

A systematic computational analysis of pharmacological options in neuroinflammatory-induced autism spectrum disorder in children: A potential for drug repositioning

Supplementary File

Table S1. Study metrics

Authors, Year	Title	Country	Study type	Age range	Sample size	Male/Female	Diagnostic tools
Pearson <i>et al.</i> ¹	Effects of extended release methylphenidate treatment on ratings of ADHD and associated behavior in children with autism spectrum disorders and ADHD symptoms	USA	Within-subject; crossover; placebo-controlled clinical trial	7.1–12.7	24	19/5	ADI-R; ADOS; DSM-IV-TR; significant ADHD symptoms; clinical interviews; clinic observations; record reviews by licensed psychologists
Hardan <i>et al.</i> ²	Efficacy and safety of memantine in children with autism spectrum disorder: Results from three phase 2 multicenter studies	USA	Randomized; double-blind; placebo-controlled; withdrawal trial; open-label extension trial	6–12	2123	1788/335	ADI-R; ADOS; DSM-IV-TR
Alsayouf <i>et al.</i> ³	Atomoxetine treatment of ADHD symptoms in 3–6-year-old children with autism spectrum disorder: A retrospective cohort study	Jordan	Retrospective cohort study	3–6	133	114/19	DSM-5; CGI-S; direct observations of the patients' behaviors; historical data; CARS2-ST; Vanderbilt ADHD diagnostic parent rating scale; clinic observations; parent reports
Luchelli and Bertschy ⁴	Low-dose fluoxetine in four children with autistic spectrum disorder improves self-injurious behavior; ADHD-like symptoms; and irritability	France	Case report	6–12	4	3/1	DSM-5; ADI-R
Cortesi <i>et al.</i> ⁵	Controlled-release melatonin; singly and combined with cognitive behavioral therapy; for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial	Italia	Randomized; double-blind; placebo-controlled	4–10	160	132/28	ADI-R; ADOS-G; DSM-IV-TR; CBCL
Hardan <i>et al.</i> ⁶	A randomized controlled pilot trial of oral N-acetylcysteine in children with autism	USA	Randomized; double-blind; placebo-controlled	3.2–10.7	33	31/2	ADI-R; ADOS; DSM-IV-TR; expert clinical evaluation; clinic visits; CGI-S
Chugani <i>et al.</i> ⁷	Efficacy of low-dose buspirone for restricted and repetitive behavior in young children with autism spectrum disorder: A randomized trial	USA	Randomized; placebo-controlled; double-blind	2–6	166	137/29	ADI-R; ADOS; DSM-IV-TR
Parker <i>et al.</i> ⁸	Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism	USA	Randomized; placebo-controlled; double-blind; parallel design	6–12	32	27/5	ADI-R; ADOS; DSM-IV-TR; DSM-5; telephone-screened; medical assessment; comprehensive psychiatric evaluation; clinic visits; Stanford-Binet Intelligence Scales fifth edition; CGI-S
Mazahery <i>et al.</i> ⁹	A randomized-controlled trial of vitamin D and omega-3 long-chain polyunsaturated fatty acids in the treatment of core symptoms of autism spectrum disorder in children	New Zealand	Randomized; double-blind; placebo-controlled	2.5–8.0	117	100/17	DSM-5; standardized psychological tests; SRS; SPM
Silva <i>et al.</i> ¹⁰	Evaluation of the efficacy and safety of cannabidiol-rich cannabis extract in children with autism spectrum disorder	Brazil	Randomized; double-blind; placebo-controlled	5–11	60	52/8	DSM-5; sociodemographic questionnaire; CARS; clinic observations; parent reports

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Table S1. (Continued)

Authors, Year	Title	Country	Study type	Age range	Sample size	Male/Female	Diagnostic tools
	: Randomized; double-blind; and placebo-controlled clinical trial						
Montazmanesh <i>et al.</i> ¹¹	Sulforaphane as an adjunctive treatment for irritability in children with autism spectrum disorder: A randomized; double-blind; placebo-controlled clinical trial	Iran	Randomized; double-blind; placebo-controlled	4–12	60	40/20	DSM-5; ADI-R; children's behavioral examination; semi-structured interviews
Zimmerman <i>et al.</i> ¹²	Randomized controlled trial of sulforaphane and metabolite discovery in children with autism spectrum disorder	USA	Randomized; placebo-controlled; double-blind	3–12	45	40/5	ADOS; VABS-II; semi-structured interview; Leiter International Test of Intelligence-Revised
Mazahery <i>et al.</i> ¹³	A randomized controlled trial of vitamin D and omega-3 long chain polyunsaturated fatty acids in the treatment of irritability and hyperactivity among children with autism spectrum disorder	New Zealand	Randomized double-blind; placebo-controlled	2.5–8.0	73	60/13	DSM-5
Ghaleiha <i>et al.</i> ¹⁴	Memantine as adjunctive treatment to risperidone in children with autistic disorder: a randomized; double-blind; placebo-controlled trial	Iran	Randomized; double-blind; placebo-controlled	4–12	40	23/17	DSM IV-TR; ADI-R; behavioral observation; semi-structured interview
Wink <i>et al.</i> ¹⁵	A randomized placebo-controlled pilot study of N-acetylcysteine in youth with autism spectrum disorder	USA	Randomized; double-blind; placebo-controlled	4–12	31	24/7	DSM-IV; ADI-R; clinical interview; Leiter International Test of Intelligence-Revised; CGI-S
Fieiras <i>et al.</i> ¹⁶	Risperidone and aripiprazole for autism spectrum disorder in children: an overview of systematic reviews	Chile	Overview of systematic reviews (SRS)	0–12	NA	NA	DSM-5; ADI-R; ADOS; CARS; ASIEP-2; CSBS (Caregiver Questionnaire); SCATA; ToPP; CBS; NCBRS; clinic observations; parent reports
Brito <i>et al.</i> ¹⁷	Effect of prednisolone on language function in children with autistic spectrum disorder: a randomized clinical trial	Brazil	Randomized; double-blind; placebo-controlled	3–7	40	40/0	DSM-IV; CARS; clinic observations; parent reports
Dai <i>et al.</i> ¹⁸	Improved symptoms following bumetanide treatment in children aged 3–6 years with autism spectrum disorder: A randomized; double-blind; placebo-controlled trial	China	Randomized; double-blind; placebo-controlled; parallel-group	3–6	119	100/19	ADI-R; ADOS; DSM-5; SRS; CARS; clinic observations; parent reports
Zhang <i>et al.</i> ¹⁹	Symptom improvement in children with autism spectrum disorder following bumetanide administration is associated with decreased GABA/glutamate ratios	China	Randomized; placebo controlled; double-blind	3–6	83	65/18	ADI-R; ADOS; DSM-5; CARS; clinic observations; parent reports
Zarnowska <i>et al.</i> ²⁰	Therapeutic use of carbohydrate-restricted diets in an autistic child; a case report of clinical and 18FDG PET findings	Poland	Case report	6	1	1/0	DSM-IV-TR; psychological and psychiatric evaluations; CARS; WISC-R; clinic observations; parent reports
Gvozdjaková <i>et al.</i> ²¹	Ubiquinol Improves Symptoms in Children with Autism	Slovakia	Open trial	3–6	24	17/7	DSM IV; CARS; clinic observations; parent reports
Duffy <i>et al.</i> ²²	Corticosteroid therapy in regressive autism: a retrospective study of effects on the FMAER; language; and behavior	USA	Retrospective study	3–5	44	36/8	DSM-IV; diagnostic by academic child neurologists and/or psychiatrists, and/or psychologists
Asadi and Theoharides ²³	Corticotropin-releasing hormone and extracellular mitochondria augment immunoglobulin E-stimulated human mast-cell vascular endothelial growth factor release; which is inhibited by luteolin	USA	<i>In vitro</i> study	NA	NA	NA	NA

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Table S1. (Continued)

Authors, Year	Title	Country	Study type	Age range	Sample size	Male/Female	Diagnostic tools
Simhal <i>et al.</i> ²⁴	Changes in the geometry and robustness of diffusion tensor imaging networks: Secondary analysis from a randomized controlled trial of young autistic children receiving an umbilical cord blood infusion	USA	Randomized; placebo-control; double-blind; single site; prospective	2–7	165	131/34	ADI-R; ADOS; DSM-5; CGI-S
Antonucci <i>et al.</i> ²⁵	Clinical experience of integrative autism treatment with a novel type of immunotherapy	Italy	Open-label; non-controlled; retrospective analysis	3.1–4.5	3	3/0	ATEC; clinical diagnostic
Pearson <i>et al.</i> ²⁶	Pancreatic replacement therapy for maladaptive behaviors in preschool children with autism spectrum disorder	USA	Randomized; placebo-controlled; double-blind parallel group; delayed-start	3–6	190	150/40	SCQ; DSM-IV-TR; ADI-R
Carpenter <i>et al.</i> ²⁷	White matter tract changes associated with clinical improvement in an open-label trial assessing autologous umbilical cord blood for treatment of young children with autism	USA	Phase I open-label trial	2–6	25	17/2	DSM-5; ADOS; ADI-R; CGI-S
Thanh <i>et al.</i> ²⁸	Outcomes of bone marrow mononuclear cell transplantation combined with interventional education for autism spectrum disorder	Vietnam	Open-label uncontrolled clinical trial	3.0–7.4	30	25/5	DSM-5; CARS

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder; ADI-R: Autism diagnostic interview-revised; ADOS-2: Autism diagnostic observation schedule, second edition; DSM-IV-TR: Diagnostic and statistical manual of mental disorders, 4th edition, text revision; DSM-5: Diagnostic and statistical manual of mental disorders, 5th edition; CGI-S: Clinical global impressions-severity; CARS: Childhood autism rating scale; CBCL: Child behavior checklist; VABS-II: Vineland adaptive behavior scales, second edition; SRS: Social responsiveness scale; SPM: Sensory processing measure; WISC-R: Wechsler intelligence scale for children-revised; SCQ: Social communication questionnaire; ATEC: Autism treatment evaluation checklist; FMAER: Frequency modulated auditory evoked response; ASIEP-2: Autism screening instrument for educational planning, second edition; CSBS: Communication and symbolic behavior scales; SCATA: Social Communication assessment for toddlers with autism; ToPP: Test of pretend play; CBS: Child behavior scale; NCBRS: Nisonger child behavior rating scales; 18FDG PET: 18 F-fluorodeoxyglucose positron emission tomography; GABA: Gamma-aminobutyric acid

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