research, including cholinergic and glutamatergic agents and oxytocin, will be of considerable interest in the future. However, research on the treatment of core symptoms is plagued by limitations in study design, statistical power and other issues inherent to the study of treatments for autism (e.g., heterogeneity of the disorder) that continue to prevent the elucidation of efficacious treatments.

Keywords

autism; pharmacologic treatment; atypical antipsychotics; antidepressants; cholinergic agents; glutamatergic agents; oxytocin; research methods

1. Introduction

Autism is a lifelong neurodevelopmental disorder characterized by current DSM-IV diagnostic guidelines as impairments in social interaction and communication and the presence of restricted and repetitive behaviors (1). According to current diagnostic guidelines, these symptoms must be observed in the first 3 years of life and must cause significant impairment for the individual. When grouped with Asperger's disorder and Pervasive Developmental Disorder-NOS, these conditions are referred to as autism spectrum disorders (ASD). The term ASD reflects the dimensional nature of the disorder, which manifests as different combinations of the core symptoms at varying levels of severity (2).

Although exact numbers vary by study and sample characteristics, recent data indicate that over half of children with ASD in the United States are prescribed psychotropic medication, and medication use increases with age (3, 4). However, pharmacologic treatment is often targeted at problems other than the core symptoms of the disorder (5). ASD is commonly associated with challenging behaviors such as irritability, aggression, self-injury, hyperactivity, and inattention (6–8), and these behaviors have often been the stated targets of

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The authors have no conflicts of interest to report.

psychopharmacologic treatment. The atypical antipsychotics aripiprazole (age 6 years and above) and risperidone (age 5 years and 20 pounds and above), clinically indicated for autism in children in the United States, are FDA-approved for the treatment of irritability only (9, 10). Other pharmacologic treatments commonly used for challenging behaviors include other atypical antipsychotics, alpha-2 agonists, mood stabilizers, stimulants, atomoxetine, and naltrexone (11). Within the core symptoms, repetitive behaviors have been most frequently targeted by pharmacologic treatments. Repetitive behaviors, along with irritability, and aggression, for instance, are considered *positive* symptoms and as indicated by the review below, have been studied more extensively than the largely *negative* core symptoms of impairments in social communication.

Here we review in a non-systematic fashion the data on pharmacological agents, specifically focusing on analyses that explore effects on the core symptoms of ASD, using findings from extant literature to categorize medications into groupings of a) those that have been shown to be not efficacious and should probably be abandoned as potential treatments, b) those that are possibly efficacious and deserve more research, and c) those that are currently proposed as new lines of investigation. While an attempt was made to limit this review to agents that have been investigated explicitly for effects on the core symptoms; we found a variety of studies that wherein core symptoms were reported upon, even when not the primary outcome of the study (e.g., the atypical antipsychotics, which have been reported to exert some effects on the core symptoms). Core symptoms are broadly defined here to include measurement of domains ranging from “social withdrawal” in the social domain to traditionally defined obsessive-compulsive symptoms in the restricted/repetitive behavior domain. In the interest of brevity, we focus on traditionally-defined psychopharmacologic agents; we do not address other types of agents such as vitamins and supplements. We also limited this review to articles written in English and this review is written from a North American perspective and may not reflect practice in other regions. We also exclude studies that focused on neurogenetic disorders that are highly associated with, but not exclusively diagnosed with autism (e.g., Fragile X). Table 1 provides a summary of the key design elements and brief results of the reviewed studies. We conclude with a summary of challenges to pharmacotherapy research in ASD, and offer suggestions for future research.

2. Review of Research

2.1 Agents Found to be Probably Not Efficacious

Several pharmacological agents have been adequately evaluated and can be eliminated as possible treatments for the core symptoms of ASD. Fenfluramine, an indirect serotonin agonist that was approved in the US to treat obesity, was pursued as a treatment for ASD due to its potential to decrease levels of serotonin in the blood (12). Initial case reports (13) and a double-blind crossover study (14) were successful in treating core symptoms. However, a double-blind parallel group study found no therapeutic effect of fenfluramine on core symptoms in tandem with adverse effects on learning (15), and subsequent trials were unable to support its use (e.g., 16, 17, 18). Further, concerns about associated cardiac valvular disease led to the removal of fenfluramine from the market in 1997.

Opioid dysregulation has been proposed as a cause of autism, owing initially to observations of autism-like symptoms in animals treated with opiates (19). A great number of case reports, open trials, and controlled trials have been published on the use of naltrexone, an opioid receptor antagonist, for self-injury and core symptoms of autism (for review, see 20). Although naltrexone has been shown to be well-tolerated, the consensus among results is that the drug does not improve core symptoms of autism. The most common positive finding in studies of naltrexone in autism has been on hyperactivity (e.g., 21, 22, 23).

Following incidental administration of porcine secretin, a polypeptide produced in the intestine, improvements were noted in the core symptoms of three children with autism (24). This observation led to many investigations of secretin, which is now among the most widely studied potential treatments for autism. Although the quality of these studies varied, no evidence has been produced to suggest that porcine secretin is efficacious in treating core symptoms (for review, see 25).

Due to the high rate of epilepsy found in individuals with ASD, anticonvulsants are used frequently in this population. Along with lithium, these types of drugs are often referred to collectively as mood stabilizers. After an initial open-label study showed improvements with divalproex on repetitive behaviors and social relatedness (26), an 8-week double-blind, placebo-controlled study was carried out (27). In 13 subjects, a significant and large effect was observed on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; 28), most strongly for an item that reflects the amount of time spent engaging in repetitive behaviors. A second double-blind, placebo-controlled study in 27 children with ASD and significant irritability found no effect of divalproex on the CY-BOCS, which was gathered as a secondary measure (29). However, it should be noted that there is a separate line of research that has questioned whether anticonvulsants may be helpful treating core symptoms of autism in subsets of children with epilepsy or epileptiform discharges (30). Other mood stabilizers, such as lamotrigine and levetiracetam, have been shown to be ineffective for repetitive behavior and social symptoms (31, 32). Although mood stabilizers may yet prove to be effective for the irritability and aggression found in ASD, the balance of evidence suggests that this class does not treat the core symptoms.

2.2 Agents Found to be Possibly Efficacious

2.2.1 Atypical antipsychotics—The atypical antipsychotics are frequently studied and prescribed for aberrant behaviors associated with autism (11). No studies of atypical antipsychotics have explicitly described the core symptoms of autism among the primary targets of treatment; however, symptoms such as social withdrawal and stereotypic behaviors are often assessed as secondary outcomes. Because improvements in these areas have been consistently reported in the atypical antipsychotic treatment literature, we review the evidence here.

As indicated in Table 1, Risperidone was evaluated in an 8-week, double-blind, placebo-controlled study in 101 children with ASD and irritability (33). As hypothesized, a large and significant effect of risperidone was observed on the Irritability subscale of the Aberrant Behavior Checklist (ABC; 34). A significant and large effect of risperidone treatment was observed on Stereotypy. Although the effect on Social Withdrawal was moderate in size, it did not reach significance after Bonferroni correction. Other scales relevant to the core symptoms of autism were collected in this study; McDougle et al. (35) reported secondary analyses of the Ritvo-Freeman Real Life Rating Scale (R-FRLRS) and the modified CY-BOCS. Significant and moderate-to-large effects of risperidone treatment were found on Sensory Motor Behaviors, Affectual Relations, and Sensory Responses of the R-FRLRS and the modified Compulsions scale of the CY-BOCS. Although the effect sizes for R-FRLRS Social Relationships and Language were large, they failed to reach statistical significance. A similar study in 77 Canadian youth found a large and significant effect of risperidone on symptoms of irritability and aggression (36). However, improvements on measures of core symptoms such as ABC Lethargy/Social Withdrawal, ABC Stereotypy, Nisonger Child Behavior Rating Form (NCBRF; 37) Self-Isolated/Ritualistic, and NCBRF Self Injurious/Stereotypic were small-to-moderate or failed to reach significance.

Secondary analyses showed statistically significant and moderately sized effects of risperidone treatment (with and without parent training) compared to placebo were observed

on the Lethargy/Social Withdrawal subscale of the ABC (38; In Press). The analyses included data from the risperidone study reviewed above (33) as well as from a randomized, controlled, 24-week study of atypical antipsychotic (risperidone or aripiprazole) plus parent training in 124 children with ASD. This latter study found a significant effect of combined treatment versus medication alone on challenging behavior (39), as well as a small statistically significant effect in favor of combined treatment on some subscales of the Vineland Adaptive Behavior Scales (40), including the Socialization subscale.

Preliminary data also suggested that paliperidone, an active metabolite of risperidone that is approved for use in the US for schizophrenia and schizoaffective disorder, may ameliorate symptoms of irritability associated with autism. In an 8-week open-label study, 25 adolescents and young adults with autism and significant irritability were treated with paliperidone (41). Significant pre-post effect sizes were greater than 2.0 on the primary outcome measures: ABC Irritability and global improvement. Relevant here, effect sizes were also large and significant for the remaining ABC subscales, including Lethargy/Social Withdrawal and Stereotypy, the Modified CY-BOCS, and the Social Responsiveness scale.

A pair of double-blind, placebo-controlled studies on aripiprazole for irritability associated with autism were published; one was 8 weeks of fixed dosage in 218 children and adolescents (42) and the other was 8 weeks of flexible dosage in 95 children and adolescents (43). A 52-week open label continuation of these studies was also reported (44). In all studies, aripiprazole was effective for the treatment of irritability, as measured by the ABC. Significant effects on ABC Stereotypy and the modified CY-BOCS were also observed, though the difference from placebo was small. No significant differences were observed on ABC Lethargy/Social Withdrawal.

Taken together, these results suggest that the atypical antipsychotics may have a modest effect on the core symptoms of autism as measured by the ABC, NCBRF, and CY-BOCS. Some cautionary notes, which apply to the studies of most drug classes reviewed here, are warranted. Most studies have recruited children specifically for irritability, so it is unclear if effects on the core symptoms of autism would be observed in children without irritability. In these samples, perceived improvements in the core symptoms may simply reflect improvement in irritability. Further, no study has evaluated the core symptoms as a primary outcome, so the measures may not have been optimally selected (see below). Finally, the side effects associated with the atypical antipsychotics (e.g., weight gain and somnolence) may override the modest potential improvement in the core symptoms.

2.2.2 Antidepressants—Perhaps owing to shared features of repetitive/restricted interests with obsessive-compulsive disorder (OCD) and some evidence of disrupted serotonin functioning in autism (12), antidepressants have become a target of interest for the treatment of autism. Most studies of antidepressants have focused upon primarily repetitive behavior. The selective serotonin reuptake inhibitors (SSRI) are the most commonly prescribed antidepressants, owing to their safer side effect profile relative to the tricyclic antidepressants (TCA).

In a 10-week, double-blind, crossover study, 12 children and adolescents with autism were assigned to a clomipramine (a TCA) versus a placebo condition and 12 were assigned to clomipramine versus desipramine (another TCA) (45). In both cases, clomipramine was superior in producing a response on the OCD subscale of the Modified Comprehensive Psychopathological Rating Scale (46). A more recent double-blind crossover study in 31 children, adolescents, and young adults with autism found no statistically significant advantage for clomipramine over placebo or haloperidol (an antipsychotic) on any of the subscales of the ABC (47).

The definitive study of an SSRI for a core symptom of autism was a double-blind, placebo-controlled, parallel-group trial of citalopram targeting repetitive behavior and restricted interests (48). One hundred forty-nine children and adolescents with ASD were assigned to 12 weeks of citalopram or placebo. There was no effect of citalopram treatment over placebo on the main outcome measure, the Repetitive Behavior Scale-Revised, or the ABC.

Controlled studies have produced mixed results for fluoxetine, which may be more effective for adults than for children. A 20-week crossover study in 39 children, found that fluoxetine produced a statistically, but not clinically, significant effect on repetitive behavior (49). However, a 12-week double-blind, placebo-controlled study in 37 adults with ASD found significant improvements in the adult Y-BOCS with fluoxetine treatment (50). Members of the fluoxetine group were 1.5 times more likely than placebo to experience improvement as judged by the Clinical Global Impressions. Fluvoxamine, another SSRI, was also judged to be effective in reducing repetitive thoughts and actions in a 12-week, double-blind, placebo-controlled study in 30 adults with autism (51).

Although the controlled data suggest that antidepressants are not effective for the treatment of the core symptoms of autism in children, some studies have found support for their use in adults. Several uncontrolled reports provide support for the use of SSRIs (52); more research is needed to fully evaluate their utility.

2.3 Newer Lines of Research

Several other classes of drugs not previously used in children or for behavioral purposes have gained traction as possible treatments for the core symptoms of autism. The rationale for the use of these classes is hypothesis-driven with biological mechanisms of action proposed, rather than resulting from incidental observations from treating other disorders. In particular, acetylcholinesterase inhibitors, glutamatergic drugs, and oxytocin have generated recent enthusiasm (53).

2.3.1 Cholinergic agents—The acetylcholinesterase inhibitors are FDA-approved for the treatment of dementia associated with Alzheimer's disease. Postmortem data suggest that cholinergic abnormalities may be implicated in autism, though a definitive link has yet to be established (54). In a double-blind, placebo-controlled, parallel-group study, 43 children with ASD or Landau-Kleffner Syndrome were treated for 6 weeks with donepezil, an acetylcholinesterase inhibitor (55). Because between-group statistics were not presented in the study publication, it is impossible to draw conclusions about the difference between the treatment conditions from this report. The researchers did observe conflicting trends *within groups*: increases in expressive and receptive language were statistically significant for the active treatment group but not in the placebo group, while improvements on the Childhood Autism Rating Scale (CARS; 56), an autism screening tool, were statistically significant in the placebo group but not the active treatment group. Open-label studies of donepezil suggest that it may be useful for irritability and hyperactivity, but not for language and social symptoms (57, 58). A preliminary study of donepezil found that it increased the proportion of REM sleep and decreased the latency to REM sleep, which the authors hypothesize may have effects on learning and cognition (59) and invites a larger, rigorously designed trial.

Uncontrolled data are available on several other cholinesterase inhibitors. Tacrine, the first available drug of this class, was found to have little therapeutic effect in three individuals with autism (60). Safety concerns, primarily regarding hepatotoxicity, have prevented further study of tacrine. Rivastigmine was evaluated in a 12-week open label study of 32 children with ASD (61). Statistically significant improvements of small magnitude were noted on the CARS and a scale of expressive language ability, and subjective parent report was positive.

Thirteen children and adolescents with autism were given galantamine in a 12-week open-label study (62). Statistically significant improvements were observed on the Autism factor of the CPRS and the Lethargy/Social Withdrawal subscale of the ABC, though the magnitude of these improvements was relatively small. In a Letter to the Editor, Niederhofer and colleagues reported the results of a placebo-controlled, double-blind, crossover trial of galantamine (63). Twenty boys with autistic disorder showed statistically significant improvements on parent and teacher rated ABC scores, though the magnitude was small.

A pilot trial of mecamylamine, active at nicotinic acetylcholine receptors, was recently published (64). This double-blind, placebo-controlled trial in 20 children with ASD failed to find a statistically or clinically significant effect of mecamylamine on core symptoms, cognition, or challenging behaviors. The authors noted that a dose-finding study may have been advisable, and that more potent drugs (e.g., varenicline) may be tested in the future.

2.3.2 Glutamatergic agents—Glutamate has been implicated in the pathophysiology of autism by mouse models, genetic findings, and post-mortem data (65). D-cycloserine, a partial agonist at *N*-methyl-D-aspartate (NMDA) glutamate receptors that has been shown to be effective in treating the negative symptoms of schizophrenia (66), was evaluated in an 8-week, single-blind, placebo controlled trial (67). For the 10 of 12 children who completed the trial, scores on the ABC Lethargy/Social Withdrawal subscale were reduced by an average of 60%. Unfortunately, no further studies of d-cycloserine have been reported. Future reports will help to elucidate the role of d-cycloserine in the treatment of autism.

Amantadine, an NMDA glutamate receptor antagonist, was evaluated in a 4-week, double-blind, placebo-controlled study (68). Thirty-nine children and adolescents with autism were enrolled in the trial. No statistically significant difference was found between groups on parent-rated measures, although there was a trend towards greater response to amantadine on clinician-rated Clinical Global Impressions (CGI) ratings. No further studies of amantadine in autism have been reported.

A different glutamatergic antagonist has been the subject of much interest in the past decade: memantine, which is FDA-approved for the treatment of dementia associated with Alzheimer's disease. Although no controlled trials have been published, several open label and retrospective reports are available. Of 18 children and adolescents treated with memantine for an average of 19 weeks, 11 (61%) patients were deemed clinical responders with CGI-Improvement ratings of "much improved" or "very much improved" (69). In another retrospective review, response in 150 children and adolescents with ASD was evaluated for three domains: expressive and receptive language, cognitive and social behaviors, and self-stimulatory activity (70). In this study, about 70% of participants were clinical responders on language and social behavior, while only 12% of the sample responded in terms of self-stimulatory behavior. None of 14 boys treated in another 8-week open label trial was considered globally improved (71). However, statistically significant improvements were observed on each of the ABC subscales, including Lethargy/Social Withdrawal and Stereotypy. A letter to the editor detailed the treatment of four individuals with ASD (72); 4 weeks of treatment with memantine resulted in no meaningful improvements on the ABC.

Two recently published trials explored other glutamatergic agents. Acamprosate is FDA-approved for the maintenance of alcohol abstinence in adults, and its mechanism of action is unclear, though it acts at NMDA glutamate receptors and is associated with antagonism at metabotropic glutamate receptors (mGluR). In an open-label trial with six children, clinical response on social communicative abilities was observed in five patients, per clinician judgment (e.g., Clinical Global Impressions) (73). Improvements were also noted on most

subscales of the ABC and the Social Responsiveness Scale. Hardan and colleagues (74) reported on the use of n-acetylcysteine, which modulates NMDA glutamate receptors, in a double-blind, placebo-controlled trial. Twenty-nine children were randomized to 12-weeks of n-acetylcysteine or placebo. Few differences were observed between groups, save for significant improvement on ABC Irritability (a target symptom for which patients were recruited).

2.3.3 Oxytocin—Oxytocin has been the target of much excitement as data has become available that may implicate it directly in autism (75). Oxytocin is a neuropeptide that is involved in the development of emotional and social affiliative behaviors (76), so the intuitiveness of its utility in autism is strong. Oxytocin is difficult to administer effectively, especially for long-acting benefit; it is quickly broken down and crosses the blood-brain barrier with difficulty. Thus, administration routes such as intranasal are being explored. Oxytocin and the related peptide vasopressin have been shown to increase social awareness in individuals with and without autism (77–79). Fifteen adults with ASD were challenged with an infusion of synthetic oxytocin (pitocin) in a placebo-controlled crossover study (80). Following the challenge, the severity of repetitive behaviors was rated by clinicians. The severity and number of repetitive behaviors was significantly reduced after oxytocin administration. Comprehension of affective qualities of speech was also evaluated as an outcome variable (81). Both subject groups improved relative to baseline following infusion; however, those who first received placebo reverted to baseline at the second challenge, while those who first received oxytocin maintained the improvement. The potential for a carryover effect in this study makes the results difficult to interpret. Results of future trials will further clarify the role of oxytocin in the treatment of core symptoms of autism.

3. Comment and Future Directions

Despite efforts in the field, this review finds that there are no definitely effective or efficacious pharmacologic treatments for the core symptoms of autism. Although many agents have been evaluated, the results are variable. Certain aspects of the research methodology used in studies of autism may contribute to the lack of consistent findings.

A primary issue illustrated by the reviewed research is statistical power, or the ability of a study to capture a treatment effect if one exists. When considering the restrictions of strict study inclusion criteria, it is understood that it will not be easy to recruit large samples, certainly in single-site studies, given limitations on the pool of possible subjects. Sample size is inversely related to effect size when calculating power; larger sample sizes are useful especially when the effect of treatment is expected to be small. For example, the studies included in the current review were largely in samples of 40 or fewer. However, the solution of ever-increasing sample size may not be practical. No magnitude of sample size can offset design issues such as lack of control, heterogeneous samples, and imprecise measurement. It is acknowledged that studies described in the current review varied considerably with respect to these factors, and in particular, there was an overrepresentation of smaller and open label studies for the more recent studies that included the cholinergic and glutamatergic classes. Future trials should address these concerns in order to improve the quality of autism research. Randomized controlled trials are the gold standard of pharmacologic research, and while it is acknowledged that when using a drug for a new target, safety may be determined through small open label pilots, a control group is especially important given the relatively high rate of placebo response observed in autism (82).

Autism is an extraordinarily heterogeneous disorder, and manifestation is influenced by any number of variables such as language level, age, and cognitive ability. In fact, there is increasing support for consideration of multiple autisms, particularly when it comes to

treatment considerations. A drug with a specific mechanism may not produce the same result in two individuals with the same diagnosis but divergent presentation or etiology (83). Studies already address this when inclusion criteria require certain thresholds of specific symptoms or exclusions for specific condition, but it is possible that even further subgrouping will be necessary to allow efficacy to be shown for certain classes of drugs. Thus, a focus on individualized medicine that utilizes biological subtypes and mechanisms to drive agent, sample selection, and treatment target, like that seen in Fragile X Syndrome (84) will be of utmost importance moving forward. It may be especially important with such approaches to utilize larger international multi-site studies in order to achieve sufficient sample sizes and representativeness.

However, reducing heterogeneity in study samples must be balanced with the need for representativeness, especially when core autism symptoms are the target. For instance, it may have been difficult to determine whether several of the antipsychotic drug studies were effective in treating core autism symptoms, because when children have been recruited for meeting a threshold of irritability, it may be very difficult to tease parents' perception of improvement in irritability from improvement in symptoms of autism. Thus, trials with explicit focus on core symptoms must recruit samples with careful consideration of key characteristics.

There is no gold-standard for the measurement of change in autism symptoms in clinical trials (85). The gold-standard diagnostic instruments, the Autism Diagnostic Interview-Revised (86) and the Autism Diagnostic Observation Schedule (87) were not created to measure severity or improvement of the disorder. None of the measures used in the reviewed studies holistically and comprehensively measures change in core symptom domains, with adequately established reliability and validity across all subgroups of individuals with ASD (e.g., developmental and chronological age levels). While we recognize this as a limitation in the field, there are several measures that have been commonly used as indicators of autism treatment outcome. The ABC is a parent report scale of challenging behaviors observed in developmental disabilities that has been used primarily for its Irritability subscale. The ABC also contains subscales that measure avoidance of social interaction (Lethargy/Social Withdrawal) and stereotypic movements (Stereotypy). However, the constructs measured by the ABC do not cleanly map onto autism symptoms. Similarly, the CY-BOCS, created for use in obsessive-compulsive disorder, is often used in a modified format to approximate the repetitive behaviors observed in children with autism (88). Given the developmental nature of the disorder, efficacy of a treatment may take the form of increased trajectory of skill development, rather than reduction in any specific symptom (89). The importance of psychometrically sound outcome measures, biological or behavioral, cannot be overstated; inaccurate measurement has been identified in other fields as responsible for failed trials (90).

The field is looking eagerly toward the advent of biomarkers of autism, which may dramatically increase power through study design that measures mechanism. In the interim, biological measurement can be used via surrogate endpoints, which may help to target treatment and more accurately measure its effects. Studies of MGLuR in fragile X and rapamycin in tuberous sclerosis are examples, in their ability to test whether methylation status moderates efficacy (84), and their ability to correct mTOR (mammalian target of rapamycin) pathway abnormalities, respectively (91). This type of design will help to streamline candidate identification and narrow the focus in the field. However, it will be important for studies to be very explicit about their primary outcome variable, which will need to be based on behavioral presentation (i.e., symptoms of autism) rather than biologic markers. Biological markers can be studied as an endpoint to determine mechanism of action, but not as an outcome measure if core symptoms of autism are the drug target.

Study characteristics such as the chronologic and mental age at which intervention occurs should also be given serious consideration (92). In nearly all of the studies reviewed here, participants were at least 5 years of age, and there were often exclusion criteria based on cognitive ability. Pharmacologic research is difficult in children; diagnoses may be unstable, parents and clinicians may be unwilling to treat very young children, and the effects of pharmacologic agents in very young and very impaired children are often not well-understood. However, autism is a developmental disorder, and logic dictates that the most dramatic effects on outcome will be observed with earlier intervention targeting those most severely affected. Future research should explore the possibility of younger samples and of longer-term follow-up to determine the possibility of cascade effects (e.g., a chain of events due to a one-time effect on a system).

Finally, as pharmacologic research for the core symptoms of autism moves forward, a greater emphasis on combined treatments, both behavioral and pharmacologic may be necessary. Not only does this more accurately reflect real-world conditions, it best utilizes the tools we have available. Currently, the only empirically supported treatments for autism are based on applied behavior analysis, which has been combined with pharmacologic treatment in at least one trial (39).

Autism treatment research is moving forward quickly, with exciting new avenues and ever-increasing attention to study design. Even as we identify new agents, however, there are some major methodological issues that will constrain our ability to detect the effects. Improvements to study design and instrumentation will help to ensure that future research is as efficient as possible.

Acknowledgments

This work was supported by the Intramural Program of the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH). The views expressed in this paper do not necessarily represent the views of the NIMH, NIH, HHS, or the United States Government.

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Table 1

Selected evidence for “possibly efficacious” and “newer lines of research”

Agent	Ref	Sample	Study Design	Target Symptoms	Study Results (Relevant to Core Symptoms Only)	Reported Serious AEs ¹
Risperidone	33	N = 101. Autism. Children. Recruited for irritability.	8-week, R, DB, PBO, PG.	Irritability.	Moderate effect of RIS on ABC Stereotypy. N.S. effect on ABC Social Withdrawal and Inappropriate Speech. CY-BOCS NR.	None.
	36	N = 79, ASD. Children.	8-week, R, DB, PBO, PG.	Behavioral symptoms.	Moderate effects of RIS on ABC Inappropriate Speech, Social Withdrawal, and Stereotypy.	No serious AEs reported.
Puliperidone	41	N = 25. Autism. Children & adults. Recruited for irritability.	8-week, prospective, OL.	Irritability.	Large pre-post effects on ABC Social Withdrawal, Stereotypy, Inappropriate Speech; SRS Total score, CY-BOCS.	None.
Aripiprazole	42, 43, 44	N = 218 [42]; N = 164 [43]; N = 330 [44]. Children. Recruited for irritability.	8-week, DB, PBO, PG [42, 43]. Fixed-dose [42], flexible-dose [43]. 52-week, OL [44].	Irritability	ARI superior to PBO on ABC Stereotypy, Inappropriate Speech, CY-BOCS Compulsions [42, 43]. Pre-post improvements on these subscales in OL [44].	Presyncope and agitation [42]. Aggression, impulsivity, acute otitis media, pharyngotonsillitis, sinusitis, dysphagia, cholecystitis, cholelithiasis, asthma, suicidal ideation, skin infection, convulsion [44].
Clomipramine	45	N = 30. Autism. Children.	10-week, DB, R, crossover v. PBO or desipramine (DES).	RRB.	CLO superior to placebo and DES on all primary outcome measures and secondary outcome measures.	No serious AEs reported.
	47	N = 36. Autism. Children and adults.	7-week, DB, R, crossover (CLO, haloperidol [HAL], PBO).	RRB.	Significant improvement from BL observed on CARS and ABC Irritability for HAL but not CLO. Without intent-to-treat, CLO was equally superior to placebo.	No serious AEs reported.
Citalopram	48	N = 149, ASD. Children.	12-week, DB, R, PBO.	RRB.	No effect of treatment.	Prolonged seizure with loss of consciousness.
Fluoxetine	49	N = 39, ASD. Children.	16 week DB PBO cross-over.	RRB.	Significant effect of treatment on CY-BOCS. No difference on modified CGI.	No serious AEs reported.
	50	N = 37 ASD. Adults.	12 week DB, PBO.	RRB, global autism severity.	Significant effect of treatment on Y-BOCS and CGI-I.	No serious AEs reported.

Agent	Ref	Sample	Study Design	Target Symptoms	Study Results (Relevant to Core Symptoms Only)	Reported Serious AEs ¹
Fluvoxamine	51	N = 30 Autism. Adults.	12-week, DB, PBO.	Targets: RRB, aggression, social relatedness.	Treatment associated with significant global improvement and reduction in repetitive thoughts and behaviors.	None.
Donepezil	55	N = 43. ASD. Children.	6-week, DB, PBO plus OL extension and cross-over for placebo.	Core symptoms.	Vocabulary improved within the treatment group but was not compared statistically to placebo group.	No serious AEs reported.
	57	N = 8. Autism. Children.	Retrospective chart review.	Core symptoms, disruptive behavior.	Pre-post significant improvement on ABC Social Withdrawal and CGI-I.	No serious AEs reported.
Tacrine	60	N = 3. Autism. Children and adults.	OL, length NR.	Core symptoms.	Small significant pre-post improvement on all ABC subscales except Stereotypy.	No serious AEs reported.
Rivastigmine	61	N = 32. ASD. Children.	12-week OL.	Language, core symptoms.	Small significant pre-post improvement in CARS, expressive vocabulary, CPRS. No treatment effect on receptive vocabulary.	No serious AEs reported.
Galantamine	62	N = 13. Autism. Children.	12-week prospective, OL.	Disruptive behavior.	Modest improvement on CPRS autism subscale, ABC Social Withdrawal.	No serious AEs reported.
Mecamylamine	63	N = 20. Autism. Children. Recruited for irritability.	R, DB, PBO, crossover, trial length NR.	NR.	Modest improvement on parent-rated ABC Social Withdrawal, Inappropriate Speech. No diff on clinician scale.	No serious AEs reported.
	64	N = 20. Autism. Children.	14-week, DB, PBO, PG. Plus 10-week OL for placebo.	Core and associated symptoms.	No effect of treatment. Some indication that moderate dose of drug was superior to higher dose.	No serious AEs reported.
D-cycloserine	67	N = 10. Autism. Children and adults.	8-week, prospective, single-blind.	Social, communication impairment.	Pre-post improvement on CGI-S and I noted. Moderate improvements in ABC Social Withdrawal. No change on other (sub)scales.	No serious AEs reported.
Amantadine	68	N = 39. Autism. Children. Recruited for irritability.	4-week, R, DB, PG, PBO.	Irritability, Hyper-activity.	No difference on parent ratings. Clinician-rated ABC showed small differences on Inappropriate Speech.	None.
Memantine	69	N = 18. ASD. Children.	OL, retrospective, mean duration 19 weeks.	Social use of language, inattention/hyperactivity, irritability.	Improvement noted in about 60% of the sample.	No serious AEs reported.

Agent	Ref	Sample	Study Design	Target Symptoms	Study Results (Relevant to Core Symptoms Only)	Reported Serious AEs ¹
	70	N = 151. ASD. Children and adults.	OL, prospective, trial range 1–21 months.	Language, social behavior, self-stimulation.	Significant improvements on CGI-I for all target symptoms.	No serious AEs reported.
	71	N = 14. ASD. Children.	8-week, prospective, OL.	Language, cognition, memory, behavior.	No pre-post differences on language or CGI. Small-to-moderate improvements in ABC Social Withdrawal, Stereotypy, and Inappropriate Speech.	No serious AEs reported.
	72	N = 4. ASD. Children and adults. Recruited for high ABC.	4-week, OL, (pro/retrospective NR).	Core and associated symptoms.	No pre-post differences.	No serious AEs reported.
Acamprosate	73	N = 6. Autism. Children.	OL, naturalistic; trial length range 10–30 weeks.	Social Impairment.	Global improvement noted in most subjects. Significant pre-post improvement on ABC Social Withdrawal.	No serious AEs reported.
N-Acetylcysteine	74	N = 33. Autism. Children. Recruited for irritability.	12-week, DB, PBO.	Irritability.	Some improvement noted on SRS-Social Cognition and Social Motivation and RBS-R Stereotypies.	No serious AEs reported.
Oxytocin	80, 81	N = 15. ASD. Adults.	R, DB, PBO, crossover, challenge (single administration).	RRB; comprehension of affect.	Repetitive behaviors and affective speech recognition improved with OXY.	No serious AEs reported.

¹ Many reports did not positively confirm that no serious AEs occurred (i.e., no mention was made of serious AEs) and are classified as “No serious AEs reported.” Reports that positively confirmed that no serious AEs occurred are classified with “None.” If not reported as Serious, individual AEs are not included in this table.

Note: The studies included in this table do not represent an exhaustive review of the literature and are meant to be illustrative. Ref = reference number. R = randomized. DB = double-blind. PBO = placebo. PG = parallel groups. RIS = risperidone. ABC = Aberrant Behavior Checklist. NS = non-significant. CY-BOCS = Children’s Yale-Brown Obsessive Compulsive Scale. NR = not reported. AE = adverse effect. ASD = autism spectrum disorders. OL = open-label. SRS = Social Responsiveness Scale. ARI = aripiprazole. RRB = restricted and repetitive behavior. CLO = clomipramine. BL = baseline. CARS = Childhood Autism Rating Scale. Y-BOCS = Yale-Brown Obsessive Compulsive Scale. CGI = Clinical Global Impressions (-1 = Improvement, -5 = Severity). CPRS = Conners’ Parent Rating Scale. RBS-R = Repetitive Behavior Scale-Revised. OXY = oxytocin.