Autism Facts in the Age of Disinformation

Douglas Vanderbilt, MD, MS, MBA
CHLA Developmental-Behavioral Pediatrics (DBP)

AAP Chapter 2
Advances in Pediatrics Symposium
April 18, 2026

Disclosure

I have no financial relationship or interest with any proprietary entity producing health care goods or services related to the content of this CME activity.

I do not intend to discuss an unapproved/ investigative use of a commercial product/device in my presentation.

Goals

1. Explain what is known about the causes of autism spectrum disorder
2. Recommend evidenced-based treatment interventions for autism management
3. Manage questions about leucovorin, cerebral folate deficiency, and Tylenol

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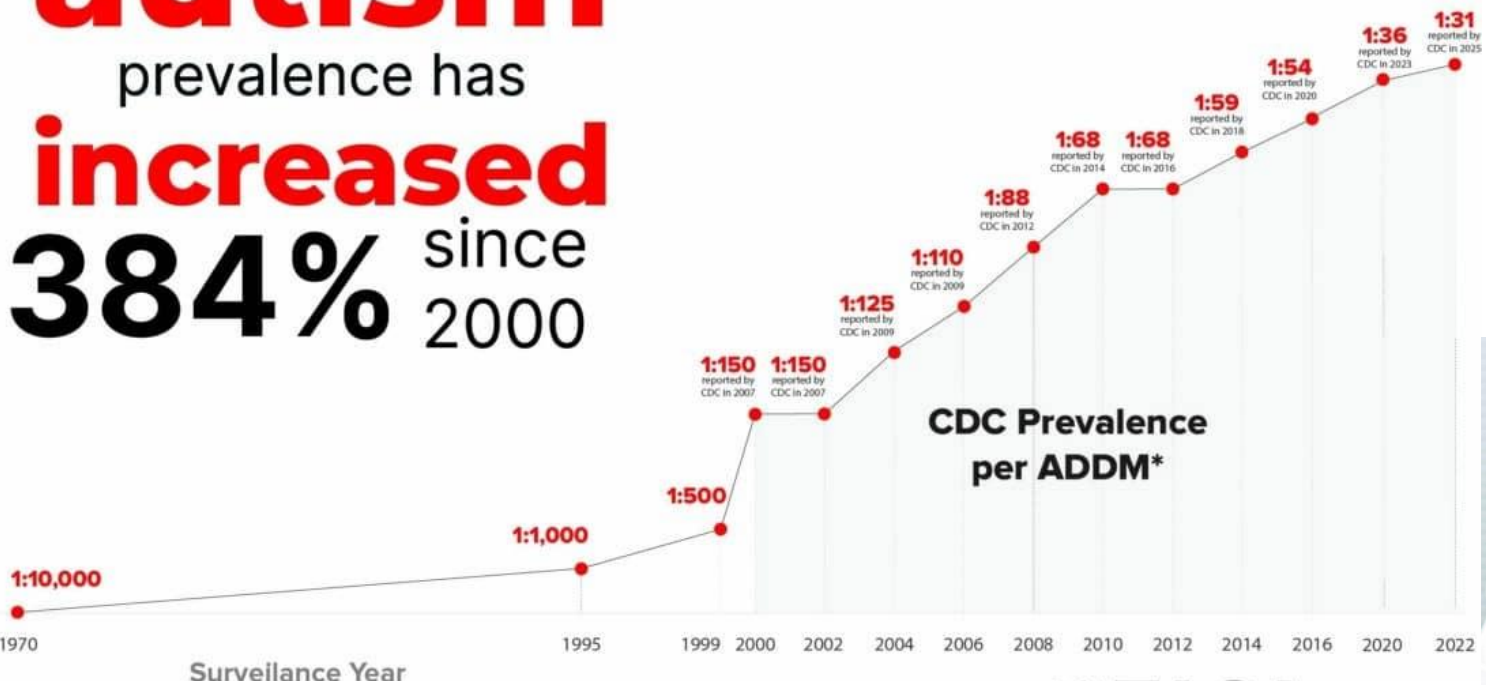
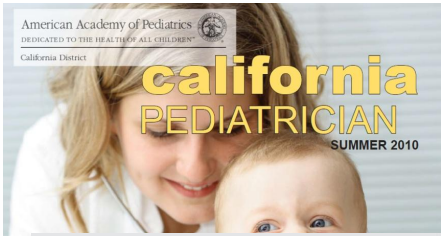
ASD Increase?

autism prevalence has **increased** **384%** since 2000





Autism:
Diagnosis in Evolution and Opportunity for Pediatric Intervention

Douglas Vanderbilt, MD;
Marian E. Williams, PhD

Because…

1. Broader diagnostic criteria
2. Increased awareness
3. Improved screening tools/processes

Shaw KA, et al. Autism Developmental Disabilities Monitoring Network, MMWR Surveill Summ 2025;74(No. SS-2):1–22; www.autismspeaks.org

Social Communication

SC

Interests

Social-Communication (all):

- Social-emotional reciprocity- back and forth
- Nonverbal communicative behaviors- eye contact
- Relationships- friends

Interests (2):

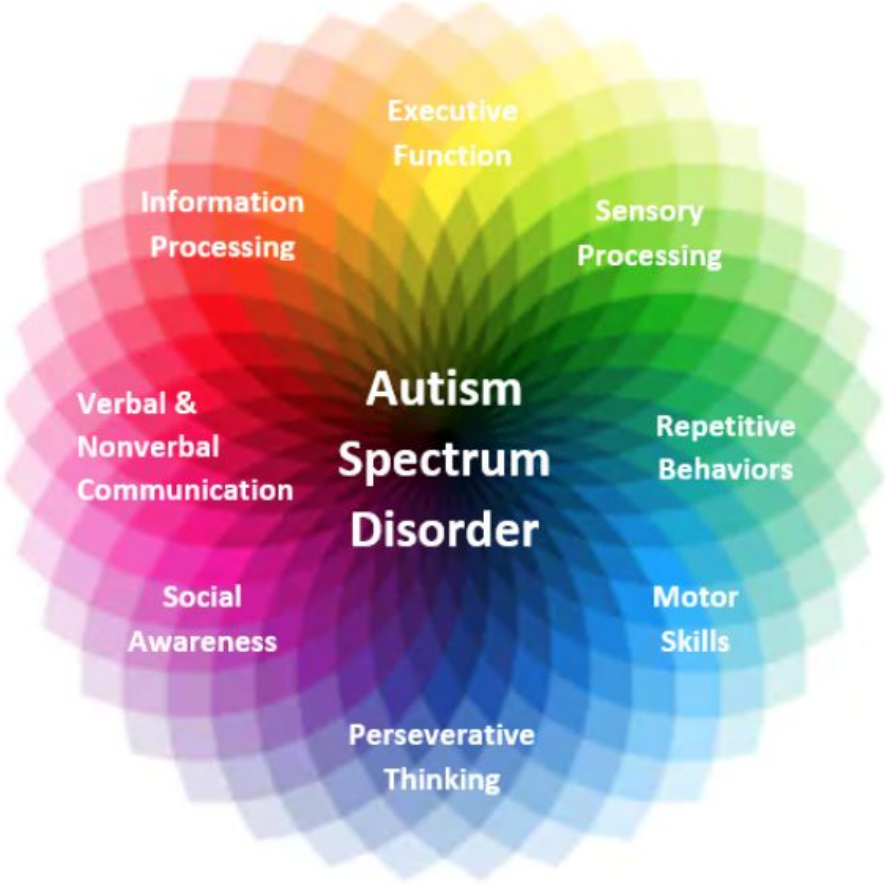
- Stereotyped/repetitive speech- echolalia
- Excessive routines/ritualized patterns- flapping
- Restricted/fixated interests- trains
- Sensory Integration problems- hypo/hyper

www.dsm5.org 2013

Facts

- 1 in 31 children
- 3X males
- Most diagnosed >4 years, possible by age 2
- All ethnic/SES groups but minority diagnosed later/less often

- No medical detection
- Vaccines do not cause autism
- Early Intervention and Supports
  - Behavioral therapy
  - Improves learning, communication, social skills



www.ncsautism.org; CDC, 2025

DBP History Risk Factors

- Boys > Girls
- Positive family history
  - Prior child with ASD (2-20%)
  - Identical twins (36-95%)
  - Non-identical twins (31%)
- Having neurodevelopmental disorders:
  - Fragile X syndrome
  - Tuberous sclerosis
  - Tourette's syndrome
  - Epilepsy
- Advanced maternal age
- Paternal age > 40 years 6x more likely than < 30 years
- Prematurity / low birth weight / perinatal risks
  - Gestational diabetes (40% risk)

www.mayoclinic.com/autism; Reichenberg, 2006; Limperopoulos, 2008; Indredavik, 2008; Xiang, 2015

Screening Tools

- Modified Checklist for Autism in Toddlers, Revised with Follow-Up (MCHAT)

  www.mchatscreen.com
- Parent's Observations of Social Interactions (POSI)

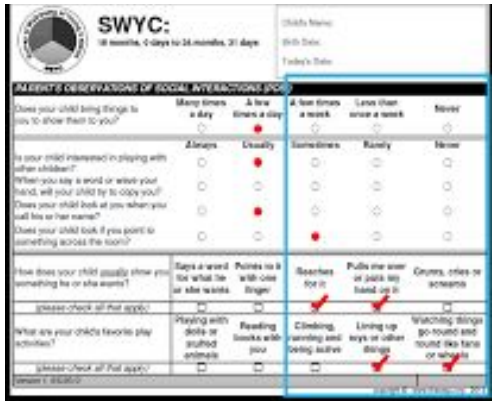
  www.teamupcenter.org/parts-of-the-swyc/parents-observations-of-social-interactions-posi
- Childhood Autism Spectrum Test (CAST) >4 yrs

  www.autismresearchcentre.com/tests/childhood-autism-spectrum-test-cast


M-CHAT

Please fill out the following about how your child usually is. Please try to answer every question. If the behavior is rare (e.g., you've seen it once or twice), please answer as if the child does not do it.

1. Does your child enjoy being swung, bounced on your knee, etc.? Yes No
2. Does your child take an interest in other children? Yes No
3. Does your child like climbing on things, such as up stairs? Yes No
4. Does your child enjoy playing peek-a-boo/hide-and-seek? Yes No
5. Does your child ever pretend, for example, to talk on the phone or take care of a doll or pretend other things? Yes No
6. Does your child ever use his/her index finger to point, to ask for something? Yes No
7. Does your child ever use his/her index finger to point, to indicate interest in something? Yes No
8. Can your child play properly with small toys (e.g. cars or blocks) without just mouthing, fiddling, or dropping them? Yes No
9. Does your child ever bring objects over to you (parent) to show you something? Yes No
10. Does your child look you in the eye for more than a second or two? Yes No
11. Does your child ever seem oversensitive to noise? (e.g., plugging ears) Yes No
12. Does your child smile in response to your face or your smile? Yes No
13. Does your child imitate you? (e.g., you make a face-will your child imitate it?) Yes No
14. Does your child respond to his/her name when you call? Yes No
15. If you point at a toy across the room, does your child look at it? Yes No
16. Does your child walk? Yes No
17. Does your child look at things you are looking at? Yes No
18. Does your child make unusual finger movements near his/her face? Yes No
19. Does your child try to attract your attention to his/her own activity? Yes No
20. Have you ever wondered if your child is deaf? Yes No
21. Does your child understand what people say? Yes No


SWYC:

PARENT'S OBSERVATIONS OF SOCIAL INTERACTIONS (POSI)

Does your child bring things to you to show them to you?	Many times a day	A few times a day	A few times a week	Less than once a week	Never
	○	●	○	○	○
	Always	Usually	Sometimes	Rarely	Never
Is your child interested in playing with other children?	○	●	○	○	○
When you say a word or wave your hand, will your child try to copy you?	○	○	○	○	○
Does your child look at you when you call his or her name?	○	●	○	○	○
Does your child look if you point to something across the room?	○	○	●	○	○
How does your child usually show you something he or she wants?	Says a word for what he or she wants	Points to it with one finger	Reaches for it	Pulls one arm or puts my hand on it	Grunts, cries or screams
please check all that apply	☐	☐	✓	✓	☐
What are your child's favorite play activities?	Playing with dolls or stuffed animals	Reading books with you	Climbing, running and being active	Lining up toys or other things	Watching things go round and round like fans or wheels
please check all that apply	☐	☐	☐	✓	✓

The Childhood Autism Spectrum Test (CAST)

Child's Name: ..... Age: ..... Sex: Male / Female

Birth Order: ..... Twin or Single Birth: .....

Parent/Guardian: .....

Parent(s) occupation: .....

Age parent(s) left full-time education: .....

Address: .....

.....

.....

Tel No: ..... School: .....

Please read the following questions carefully, and circle the appropriate answer responses are confidential.

1. Does s/he join in playing games with other children easily?	Yes	No
2. Does s/he come up to you spontaneously for a chat?	Yes	No
3. Was s/he speaking by 2 years old?	Yes	No
4. Does s/he enjoy sports?	Yes	No
5. Is it important to him/her to fit in with the peer group?	Yes	No
6. Does s/he appear to notice unusual details that others miss?	Yes	No
7. Does s/he tend to take things literally?	Yes	No
8. When s/he was 3 years old, did s/he spend a lot of time pretending (e.g., play-acting being a superhero, or holding teddy's tea parties)?	Yes	No
9. Does s/he like to do things over and over again, in the same way all the time?	Yes	No
10. Does s/he find it easy to interact with other children?	Yes	No
11. Can s/he keep a two-way conversation going?	Yes	No
12. Can s/he read appropriately for his/her age?	Yes	No
13. Does s/he mostly have the same interests as his/her peers?	Yes	No
14. Does s/he have an interest which takes up so much time that s/he does little else?	Yes	No
15. Does s/he have friends, rather than just acquaintances?	Yes	No
16. Does s/he often bring you things s/he is interested in to show you?	Yes	No
17. Does s/he enjoy joking around?	Yes	No
18. Does s/he have difficulty understanding the rules for polite behaviour?	Yes	No
19. Does s/he appear to have an unusual memory for details?	Yes	No
20. Is his/her voice unusual (e.g., overly adult, flat, or very monotonous)?	Yes	No
21. Are people important to him/her?	Yes	No
22. Can s/he dress him/herself?	Yes	No
23. Is s/he good at turn-taking in conversation?	Yes	No
24. Does s/he play imaginatively with other children, and engage in role-play?	Yes	No
25. Does s/he often do or say things that are tactless or socially inappropriate?	Yes	No
26. Can s/he count to 50 without leaving out any numbers?	Yes	No
27. Does s/he make normal eye-contact?	Yes	No
28. Does s/he have any unusual and repetitive movements?	Yes	No
29. Is his/her social behaviour very one-sided and always on his/her own terms?	Yes	No
30. Does s/he sometimes say "you" or "s/he" when s/he means "I"?	Yes	No

Autism and Genetics

Simons Foundation Autism Research Initiative (SFARI)

SFARI's mission is to advance the basic science of autism and related neurodevelopmental disorders.

SIMONS FOUNDATION

- ASD heritability
  - 87.0% males
  - 75.7% females
- Human Gene Module lists 1,254 genes with ASD link (1/2026)
- Gene Scoring Module rates genes
- Folate metabolism gene mutations *do not* indicate risk for ASD

SFARI GENE

Gene Scoring

New genetic links to autism are being discovered every day. To more accurately assess potential genetic causes, SFARI Gene assigns every gene in the database with a score reflecting the strength of the evidence linking it to the development of autism.

S	SYNDROMIC
1	CATEGORY 1 (High Confidence)
2	CATEGORY 2 (Strong Candidate)
3	CATEGORY 3 (Suggestive Evidence)

CNV LOCUS
1q21.1
15q13.3
16p11.2
16p12.2
16p13.11
16p13.3
17p11.2
17q11.2
17q12
2p16.3
2q11.2
22q11.2
22q13.3
3q29
5q35
7q11.23
8p23.1

Sandin S, et al. *JAMA Psychiatry.* 2024;81(7):673–680;
www.sfari.org

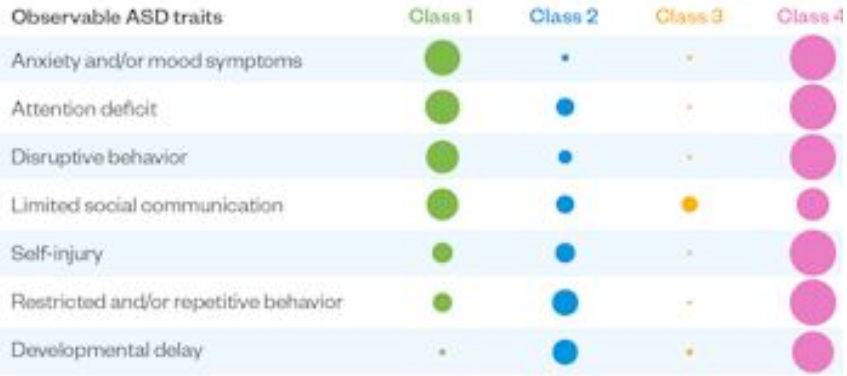
Children's Hospital LOS ANGELES | USC University of Southern California

The Genetics of Autism-Related Traits

Hundreds of genes are potentially involved in the development of autism spectrum disorde (ASD), leading to a broad variety of cognitive and behavioral traits. To gain insights into the neurobiology of ASD and to offer the potential for improved diagnosis, researchers have teased out correlations between ASD traits and the underlying genetics.

Classifying Traits

Using a statistical model, researchers analyzed 239 ASD traits present in 5,392 individuals and identified four distinct classes based on patterns in those traits. The trait distribution is visualized below, with circle size proportional to trait intensity.



Genetic Correlations

While all classes showed types of genetic mutations associated with ASD, researchers found that each class had its own biological signature:

nature genetics

Article

https://doi.org/10.1038/s41588-025-02224-z

Decomposition of phenotypic heterogeneity in autism reveals underlying genetic programs

Received: 25 July 2024

Accepted: 2 May 2025

Published online: 9 July 2025

Check for updates

Aviya Litman[1,2,12], Natalie Sauerwald[3,12], LeeAnne Green Snyder[4], Jennifer Foss-Feig[4,5,6], Christopher Y. Park[3], Yun Hao[3], Ilan Dinstein[7,8,9], Chandra L. Theesfeld[2,10] & Olga G. Troyanskaya[2,3,10,11]

Unraveling the phenotypic and genetic complexity of autism is extremely challenging yet critical for understanding the biology, inheritance,

Class 1- Social and Behavioral Challenges (37%)

- Core ASD traits + ADHD/anxiety/depression/OCD - delays
- Common variants, DNV neurons active later

Class 2- Mixed ASD + Developmental Delay (19%)

- Range ASD traits + delays - DBP conditions
- Rare inherited genetic variants early

Class 3- Moderate Challenges (34%)

- Milder core ASD traits - DBP conditions/delays
- Rare variants tolerate mutations

Class 4- Broadly Affected (10%)

- Severe ASD traits + delays + DBP conditions
- *de novo* mutations sensitive to impact

Lucy Reading-Ikkanda/Simons Foundation; www.nature.com/articles/s41588-025-02224-z

Goals

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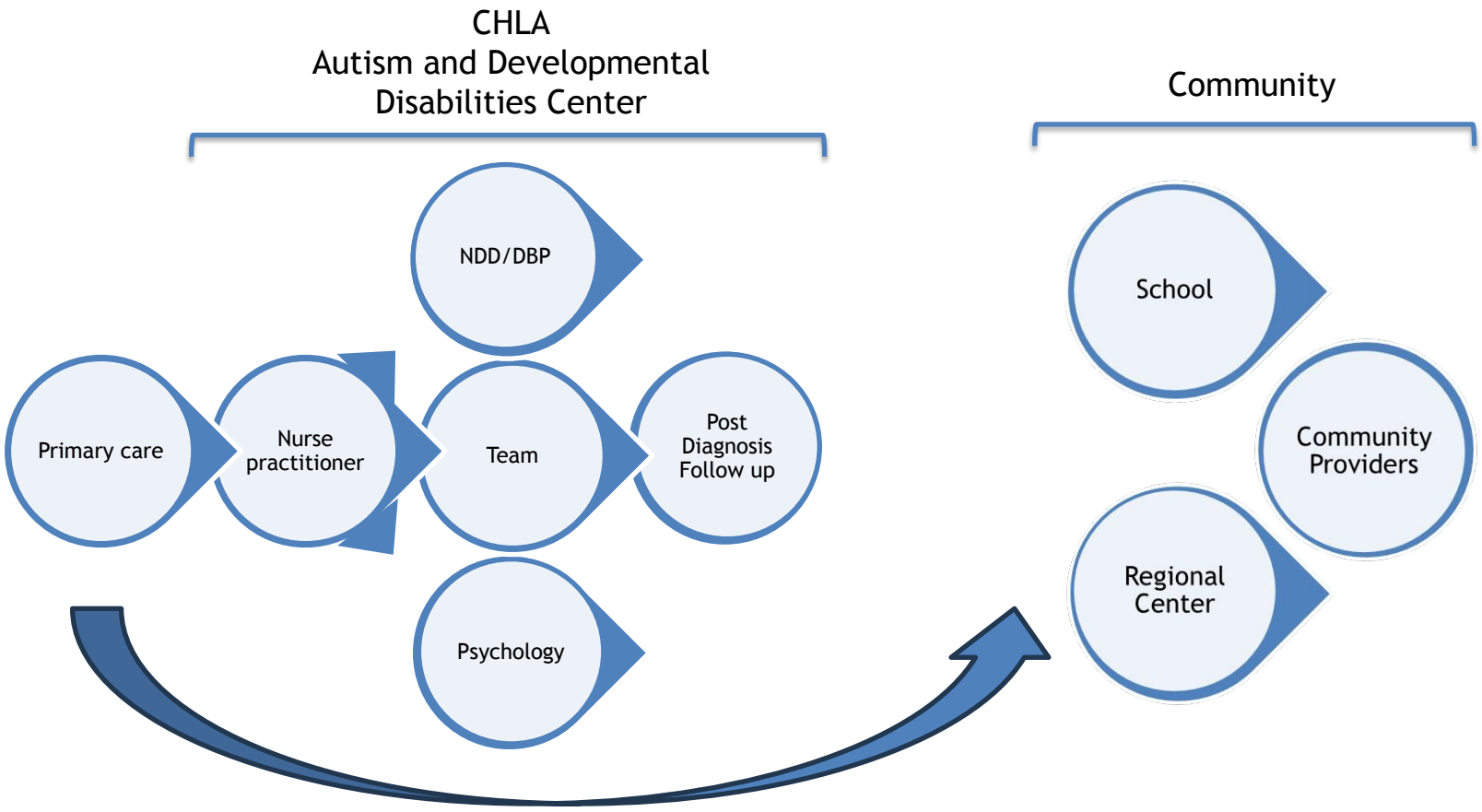
Diagnostic Assessment



Medical Evaluation

- Comprehensive medical history and examination
  - Macro/Microcephaly
  - Cutaneous stigmata
  - Facial dysmorphism
- Genetic Testing: recommended all children with ASD
  - CMA or Whole exome/genome sequencing
  - First-tier tests for GDD/ID +/- ASD
    - American Academy of Pediatrics (AAP)
    - American College of Medical Genetics and Genomics (ACMG)
- Audiology/Vision assessments
- Brain MRI and EEG: Not useful, unless..
  - MRI:
    - extreme macrocephaly, microcephaly, focal neurologic deficits, focal epilepsy, neuroregression
  - EEG:
    - question of/obvious seizures, clear abrupt language/motor regression >12 months
- Nope:
  - Metabolic / GI / Allergy studies / Heavy metal testing
  - Leucovorin initiation/work up

Rodan LH, et al. Genetic Evaluation of the Child With Intellectual Disability or Global Developmental Delay: Clinical Report. Pediatrics. 2025 Jul 1;156(1):e2025072219.

Primary Treatment

Educational Interventions

- Behavioral Therapy
- Comprehensive programs
  - Early Start Denver Model
- Developmental/relational
  - DIR Floortime
- Social skills instruction
- Speech/language therapy
- Occupational / sensory integration therapy
- Goals
  - communication
  - positive behaviors
  - disruptive behaviors

EVIDENCE-BASED PRACTICES

*Indicates practices with newly developed content (2015-2016). Select the practice to access these modules and downloadable resources.

Antecedent-based Intervention (ABI)*

Cognitive Behavioral Intervention (CBI)**

Differential Reinforcement of Alternative, Incompatible, or Other Behavior (DRA/I/O)

Discrete Trial Teaching (DTT)*

Exercise (ECE)*

Extinction (EXT)

Functional Behavior Assessment (FBA)*

Functional Communication Training (FCT)

Modeling (MD)*

Naturalistic Intervention (NI)

Parent-implemented Intervention (PII)

Peer-mediated Instruction and Intervention (PMII)*

Picture Exchange Communication System (PECS)*

Pivotal Response Training (PRT)

Prompting (PP)*

Reinforcement (R+)*

Response Interruption/Redirection (RIR)

Scripting (SC)**

Self-management (SM)*

Social Narratives (SN)*

Social Skills Training (SST)*

Previously Social Skills Groups

Structured Play Group (SPG)**

Task Analysis (TA)*

Technology-aided Instruction and Intervention (TAII)** *Previously Computer Aided Instruction and Speech Generating Devices*

Time Delay (TD)*

Video Modeling (VM)

Visual Support (VS)*

www.community.undivided.io/news/166739; www.autismpdc.fpg.unc.edu; Myers, 2007; Dawson, 2009

Medication Treatments

- Pharmacological treatments: effective for coexisting conditions
  - No medication for core features of ASD
  - FDA approved meds include
    - Risperidone and Aripiprazole for irritability/agitation in children with ASD
    - Alpha agonists and stimulants for children with ASD and co-existing ADHD
  - Anxiety, Depression, Sleep
- There is no "cure" for ASD

Volume 145, Issue 1
January 2020

PEDIATRICS

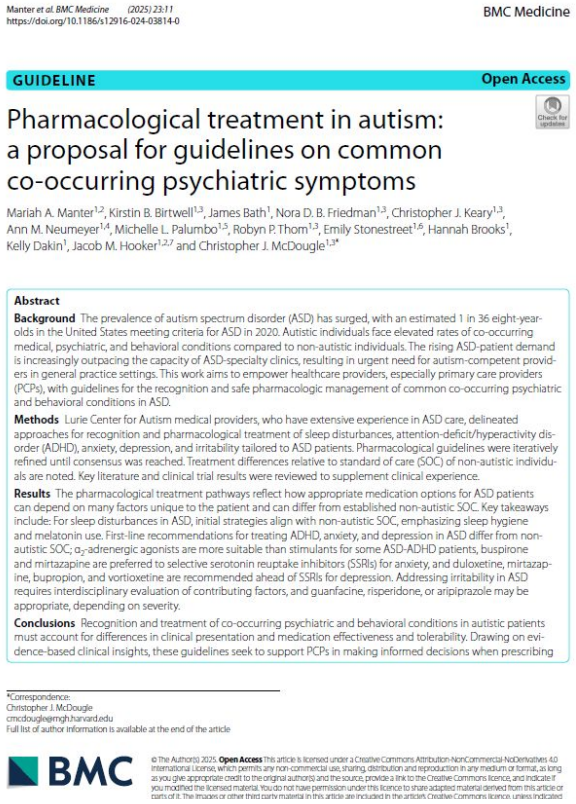
FROM THE AMERICAN ACADEMY OF PEDIATRICS | CLINICAL REPORT | JANUARY 01 2020

Identification, Evaluation, and Management of Children With Autism Spectrum Disorder FREE

Susan L. Hyman, MD, FAAP; Susan E. Levy, MD, MPH, FAAP; Scott M. Myers, MD, FAAP; COUNCIL ON CHILDREN WITH DISABILITIES, SECTION ON DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS; Dennis Z. Kuo, MD, MHS, FAAP; Susan Apkon, MD, FAAP; Lynn F. Davidson, MD, FAAP; Kathryn A. Ellerbeck, MD, FAAP; Jessica E.A. Foster, MD, MPH, FAAP; Garey H. Noritz, MD, FAAP; Mary O'Connor Leppert, MD, FAAP; Barbara S. Saunders, DO, FAAP; Christopher Stille, MD, MPH, FAAP; Larry Yin, MD, MSPH, FAAP; Carol C. Weitzman, MD, FAAP; David Omer Childers, Jr, MD, FAAP; Jack M. Levine, MD, FAAP; Ada Myriam Peralta-Carcelen, MD, MPH, FAAP; Jennifer K. Poon, MD, FAAP; Peter J. Smith, MD, MA, FAAP; Nathan Jon Blum, MD, FAAP; John Ichiro Takayama, MD, MPH, FAAP; Rebecca Baum, MD, FAAP; Robert G. Voigt, MD, FAAP; Carolyn Bridgemohan, MD, FAAP

Hyman SL, Levy SE, Myers SM; Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. Pediatrics. 2020 Jan;145(1):e20193447.

Manter MA, et al. BMC Med. 2025 Jan 7;23(1):11.



Manter et al. BMC Medicine (2025) 23:11
https://doi.org/10.1186/s12916-024-03814-0

BMC Medicine

GUIDELINE Open Access

Pharmacological treatment in autism: a proposal for guidelines on common co-occurring psychiatric symptoms

Mariah A. Manter[1,2], Kirstin B. Birtwell[1,3], James Bath[1], Nora D. B. Friedman[1,3], Christopher J. Keary[1,3], Ann M. Neumeyer[1,4], Michelle L. Palumbo[1,5], Robyn P. Thom[1,3], Emily Stonestreet[1,6], Hannah Brooks[1], Kelly Dakin[1], Jacob M. Hooker[1,2,7] and Christopher J. McDougle[1,3*]

Abstract

Background The prevalence of autism spectrum disorder (ASD) has surged, with an estimated 1 in 36 eight-year-olds in the United States meeting criteria for ASD in 2020. Autistic individuals face elevated rates of co-occurring medical, psychiatric, and behavioral conditions compared to non-autistic individuals. The rising ASD-patient demand is increasingly outpacing the capacity of ASD-specialty clinics, resulting in urgent need for autism-competent providers in general practice settings. This work aims to empower healthcare providers, especially primary care providers (PCPs), with guidelines for the recognition and safe pharmacologic management of common co-occurring psychiatric and behavioral conditions in ASD.

Methods Lurie Center for Autism medical providers, who have extensive experience in ASD care, delineated approaches for recognition and pharmacological treatment of sleep disturbances, attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, and irritability tailored to ASD patients. Pharmacological guidelines were iteratively refined until consensus was reached. Treatment differences relative to standard of care (SOC) of non-autistic individuals are noted. Key literature and clinical trial results were reviewed to supplement clinical experience.

Results The pharmacological treatment pathways reflect how appropriate medication options for ASD patients can depend on many factors unique to the patient and can differ from established non-autistic SOC. Key takeaways include: For sleep disturbances in ASD, initial strategies align with non-autistic SOC, emphasizing sleep hygiene and melatonin use. First-line recommendations for treating ADHD, anxiety, and depression in ASD differ from non-autistic SOC; α_2-adrenergic agonists are more suitable than stimulants for some ASD-ADHD patients, buspirone and mirtazapine are preferred to selective serotonin reuptake inhibitors (SSRIs) for anxiety, and duloxetine, mirtazapine, bupropion, and vortioxetine are recommended ahead of SSRIs for depression. Addressing irritability in ASD requires interdisciplinary evaluation of contributing factors, and guanfacine, risperidone, or aripiprazole may be appropriate, depending on severity.

Conclusions Recognition and treatment of co-occurring psychiatric and behavioral conditions in autistic patients must account for differences in clinical presentation and medication effectiveness and tolerability. Drawing on evidence-based clinical insights, these guidelines seek to support PCPs in making informed decisions when prescribing

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Full list of author information is available at the end of the article

After the Diagnosis...Service Navigation

1. Recommendations in our reports
2. Team members
   - Social workers
   - Family navigators
   - Community Health Workers
   - Tech platforms
     - Supports for children with developmental disabilities and delays
     - Web resources & mobile app

Undivided www.undivided.io/

- Educational support: Assistance with requesting assessments, securing more support, developing effective IEP and 504 plans, tracking progress, and more.
- Public benefits: Discover the benefits your child is eligible for.
- Stay organized: Keep all documents and notes in a secure digital binder for easy access.
- Learn from experts: Get 1:1 support with a Navigator, and join office hours with special education and public benefits specialists to get answers to your questions.

I am a... *

My Child's Roadmap

Optimize my child's IEP acc

Find an new therapist

Apply for Medi-Cal

Plan for my child's finc

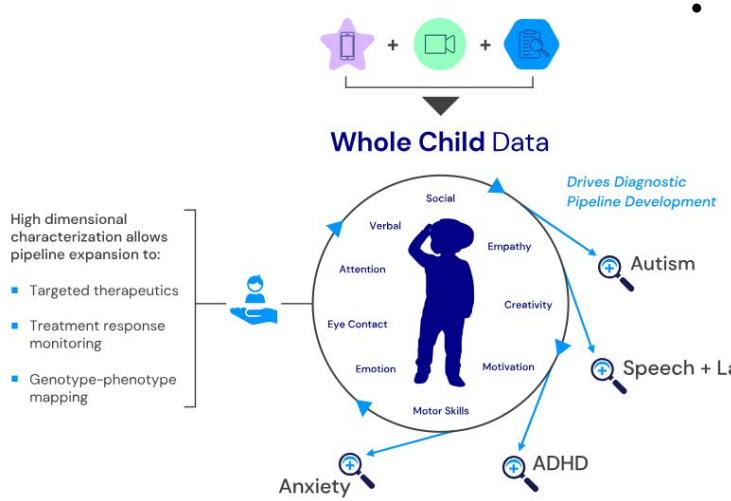
Apply for In-Home Su

www.helpmegrowla.org or call 833.903.3972

Other ASD Referrals

- Regional Center or Early Intervention (IDEA Part C)
  - Respite
  - Family Resource Centers
  - Behavioral classes / therapy
- Individualized Education Programs (IDEA Part B)
  - Comprehensive programs
  - Social skills groups
  - OT, SLT, Behavioral therapy
- Consultation on services/meds
  - DBP/Psychiatry Child Psychiatry

Future of Primary Care: after the ASD Screening..



Diagnostic Decision Aid

- Parent Questionnaire
  - Video of Child- Play and Face to Face
    - Clinician Questionnaire

ASD: Yes, No, Indeterminate

canvas Dx™ by cognoa

FOR PRESCRIPTION USE ONLY

Introducing Canvas Dx, the first and only FDA authorized diagnostic that equips more clinicians to rapidly and accurately diagnose or rule out autism in children ages 1.5 to 6 years, better plan for next steps, and unlock services.

JMIR FORMATIVE RESEARCH Sohl et al

Original Paper

Integration of an Artificial Intelligence–Based Autism Diagnostic Device into the ECHO Autism Primary Care Workflow: Prospective Observational Study

Kristin Sohl[1], MD, FAAP; Erik Linstead[2], PhD; Kelianne Heinz[3], MIDS; Elia Eiroa Lledo[2], PhD; Alicia Brewer Curran[1], BS; Melissa Mahurin[1], BA; Valeria Nanclares-Nogués[1], PsyD; Carmela Salomon[3], PhD; Minda Seal[3], MSA; Sharief Taraman[3,4,5], MD

[1]ECHO Autism Communities, University of Missouri School of Medicine, Columbia, MO, United States
[2]Fowler School of Engineering, Chapman University, Orange, CA, United States
[3]Cognoa Inc, Newport Beach, CA, United States
[4]Pediatric Neurology and Clinical Informatics, Children's Health of Orange County, Orange, CA, United States
[5]School of Medicine, University of California Irvine, Irvine, CA, United States

Results: Eighty children and 7 clinicians completed the study. On average, time from clinical concern at study enrollment to final autism diagnosis was 39.22 days, compared to 180- to 264-day waits at adjacent specialist referral centers. The vast

Conclusion

The ECHO Autism: EDx plus device workflow was feasible and reduced barriers to diagnosis for both caregiver and clinician users. Compared to referral to adjacent specialist waitlists, use of the ECHO Autism: EDx plus device workflow resulted in a reduced travel burden for families and significantly shortened patient delays from first clinical question to diagnosis and treatment initiation.

Goals

1. Explain what is known about the causes of autism spectrum disorder
2. Recommend evidenced-based treatment interventions for autism management
3. **Manage questions about leucovorin, cerebral folate deficiency, and Tylenol**

nature human behaviour

Article

https://doi.org/10.1038/s41562-025-02256-9

Complementary, alternative and integrative medicine for autism: an umbrella review and online platform

Received: 29 December 2024

Accepted: 28 May 2025

A list of authors and their affiliations appears at the end of the paper

- 90% reporting they have tried it at least once
- Several meta-analyses to look at 19 different complementary, alternative and integrative medicine approaches for ASD

Gosling, C.J., Boisseleau, L., Solmi, M. *et al*. Complementary, alternative and integrative medicine for autism: an umbrella review and online platform. *Nat Hum Behav* (2025). https://doi.org/10.1038/s41562-025-02256-9

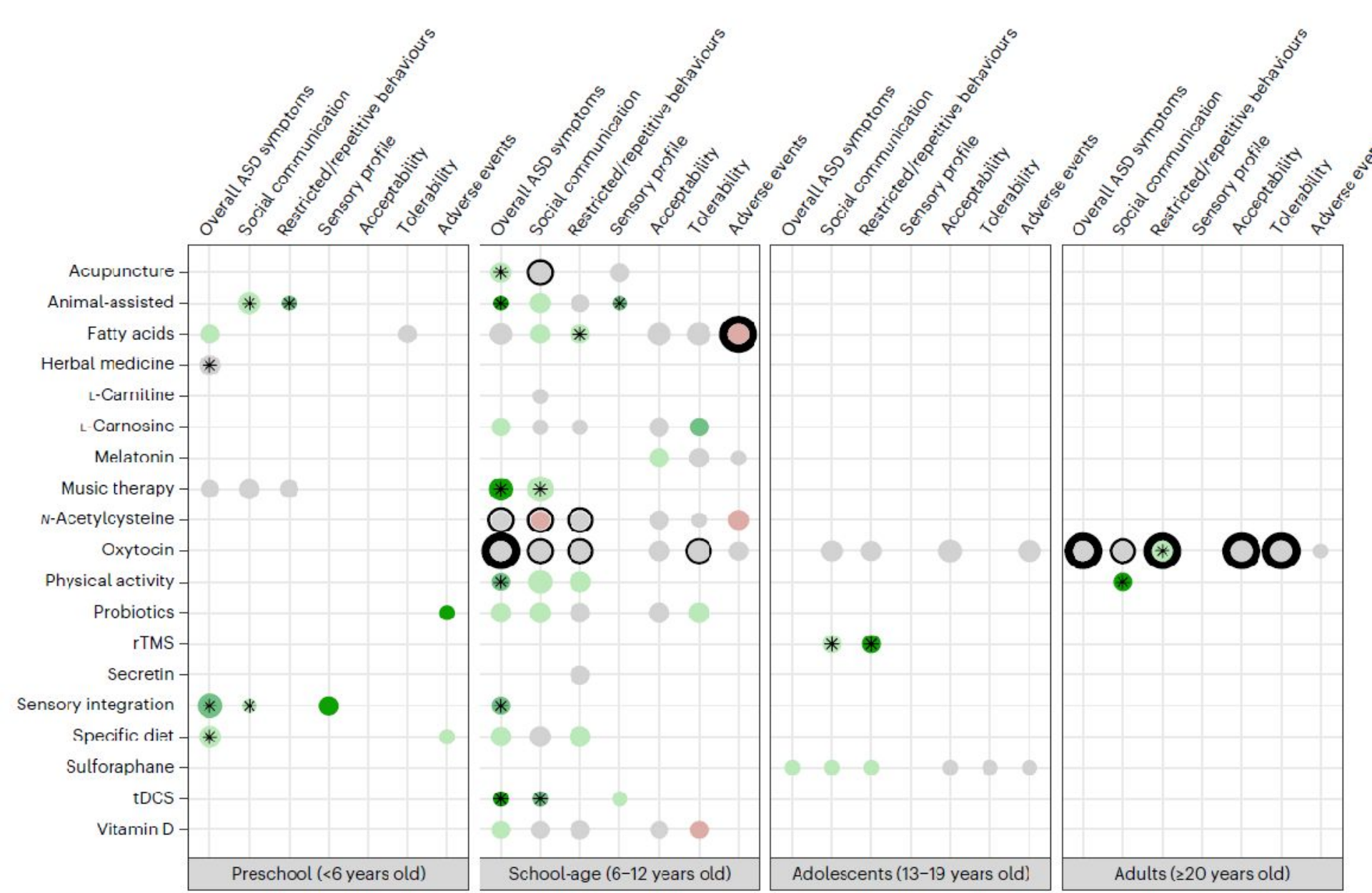


Fig. 2 | Primary outcome comparisons. Scatter plot indicating, for each PICO combination, the magnitude of the pooled effect sizes (grey: absence of effect (SMD ranging from −0.20 to 0.20, OR/RR ranging from 0.80 to 1.25); green: positive effect; red: negative effect; darker colour indicates larger magnitude), the statistical significance (black stars indicate a two-sided *P* value <0.05), the confidence GRADE rating (no surrounding circle: 'very low'; light circle: 'low'; bold circle: 'moderate') and the size of the meta-analysis (greater dot width indicates larger meta-analysis). All pooled effect sizes were estimated using random-effects meta-analysis, with no adjustment for multiple testing.

Fig. 3 | Secondary outcome comparisons. Scatter plot indicating, for each PICO combination, the magnitude of the pooled effect sizes (grey: absence of effect (SMD ranging from −0.20 to 0.20, OR/RR ranging from 0.80 to 1.25); green: positive effect; red: negative effect; darker colour indicates larger magnitude), the statistical significance (black stars indicate a two-sided *P* value <0.05), the confidence GRADE rating (no surrounding circle: 'very low'; light circle: 'low'; bold circle: 'moderate') and the size of the meta-analysis (greater dot width indicates larger meta-analysis). All pooled effect sizes were estimated using random-effects meta-analysis, with no adjustment for multiple testing.

Umbrella Main Finding

- Very low-quality evidence to support many of the CAIMs studied
- Lack of safety parameters evaluated
- Oxytocin-> adult restricted, repetitive behavior
  - small statistically significant effect size
  - high level of evidence

Little Evidence to Support Complementary, Alternative, or Integrative Medicine for Autism

Damian McNamara, MA
September 19, 2025

Medscape

"*Things that work for one child may not work for another no matter how well-designed a study is*," Vanderbilt said.

Leucovorin (folinic acid)

Leucovorin helped son with autism speak, parents say

CBS Evening News ✓ 178K views • 8 months ago

After 2-year-old Mason Connor was diagnosed with autism, his parents turn to leucovorin, also known as folinic acid, an off-label drug being studied for its potential to help some kids improve...

CC

March 2025

Parents express optimism over possible treatment for autism

Leucovorin: A surprising autism treatment

Frye first turned to leucovorin as a potential treatment in the early 2000s after observing a striking pattern in children with autism.

"I started to realize that the neurochemistry in the brain was off," he said.

MEDICINE EXCLUSIVE

Children with autism are showing 'dramatic improvement' with this cheap drug — and doctor behind its research says it may one day prevent the disorder

By McKenzie Beard
Published March 19, 2025, 6:00 a.m. ET

126 Comments

"Frye's patients respond to therapies targeting the mitochondria."

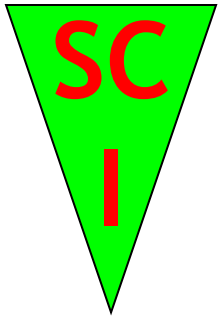
"Dr. Frye is able to ameliorate clinical presentation of autism in his patients, and in some cases reverse their symptoms to the points where they no longer meet the diagnostic criteria for autism spectrum disorder (ASD)"

https://www.youtube.com/watch?v=b9ti03pTWnE

Leucovorin (folinic acid)?

- Active isomer of 5-formyl tetrahydrofolic acid
- FDA approved
  - Reducing toxic side effects of chemotherapy: methotrexate
  - Chemotherapy adjunct: 5-FU/leucovorin (5FU/LV)
  - Megaloblastic anemia due to B9 deficiency but not:
    - Pernicious/megaloblastic anemias- B12 vitamin deficiency
  - Cerebral folate deficiency (CFD)
    - Developmental delays/regression
    - Head growth deceleration
    - Hypo/hypertonia
    - Ataxia
    - Seizures

vs



Children's Hospital LOS ANGELES | USC University of Southern California

For Immediate Release: September 22, 2025

The U.S. Food and Drug Administration today initiated the approval of leucovorin calcium tablets for patients with cerebral folate deficiency (CFD), a neurological condition that affects folate (a vitamin essential for brain health) transport into the brain. Individuals with cerebral folate deficiency have been observed to have developmental delays with autistic features (e.g., challenges with social communication, sensory processing, and repetitive behaviors), seizures, and problems with movement and coordination.

FDA NEWS RELEASE

FDA Takes Action to Make a Treatment Available for Autism Symptoms

"We have witnessed a tragic four-fold increase in autism over two decades," **said FDA Commissioner Marty Makary, M.D., M.P.H.** "Children are suffering and deserve access to potential treatments that have shown promise. We are using gold standard science and common sense to deliver for the American people."

Children's Hospital LOS ANGELES | USC University of Southern California

NATIONAL ARCHIVES

FEDERAL REGISTER

The Daily Journal of the United States Government

The FDA's relabeling of leucovorin is limited to genetic CFD (i.e pathogenic variants in *FOLR1)*

Approval of Previously Withdrawn New Drug Application for WELLCOVORIN (Leucovorin Calcium) Tablets

SUMMARY:

The Food and Drug Administration (FDA or Agency) is announcing approval of the previously withdrawn new drug application (NDA) for Wellcovorin (leucovorin calcium) tablets, equivalent to (EQ) 5 milligrams (mg) base and EQ 25 mg base. FDA is initiating this action on the basis of new data and is required to publish notice of approval of an NDA for which the Agency had previously withdrawn approval.

Under 21 CFR 314.160, FDA, on its own initiative or upon request of an applicant, may, on the basis of new data, approve an application or abbreviated application which it had previously refused, suspended, or withdrawn approval. With respect to leucovorin calcium tablets, FDA has conducted a systematic analysis of literature published between 2009-2024 and has determined that the information supports a finding that orally administered leucovorin calcium tablets improve certain symptoms in adults and pediatric patients with cerebral folate deficiency (CFD). Published case reports provided patient-level data on over 40 patients, including both adults and pediatric patients, with genetically confirmed CFD due to variants in the FOLR1 gene who were treated with oral leucovorin. Patients had heterogenous

https://www.federalregister.gov/d/2025-18510/p-7

Leucovorin?

- No well powered studies show ASD = CFD
- No well powered RCT with generalizable results that have been reproduced, showing Leucovorin improves language or core autism features
  - 4 methodologically flawed studies with small sample sizes- 1 group
- CFD is a rare degenerative condition
  - ASD is not a core feature of CFD
  - FOLR1; MTHFR; SLC46A1 gene tests

European Journal of Pediatrics (2026) 185:109
https://doi.org/10.1007/s00431-026-06769-x

RETRACTION NOTE

Retraction Note: Efficacy of oral folinic acid supplementation in children with autism spectrum disorder: a randomized double-blind, placebo-controlled trial

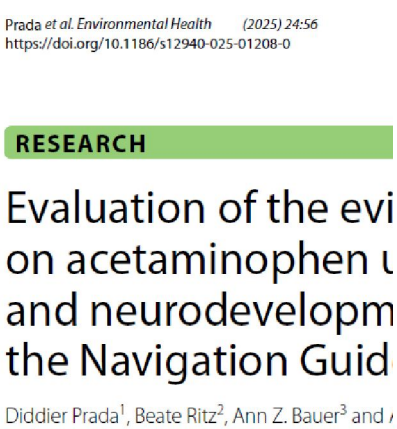
Prateek Kumar Panda[1] · Indar Kumar Sharawat[1] · Sarama Saha[2] · Diksha Gupta[1] · Achanya Pa
Kiran Meena[2]

Retraction Note: European Journal of Pediatrics (2024) 183:4827-4835
https://doi.org/10.1007/s00431-024-05762-6

"By September [2025], we will know what has caused the autism epidemic and we'll be able to eliminate those exposures," Kennedy said.

Tylenol

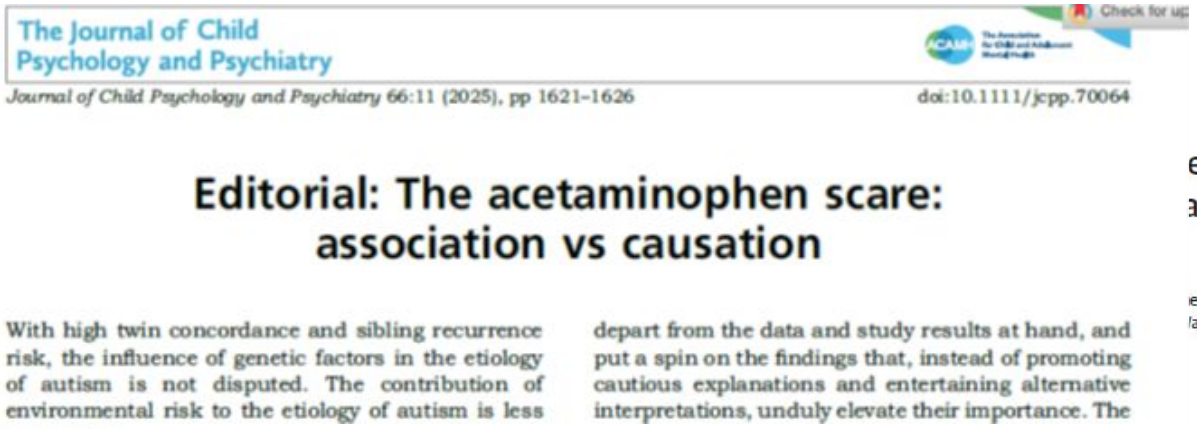
Don't Take Tylenol?


Prada et al. Environmental Health (2025) 24:56
https://doi.org/10.1186/s12940-025-01208-0

RESEARCH

Evaluation of the evi
on acetaminophen u
and neurodevelopm
the Navigation Guid

Diddier Prada[1], Beate Ritz[2], Ann Z. Bauer[3] and


The Journal of Child Psychology and Psychiatry

Journal of Child Psychology and Psychiatry 66:11 (2025), pp 1621–1626 doi:10.1111/jcpp.70064

Editorial: The acetaminophen scare: association vs causation

With high twin concordance and sibling recurrence risk, the influence of genetic factors in the etiology of autism is not disputed. The contribution of environmental risk to the etiology of autism is less

depart from the data and study results at hand, and put a spin on the findings that, instead of promoting cautious explanations and entertaining alternative interpretations, unduly elevate their importance. The

ero Acetaminophen
activity Disorder

ei Hong, MD, PhD;
ang, MD, MPH, ScD

- Association is not causation
  - Many correlations- eg. psychiatric disorders, chronic pain
  - Well studied: valproic acid and advanced parental age
- Methodology
  - Confirmation bias
  - Acetaminophen maternal recall and caregiver autism screening tools
- Residual confounding
  - Why was the pain medicine used…. 3rd unmeasured variable
  - Negative controls on exposures and outcomes (no biological pathway)
- Confounding by genetic factors
  - Shared familial influences (sibling control analysis)

Fombonne, E. J Child Psychol Psychiatr, 66: 1621-1626.

Children's Hospital LOS ANGELES

SDBP
Society for Developmental & Behavioral Pediatrics

SDBP Mission Statement:
Optimizing the development and behavioral (DB) health of all children and families through interprofessional collaboration.

6728 Old McLean Village Drive, McLean, VA 22101
www.sdbp.org • info@sdbp.org

A Statement from the Society for Developmental and Behavioral Pediatrics On Recent Autism Claims

The Society for Developmental and Behavioral Pediatrics (SDBP) stands with concerned families, scientists, and clinicians in emphasizing that messaging about autism and its causes must be based on clear, unbiased scientific findings. We understand that parents, as well as clinicians and scientists, want more answers about what causes autism, and we're committed to sharing what the research actually tells us.

What We Know About Autism's Causes

Decades of research shows that autism has complex causes involving both genetics and environmental influences working together. Importantly, autism is not caused by anything parents did or did not do. No single factor—whether genetic or environmental—causes autism on its own. Instead, autism likely results from many different genetic variations interacting with environmental factors during critical periods of brain development.

About Recent Claims

Regarding acetaminophen (Tylenol) use during pregnancy: There is no strong evidence showing a direct relationship between the appropriate use of acetaminophen during pregnancy and harmful effects on fetal development. Some recent studies have suggested associations, but these do not prove causation. Importantly, when researchers used more sophisticated study designs that compared siblings within the same family—which better controls for genetic and maternal health factors—any previously observed associations between acetaminophen use and autism disappeared. This suggests that family genetics and maternal health, rather than acetaminophen itself, may explain earlier findings. *Acetaminophen continues to be considered safe when used as directed during pregnancy by the American College of Obstetricians and Gynecologists and other leading medical groups.*

Regarding folate, folate receptor autoantibodies, and leucovorin treatment: While evidence suggests that getting adequate folate during critical windows of pregnancy may reduce autism risk, appropriate supplementation is already recommended for all pregnant women. Much more research is needed on folate

sdbp.org

Interim Guidance from the American Academy of Pediatrics: Use of Leucovorin in Autistic Pediatric Patients

- **At this time, the American Academy of Pediatrics (AAP) does not recommend the routine use of leucovorin (folinic acid) for autistic children.**
- The AAP does not have prescribing guidelines for leucovorin for the indication of autism.
- Early, small-scale studies have explored its use—with documented cerebral folate deficiency—and some findings suggest potential benefit in carefully selected cases.
- Preliminary results are promising and have laid the groundwork for further investigation.
- Current evidence base remains too limited to support specific clinical recommendation

- Providers should engage in shared decision-making
- Provide clear information about current evidence and potential risks
- Support robust supports and services based on individual need
- Optimize recommended services and emphasize continuation of well-established evidenced based therapies that are beneficial to the well-being of the child.
- Prioritize *harm mitigation*
- Support families in navigating complex therapeutic decisions grounded in compassion, transparency, and scientific integrity.

CHLA Parent Handouts

Common questions about autism, leucovorin, and acetaminophen

You may have seen stories about autism in the news and on social media in recent days. There is a lot of information about what may cause autism, and it may be confusing. The information below has common questions and answers from medical professionals.

What is autism?

Autism spectrum disorder (ASD) refers to a difference in the way a child's brain develops that can affect how they communicate and interact with others. Children with autism may also have trouble understanding the world around them. They may move in an unusual way (like flapping their hands) or do the same thing over and over (like saying the same word).

Autistic symptoms are different for each person. Some autistic people are verbal, while others have mild or moderate speech difficulties. Others have a very hard time with language or are not verbal.

What causes autism?

Over 30 years of research show that there are many different causes of autism. Factors such as personal health, the environment, and our genes can all play a role in what causes autism.

Hundreds of genes are important to how the brain develops. About 3 out of 10 cases of autism and other intellectual and developmental disabilities may be caused by a change in one of these genes.

Հաճախ տրվող հարցեր աուտիզմի, լեյկովորինի և ացետամինոֆենի մասին

Վերջերս զանգվածային լրատվության միջոցներում և սոցիալական ցանցերում դուք երևի տեսել եք հոդվածներ աուտիզմի մասին: Աուտիզմի առաջացման պատճառների մասին շատ տեղեկություններ կան, և դա կարող է շփոթեցնել: Ստորև ներկայացված են հաճախ տրվող հարցերը և առողջապահության ոլորտի մասնագետների պատասխանները:

Preguntas frecuentes sobre el autismo, la leucovorina y el acetaminofeno

Es posible que haya visto historias sobre el autismo en las noticias y en las redes sociales en los últimos días. Existe mucha información sobre qué causa el autismo y eso puede ser confuso. La siguiente información contiene preguntas frecuentes y respuestas de profesionales médicos.

关于自闭症、亚叶酸钙和对乙酰氨基酚的常见问题

近日，您可能在新闻和社交媒体上看到了自闭症的相关报道。关于自闭症可能病因的信息纷繁复杂，可能会令人困惑。以下是医疗专业人员针对常见问题给出的解答。

Art of DBP Medicine

How you treat the patient, is as important as what you treat them with.

Change Summary

I will…

1. Share that autism spectrum disorder has varied origins with environmental and genetic bases
2. Support families in evidenced-based treatment interventions
3. Dispel false information about leucovorin, cerebral folate deficiency, and Tylenol