An Evidence-based Medication Overview for Autism Spectrum Disorders

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Disclaimer

While Dr. Rossignol has attempted to make the information in this presentation as accurate as possible, the information is provided without any expressed or implied warranty. The purpose of this lecture is to provide information about different conditions or treatments that may affect individuals with autism and other conditions. Please be advised that Dr. Rossignol is not giving medical advice and that circumstances may dictate different treatments. All of the reviewed treatments in this lecture are considered off-label and not FDA-approved. Before beginning any treatment, please consult with your or your child's physician.

The use of every treatment in autism is "off-label" except for Risperidone and Aripiprazole for the treatment of irritability

What is Autism?

- **Is classified as a disorder, not a disease**
- **Is a spectrum disorder**
- **There are no defining biomarkers**
- **Is diagnosed solely by behavioral observations: has + and - symptoms**
- **Therefore, the diagnosis of autism tells us nothing about the potential causes of the disorder**

Approved Medications: ASD

- **Risperidone (Risperdal®)**
- **Aripiprazole (Abilify®)**
- **Both are atypical antipsychotic medications approved for treating irritability associated with ASD and thus do not treat core autistic symptoms or behaviors**
- **There are currently no approved med-ications for the core symptoms of ASD**

Evidence Based Medicine (EBM)

- **Using the best available evidence to aid clinical decision making**
- **Uses strength or level of evidence (LOE)**
  - **Benefit(s) of treatment**
  - **Risk(s) of treatment**
  - **Can apply to diagnostic testing**
- **Basis is often randomized controlled trials (RCT), systematic reviews and meta-analysis**

Evidence-based Medicine: Strength of Evidence (Efficacy)

- A: Supported by at least 2 prospective randomized controlled trials (RCTs) *or* 1 systematic review
- B: Supported by at least 1 prospective RCT *or* 2 nonrandomized controlled trials
- C: Supported by at least 1 nonrandomized controlled trial *or* 2 case series
- D: Troublingly inconsistent *or* inconclusive studies *or* studies reporting no improvements

STEPS: Evidence for Treatments

- **S**afety: Has it been studied in children?
- **T**olerability: What are the side effects?
- **E**fficacy: Does it work?
- **P**rice: How much will it cost?
- **S**implicity: How easy is it to do?

STEPS: Melatonin

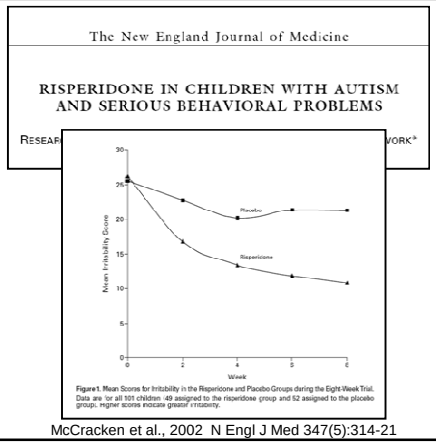
- Safety: 20 studies showing safety in children with autism
- Tolerability: Very little side effects
- Efficacy: 5 double-blind studies showing improvements compared to placebo
- Price: Less than $30 per month
- Simplicity: Pill taken at bedtime

Ideal Treatment

- Backed by Strength of Evidence: A
- Safe
- Tolerable
- Efficacious: Treatment works
- Price: Cheap
- Simple: In-home treatment
- POEM: Outcome matters to child/parent

Medications Strength of Evidence: A And On-Label

Supported by at least 2 prospective randomized controlled trials


The New England Journal of Medicine

RISPERIDONE IN CHILDREN WITH AUTISM AND SERIOUS BEHAVIORAL PROBLEMS

RESEAR… …VORK*

Mean Irritability Score

Week

Figure 1. Mean Scores for Irritability in the Risperidone and Placebo Groups during the Eight-Week Trial. Data are for all 101 children: 49 assigned to the risperidone group and 52 assigned to the placebo group. Higher scores indicate greater irritability.

McCracken et al., 2002 N Engl J Med 347(5):314-21

Efficacy of Risperidone in Managing Maladaptive Behaviors for Children With Autistic Spectrum Disorder: A Meta-Analysis

This meta-analysis examined research regarding the effectiveness of risperidone use among children with ASD using articles published since the year 2000. The database for the analyses comprised 22 studies including 16 open-label and six placebo-controlled studies. RESULTS: The mean effect size for the database was 1.047 and the sample weighted mean effect size was 1.108, with a variance of 0.18. Outcome measures demonstrated mean improvement in problematic behaviors equaling one standard deviation, and thus current evidence supports the effectiveness of risperidone in managing behavioral problems and symptoms for children with ASD. Although Risperdal has several adverse effects, most are manageable or extremely rare. An exception is rapid weight gain, which is common and can create significant health problems.

Sharma and Shaw, 2012 J Pediatr Health Care 26(4):291-9

Cochrane Database Syst Rev. 2012 May 16;5:CD009043.

Aripiprazole for autism spectrum disorders (ASD).

Ching H, Pringsheim T.

Two randomized controlled trials with similar methodology have evaluated the use of aripiprazole for a duration of eight weeks in 316 children with ASD. Although we searched for studies across age groups, only studies in children and youths were found. Meta-analysis of study results revealed a mean improvement of 6.17 points on the Aberrant Behavior Checklist (ABC) irritability subscale, 7.93 points on the ABC hyperactivity subscale, and 2.66 points in the stereotypy subscale in children treated with aripiprazole relative to children treated with a placebo. In terms of adverse side effects, children treated with aripiprazole had a greater increase in weight with a mean increase of 1.13 kg relative to placebo, and had a higher risk ratio for sedation (RR 4.28) and tremor (RR 10.26).

Ching and Pringsheim, 2012 Cochrane Database Syst Rev. 5:CD009043

Off-label from here on…

Medications Strength of Evidence: A

Supported by at least 2 prospective randomized controlled trials

Efficacy and Safety of Naltrexone Use in Pediatric Patients with Autistic Disorder

OBJECTIVE: To review the efficacy and safety of naltrexone in pediatric patients with autistic disorder (AD). Naltrexone has been used most commonly at doses ranging from 0.5 to 2 mg/kg/day and found to be predominantly effective in decreasing self-injurious behavior. Naltrexone may also attenuate hyperactivity, agitation, irritability, temper tantrums, social withdrawal, and stereotyped behaviors. Patients may also exhibit improved attention and eye contact. Transient sedation was the most commonly reported adverse event.

Elchaar et al., 2006 Ann Pharmacother 40(6):1086-95

Effect of propranolol on verbal problem solving in autism spectrum disorder

Some studies suggest drugs decreasing noradrenergic activity are beneficial in ASD. In individuals without neurodevelopmental diagnoses, propranolol is beneficial only for difficult NF-dependent problems. However, in populations with altered noradrenergic regulation, propranolol also benefits performance for simple problems. Due to decreased flexibility of access to networks in ASD, we wished to examine the effect of propranolol on NF in ASD. ASD subjects benefited from propranolol on simple anagrams, whereas control subjects were impaired by propranolol. Further study will be necessary to confirm this finding in a larger sample and to compare clinical response with cognitive response to propranolol.

Beversdorf et al., 2008 Neurocase 14(4):378-83

TABLE 1

Average solution latencies (A), numbers of problems solved (B), and numbers of pictures recognized (out of 30) for each condition with in each group (±*SD*)

	Propranolol	*Placebo*
(A) Average solution latencies (s)		
ASD	22.0 ± 14.0	28.4 ± 17.6
Control	22.5 ± 16.9	20.3 ± 14.4
(B) Number of problems solved		
ASD	12.6 ± 2.0	12.3 ± 2.0
Control	12.8 ± 1.6	13.0 ± 1.1
(C) Number of pictures recognized (out of 30)		
ASD	12.9 ± 6.2	11.6 ± 7.8
Control	13.6 ± 6.0	13.2 ± 8.2

Beversdorf et al., 2008 Neurocase 14(4):378-83

Effect of Propranolol on Functional Connectivity in Autism Spectrum Disorder—A Pilot Study

Ananth Narayanan · Catherine A. White · Sanjida Saklayen · Mary J. Scaduto · Allen L. Carpenter · Amir Abdaljalil · Petra Schmalbrock · David Q. Beversdorf

Our goal was to determine the effect of propranolol on functional connectivity in ASD during a verbal decision making task as compared to nadolol, thereby accounting for the potential spurious fMRI effects due to peripheral hemodynamic effects of propranolol. Ten ASD subjects underwent fMRI scans after administration of placebo, propranolol or nadolol, while performing a phonological decision making task. Comparison of functional connectivity between pre-defined ROI-pairs revealed a significant increase with propranolol compared to nadolol, suggesting a potential imaging marker for the cognitive effects of propranolol in ASD.

Narayanan et al., 2010 Brain Imaging Behav 4(2):189-97

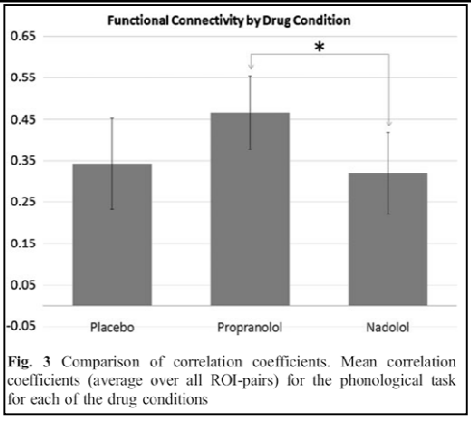


Fig. 3 Comparison of correlation coefficients. Mean correlation coefficients (average over all ROI-pairs) for the phonological task for each of the drug conditions

Narayanan et al., 2010 Brain Imaging Behav 4(2):189-97

Effect of Propranolol on Word Fluency in Autism

David Q. Beversdorf, MD,† ‡§‖ Sanjida Saklayen, PhD,§‖ Katherine F. Higgins,¶ Kimberly E. Bodner, MA, MS,† Stephen M. Kanne, PhD,‡# and Shawn E. Christ, PhD† ‡*

METHODS: A sample of 14 high-functioning adolescent and adult participants with autism and 14 matched controls were given letter and category word fluency tasks on 2 separate testing sessions; 1 test was given 60 minutes after the administration of 40 mg propranolol orally, and 1 test was given after placebo, administered in a double-blinded, counterbalanced manner. RESULTS: Participants with autism were significantly impaired compared with controls on both fluency tasks. Propranolol significantly improved performance on category fluency, but not letter fluency among autism participants. No drug effect was observed among controls. Expected drug effects on heart rate and blood pressure were observed in both the groups.

Beversdorf et al., 2011 Cogn Behav Neurol 24(1):11-7

Intranasal Oxytocin Improves Emotion Recognition for Youth with Autism Spectrum Disorders

Adam J. Guastella, Stewart L. Einfeld, Kylie M. Gray, Nicole J. Rinehart, Bruce J. Tonge, Timothy J. Lambert, and Ian B. Hickie

In a double-blind, randomized, placebo-controlled, crossover design, we administered oxytocin nasal spray (18 or 24 IU) or a placebo to 16 male youth aged 12 to 19 who were diagnosed with Autistic or Asperger's Disorder. In comparison with placebo, oxytocin administration improved performance on the Reading the Mind in the Eyes Task. This study provides the first evidence that oxytocin nasal spray improves emotion recognition in young people diagnosed with autism spectrum disorders. Findings suggest the potential of earlier intervention and further evaluation of oxytocin nasal spray as a treatment to improve social communication and interaction in young people with autism spectrum disorders.

Guastella et al., 2009 Biol Psychiatry, in press

Promoting social behavior with oxytocin in high-functioning autism spectrum disorders

Elissar Andari[a], Jean-René Duhamel[a], Tiziana Zalla[b], Evelyn Herbrecht[b], Marion Leboyer[b], and Angela Sirigu[a,1]

We investigated the behavioral effects of oxytocin in 13 subjects with autism. In a simulated ball game where participants interacted with fictitious partners, we found that after oxytocin inhalation, patients exhibited stronger interactions with the most socially cooperative partner and reported enhanced feelings of trust and preference. Also, during free viewing of pictures of faces, oxytocin selectively increased patients' gazing time on the socially informative region of the face, namely the eyes. Thus, under oxytocin, patients respond more strongly to others and exhibit more appropriate social behavior and affect, suggesting a therapeutic potential of oxytocin through its action on a core dimension of autism.

Andari et al., 2010 Proc Natl Acad Sci USA, in press

Long-Term Administration of Intranasal Oxytocin Is a Safe and Promising Therapy for Early Adolescent Boys with Autism Spectrum Disorders

We conducted a singled-armed, open-label study in which OT was administered intranasally over the long term to eight male youth with ASD. The OT administration was performed in a stepwise increased dosage manner every 2 months (8, 16, 24 IU/dose). A placebo period (1-2 weeks) was inserted before each step. In addition, side effects were monitored by measuring blood pressure and examining urine and blood samples. Results: Six of the eight participants showed improved scores on the communication and social interaction domains of the ADOS-G. Caregivers of 5 of the eight participants reported certain positive effects of the OT therapy, especially on the quality of reciprocal communication. All participants showed excellent compliance and no side effects.

Tachibana et al., 2013 J Child Adolesc Psychopharmacol, in press

A prospective double-blind, randomized clinical trial of levocarnitine to treat autism spectrum disorders

Thirty subjects diagnosed with an ASD were randomly assigned to receive a standardized regimen (50 mg L-carnitine/kg bodyweight/day) of liquid L-carnitine (n=19) or placebo (n=11) for 3-months. Significant improvements were observed in CARS (-2.03, 95% CI=-3.7 to -0.31), CGI (-0.69, 95% CI=-1.1 to -0.06), and ATEC scores. Significant correlations between changes in serum free-carnitine levels and positive clinical changes were observed for hand muscle strength (R2=0.23, P=0.046), cognitive scores (R2=0.27, P=0.019), and CARS scores (R2=0.20, P=0.047).

Geier et al., 2011 Med Sci Monit 17(6):PI15-23

L-Carnitine supplementation improves the behavioral symptoms in autistic children

Thirty children diagnosed with autism were randomly assigned to receive (100 mg/kg bodyweight/day) of liquid l-carnitine (n = 16) or placebo (n = 14) for 6 months. Results showed significant improvement in CARS scores (P-groups <0.001) and (P-overtime = 0.006), with statistically significant differences in free carnitine levels (P = 0.027) and total carnitine levels (P = 0.036). There was no correlation between baseline free and total carnitine levels with changes in CARS scores from zero to 6 months (r > 0.5, P > 0.05) and generally l-carnitine therapy was well tolerated. In conclusion, l-carnitine therapy (100 mg/kg bodyweight/day) administered for 6 months significantly improved the autism severity, but subsequent studies are recommended.

Fahmy et al., 2013 RASD 7(1):159-166

Medications
Strength of Evidence: B

Supported by at least 1 prospective randomized controlled trial

Galantamine may be effective in treating autistic disorder

When parent and teacher scores were combined, mean scores were slightly lower during treatment with galantamine than during treatment with placebo for irritability classified by ratings of the aberrant behaviour checklist (galantamine 11.5 (7.6) *v* placebo 15.1 (5.4), P=0.039), hyperactivity (17.2 (12.8) *v 21.7 (15.4), P=0.038),* inadequate eye contact (placebo 7.6 (3.2) *v 8.4 (5.2),* P=0.049), and inappropriate speech (4.7 (3.1) *v 6.2 (2.4), P=0.045).*

Niederhofer et al., 2002 BMJ 325:1422

Donepezil hydrochloride: a double-blind study in autistic children

Forty-three patients (35 males, 8 females, average age 6.8 yrs., range 2.1-10.3 yrs), with diagnoses of Autistic Spectrum Disorders enrolled in a randomized six-week, double blind, placebo-controlled trial of donepezil hydrochloride, with an additional six weeks of open-label treatment. Expressive and receptive speech gains, as well as decreases in severity of overall autistic behavior, were documented after 6-weeks for the treatment group. These improvements were statistically significant when compared to placebo, and were clinically meaningful as assessed over time.

Chez et al., 2003 Journal of Pediatric Neurology 1(2):83-88

An Open Label Trial of Donepezil for Enhancement of Rapid Eye Movement Sleep in Young Children with Autism Spectrum Disorders

Five subjects found to have an ASD (ages 2.5-6.9 years) and demonstrated deficits in REM sleep compared with within-lab controls were enrolled in a dose finding study of donepezil. Each subject was examined by polysomnography for REM sleep augmentation after drug administration. Results: REM sleep as a percentage of Total Sleep Time was increased significantly and REM latency was decreased significantly after drug administration in all subjects. No other observed sleep parameter was changed significantly.

Buckley et al., 2011 J Child Adolesc Psychopharmacol 21(4):353-357

Safety and Efficacy of Donepezil in Children and Adolescents with Autism: Neuropsychological Measures

The goal of this study was to assess the tolerability, safety, and efficacy of donepezil on EF in a sample of children and adolescents with ASD. METHOD: Thirty-four children and adolescents with ASD (age range 8-17 years; IQ >75) were enrolled in a 10-week, double-blind, placebo-controlled trial of donepezil (doses of 5 and 10 mg), followed by a 10-week open label trial for placebo nonresponders. RESULTS: The effect of donepezil treatment on EF was examined. Despite improvement on a number of EF measures, no statistically significant between-group differences were found (with gains observed for both the placebo and donepezil groups). CONCLUSIONS: The results suggest that short-term treatment with donepezil may have limited impact on cognitive functioning in ASD.

Handen et al., 2011 J Child Adolesc Psychopharmacol 21(1):43-50

Clonidine Treatment of Hyperactive and Impulsive Children with Autistic Disorder

Subjects were included in the study if they had inattention, impulsivity, and hyperactivity that was excessive for their developmental level. Subjects had not tolerated or responded to other psychopharmacologic treatments (neuroleptics, methylphenidate, or desipramine). Teacher ratings on the Aberrant Behavior Checklist irritability, stereotypy, hyperactivity, and inappropriate speech factors were lower during treatment with clonidine than during treatment with placebo.

Jaselskis et al., 1992 J Clin Psychopharmacol12(5):322-7

Original article

Use of clonidine in children with autism spectrum disorders

An open labeled retrospective study of clonidine in treatment of insomnia, and/or hyperactivity, inattention, mood disorder, and aggressive behaviors was conducted using parent reports of sleep initiation and maintenance, as well as behaviors prior and during clonidine treatment. Clonidine was effective in reducing sleep initiation latency and night awakening, to a less degree in improving attention deficits hyperactivity, mood instability and aggressiveness in this cohort of 19 children with ASD. The side effects were largely tolerable.

Ming et al., 2008 Brain Dev 30(7):454-460

Double-Blind, Placebo-Controlled Study of Amantadine Hydrochloride in the Treatment of Children With Autistic Disorder

After a 1-week, single-blind placebo run-in, patients received a single daily dose of amantadine (2.5 mg/kg per day) or placebo for the next week, and then bid dosing (5.0 mg/kg per day) for the subsequent 3 weeks. RESULTS: When assessed on the basis of parent-rated ABC-CV ratings of irritability and hyperactivity, the mean placebo response rate was 37% versus amantadine at 47% (not significant). However, in the amantadine-treated group there were statistically significant improvements in absolute changes in clinician-rated ABC-CVs for hyperactivity (amantadine -6.4 versus placebo -2.1; p = .046) and inappropriate speech (-1.9 versus 0.4; p = .008). CGI scale ratings were higher in the amantadine group: 53% improved versus 25% (p = .076). Amantadine was well tolerated.

King et al., 2001 J Am Acad Child Adolesc Psychiatry 40(6):658-65

Cyproheptadine in the treatment of autistic disorder: a double-blind placebo-controlled trial

Patients were randomly allocated to cyproheptadine + haloperidol (Group A) or haloperidol + placebo (Group B) for an 8-week, double-blind, placebo-controlled study. The primary measure of the outcome was the Aberrant Behaviour Checklist-Community (ABC-C) and the secondary measure of the outcome was the Childhood Autism Rating Scale (relating to people and verbal communication). RESULTS: The ABC-C and the Childhood Autism Rating Scale scores improved with cyproheptadine. The difference between the two treatments was significant as indicated by the effect of group. The results suggest that the combination of cyproheptadine with a conventional antipsychotic may be superior to conventional antipsychotic alone for children with autistic disorder..

Akhondzadeh et al., 2004 J Clin Pharm Ther 29(2):145-50

Celecoxib as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial

In a 10-week randomized double-blind placebo-controlled study, 40 outpatient children with a Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision clinical diagnosis of autism were randomly allocated to celecoxib plus risperidone or placebo plus risperidone. The dose of risperidone and celecoxib were titrated up to 3 and 300 mg/day, respectively. RESULTS: By week 10, patients in the celecoxib group showed significantly greater improvement in the Irritability (P < 0.001), Lethargy/Social Withdrawal (P < 0.001), and Stereotypic Behavior (P < 0.00) but not in Hyperactivity/Noncompliance (P = 0.202) and Inappropriate Speech (P = 0.802) subscales than the placebo group.

Asadabadi et al., 2012 Psychopharmacology (Berl), in press

A Double-Blind Placebo-Controlled Trial of Fluoxetine for Repetitive Behaviors and Global Severity in Adult Autism Spectrum Disorders

Adults with ASDs were enrolled in a 12-week double-blind placebo-controlled fluoxetine trial. Thirty-seven were randomly assigned to fluoxetine (N=22) or placebo (N=15). Dosage followed a fixed schedule, starting at 10 mg/day and increasing as tolerated up to 80 mg/day. There was a significant treatment-by-time interaction indicating a significantly greater reduction in repetitive behaviors across time for fluoxetine than for placebo. With overall response defined as a CGI global improvement score of 2 or less, there were significantly more responders at week 12 in the fluoxetine group than in the placebo group. The risk ratio was 1.5 for CGI global improvement (responders: fluoxetine, 35%; placebo, 0%) and 1.8 for CGI-rated improvement in obsessive-compulsive symptoms (responders: fluoxetine, 50%; placebo, 8%). Only mild and moderate side effects were observed.

Hollander et al., 2012 Neuropsychopharmacology 30(3):582-9

Lack of Efficacy of Citalopram in Children With Autism Spectrum Disorders and High Levels of Repetitive Behavior

PARTICIPANTS: One hundred forty-nine volunteers 5 to 17 years old (mean [SD] age, 9.4 [3.1] years) were randomized to receive citalopram (n = 73) or placebo (n = 76). RESULTS: There was no significant difference in the rate of positive response on the Clinical Global Impressions, Improvement subscale between the citalopram-treated group (32.9%) and the placebo group (34.2%) (relative risk, 0.96; 95% confidence interval, 0.61-1.51; P > .99).

King et al., 2009 Arch Gen Psychiatry 66(6):583-90

A randomised controlled trial of bumetanide in the treatment of autism in children

Sixty children with autism or Asperger syndrome (3-11 years old) received for 3 months placebo or bumetanide (1 mg daily), followed by 1-month wash out. Bumetanide reduced significantly the Childhood Autism Rating Scale (CARS) (D90-D0; P<0.004 treated vs placebo), Clinical Global Impressions (P<0.017 treated vs placebo) and ADOS values when the most severe cases (CARS values above the mean+/-s.d.; n=9) were removed (Wilcoxon test: P-value=0.031; Student's t-test: P-value=0.017). In a companion study, chronic bumetanide treatment significantly improved accuracy in facial emotional labelling, and increased brain activation in areas involved in social and emotional perception (Hadjikhani et al., submitted).

Lemonnier et al., 2012 Transl Psychiatry 2:e202

Riluzole as an Adjunctive Therapy to Risperidone for the Treatment of Irritability in Children with Autistic Disorder: A Double-Blind, Placebo-Controlled, Randomized Trial

Subjects received riluzole (titrated to 50 or 100 mg/day based on bodyweight) or placebo in addition to risperidone (titrated up to 2 or 3 mg/day based on bodyweight) for 10 weeks. A significantly greater improvement in the study primary outcome (the ABC-C irritability subscale score) was achieved by the riluzole-treated children compared with the placebo group (P = 0.03). Patients in the riluzole group also showed significantly greater improvement on the lethargy/social withdrawal (P = 0.02), stereotypic behavior (P = 0.03), and hyperactivity/non-compliance subscales (P = 0.005), but not on the inappropriate speech subscale (P = 0.20) than patients in the placebo group.

Ghaleiha et al., 2013 Paediatr Drugs, in press

Medications
Strength of Evidence: C

Supported by at least 1 nonrandomized controlled trial or 2 case series

A retrospective study of memantine in children and adolescents with pervasive developmental disorders

Medical records of 18 patients with PDDs consecutively treated with open-label memantine were retrospectively reviewed. The data reviewed included prospectively obtained assessments of severity (S) and improvement (I) using the Clinical Global Impressions Scale (CGI). Pretrial and follow-up parent ratings were also available on six patients using the Aberrant Behavior Checklist (ABC). RESULTS: Eleven of 18 (61%) patients were judged responders to memantine based on a rating of "much improved" or "very much improved" on the CGI-I. Significant improvement was also seen on the CGI-S. Improvement was primarily seen clinically in social withdrawal and inattention. Adverse effects occurred in 7 of 18 (39%) patients and led to drug discontinuation in 4 of 18 (22%) patients.

Erickson et al., 2007 Psychopharmacology (Berl) 191(1):141-7

Memantine as Adjunctive Therapy in Children Diagnosed With Autistic Spectrum Disorders: An Observation of Initial Clinical Response and Maintenance Tolerability

Open-label add-on therapy was offered to 151 patients with prior diagnoses of autism or Pervasive Developmental Disorder Not Otherwise Specified over a 21-month period. Results showed significant improvements in open-label use for language function, social behavior, and self-stimulatory behaviors, although self-stimulatory behaviors comparatively improved to a lesser degree.

Chez et al., 2007 J Child Neurol 22(5):574-9

Case Study: Corticosteroid Treatment of Language Regression in Pervasive Developmental Disorder

The authors describe a child whose language and behavior regressed at 22 months and in whom pervasive developmental disorder was later diagnosed. At 6 years, he displayed a profound receptive-expressive aphasia accompanied by behavioral disturbances characterized by hyperactivity, impaired social interactions, tantrums, gestural stereotypies, and echolalia. Corticosteroid treatment resulted in amelioration of language abilities and behavior.

Stefanatos et al., 1995 J Am Acad Child Adolesc Psychiatry 34(8):1107-11

Response to steroid therapy in autism secondary to autoimmune lymphoproliferative syndrome

Previously developmentally normal, he had symptoms of autism with rapid regression in developmental milestones coincident with the onset of lymphoproliferation and autoimmune hemolytic anemia. Low-dose steroid therapy induced early and complete remission in the ALPS phenotype. There was subjective improvement, followed by objective improvement in speech and developmental milestones. We propose that autism may be part of the autoimmune disease spectrum of ALPS in this child.

Shenoy et al., 2000 J Pediatr 136(5):682-7

18. Pulse High-Dose Steroids as Combination Therapy with Valproic Acid in Epileptic Aphasia Patients with Pervasive Developmental Delay or Autism

A prospective study was done with 44 children with language regression and abnormal Digitrace 24 EEG epileptiform activity in sleep. All the patients were treated with a form of Depakote or Depakene for 8 to 12 weeks and were reassessed with a 24-hour EEG before the addition of weekly bolus high-dose prednisone or methylprednisolone (10 mg/kg/wk). Results of poststeroid add-on treatment were available for 25 cases. Of these patients, EEG showed further improvement in 60% (n = 15), with no improvement seen in 40% (n = 10). Clinical speech data showed the combination of Depakote/Depakene and pulse dose steroid treatment yielding improvement in 82% (n=36). Side effects were unremarkable with no cushingoid complications even after 18 months of therapy.

Chez et al., 1998 Annals Neurology 44(3):539

Improvement in children with autism treated with intravenous gamma globulin

In documented autistic children, 400mg/kg IVIG was administered each month for 6 months. Baseline and monthly Aberrant Behavior Checklists were completed on each child in order to measure the child's response to IVIG. The participants' overall aberrant behaviors decreased substantially soon after receiving their first dose of IVIG. Further analysis of the total scores revealed decreases in hyperactivity, inappropriate speech, irritability, lethargy and stereotypy. However, 22 of the 26 children regressed to their pre-IVIG status within 2–4 months of discontinuing the IVIG.

Boris et al., 2006 J Nut Environ Med 15(4):1-8

Brief Report: Dysregulated Immune System in Children with Autism: Beneficial Effects of Intravenous Immune Globulin on Autistic Characteristics[1]

In an open-label study of 10 children with autism who also had abnormal serum immunoglobulin levels, IVIG (400 mg/kg) was given monthly for at least 6 months. No adverse effects were noted, and improvements were observed in social interaction, eye contact, speech, and response to commands; in 2 children, the improvements in speech were large, and one child "almost completely recovered speech."

Gupta et al., 1996 J Autism Dev Disord 26(4):439-52

Open

Molecular Psychiatry (2012), 1–13

www.nature.com/mp

ORIGINAL ARTICLE

Cerebral folate receptor autoantibodies in autism spectrum disorder

RE Frye[1], JM Sequeira[2], EV Quadros[2], SJ James[1] and DA Rossignol[3]

Frye et al., 2012 Mol Psych, in press

Patient data

- **93 children with ASD**
- **70/93 (75%) positive for at least one FR antibody**
- **16 children had CSF 5MTHF measured**
- **44 children (mean age 6 years 10 months) with + antibody present treated with oral folinic acid at 2 mg/kg/day divided bid (max 50 mg) for mean of 4 months**
- **9 wait list control children with + antibody (mean age 6 years 11 months)**

Frye et al., 2012 Mol Psych, in press

Response Measure	Worse	No Change	Any Improvement	Moderate or Much Improved
Receptive Language	2%	32%	66%	39%
Expressive Language	2%	34%	63%	34%
Verbal Communication	2%	34%	63%	32%
Non-verbal Communication	0%	59%	41%	24%
Stereotyped Behavior	5%	44%	51%	34%
Hyperactivity	17%	56%	27%	12%
Mood	5%	49%	51%	15%
Attention	0%	41%	59%	24%
Aggression	5%	78%	17%	12%

Frye et al., 2012 Mol Psych, in press

A review of traditional and novel treatments for seizures in autism spectrum disorder: Findings from a systematic review and expert panel.

Several lines of evidence point to valproate, lamotrigine and levetiracetam as the most effective and tolerable AEDs for individuals with ASD. Limited evidence supports the use of traditional non-AED treatments, such as the ketogenic and modified Atkins diet, multiple subpial transections and immunomodulation and neurofeedback treatments. Although specific treatments may be more appropriate for specific genetic and metabolic syndromes associated with ASD and seizures, there are few studies which have documented the effectiveness of treatments for seizures for specific syndromes. Limited evidence supports L-carnitine, multivitamins and N-acetyl-L-cysteine in mitochondrial disease and dysfunction, folinic acid in cerebral folate abnormalities and early treatment with vigabatrin in tuberous sclerosis complex

Frye et al., 2013 Frontiers in Public Health, in press

Medications
Strength of Evidence: D

Supported by inconclusive studies or only 1 case study

Cochrane Database Syst Rev. 2012 Apr 18;4:CD003495.

Intravenous secretin for autism spectrum disorders (ASD).

CONCLUSION: There is no evidence that single or multiple dose intravenous secretin is effective and as such currently it should not be recommended or administered as a treatment for ASD. Further experimental assessment of secretin's effectiveness for ASD can only be justified if there is new high-quality and replicated scientific evidence that either finds that secretin has a role in neurotransmission in a way that could benefit all children with ASD or identifies important subgroups of children with ASD who could benefit from secretin because of a proven link between the action of secretin and the known cause of their ASD, or the type of problems they are experiencing.

Williams et al., 2012 Cochrane Database Syst Rev. 2012 Apr 18;4:CD003495

15 children

Randomized controlled trial of transdermal secretin on behavior of children with autism

Previous trials of secretin for the treatment of autism have utilized a single or double dose administered intravenously. Secretin or placebo was applied daily, in ointment form, to the backs of the children in randomized, successive 4 week periods with an intermediate 6 week washout period. Overall, there were no statistically significant differences in speech, sociability, sensory, and health scores for treatment versus placebo periods. Improvement in speech was found during the treatment phase of the trial (p=0.0479 for secretin versus placebo) only in children not using other medications.

Ratliff-Schaub et al., 2005 Autism 9(3):256-65

ANNALS OF CLINICAL PSYCHIATRY 2009;21(3):XX-XX REVIEW ARTICLE

www.aacp.com/pdf%2F2104%2F2104ACP_Review2.pdf

Novel and emerging treatments for autism spectrum disorders: A systematic review

RESULTS: Grade A treatments for ASD include melatonin, acetylcholinesterase inhibitors, naltrexone, and music therapy. Grade B treatments include carnitine, tetrahydrobiopterin, vitamin C, alpha-2 adrenergic agonists, hyperbaric oxygen treatment, immunomodulation and anti-inflammatory treatments, oxytocin, and vision therapy. Grade C treatments for ASD include carnosine, multivitamin/mineral complex, piracetam, polyunsaturated fatty acids, vitamin B_6/magnesium, elimination diets, chelation, cyproheptadine, famotidine, glutamate antagonists, acupuncture, auditory integration training, massage, and neurofeedback.

Rossignol, 2009 Annals Clin Psych 21(4):213-236

TABLE 7

Summary of treatments and their effects on certain autistic behaviors

Speech/communication	Carnitine Carnosine GFCF diet Alpha-2 adrenergic agonists Cyproheptadine Glutamate antagonists AIT	Tetrahydrobiopterin B6/magnesium AI HBOT Famotidine Music therapy Neurofeedback
Autistic behavior	Carnosine B_6/magnesium Probiotics GFCF diet Alpha-2 adrenergic agonists Cyproheptadine Vision therapy	Piracetam Folic acid/B_{12} Digestive enzymes AI HBOT Music therapy
Social interaction	Tetrahydrobiopterin B6/magnesium AI HBOT Famotidine Massage	Carnosine GFCF diet Naltrexone Oxytocin Glutamate antagonists Neurofeedback
Stereotypy	Vitamin C B6/magnesium Alpha-2 adrenergic agonists Famotidine AIT	Omega 3 fatty acids Naltrexone Cyproheptadine Glutamate antagonists Massage
Hyperactivity	Omega 3 fatty acids AI Alpha-2 adrenergic agonists Glutamate antagonists Massage	Magnesium Naltrexone Chelation AIT
Eye contact	Tetrahydrobiopterin AI Famotidine	Omega 3 fatty acids HBOT Music therapy
Attention	Omega 3 fatty acids Alpha-2 adrenergic agonists Music therapy	AI Glutamate antagonists
Sleep	Melatonin Multivitamin Alpha-2 adrenergic agonists	Carnitine Iron

AI: Acetylcholinesterase inhibitors; AIT: auditory integration training; GFCF: gluten-free, casein-free diet; HBOT: hyperbaric oxygen treatment;

Rossignol, 2009 Annals Clin Psych 21(4):213-36