A Natural Approach to Oppositional Defiant Disorder

Naturopathic Pediatrics PRO Module #3
Erika Krumbeck, ND, FABNP

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- **August 8th, 12:00 p.m. PST - Evidence-Based Nutritional Interventions for ADHD in children**
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A Natural Approach to Oppositional Defiant Disorder

Naturopathic Pediatrics PRO Module #3
Erika Krumbeck, ND, FABNP

An estimated

2-16%

of children and adolescents have Oppositional Defiant Disorder.

#1

Cause of referrals for youth mental health.

92%

of children with ODD have another mental health disorder in their lifetime

Nock, M. K., Kazdin, A. E., Hiripi, E., & Kessler, R. C. (2007). Lifetime prevalence, correlates, and persistence of oppositional defiant disorder: Results from the National Comorbidity Survey Replication. Journal of Child Psychology and Psychiatry, 48(7), 703–713. https://doi.org/10.1111/j.1469-7610.2007.01733.x

What is Oppositional Defiant Disorder?

Symptoms of ODD:

- Argumentative
- Angry or resentful
- Frequent temper tantrums
- Refusing to comply with requests, rules
- Deliberately disruptive
- Blames others for mistakes
- Frequent outbursts
- Questions rules/authority
- Gender differences: Boys are often aggressive, Girls are often manipulative or lying

Screening questions for ODD in practice

- Has your child in the past three months been spiteful or vindictive, or blamed others for his or her own mistakes? (Any “yes” is a positive response.)
- How often is your child touchy or easily annoyed, and how often has your child lost his or her temper, argued with adults, or defied or refused adults' requests? (Two or more times weekly is a positive response.)
- How often has your child been angry and resentful or deliberately annoying to others? (Four or more times weekly is a positive response.)

Diagnostic Criteria of ODD:

- At least four symptoms from the list below should have been present on most days **for at least 6 months** demonstrating a pattern of **angry or irritable mood, argumentative or defiant behavior, or vindictiveness**:
  - Often loses temper
  - Often touchy or easily annoyed
  - Often angry and resentful
  - Often argue with authority figures
  - Often actively refuse or defy to comply
  - Often deliberately annoys others
  - Often blames others for mistakes or behavior
  - Spiteful or vindictive at least twice in the past 6 months

Diagnostic Criteria of ODD:

- There should be evidence of impairment either in the form of distress (in the individual, family, peers, etc.) and/or negative impact on social, educational, occupational, or other important areas of functioning. The behaviors do not occur exclusively during substance use, psychotic, depressive, or bipolar disorder. The patients must not meet the criteria for disruptive mood dysregulation disorder.
- Severity: ODD is considered mild if symptoms are confined to only one setting, moderate if at least two settings and severe if symptoms are present in three or more settings.

What is Conduct Disorder?

Diagnostic Criteria of Conduct Disorder:

- A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated.

Signs:

- Bullies, threatens, intimidates
- Initiates physical fights
- Uses weapons to cause serious physical harm
- Physically cruel to others
- Commits robberies
- Forced sexual activity
- Destruction of property
- Serious violation of parental guidance or rules
- School truancy, beginning before age 13

Why is it important to diagnose and treat ODD?

- Lack of treatment, poor parenting strategies, social stressors and poor support for children with ODD can lead to a child developing conduct disorder.
- On the other hand, adequate treatment, co-treatment of other coexisting conditions (ADHD, OCD, etc), family therapy and positive parenting are associated with a GOOD prognosis for kids with ODD.

What is the etiology of Oppositional Defiant Disorder? What are the risk factors?

The etiology of ODD

- The etiology of oppositional defiant disorder (ODD) is complex and multifaceted, involving a combination of biological, psychological, and social factors.
- Children with ODD may have **deficits in specific cognitive and emotional skills** that contribute to their oppositional behaviors. These deficits can include **problems with executive functions such as working memory, task switching**, and **organized problem solving,** as well as **difficulties in emotional regulation, such as affective modulation.**

> Int J Dev Neurosci. 2024 May 25. doi: 10.1002/jdn.10349. Online ahead of print.

Decreased gray matter volume in the anterior cerebellar of attention deficit/hyperactivity disorder comorbid oppositional defiant disorder children with associated cerebellar-cerebral hyperconnectivity: insights from a combined structural MRI and resting-state fMRI study

Xin Wang [1], Yan Guo [2], Jin Xu [1], Yong Xiao [1], Yigang Fu [1]

Affiliations + expand

PMID: 38795021 DOI: 10.1002/jdn.10349

Abstract

Attention deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) are highly comorbid. Many prior investigations have found that ADHD relates to anatomical abnormalities in gray matter. The abnormal gray matter of ADHD comorbid ODD is still poorly understood. This study aimed to explore the effect of comorbid ODD on gray matter volume (GMV) and functional alterations in ADHD. All data were provided by the ADHD-200 Preprocessed Repository, including 27 ADHD-only children, 27 ADHD + ODD children, and 27 healthy controls aged 9-14 years. Voxel-

Genetics?

- There is no single known gene responsible for ODD, but several single nucleotide polymorphisms have been shown to be associated with increased risk for ODD: MAOA-uVNTR and 5-HTTLPR (SLC6A4)
- (We will review these thoroughly in a few slides…)

Parenting

- Unpredictable, inconsistent, negative, abusive or escalating parenting practices are associated with ODD.
- **Encouraging the connection between the parent and child is the most critical thing that healthcare providers can do. Never criticize a parent or cut down a parent for their decisions.**
- I highly recommend the Promoting First Relationships training.

Risk factors for developing ODD:

- Parent with history of ADHD, ODD or Conduct Disorder
- Parent with a mood disorder like depression or bipolar disorder
- Mother who smoked during pregnancy
- Parent who has drinking or substance abuse
- Exposure to lead or other toxins affecting brain growth
- Fetal alcohol syndrome
- Neglectful or absent parent
- Inconsistent discipline or corporal punishment
- Poor nutrition
- Abuse or neglect
- Family instability
- Developmental disorders

Why is there a higher rate in boys?

- Higher testosterone levels are linked to increased aggression and oppositional behaviors.
  - Studies have shown that testosterone can influence brain areas related to aggression and social dominance.
- Vasopressin and oxytocin may also be involved.
  - Oxytocin = "the love hormone" is critical for social bonding. Oxytocin fosters nurturing, trust, social attachment, social connections, maternal bonds.
  - Vasopressin is associated with protective and territorial behaviors, especially in males.
  - High testosterone dampens bonding effects of oxytocin and enhances aggressive effects of vasopressin. High levels of testosterone can decrease sensitivity to social cues and reduce social behaviors, impacting social bonding and empathy. This makes it harder for boys with ODD to form positive social bonds.

Why is there a higher rate in boys?

- Studies suggest that **boys are more likely to externalize their stress through behaviors such as aggression and defiance,** while girls may internalize stress, leading to anxiety and depression.
- The interaction between testosterone and social environment is crucial. Boys with higher levels of testosterone might be more sensitive to environmental triggers and stressors, which can lead to an increased risk of developing ODD when coupled with adverse social conditions such as inconsistent discipline, exposure to violence, or lack of positive role models.

Tools for diagnosis of ODD

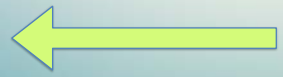
Diagnostic Tools in Primary Care

- Clinical interviews: structured interviews with child and parent is very important for documenting parental concerns
- Questionnaires and rating scales can be used to assess symptoms of ODD.
  - **Vanderbilt ADHD Assessment** - also includes sections on ODD
  - Connors Rating Scales
  - Child Behavior Checklist (CBCL)
  - Behavior Assessment System for Children (BASC)

Referral to Neuropsychology or Psychiatry

- Primary care providers may refer a child to a specialist such as a child psychologist, psychiatrist, or neuropsychologist for further assessment. This is especially likely if:
  - The diagnosis needs to be confirmed. (E.g., to set up educational resources, generate a 504 plan or IEP for a child.)
  - The diagnosis is unclear or the child's symptoms are complex.
  - There are co-occurring conditions (such as ADHD, anxiety, or mood disorders) that need to be evaluated.

Differential Diagnosis and Comorbidities



ODD vs. ADHD

- High overlap! 40% of children with ADHD also exhibit signs of ODD.
- Symptom overlaps:
  - ADHD is primarily characterized by inattention, hyperactivity, and impulsivity. It affects the person's ability to maintain focus, stay organized, and follow through on tasks.
  - ODD is characterized by a pattern of angry or irritable mood, argumentative/ defiant behavior, or vindictiveness lasting at least six months.
- Use Vanderbilt ADHD assessment to clarify ADHD vs. ODD, or co-existing.

ODD vs. Depression

- Pediatric depression does not present clinically the same as adult depression. Children with depression are withdrawn, irritable, "moody," guilty, feelings of worthlessness. Some present with anger, refusal to do schoolwork, engage in social activities.
- Evaluation:
  - PHQ-9 for adolescents
  - Bright Futures CES-DC: cut-off score of 15 suggestive of depressive symptoms in children and adolescents.

Depression or other medical condition?

- Reminder: always check for medical issues that present as pediatric mood disorders. Thyroid, lead, iron deficiency anemia, constipation, headaches, ear infections, etc, very often present as an irritable child.

ODD vs. Intellectual Disability or Language Disorders

- In individuals with **intellectual disability,** a diagnosis of oppositional defiant disorder is given only if the oppositional behavior is markedly greater than is commonly observed among individuals comparable mental age and with comparable severity of intellectual disability.
- In patients with **Language Disorders**: It is important to distinguish ODD from a failure to follow directions that is a result of impaired language comprehension (e.g., hearing loss.) **Check the ears!**

ODD vs. Autism Spectrum Disorder

- Patients with level 1 ASD (F.K.A. as Asperger's) can have some similar symptoms of ODD, however the syndrome looks somewhat different.
  - Level 1 ASD is characterized by missed social and communication cues, restricted or repetitive patterns of behavior or interests, plus noticeable sensory issues.

Characteristics of ASD

- Persistent Deficits in Social Communication and Social Interaction:
  - Deficits in social-emotional reciprocity, e.g., failure of normal back-and-forth conversation
  - Deficits in nonverbal communication, e.g., lack of eye contact or inability to read body language.
  - Deficits in developing, maintaining and understanding relationships

Characteristics of ASD

- Restricted, Repetitive Patterns of Behavior, Interests, or Activities (at least 2 of the following):
  - Stereotyped or repetitive motor movements, use of objects, or speech: Examples: lining up toys or flipping objects, echolalia, idiosyncratic phrases.
  - Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior: Examples are extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat the same food every day.

Characteristics of ASD

- Sensory issues: Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment: Examples might include either increased sense of pain, or apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement, or hypersensitivity to bright lights or sounds.

ODD vs. ASD with Pathological Demand Avoidance

- **Pathological Demand Avoidance (PDA) is a proposed sub-type of Autism Spectrum Disorder (ASD) characterized by an extreme avoidance of everyday demands and an anxiety-driven need to control situations.** It is not officially recognized in all diagnostic manuals, such as the DSM-5, but it is gaining recognition, particularly in the UK, where it was first described. The concept of PDA helps explain the behaviors of some individuals on the autism spectrum who do not respond well to traditional approaches used for autism. **The most essential part of PDA to acknowledge is that every day demands cause a crippling anxiety for the patient, leading to resistance.**

Characteristics of Pathological Demand Avoidance

- Extreme avoidance of everyday demands: Individuals with PDA might resist typical daily activities and requests that most people would find reasonable. This resistance is believed to stem from an anxiety-based need to control situations and avoid demands that feel overwhelming.
  - An overwhelming desire to be in in control and to avoid being controlled by others is key in seeing this diagnosis.
- Otherwise kids with PDA also show signs of ASD, including missed social signs. Some have manipulative or socially inappropriate behaviors.

Characteristics of Pathological Demand Avoidance

- Other characteristics:
  - Mood swings, impulsivity
  - Comfort in role play, or playing pretend
  - Obsessive behavior, repetitive interests, or controlling behavior
  - Emotional outbursts

Why is this important?

- In my opinion, teaching parents parenting techniques to help Pathological Demand Avoidance is highly effective, even if the patient does not meet criteria for PDA or ASD.

Other conditions:

- Substance Use Disorder
- Sleep apnea or poor sleep quality:
  - Can cause irritability, hyperactivity, inattention, aggressive behavior, mood swings
- Constipation:
  - Can cause irritability, behavior problems including rule-breaking, aggression.
  - Cause or effect?? Much research on gut-brain relationship…

Other conditions:

- Reactive hypoglycemia
  - Symptoms include irritability, mood swings, aggressiveness, anxiety, fatigue, poor concentration.
  - Key: children whose behavior problems worsen 60-90 minutes after high carbohydrate meals, or children whose behavior problems resolve after eating.

Single nucleotide polymorphisms and ODD

MAOA-uVNTR

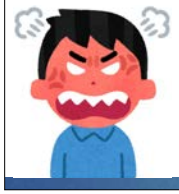
- Monoamine oxidase A is responsible for breaking down neurotransmitters serotonin, norepinephrine and dopamine in the brain.
- Variations in this gene, particularly low-activity variants (MAOA-L) have been studied for their potential link to behaviors such as increased aggression or risk of psychiatric disorders under certain conditions.
- MAOA-uVNTR is a variation in the genetic sequence in the promotor region of the MAOA gene, and corresponds with low enzymatic function. The result = excessively high levels of serotonin, norepinephrine and dopamine.

and gene systems that are most likely to contribute to antisocial behaviors are those that are involved in neurotransmission (Ferguson & Beaver, 2009).

Of all the genes that have been studied in relation to antisocial phenotypes, the monoamine oxidase A (MAOA) gene has produced the most consistent results. The MAOA gene is located on the X chromosome (Xp11.23-11.4) and is responsible for encoding the MAOA enzyme which degrades neurotransmitters, such as serotonin, dopamine, and norepinephrine. The MAOA gene has a polymorphism (MAOA-uVNTR) that is the result of a 30-base-pair (bp) variable number of tandem repeats upstream in the 5′ regulatory region of the gene. This polymorphism has been shown to affect the functioning of the MAOA enzyme with some of the alleles encoding a low activity MAOA enzyme and others encoding a high activity MAOA enzyme. Genotyping MAOA via PCR typically produces the following five fragment sizes: 2 repeats (2R), 3 repeats (3R), 3.5 repeats (3.5R), 4 repeats (4R), and 5 repeats (5R). A general consensus has been reached in that the 2R and 3R alleles correspond to low MAOA activity, while the 3.5R and 4R alleles correspond to high MAOA activity. The 5R allele, however, has been shown to produce both low MAOA activity (Sabol, Hus, & Hamer, 1998) and high MAOA activity (Deckert et al., 1999).

Human genetic research has examined the direct association between MAOA genotypes and antisocial behaviors, revealing that the alleles that encode the low activity MAOA enzyme confer an increased risk to antisocial phenotypes. For example, the low MAOA activity alleles have been linked to delinquent behavior in adolescents and young adults (Guo, Ou, Roettger, & Shih, 2008) as well as more serious types of violence, such as

Clinical symptoms of MAOA-L



- Excessively high levels of serotonin, norepinephrine and dopamine that lasts an excessively long time! They are borderline panic attack threshold constantly.
- When these kids are exposed to a stressor their adrenaline spike is HIGH and does not come down for a LONG time.
- Insomnia, anxiety, stomachaches, mood swings, impulsivity, violence are common.
- Many of these kids “explode” and then feel incredibly remorseful afterwards. The “explosion” of energy “burns off” adrenaline and helps them come back down.

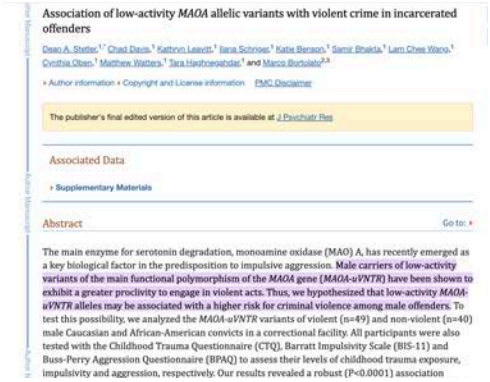
Clinical effects of MAOA-L

- The impact of the MAOA-uVNTR polymorphism is particularly pronounced when combined with adverse environmental factors. For example, individuals with low-activity MAOA who also experience childhood adversity may have a higher risk of developing behavioral disorders like ODD due to their increased biological vulnerability to environmental stresses.

Why so much worse in boys?

- MAOA is X-linked, males only inherit one copy.
- Testosterone affects MAOA gene expression, as well as modulate brain chemistry and enhance aggression.
- Female benefit from protective effects of estrogen and progesterone. Estrogen can increase transcription of MAOA gene, and progesterone can provide neurostabilizing effects through allopregnanolone (which acts of GABA-A receptors, thus calming the brain).

Why does this matter?



Association of low-activity *MAOA* allelic variants with violent crime in incarcerated offenders

Dean A. Stetler,[1,*] Chad Davis,[1] Kathryn Leavitt,[1] Ilana Schrijver,[1] Katie Benson,[1] Samir Bhakta,[1] Lam Chee Wang,[1] Cynthia Olsen,[1] Matthew Watters,[1] Tara Haghnegahdar,[1] and Marco Bortolato[2,3]

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The publisher's final edited version of this article is available at J Psychiatr Res

Associated Data

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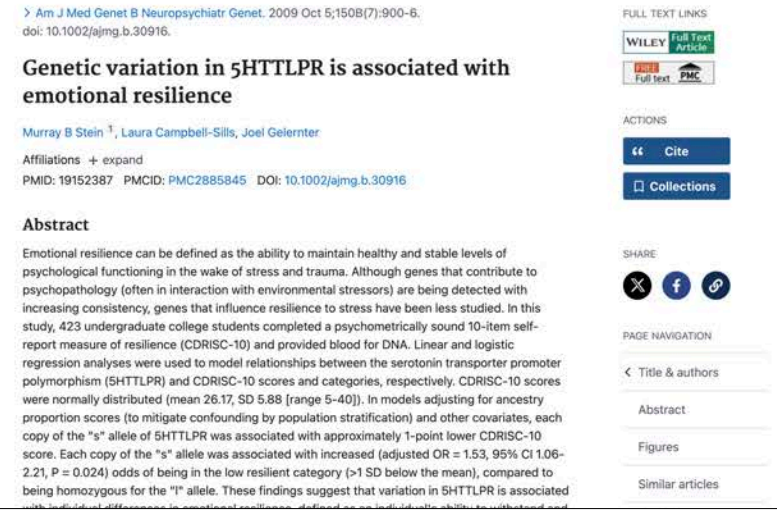
Abstract Go to: ›

The main enzyme for serotonin degradation, monoamine oxidase (MAO) A, has recently emerged as a key biological factor in the predisposition to impulsive aggression. **Male carriers of low-activity variants of the main functional polymorphism of the *MAOA* gene (*MAOA-uVNTR*) have been shown to exhibit a greater proclivity to engage in violent acts. Thus, we hypothesized that low-activity *MAOA-uVNTR* alleles may be associated with a higher risk for criminal violence among male offenders.** To test this possibility, we analyzed the *MAOA-uVNTR* variants of violent (n=49) and non-violent (n=40) male Caucasian and African-American convicts in a correctional facility. All participants were also tested with the Childhood Trauma Questionnaire (CTQ), Barratt Impulsivity Scale (BIS-11) and Buss-Perry Aggression Questionnaire (BPAQ) to assess their levels of childhood trauma exposure, impulsivity and aggression, respectively. Our results revealed a robust (P<0.0001) association

5-HTTLPR (SCL6A4 serotonin transporter gene)

- 5-HTTLPR is a genetic variant of the serotonin transporter gene (known scientifically as SLC6A4). This variant affects how serotonin is transported in the brain. Serotonin (5-HT) plays a vital role as a neurotransmitter, influencing various behaviors including appetite, movement, aggression, and focus.
- Research has shown that impaired serotonin function can lead to significant issues, such as enhanced pain perception, anxiety, aggression, symptoms of attention deficit hyperactivity disorder (ADHD), and impulsivity, which are often observed in cases of substance abuse, oppositional defiant disorder (ODD), and personality disorders.



› Am J Med Genet B Neuropsychiatr Genet. 2009 Oct 5;150B(7):900-6.
doi: 10.1002/ajmg.b.30916.

Genetic variation in 5HTTLPR is associated with emotional resilience

Murray B Stein [1], Laura Campbell-Sills, Joel Gelernter

Affiliations + expand

PMID: 19152387 PMCID: PMC2885845 DOI: 10.1002/ajmg.b.30916

Abstract

Emotional resilience can be defined as the ability to maintain healthy and stable levels of psychological functioning in the wake of stress and trauma. Although genes that contribute to psychopathology (often in interaction with environmental stressors) are being detected with increasing consistency, genes that influence resilience to stress have been less studied. In this study, 423 undergraduate college students completed a psychometrically sound 10-item self-report measure of resilience (CDRISC-10) and provided blood for DNA. Linear and logistic regression analyses were used to model relationships between the serotonin transporter promoter polymorphism (5HTTLPR) and CDRISC-10 scores and categories, respectively. CDRISC-10 scores were normally distributed (mean 26.17, SD 5.88 [range 5-40]). In models adjusting for ancestry proportion scores (to mitigate confounding by population stratification) and other covariates, each copy of the "s" allele of 5HTTLPR was associated with approximately 1-point lower CDRISC-10 score. Each copy of the "s" allele was associated with increased (adjusted OR = 1.53, 95% CI 1.06-2.21, P = 0.024) odds of being in the low resilient category (>1 SD below the mean), compared to being homozygous for the "l" allele. These findings suggest that variation in 5HTTLPR is associated

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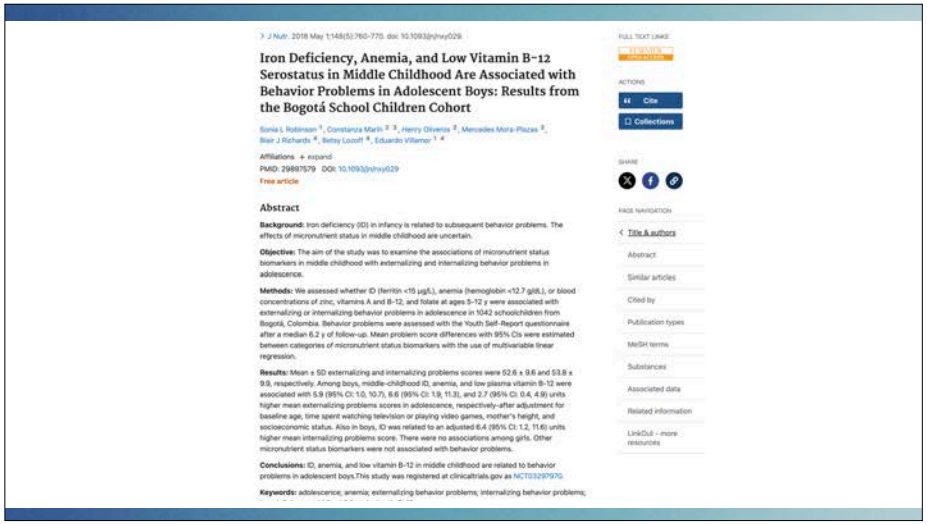
Combinations of the genes + social stressors = highly increased risk

- 5-HTTLPR x+ MAOA uVNTR + family conflicts OR sexual abuse = highest rates of teenage delinquency, mental health issues.
- One study suggested that those with 5-HTTLPR or MAOA uVNTR with positive family homes actually have the best outcomes. Environment matters!

Laboratory evaluation

Laboratory testing

- Goal of laboratory testing is to rule out nutritional factors that may be affecting mental health, or uncover missed diagnoses (e.g., lead toxicity, iron deficiency anemia).
- Standard pediatric labs: **CBC with diff, CMP, TSH & free T4, whole blood lead, ferritin, lipid panel.** Strongly consider the following testing if the parent/caregiver can afford it, especially if the child has picky eating behaviors: **B12 & folate, RBC zinc, RBC Mg, serum copper**. Consider **celiac disease testing.**



J Nutr. 2018 May 1;148(5):760–770. doi: 10.1093/jn/nxy029

Iron Deficiency, Anemia, and Low Vitamin B–12 Serostatus in Middle Childhood Are Associated with Behavior Problems in Adolescent Boys: Results from the Bogotá School Children Cohort

Sonia L Robinson [1], Constanza Marin [2, 3], Henry Oliveros [2], Mercedes Mora-Plazas [3], Blair J Richards [4], Betsy Lozoff [4], Eduardo Villamor [1, 4]

Affiliations + expand

PMID: 29897579 DOI: 10.1093/jn/nxy029

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Abstract

Background: Iron deficiency (ID) in infancy is related to subsequent behavior problems. The effects of micronutrient status in middle childhood are uncertain.

Objective: The aim of the study was to examine the associations of micronutrient status biomarkers in middle childhood with externalizing and internalizing behavior problems in adolescence.

Methods: We assessed whether ID (ferritin <15 μg/L), anemia (hemoglobin <12.7 g/dL), or blood concentrations of zinc, vitamins A and B–12, and folate at ages 5–12 y were associated with externalizing or internalizing behavior problems in adolescence in 1042 schoolchildren from Bogotá, Colombia. Behavior problems were assessed with the Youth Self–Report questionnaire after a median 6.2 y of follow-up. Mean problem score differences with 95% CIs were estimated between categories of micronutrient status biomarkers with the use of multivariable linear regression.

Results: Mean ± SD externalizing and internalizing problems scores were 52.6 ± 9.6 and 53.8 ± 9.8, respectively. Among boys, middle-childhood ID, anemia, and low plasma vitamin B–12 were associated with 5.9 (95% CI: 1.0, 10.7), 6.6 (95% CI: 1.9, 11.3), and 2.7 (95% CI: 0.4, 4.9) units higher mean externalizing problems scores in adolescence, respectively–after adjustment for baseline age, time spent watching television or playing video games, mother's height, and socioeconomic status. Also in boys, ID was related to an adjusted 6.4 (95% CI: 1.2, 11.6) units higher mean internalizing problems score. There were no associations among girls. Other micronutrient status biomarkers were not associated with behavior problems.

Conclusions: ID, anemia, and low vitamin B–12 in middle childhood are related to behavior problems in adolescent boys.This study was registered at clinicaltrials.gov as NCT03297970.

Keywords: adolescence; anemia; externalizing behavior problems; internalizing behavior problems;

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J Nutr. 2020 Jan 1;150(1):140–148. doi: 10.1093/jn/nxz185.

Vitamin D Deficiency in Middle Childhood Is Related to Behavior Problems in Adolescence

Sonia L Robinson [1], Constanza Marin [2, 3], Henry Oliveros [2], Mercedes Mora-Plazas [3], Betsy Lozoff [4, 5], Eduardo Villamor [1]

Affiliations + expand

PMID: 31429909 DOI: 10.1093/jn/nxz185

Free article

Abstract

Background: Vitamin D deficiency (VDD) is associated with depression and schizophrenia in adults. The effect of VDD in childhood on behavioral development is unknown.

Objectives: We aimed to study the associations of VDD and vitamin D binding protein (DBP) in middle childhood with behavior problems in adolescence.

Methods: We quantified plasma total 25-hydroxyvitamin D [25(OH)D] and DBP in 273 schoolchildren aged 5–12 y at recruitment into a cohort study in Bogota, Colombia. Externalizing and internalizing behavior problems were assessed after a median 6–y follow-up by parental report [Child Behavior Checklist (CBCL)] and self-report [Youth Self-Report (YSR)]. We estimated mean problem score differences with 95% CIs between exposure categories using multivariable linear regression. We also compared the prevalence of clinical behavior problems (score >63) between exposure groups. We assessed whether the associations between DBP and behavior problems were mediated through VDD.

Results: Mean ± SD CBCL and YSR externalizing problems scores were 56.5 ± 9.3 and 53.2 ± 9.5, respectively. Internalizing problems scores averaged 57.1 ± 9.8 and 53.7 ± 9.8, respectively. VDD [25(OH)D <50 nmol/L] prevalence was 10.3%. VDD was associated with an adjusted 6.0 (95% CI: 3.0, 9.0) and 3.4 (95% CI: 0.1, 6.6) units higher CBCL and YSR externalizing problems scores, respectively, and an adjusted 3.6 (95% CI: 0.3, 6.9) units higher CBCL internalizing problems scores. The prevalence of clinical total externalizing problems was 1.8 (95% CI: 1.1, 3.1) times higher in children with VDD than that in children without VDD. DBP concentration below the population median was related to higher YSR aggressive behavior and anxious/depressed subscale scores and to higher prevalence of clinical total externalizing problems. The associations between DBP and behavior problems were not mediated through VDD.

Conclusions: VDD and low DBP in middle childhood are related to behavior problems in adolescence.

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> Biol Trace Elem Res. 2024 Feb 23. doi: 10.1007/s12011-024-04098-4. Online ahead of print.

Association of Magnesium, Iron, Copper, and Zinc Levels with the Prevalence of Behavior Problems in Children and Adolescents

Ying Shen [# 1], Huyi Jin [# 2], Fanjia Guo [2 3], Wanting Zhang [2 4], Hao Fu [2], Mingjuan Jin [5], Guangdi Chen [6]

Affiliations + expand

PMID: 38388752 DOI: 10.1007/s12011-024-04098-4

Abstract

Magnesium (Mg), iron (Fe), copper (Cu), and zinc (Zn) are indispensable elements in children's growth and development. However, epidemiological evidence regarding essential elements and their mixed exposure to behavior problems remains in its infancy. The objective of the present study was to evaluate the association between essential elements and the manifestation of behavior problems, with an additional focus on the implications of their mixture. An electronic medical records review was performed among 4122 subjects aged 6-18 years who underwent examinations at Children's Hospital, Zhejiang University School of Medicine, between January 2019 and July 2022. The concentrations of essential elements were measured by atomic absorption spectrometry, and behavior problems were assessed by using the Conners' Parent Rating Scale (CPRS). A total of 895 (21.7%) children and adolescents were identified as having behavior problems. For single exposure, inversely linear dose-response relationships were identified between continuous Mg and Zn levels and the prevalence of behavior problems, and the prevalence ratios (PRs) in the categorical lowest tertile were 1.28 (95% confidence interval, CI: 1.07-1.54) for Mg and 1.31 (95% CI: 1.05-1.63) for Zn compared to the highest tertile. For mixture exposure, an inverse association between essential elements and behavior problems was also found, mainly contributed by Mg (posterior inclusion probability, PIP = 0.854). Whole blood levels of Mg and Zn were significantly inversely associated with behavior problems. The findings highlight the pivotal role of essential elements in behavior problems and emphasize the importance of maintaining adequate levels of essential elements during children's maturation.

Keywords: BKMR analysis; Behavior problems; Essential element; Magnesium; Zinc.

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Assessing the stability of the parent/caregiver-child bond

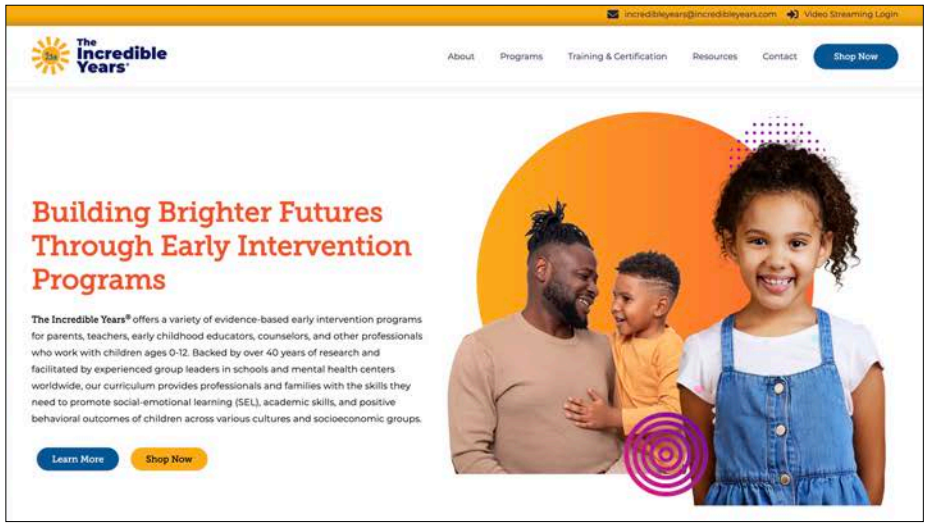
How is the child's behavior affecting the caregiver??

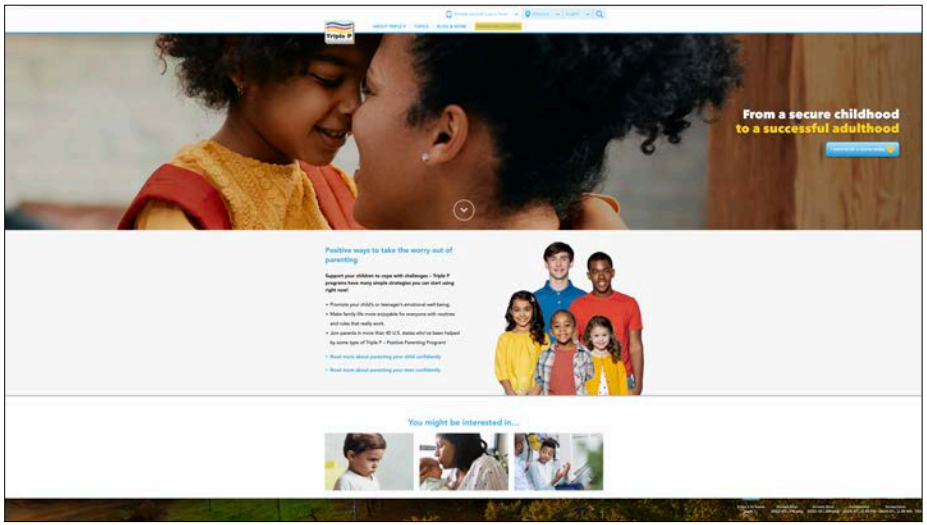
- [See the charting templates for more examples]
- "Can you describe a typical day with your child?"
- "Can you give an example of a recent situation where your child was defiant? How did you handle it?"
- "How do you take care of yourself when dealing with your child's challenging behavior?"
- "Do you have support from family, friends or professionals when dealing with your child's behavior?"

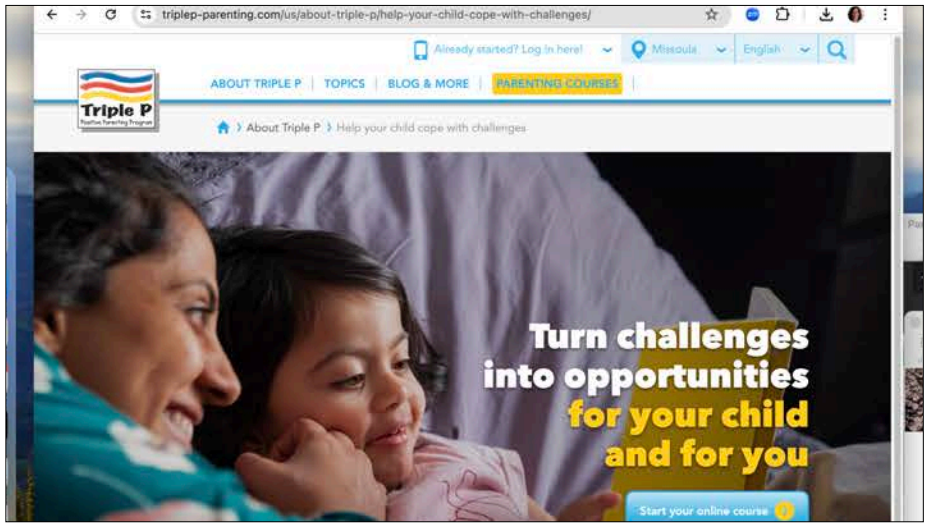
Why is this so important?

Treatment strategies

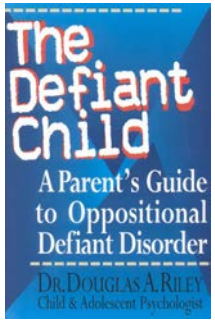
Parenting strategies

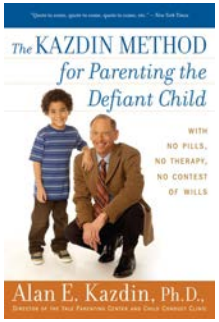


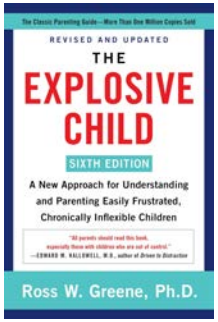




Book recommendations:







Consider TBRI

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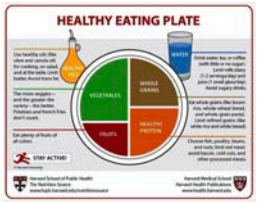
Nutritional strategies

Blood sugar balancing

- This has no scientific evidence supporting its use, it is based on my experience and in general knowledge that hypoglycemic episodes often cause behavior problems in children. (And a general diet like this would be very difficult to study in research.)
- Key points: encourage children to consume **protein, fiber and healthy fats at every meal and snack** in order to prevent blood sugar drops throughout the day.



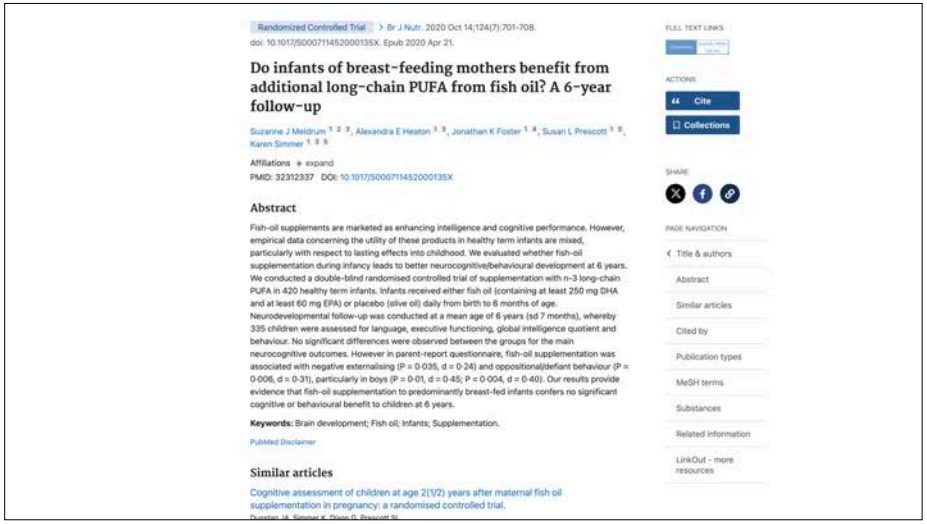
Feingold Diet?

- The Feingold Diet is an elimination diet designed to manage hyperactivity and behavioral issues by removing certain artificial additives and naturally occurring substances. Developed by Dr. Benjamin Feingold in the 1970s, this diet primarily excludes artificial colors, artificial flavors, and certain preservatives such as BHA, BHT, and TBHQ.
- **It has not been studied directly for Oppositional Defiant Disorder but it *has* been studied (with mixed results) in patients with ADHD.** Consider this diet as a trial in children with both ADHD and ODD.
- In my experience only a subset of ADHD children have sensitivities to artificial colors/flavors/preservatives, but in those cases it is dramatic.

Nutritional supplementation

Omega-3 Fatty Acids

- A few studies support the use of Omega-3 Fatty Acids in children with ODD, especially in those who also have ADHD.



Randomized Controlled Trial > Br J Nutr. 2020 Oct 14;124(7):701-708.
doi: 10.1017/S000711452000135X. Epub 2020 Apr 21.

Do infants of breast-feeding mothers benefit from additional long-chain PUFA from fish oil? A 6-year follow-up

Suzanne J Meldrum [1 2 3], Alexandra E Heaton [1 3], Jonathan K Foster [1 4], Susan L Prescott [1 5], Karen Simmer [1 3 6]

Affiliations + expand
PMID: 32312337 DOI: 10.1017/S000711452000135X

Abstract

Fish-oil supplements are marketed as enhancing intelligence and cognitive performance. However, empirical data concerning the utility of these products in healthy term infants are mixed, particularly with respect to lasting effects into childhood. We evaluated whether fish-oil supplementation during infancy leads to better neurocognitive/behavioural development at 6 years. We conducted a double-blind randomised controlled trial of supplementation with n-3 long-chain PUFA in 420 healthy term infants. Infants received either fish oil (containing at least 250 mg DHA and at least 60 mg EPA) or placebo (olive oil) daily from birth to 6 months of age. Neurodevelopmental follow-up was conducted at a mean age of 6 years (sd 7 months), whereby 335 children were assessed for language, executive functioning, global intelligence quotient and behaviour. No significant differences were observed between the groups for the main neurocognitive outcomes. However in parent-report questionnaire, fish-oil supplementation was associated with negative externalising (P = 0·035, d = 0·24) and oppositional/defiant behaviour (P = 0·006, d = 0·31), particularly in boys (P = 0·01, d = 0·45; P = 0·004, d = 0·40). Our results provide evidence that fish-oil supplementation to predominantly breast-fed infants confers no significant cognitive or behavioural benefit to children at 6 years.

Keywords: Brain development; Fish oil; Infants; Supplementation.

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Cognitive assessment of children at age 2(1/2) years after maternal fish oil supplementation in pregnancy: a randomised controlled trial.

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Omega-3 Fatty Acids

- Children with behavioral problems and depression also benefit from a combination of omega-3 fatty acids and counseling combined, with superior effect to counseling alone: Young AS, Arnold LE, Wolfson HL, Fristad MA. Psychoeducational Psychotherapy and Omega-3 Supplementation Improve Co-Occurring Behavioral Problems in Youth with Depression: Results from a Pilot RCT. J Abnorm Child Psychol. 2017 Jul;45(5):1025-1037. doi: 10.1007/s10802-016-0203-3. PMID: 27604240; PMCID: PMC5342950.
- Fatty acids reduce aggression in children: Raine A, Ang RP, Choy O, Hibbeln JR, Ho RM, Lim CG, Lim-Ashworth NSJ, Ling S, Liu JCJ, Ooi YP, Tan YR, Fung DSS. Omega-3 (ω-3) and social skills interventions for reactive aggression and childhood externalizing behavior problems: a randomized, stratified, double-blind, placebo-controlled, factorial trial. Psychol Med. 2019 Jan;49(2):335-344. doi: 10.1017/S0033291718000983. Epub 2018 May 10. PMID: 29743128.
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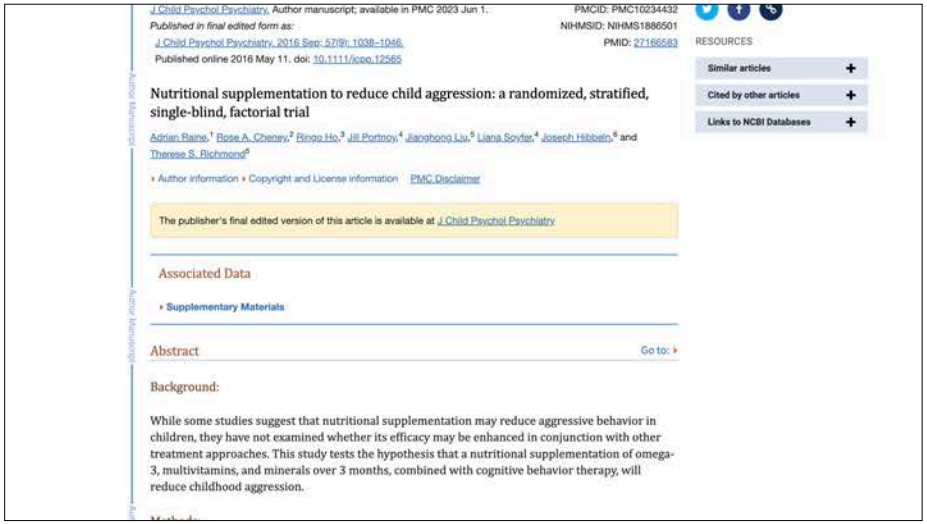

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Published online 2016 May 11. doi: 10.1111/jcpp.12565

PMCID: PMC10234432
NIHMSID: NIHMS1886501
PMID: 27166583

Nutritional supplementation to reduce child aggression: a randomized, stratified, single-blind, factorial trial

Adrian Raine,[1] Rose A. Cheney,[2] Ringo Ho,[3] Jill Portnoy,[4] Jiangbong Liu,[5] Liana Soyfer,[4] Joseph Hibbeln,[6] and Therese S. Richmond[6]

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Background:

While some studies suggest that nutritional supplementation may reduce aggressive behavior in children, they have not examined whether its efficacy may be enhanced in conjunction with other treatment approaches. This study tests the hypothesis that a nutritional supplementation of omega-3, multivitamins, and minerals over 3 months, combined with cognitive behavior therapy, will reduce childhood aggression.

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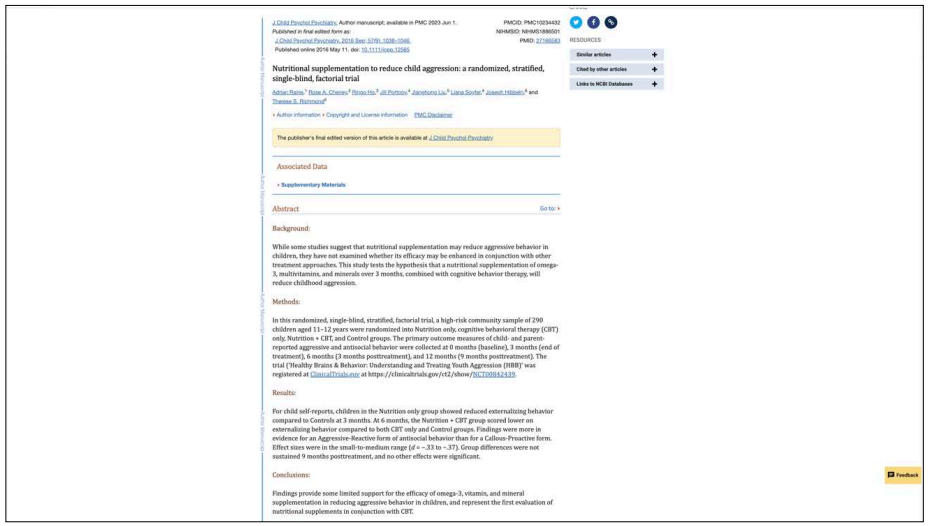

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NIHMSID: NIHMS1986501
PMID: 27180683

Nutritional supplementation to reduce child aggression: a randomized, stratified, single-blind, factorial trial

Adrian Raine,[1] Rose A. Cheney,[2] Ringo Ho,[3] Jill Portnoy,[4] Jianghong Liu,[5] Liana Soyfer,[4] Joseph Hibbeln,[6] and Theresa S. Richmond[4]

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Background:

While some studies suggest that nutritional supplementation may reduce aggressive behavior in children, they have not examined whether its efficacy may be enhanced in conjunction with other treatment approaches. This study tests the hypothesis that a nutritional supplementation of omega-3, multivitamins, and minerals over 3 months, combined with cognitive behavior therapy, will reduce childhood aggression.

Methods:

In this randomized, single-blind, stratified, factorial trial, a high-risk community sample of 290 children aged 11–12 years were randomized into Nutrition only, cognitive behavioral therapy (CBT) only, Nutrition + CBT, and Control groups. The primary outcome measures of child- and parent-reported aggressive and antisocial behavior were collected at 0 months (baseline), 3 months (end of treatment), 6 months (3 months posttreatment), and 12 months (9 months posttreatment). The trial ("Healthy Brains & Behavior: Understanding and Treating Youth Aggression (HBB)") was registered at ClinicalTrials.gov at https://clinicaltrials.gov/ct2/show/NCT00842439.

Results:

For child self-reports, children in the Nutrition only group showed reduced externalizing behavior compared to Controls at 3 months. At 6 months, the Nutrition + CBT group scored lower on externalizing behavior compared to both CBT only and Control groups. Findings were more in evidence for an Aggressive-Reactive form of antisocial behavior than for a Callous-Proactive form. Effect sizes were in the small-to-medium range (d = –.33 to –.37). Group differences were not sustained 9 months posttreatment, and no other effects were significant.

Conclusions:

Findings provide some limited support for the efficacy of omega-3, vitamin, and mineral supplementation in reducing aggressive behavior in children, and represent the first evaluation of nutritional supplements in conjunction with CBT.

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Feedback

Combined omega-3 + Multivitamin/mineral

- 16-week open-label trial with micronutrient mix containing alpha-tocopherol, ascorbic acid, biotin, chromium, P5P, selenium and zinc (note that it did NOT include folate or B12!) - significant improvement in aggressive and violent behaviors, family function and higher quality of life. Hambly JL, Francis K, Khan S, Gibbons KS, Walsh WJ, Lambert B, Testa C, Haywood A. Micronutrient Therapy for Violent and Aggressive Male Youth: An Open-Label Trial. J Child Adolesc Psychopharmacol. 2017 Nov;27(9):823-832. doi: 10.1089/cap.2016.0199. Epub 2017 May 8. PMID: 28481642.

Received: 15 May 2017 | Revised: 13 April 2018 | Accepted: 15 April 2018
DOI: 10.1002/ab.21769

RESEARCH ARTICLE

WILEY AGGRESSIVE BEHAVIOR

Reductions of intimate partner violence resulting from supplementing children with omega-3 fatty acids: A randomized, double-blind, placebo-controlled, stratified, parallel-group trial

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Funding information
Smartfish AA, Oslo, Norway; National Institute on Alcohol Abuse and Alcoholism: Intramural Research Program; University of Pennsylvania

Omega-3 supplementation has been found to reduce externalizing behavior in children. Reciprocal models of parent-child behavior suggest that improving child behavior could lead to improvements in parent behavior, however no study has examined whether omega-3 supplementation in children could reduce intimate partner violence or child maltreatment by their adult caregivers. In this randomized, double-blind, placebo-controlled, stratified, parallel group trial, a community sample of children were randomized to receive either a fruit drink containing 1 gm of omega-3 fats (Smartfish Recharge; Omega-3 group, n = 100) or the same fruit drink without omega-3's (Placebo group, n = 100). Child participants, adult caregivers, and research staff were blinded to group assignment. Adult caregivers reported inter-partner and child-directed physical assault and psychological aggression at baseline, 6 months (end of treatment) and 12 months (6 months post-treatment) using the Conflicts Tactics Scale. Caregivers of children in the omega-3 group reported long-term reductions in psychological aggression in a group × time interaction. Improvements in adult psychological aggression were correlated with improvements in child externalizing behavior scores. No differences were reported for child maltreatment. This study is the

Other considerations

- Most important is to replete deficiencies that were discovered with laboratory testing. Vitamin D, Zinc, Iron, etc.
- Strongly consider supplemental zinc, as there are multiple research studies showing positive results for children with multiple mental health disorders (BUT, no positive studies on Oppositional Defiant Disorder). The one study on ODD and 10 mg zinc supplementation showed no improvement in reducing aggressive behaviors in children, *however*, authors noted that dietary changes were occurring in the school at the same time as the trial, which affected the placebo group as well.

MAOA treatment plan

Addressing MAOA-uVNTR

- **Teaching parents about MAOA: from my MAOA - The "Warrior Gene" handout**
  - MAOA genetic mutations have been associated with various behavioral problems. The MAOA gene is often called the "warrior" gene. Here is a quick summary of what happens: the process of methylation (and many other steps) "turns on" stimulating neurotransmitters (brain chemicals) in the brain. These include neurotransmitters like dopamine, norepinephrine and serotonin. MAOA and COMT enzymes are responsible for breaking them down. When patients have genetic defects in the MAOA or COMT genes **they have difficulty breaking down these stimulating brain chemicals.** This leads to an excess of these brain chemicals. This creates something similar to a constant "adrenaline rush" that a patient cannot come down from.

…more from my MAOA handout

- **Remember that humans are not simply a product of genes or environment. We are complex! Social, environmental, emotional, genetic and many, many factors influence who we are as human beings. In other words, MAOA patients are not "doomed" to anything!**
- **High intensity exercise** can help "burn off" adrenaline.
- Check iron status, as iron deficiency worsens MAOA function.
- Some, but not all MAOA patients tend to thrive in highly stressful situations. MAOA is increased in times of stress, so some patients notice a sudden "clear head" in times of acute stress. This is why many MAOA patients have joined the military or participate in athletics.

…more from my MAOA handout

- **I highly encourage patients to find an appropriate athletic outlet.** Focused individual sports are often good for MAOA patients, like Karate, Tai Kwon Do, Jiu Jitsu or other martial arts, running, swimming, biking, skiing, etc. Many do not do well in cooperative sports.
- Support sleep! Sleep can be a huge problem for MAOA patients, because they have a very hard time "winding down." Again, high intensity exercise is key. Some, but not all, patients **worsen with melatonin** supplementation, as there is an upstream link between serotonin and melatonin. Children who get vivid dreams or nightmares with melatonin supplementation should lower their dosage or stop.
  - Consider milder herbs like passionflower, lavender or lemon balm. Passionflower acts on GABA receptors, but be aware that it can actually slow MAOA activity in high doses.

…more from my MAOA handout

- **Stomachaches are common.** Too many "sympathetic" neurotransmitters means the body has a hard time relaxing. This "rest and digest" nervous system response is called the Parasympathetic nervous system. The body **must** be able to rest and have good parasympathetic tone in order to digest food properly. Many children and adults with MAOA end up with digestive imbalances and food intolerances.
  - See dietary recommendations. Consider a short-term elimination diet, blood sugar-balancing diet, or Feingold-type diet.

…more from my MAOA handout

- **Medications:**
  - Most, but not all, **worsen on SSRI's** like Prozac or Zoloft, as they increase serotonin. Rarely a patient will actually improve. (Better results with escitalopram or fluvoxamine, NOT fluoxetine.)
  - Most, but not all patients worsen on stimulant medications (Adderall, Ritalin, etc).
  - Many patients have paradoxical reactions to medications. Be VERY cautious when using new meds!
  - Mood stabilizers may be better tolerated than antipsychotic medications

…more from my MAOA handout

- **Medications (continued)…**
  - **MAOI medications** are strongly contraindicated.
  - Many MAOA patients are worse with caffeine.
  - Quetiapine (Seroquel) tends to be well-tolerated (but is very sedating and can have side effects like weight gain). Quetiapine is an antagonist of serotonin, dopamine, histamine and adrenergic alpha a1 and a2 receptors. This is a VERY strong medication, and extremely difficult to wean off of.
  - **MAOA patients should avoid over-medicating with methylfolate (5-MTHF)**, as this will "turn on" more neurotransmitters and exacerbate the problem.

…more from my MAOA handout

- **Supplements:**
  - **Riboflavin** (vitamin B2). MAOA is FAD-dependent. (FAD = flavin adenine dinucleotide, which is the active form of riboflavin.) We can speed up the enzyme by giving more cofactor, which is B2. **Note that riboflavin will turn their urine bright yellow, which is harmless.** Dose:
    - Riboflavin has been studied for migraine prophylaxis in children and has proven safety. Recommend doses between 50-200 mg twice daily.
    - Riboflavin-5-Phosphate (active form B2) = 70-75 mg twice daily is the correct dose for ~150 lb adult. Adjust dose based on weight. (E.g., 75 lb child would take 37.5 mg twice daily.)

…more from my MAOA handout

- **Supplements:**
  - **Magnesium:** Magnesium plays a critical role in brain health and in mood regulation. It is essential for the formation of many neurotransmitters and to make membrane phospholipids. **Magnesium threonate has the best brain effect**, but it can be more expensive and is more difficult to find in a form that children will take. **Magnesium glycinate** is the next most effective form, but again can be difficult to find in a form that children will take. **Magnesium citrate** is the least effective form that I recommend, and is easily available.
    - Magnesium is often dosed "to bowel tolerance" (for magnesium citrate).
    - Otherwise dose at 100-400 mg/day of supplemental magnesium, **in addition to food sources.**

…more from my MAOA handout

- **Other supplements:**
  - **Omega-3 Fatty Acids**, recommended dose is over 1 gram of combined EPA/DHA, preferred over 3 grams of combined EPA/DHA.
  - **Iron,** if the child has iron deficiency. I prefer iron bisglycinate, as it is easier absorbed than ferrous sulfate, with less risk of constipation.
  - **Zinc** - Zinc is involved in the synthesis and regulation of multiple neurotransmitters. I typically recommend 10 mg in lozenge form, which also helps prevent URI's in cold/flu season. Take WITH food to avoid nausea.

Pathological Demand Avoidance Treatment Plan

…from my "understanding PDA" handout

- Pathological Demand Avoidance (PDA) is a profile on the autism spectrum that is characterized by an extreme resistance to everyday demands and expectations. Unlike other forms of autism, where repetitive behaviors and communication difficulties are more prominent, **PDA is distinguished by a pervasive and often intense avoidance of demands, rooted in high anxiety and a need to control…**
- Children with PDA often appear sociable and can engage in sophisticated social interactions, which may mask their underlying difficulties. However, this apparent sociability can be misleading as these children may still struggle with genuine social understanding and interaction. **Their need for control is driven by an overwhelming sense of anxiety that can be triggered by seemingly simple requests or routine tasks.** This anxiety can cause them to experience severe stress, leading to a range of behaviors aimed at avoiding demands, which can sometimes be misinterpreted as defiance or oppositional behavior.

Why do simple demands cause severe anxiety?

- For a child with Pathological Demand Avoidance (PDA), even the simplest demands can trigger severe anxiety due to a combination of factors. **A primary reason is the loss of control;** simple requests can make the child feel as if they are losing autonomy, which heightens their anxiety. This sense of being out of control can lead to panic and a strong desire to avoid the demand. Additionally, children with PDA often have a deep-seated fear of failure. They worry that they cannot meet the expectations placed on them, which can cause them to panic and resist even more. **It is critical to understand that even simple, small requests cause a full-blown panic attack.**

Parenting strategies for children with PDA:

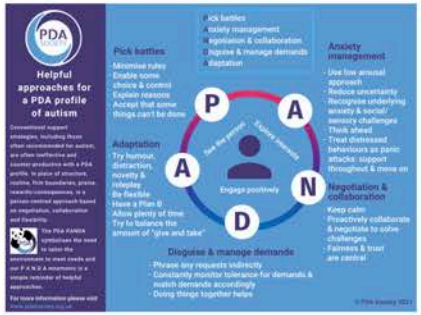
- Pick Your Battles: Focus on essential demands and let go of less critical ones. Prioritize what truly matters and be prepared to compromise on less important issues.
- Use Indirect Language: Frame requests in a way that doesn't feel like direct commands. For example, instead of saying "Put your shoes on," you might say, "The shoes are on the mat for you, I'm happy to help if you need it" Using language like "I wonder whether…," "Let's see if…," or "That's not possible right now" (for denying requests).
- Offer Choices: Providing options can give your child a sense of control. Simple choices, like selecting between two activities or choosing their clothes, can make a big difference.

Parenting strategies for children with PDA:

- Build Trust: Establish a trusting relationship by showing understanding and empathy. Recognize and validate your child's feelings and experiences.
- Be Flexible: Be ready to adapt plans and routines based on your child's current capacity for demands. Flexibility helps in reducing pressure and anxiety.
- Use Humor and Distraction: Lighten the mood with jokes or divert attention to ease the situation. Making tasks fun can often help in getting them done. Turning tasks into a game is a strategy that works for many children.

Parenting strategies for children with PDA:

- Collaborate and Negotiate: Work together with your child to find mutually acceptable solutions. Engage them in problem-solving and make them feel involved in decision-making.
- Recognize and Reduce Anxiety: Be aware of triggers and try to minimize them. Create a calm and predictable environment to help your child feel more secure.
- Plan Ahead: Anticipate potential challenges and prepare strategies in advance. Having a plan B can help manage unexpected difficulties and reduce stress.



Pharmaceutical interventions

Simulants

- Methylphenidate, e.g.,
  - Studies clearly show that treating ADHD also improved Oppositional Defiant Disorder symptoms. Theory is that amphetamine-based options work by increasing dopamine and norepinephrine levels in the brain, which improves attention, focus and self-control.
  - Remember that the use of stimulants is often accompanied by side effects like appetite suppression, insomnia, stomachaches, and headaches, and some children may experience increased irritability or anxiety. Regular monitoring and adjustments by a healthcare provider are essential to manage these side effects and ensure the medication's effectiveness.

Randomized Controlled Trial > Clin Ther. 2006 Mar;28(3):402-18.
doi: 10.1016/j.clinthera.2006.03.006

Efficacy and safety of mixed amphetamine salts extended release (adderall XR) in the management of oppositional defiant disorder with or without comorbid attention-deficit/hyperactivity disorder in school-aged children and adolescents: A 4-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, forced-dose-escalation study

Thomas J Spencer [1], Howard B Abikoff, Daniel F Connor, Joseph Biederman, Steven R Pliszka, Samuel Boellner, Stephanie C Read, Raymond Pratt

Affiliations + expand
PMID: 16750455 DOI: 10.1016/j.clinthera.2006.03.006

Abstract

Background: Oppositional defiant disorder (ODD)is associated with a high degree of impairment in social skills, family interaction, and academic functioning. Comorbid ODD is reportedly present in 40% to 70% of children and adolescents with attention-deficit/hyperactivity disorder (ADHD).

Objective: The goal of this study was to assess the efficacy and safety of mixed amphetamine salts extended release (MAS XR) for the treatment of ODD in children and adolescents aged 6 to 17 years.

Methods: This was a 4-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, forced-dose-escalation study. Patients were randomized to receive active treatment with MAS XR 10, 20, 30, or 40 mg/d or placebo. The primary efficacy end point was the ODD subscale of the Swanson, Nolan, and Pelham-IV (SNAP-IV) parent rating. Primary safety measures included adverse events recorded at each visit and for 30 days after study drug discontinuation, and changes in vital signs, 12-lead electrocardiographic (ECG) findings, laboratory tests and physical examinations, and body weight. A post hoc efficacy reanalysis was completed based on the results for the per-protocol population. For this analysis, patients were divided into high and low baseline severity categories according to the dichotomized baseline ODD parent or teacher score or dichotomized baseline ADHD parent or teacher score (high defined as scores at the median or

Clinical Trial. J Am Acad Child Adolesc Psychiatry. 2003 Aug;42(8):886-94.
doi: 10.1097/01.CHI.0000046908.27264.00.

A randomized controlled trial of clonidine added to psychostimulant medication for hyperactive and aggressive children

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Abstract

Objective: To compare clonidine with placebo added to ongoing psychostimulant therapy for the treatment of attention-deficit/hyperactivity disorder with comorbid oppositional defiant disorder or conduct disorder.

Method: Children 6 to 14 years of age recruited through 2000 to 2001 were randomized to receive clonidine syrup 0.10 to 0.20 mg/day (n = 38) or placebo (n = 29) for 6 weeks. Primary outcome measures were the Conduct and Hyperactive Index subscales of the parent-report Conners Behavior Checklist. Side effects were monitored using physiological measures and the Barkley Side Effect Rating Scale.

Results: Evaluable patient analysis showed that significantly more clonidine-treated children than controls were responders on the Conduct scale (21 of 37 versus 6 of 29; chi2(1) = 8.75, p <.01) but not the Hyperactive Index (13 of 37 versus 5 of 29). Compared with placebo, clonidine was associated with a greater reduction in systolic blood pressure measured standing and with transient sedation and dizziness. Clonidine-treated individuals had a greater reduction in a number of unwanted effects associated with psychostimulant treatment compared with placebo.

Conclusions: The findings support the continued use of clonidine in combination with psychostimulant medication to reduce conduct symptoms associated with attention-deficit/hyperactivity disorder. Treatment is well tolerated and unwanted effects are transient.

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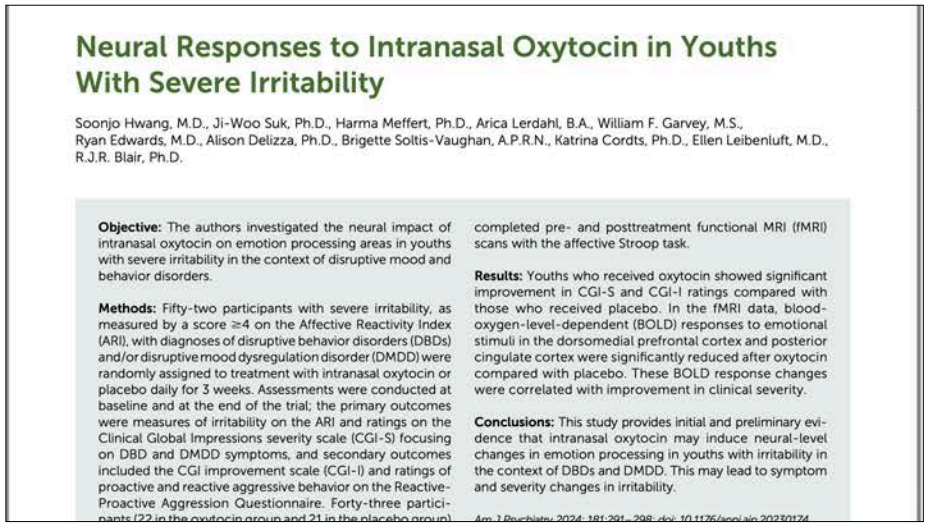
Intranasal oxytocin

- Intranasal oxytocin has been suggested as a potential treatment for Oppositional Defiant Disorder (ODD) due to its role in enhancing social bonding and emotional regulation.
- A new study indicates that administering oxytocin intranasally can lead to significant improvements in behaviors associated with ODD, such as reducing aggression and increasing prosocial behaviors. This treatment may help children with ODD form better connections with others, increasing empathy and reducing oppositional behaviors. The study suggests that oxytocin's ability to enhance emotional and social processing could be particularly beneficial in mitigating the challenging behaviors seen in ODD.
- Treatment was with intranasal oxytocin (24 IU daily, or 12 IU daily if the weight is < 40kg).



Neural Responses to Intranasal Oxytocin in Youths With Severe Irritability

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Objective: The authors investigated the neural impact of intranasal oxytocin on emotion processing areas in youths with severe irritability in the context of disruptive mood and behavior disorders.

Methods: Fifty-two participants with severe irritability, as measured by a score ≥4 on the Affective Reactivity Index (ARI), with diagnoses of disruptive behavior disorders (DBDs) and/or disruptive mood dysregulation disorder (DMDD) were randomly assigned to treatment with intranasal oxytocin or placebo daily for 3 weeks. Assessments were conducted at baseline and at the end of the trial; the primary outcomes were measures of irritability on the ARI and ratings on the Clinical Global Impressions severity scale (CGI-S) focusing on DBD and DMDD symptoms, and secondary outcomes included the CGI improvement scale (CGI-I) and ratings of proactive and reactive aggressive behavior on the Reactive-Proactive Aggression Questionnaire. Forty-three participants (22 in the oxytocin group and 21 in the placebo group) completed pre- and posttreatment functional MRI (fMRI) scans with the affective Stroop task.

Results: Youths who received oxytocin showed significant improvement in CGI-S and CGI-I ratings compared with those who received placebo. In the fMRI data, blood-oxygen-level-dependent (BOLD) responses to emotional stimuli in the dorsomedial prefrontal cortex and posterior cingulate cortex were significantly reduced after oxytocin compared with placebo. These BOLD response changes were correlated with improvement in clinical severity.

Conclusions: This study provides initial and preliminary evidence that intranasal oxytocin may induce neural-level changes in emotion processing in youths with irritability in the context of DBDs and DMDD. This may lead to symptom and severity changes in irritability.

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Other thoughts:

Other considerations

- Neurofeedback
  - Studies suggest that children with ODD often exhibit dysregulated brainwave patterns similar to those seen in ADHD, with an excess of low-frequency brainwaves. Neurofeedback aims to reduce these low-frequency waves and increase mid-range waves, promoting more balanced brain activity.
  - Works really well in patients with ADHD. (I have not tried for ODD alone.)

Herbal Medicine / Supplements

- I would consider the following supplements and/or treatment considerations in children with ODD:
  - L-Theanine, especially if presenting symptom is anxiety
  - St. John's Wort, especially if presenting symptom is depression
  - Resveratrol, to decrease neurological inflammation. Resveratrol has been shown to decrease the need for stimulant medications.
  - NAC, especially if symptoms of OCD are present
  - Saffron, especially if presenting with combined depression and anxiety, with cognitive deficits/ brain fog.

Cases

7 y/o male with ODD

- Behaviors: refusal to go to school, refusal to get out of bed, saying "You're not in control of my body, you're not in control of me!" Progresses to kicking, hitting, punching, spitting, forcing himself out of his room. Has kicked the dog, encouraged brother to kick, hit or spit on Mom. When it is over he feels bad and feels remorse.
- Worse in transitions, e.g., going skiing, sledding, going to school. Gets overwhelmed by getting his stuff on and getting going.
- Associated fatigue. Difficulty going to bed, some insomnia.
- No major changes in the last 4 months, but Dad had spanked him several times while very upset.

7 y/o male with ODD

- Treatment:
  - Mom had already asked Dad to stop spanking. Mom started to use language like “What sort of weather are you experiencing in your body?” His answer: “A volcano.”
  - I diagnosed him with anxiety.

7 y/o male with ODD

- “It absolutely sounds like he is experiencing anxiety. To me it sounds similar to a condition called Pathological Demand Avoidance (PDA), which is a subset of autism. I don't see any other signs of autism per-se, but he definitely fits the rest of the criteria. PDA is characterized by overwhelming anxiety when asked to do simple tasks (like getting his clothes on, etc). Because he has no other autism-like traits I will diagnose him with Anxiety. However, I would like you guys to read about Pathological Demand Avoidance because many of the strategies will be extremely helpful for you. Be aware that during his outbursts he is really experiencing the physical manifestations of a full-blown panic attack. His body is perceiving even simple demands the same as he would a bear attack. For example, he is either shutting down (freeze), or hitting (fight).”

7 y/o male with ODD

- Recommended my favorite anxiety book for kids: “Anxiety Relief for Kids: On-the-Spot Strategies to Help your Child Overcome Worry, Panic and Avoidance.
- Recommended some articles on Pathological Demand Avoidance, so Mom and Dad could reduce the demands on this kiddo.
- Nutritional supplementation:
  - L-Theanine + GABA
  - Multivitamin
  - CALM Magnesium
  - Consider low dose melatonin

7 y/o male with ODD

- Recommended bloodwork - CBC, TSH, CMP, ferritin, Vitamin D, B12, folate, lead, etc.
- Mom ended up not getting bloodwork done, at next well child check he was significantly improved with just behavioral modifications in the home. No other interventions needed.

13 y/o male with ADHD and ODD

- In and out of public school with concerns of behavior, impulsivity, ODD. Psychiatrist the prior year diagnosed him with ADHD.
- Symptoms: severe anxiety, impulsivity, difficulty staying on task, time-blindness, defiant behaviors, difficulty regulating emotions. Socially he can get easily excitable, high-energy, sometimes impulsive, sometimes does/says things outside of normal. Sometimes misses social cues.
- History of sexual abuse by a fellow student age 6.
- History of low weight, stomach issues like diarrhea.
- Family history significant for anxiety, depression, ADHD

13 y/o male with ADHD and ODD

- Had tried previous to our visit:
  - Concerta: side effects like stomachaches, difficulty sleeping, headaches, joint pains. Helped focus for a time, then effects wore off. Increased dose which worked for a while, then again wore off.
  - Vyvanse: helped, but had significant loss of appetite, difficulty sleeping.
  - Guanfacine: severe anxiety
  - L-Theanine, L-Tyrosine, Methylfolate, MethylB12.
  - GF diet.

13 y/o male with ADHD and ODD

- Treatment:
  - Discussed PDA briefly so Mom would be aware of demand triggers
  - Labwork: Thyroid, CBC, CMP, ferritin, vitamin D, B12, folate, lead, lipids, HbA1c, celiac
  - Organic Acid Testing ordered
  - Continue L-Theanine
  - Recommended pause on methylB's before we find out about the rest of his SNPs
  - Omega 3's

13 y/o male with ADHD and ODD

- Treatment:
  - "Happy Brain Diet" - Feingold-type diet, focusing on balancing blood sugar. Eliminate colorings and additives for 30 days, optional GF/DF diet as well.

13 y/o male with ADHD and ODD

- 1st follow-up:
  - Labs showed low ferritin, low cholesterol (remember low cholesterol is associated with anxiety), low vitamin D, negative celiac, negative lead, normal HbA1c
  - Organic Acid Test showed VMA borderline high, 5-HIAA high, pyroglutamate high.
  - Recommended: Iron bisglycinate, eggs, grass-fed fatty meats, colorful fruits and veggies, a multivitamin, vitamin D, continued fish oil, continued L-Theanine.
  - HIGH intensity physical exercise. (To reduce catecholamines)
  - Discussed potential doing targeted therapies based on OAT, but I wanted to clear nutritional deficiencies first.

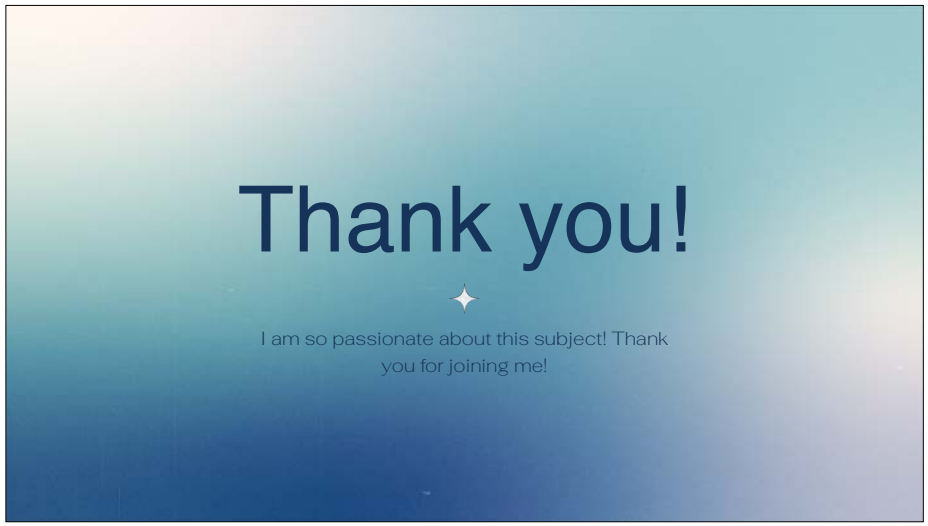
13 y/o male with ADHD and ODD

- In between visits Mom requested functional stool test (stool culture, O&P, pancreatic function markers, fecal calprotectin, IgA, Eosinophilic protein X), discussed doing SNP testing.
- 3rd visit: Symptoms were getting better, more mature, not arguing as much.
  - Reviewed the stool testing, showing impaired exocrine pancreatic function, low lactobacillus levels. Recommended digestive enzymes, lactobacillus probiotic.
  - VERY brief review of SNP testing, showing MAOA SNP's (did not test uVTNR, which does not come in the commercially available test). Recommended Riboflavin 5' Phosphate 2 capsules per day.

13 y/o male with ADHD and ODD

- 4th visit: (Now age 14)
  - Is consistently taking his supplements. Improved symptoms since initiation of treatment, and Mom notes that it also coincides with pubertal changes.
  - Mom is conscious to lower expectations and reduce frustration at home.
  - Reviewed SNP report - showed he is heterozygous COMT, homozygous MAOA (does NOT show uVTNR gene, though). Discussed how it will be very hard for him to come down from anxious events. Recommended other solo sports, running, etc. ALL MAOA patients need high intensity exercise. Discussed dopamine genes, DBH and DRD (probably related to Dad's ADHD), discussed strategies for increasing dopamine in the brain.
  - Continue the supplements, exercise, consistent protein intake.

Q&A time!


Thank you!
I am so passionate about this subject! Thank you for joining me!