METHYLCOBALAMIN

Pharmacy Compounding Advisory Committee Meeting
June 9, 2021

A.J. Day, PharmD
Vice President of Clinical Services
PCCA

PRESENTATION ON BEHALF OF

NATIONAL COMMUNITY PHARMACISTS ASSOCIATION

ALLIANCE FOR PHARMACY COMPOUNDING

Source: FDA Briefing Document; Pharmacy Compounding Advisory Committee (PCAC) Meeting; June 9, 2021, Tab 2c page 46

Methylcobalamin is a vitamer of vitamin B_{12} and based upon the use of other cobalamins would be expected to be effective in treating vitamin B_{12} deficiency. However, it is not clear that treatment of vitamin B_{12} deficiency is currently the primary use of compounded methylcobalamin in the U.S. or that methylcobalamin provides a unique benefit over other

46

vitamers of vitamin B_{12} that are available in FDA approved drug products. It appears that the primary use of compounded methylcobalamin is to treat patients with conditions, in some cases serious, for which there is little evidence to support the effectiveness. We do not have information on the range of doses or the frequency of administration and cannot make a judgement on the safety of the current use of injectable products in patients.

Use of cyanocobalamin or hydroxocobalamin in ASD

- There are no clinical trials to assess the safety or efficacy of either cyanocobalamin or hydroxocobalamin for patients with Autism Spectrum Disorders (ASD)

- Clinicians would be starting from scratch
- No dosing information
- No safety data for this population
- No anecdotal data

Pharmacokinetics

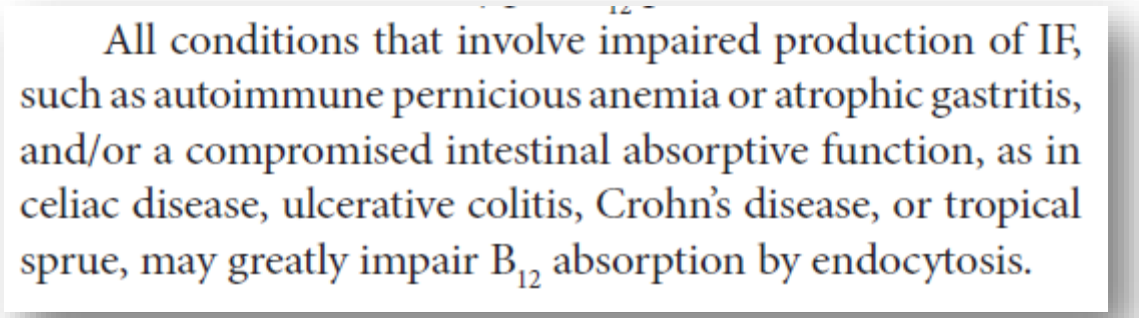
- FDA notes that exogenously administered methylcobalamin is not biologically active (Figure 4)
  - Absorption requires functional Intrinsic Factor
  - Transport to cells requires binding to specific transport proteins
  - Intracellular reduction of methylcobalamin to inactive cobalamin and methyl ligand

- This typical absorption pathway relies on fully functional gastrointestinal lining, transport proteins, and Intrinsic Factor

Pharmacokinetics

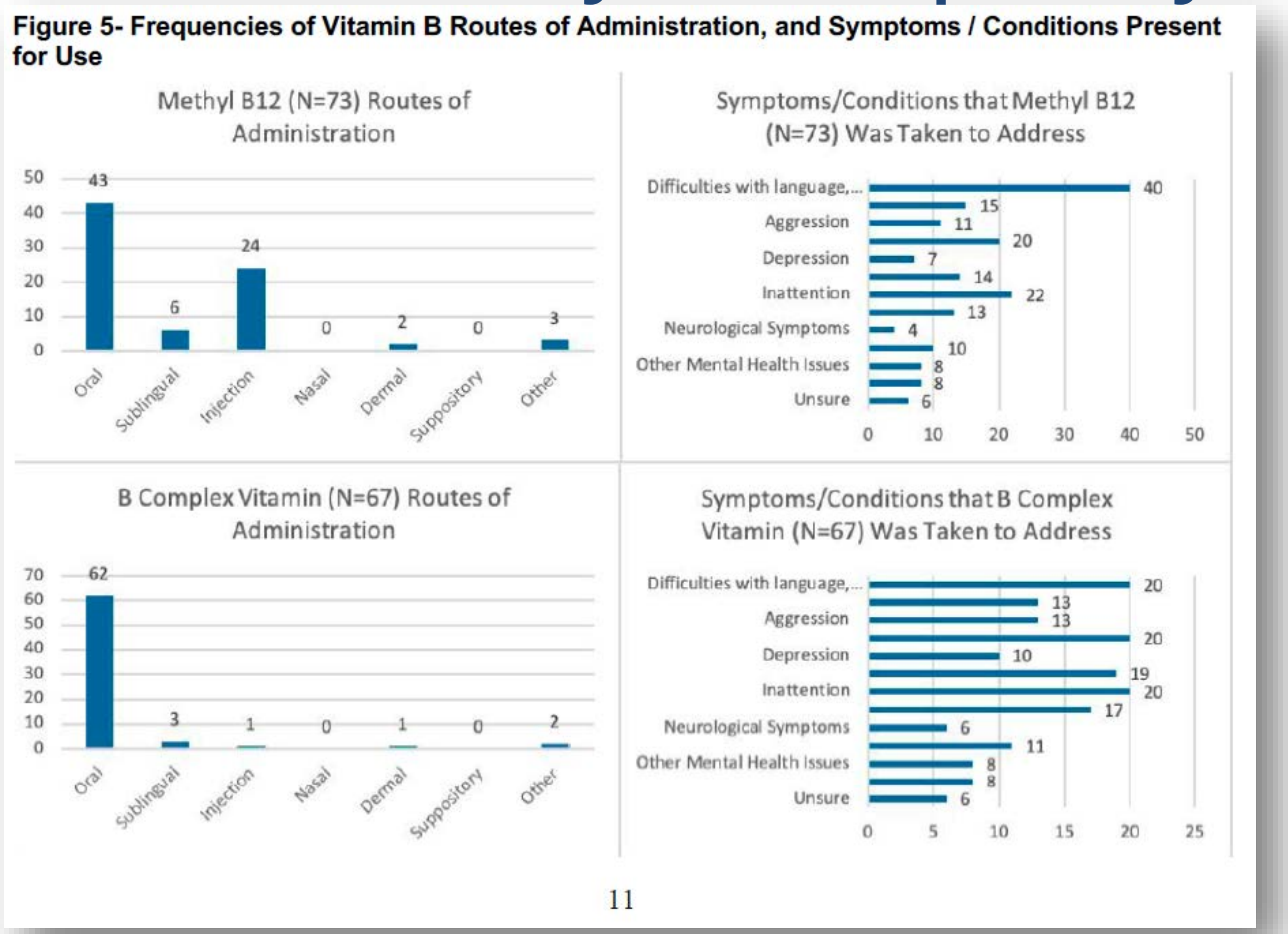
- A hallmark feature for many patients with ASD is compromised gut/intestinal health, sensitivity to proteins and foods, therefore oral absorption of cobalamins may not be the same in ASD patients
- Data assessed by Paul and Brady 2017, and their references, does not explore altered gastrointestinal health or function in patients with ASD

- Paul and Brady 2017, page 44



All conditions that involve impaired production of IF, such as autoimmune pernicious anemia or atrophic gastritis, and/or a compromised intestinal absorptive function, as in celiac disease, ulcerative colitis, Crohn's disease, or tropical sprue, may greatly impair B_{12} absorption by endocytosis.

Johns Hopkins University – Frequency of Use



https://www.jhsph.edu/research/centers-and-institutes/center-of-excellence-in-regulatory-science-and-innovation/research/JHU_CERSI_%20BulkSubstancesASD_FinalReport_20Nov20docx.pdf

Safety Assessment

- Reviews by FDA and Johns Hopkins University researchers did not identify significant safety concerns
- There are many trials which report safety measures and the safety profile is consistent

Among the United States (U.S.) reports, there were no deaths reported and no events considered by OSE to be probably or certainly related to methylcobalamin. There were four reports that

Source: FDA Briefing Document; Pharmacy Compounding Advisory Committee (PCAC) Meeting; June 9, 2021, Tab 2c page 14

No published clinical trials were found that were conducted to specifically assess the safety of methylcobalamin in humans. In some studies investigating the use of oral, intramuscular, intrathecal and intravenous methylcobalamin at different doses as a treatment for various disorders, safety data is reported. Adverse events reported with methylcobalamin use are infrequent and non-serious. Adverse events in studies that reported safety outcomes are summarized below.

Source: FDA Briefing Document; Pharmacy Compounding Advisory Committee (PCAC) Meeting; June 9, 2021, Tab 2c page 16

Safety Assessment

- Package Insert - Japan

Eisai Co., Ltd. 1

Revised: April 2005 (4th version, Revisions associated with the amendment of the Pharmaceutical Affairs Law)

Standard Commodity Classification No. of Japan
873136

- Drug for peripheral neuropathies -

Methycobal® injection 500 μg

<Mecobalamin preparation>

Prescription drug

Storage
METHYCOBAL should be stored in LPE pack (Light Protect Easy open pack) at room temperature. (If ampules are not kept in the LPE pack, mecobalamin decomposes by light and decreases the content).

Expiration date
METHYCOBAL should be used before the expiration date indicated on the package or label.

Approval No.	57AM-1221
Date of listing in the NHI reimbursement price	Jun 1984
Date of initial marketing in Japan	Jun 1984
Date of latest reexamination	Mar 1998
Date of latest approval of indications	Jul 1983

Caution: See "PRECAUTION FOR HANDLING" section.
Caution : Use only as directed by a physician.

DESCRIPTION

METHYCOBAL is a clear, red injection containing the following ingredients, and contained in brown ample (one-point-cut type).

Ingredients		Content per ampule (1 mL)
Active ingredient	Mecobalamin	500 μg
Inactive ingredient	D-Mannitol	50 mg
Product description		Methycobal is a clear, red liquid
pH		5.3 - 7.3
Osmotic pressure ratio		about 1 (ratio relative to isotonic sodium chloride solution)

INDICATIONS

Peripheral neuropathies

(1) **Clinically significant adverse reactions** (incidence unknown)

Anaphylactoid reaction

Anaphylactoid reaction such as decrease in blood pressure or dyspnea, may occur. Patients should be carefully observed. In the event of such symptoms, treatment should be discontinued immediately and appropriate measures taken.

(2) **Other adverse reactions**

	<0.1%	Incidence unknown
Hypersensitivity [note]	Rash	
Others	Headache and hot sensation	Diaphoresis and pain/induration at the site of intramuscular injection

- Package Insert - Australia

Australian Product Information
Biological Therapies Methylcobalamin 10 mg in 2 mL Injection
(Mecobalamin (co-methylcobalamin))

AUST R: 22435

1. Name of the Medicine

Mecobalamin (co-methylcobalamin)

2. Qualitative and Quantitative Composition

Each vial contains a minimum of 2 mL of solution and has mecobalamin (co-methylcobalamin) 10 mg as an active ingredient.

3. Pharmaceutical Form

Biological Therapies Methylcobalamin 10 mg in 2 mL Injection is a clear bright red coloured solution for injection supplied in amber glass vials. The pH of the solution is 6.0-8.0.

For the full list of excipients, see Section 6.1 List of Excipients.

4. Clinical Particulars

4.1 Therapeutic Indications

Cobalamin deficiency may exist that is unable to be corrected by oral intake and in these cases parenteral administration may be preferable. Oral administration of vitamin B_{12} may be insufficient in pernicious anaemia, malabsorption disorders, gastrectomy and gastrointestinal pathologies.

Safety Assessment

- Package Insert - Japan

PRECAUTIONS

1. Adverse Reactions

Adverse reactions were reported in 13 of 2,872 patients (0.45 %). (At the end of the reexamination period)

(1) Clinically significant adverse reactions (incidence unknown)

Anaphylactoid reaction

Anaphylactoid reaction such as decrease in blood pressure or dyspnea, may occur. Patients should be carefully observed. In the event of such symptoms, treatment should be discontinued immediately and appropriate measures taken.

(2) Other adverse reactions

	<0.1%	**Incidence unknown**
Hypersensitivity note)	Rash	
Others	Headache and hot sensation	Diaphoresis and pain/induration at the site of intramuscular injection

Note: In the event of such symptoms, treatment should be discontinued.

Safety Assessment

Australian Government
Department of Health
Therapeutic Goods Administration

Database of Adverse Event Notifications - medicines

Medicine summary

You searched for the following **3 medicines** between **01/01/1991 – 01/03/2021**:

- Blackmores B12 Rapi-Melt 1000mcg AUST L 269572 (mecobalamin (co-methylcobalamin))
- Herbs of Gold Activated Sublingual B12 - AUST L 266757 (mecobalamin (co-methylcobalamin))
- Methyl B12 Chewable - AUSTL 260090 (mecobalamin (co-methylcobalamin))

Database of Adverse Event Notifications - medicines — Medicine summary

Results

Number of reports (cases): 4

(Multiple adverse events have been reported for some patients)

Number of cases with a single suspected medicine: 4

(The TGA thinks there is a possibility that the medicine caused the adverse event)

Number of cases where death was a reported outcome: 0

(These reports of death may or may not have been a result of taking a medicine)

MedDRA system organ class[i]	MedDRA reaction term[ii]	Number of cases[iii]	Number of cases with a single suspected medicine[iv]	Number of cases where death was a reported outcome[v]
Cardiac disorders	Tachycardia	2	2	0
Psychiatric disorders	Anxiety	2	2	0
Product issues	Product complaint	1	1	0
General disorders and administration site conditions	Pain	1	1	0
Investigations	Blood pressure increased	1	1	0
Nervous system disorders	Burning sensation	1	1	0
General disorders and administration site conditions	Fatigue	1	1	0
Psychiatric disorders	Insomnia	1	1	0
General disorders and administration site conditions	Malaise	1	1	0
Musculoskeletal and connective tissue disorders	Muscle spasms	1	1	0

Author (year of pub.)	Duration of Trial	N	Dose and Route	Adverse event (report)
Hendren (2015) (ASD)	8 weeks	57	Methylcobalamin 75 µg/kg every 3 days. Subcutaneous	Treatment: 28; Control 29 3/27 (Cold); 2/27 (Fever); 1/27 (flu); 1/27 (growing pain); (2/27) Increasing hyperactivity; 1/27 (Increasing irritability); 1/27 (Lack of focus); 5/27 (mouthing); 2/27 (Nose bleeds); 1/27 (Rash); 1/27 (stomach flu); 1/27 (trouble sleeping);
Bertoglio (2010) (ASD)	12-weeks	30	All subjects received 6 weeks of placebo and 6 weeks of Methylcobalamin 64.5 µg/kg every 3 days Subcutaneously	Side effects were limited to increased hyperactivity and increased mouthing of objects. No serious adverse events were reported.
Frye (2013) (ASD)	3 months	48	Methylcobalamin 75 µg/kg twice weekly 400 µg folinic acid PO twice daily Subcutaneous	6/44 (Hyperactivity); 3/44 (reduced sleep); 2/42 (Discomfort with injections); 1/42 (insomnia); 1/44 (Impulsivity); 1/44 (irritability). Four patients (2 had hyperactivity) dropped out of trial.
James (2004) (ASD)	4 months	53	Folinic acid 800 µg PO BID and 1000 mg betaine PO BID (intervention 1) administered after baseline blood draw for 3 months. Another baseline blood draw was compared with initial blood draw. Methylcobalamin 75 µg/kg twice a week in addition to the oral folinic acid and betaine for an additional month (2^{nd} intervention) Subcutaneous	Treatment: 20; Control 33 Not reported
James (2009) (ASD)	3 months	82	Methylcobalamin 75 µg/kg 2 times per week and 400 µg folinic acid PO twice a day for 3 months Subcutaneous	Treatment: 40; Control 42 4/44 (moderate hyperactivity that was reduced with decreased dose of Folinic acid to 400 µg/d) 1/44 (sleep disruption) 1/44 (getting to sleep) 1/44 (Increased impulsiveness) 1/44 (Irritability).

Author (year of pub.)	Duration of Trial	N	Dose and Route	Adverse event (report)
Zhang (2017) (BIPN) Bortizomib (Velcade) induced peripheral Neuropathy	5 months (5 cycles of Velcade therapy*)	65	Methylcobalamin, 2000 µg per dose in 100ml saline one hour before chemotherapy for >1h, and continuously for 28 days to prevent BIPN Intravenous	Treatment: 27; Control 38 1/28 (Rash)
Shibuya (2014) (Peripheral neuropathy)	12 months	14	Methylcobalamin 25 mg/day for 10 days followed by monthly 25 mg for 5 months Intravenous	2/14 (Pneumonia related to AIDP seborrheic dermatitis due to CMT) AIDP = acute inflammatory demyelinating polyneuropathy , CMT = Charcot-Marie-Tooth disease
Chiu (2011) (Chronic back pain)	9 months	60	Methylcobalamin 500 µg three times a week for 2 weeks Intramuscular	Treatment:33; Control 27 1/33 (pain, hematoma and lack of improvement in symptoms).
Kaji (2019) (Amyotrophic lateral sclerosis)	< 36 months	373	Methylcobalamin 25 mg or 50 mg twice per week starting from the end of the observation period (12 weeks) and continued for 182 weeks Intramuscular	Treatment: 124 (25 mg), 123 (50 mg); Placebo 123 Placebo (5/123), methylcobalamin: 9/124 (25 mg) and 7/123 (50 mg) Serious adverse events was similar 64.2%, 62.1% and 65.0%, 6 died of causes other than ALS progression. 1 death in the 50 mg methylcobalamin group was due to cardiac arrest following MI or arrhythmia considered unrelated to medication based on patient's history
	* Not clear or not specified			

Author (year of pub.)	Duration of Trial	N	Dose and Route	Adverse event (report)
Kuwabara (1999) (Uremic and diabetic neuropathy)	6 months	10	Methylcobalamin 500 µg three times a week for 6 months after each hemodialysis Intravenous	2/10 (pain scale unchanged) No adverse effect reported.
Tamura (1999) (Immunomodulation of B12 deficient anemia)	2 years	19	Methylcobalamin 500 µg/day every other day for 2 weeks and 1000 µg every 3 months as out-patients Intramuscular	Treatment: 11; Control 8 0/11 (No adverse effects)
Nakano (2005) (ASD)	6-25 months	13	Methylcobalamin 25-30 µg/kg/day to max of 1500 µg/day max Parenteral (not specified)	0/11 (No adverse effects)
Dave (2021) (Bioavailability study)	3 weeks	18	Methylcobalamin nasal spray 500 µg, or methylcobalamin 100 µg IM injection (15 day washout)	Nasal spray (1/18 dizziness) IM (0/18 no adverse effect)
Total	**531 weeks**	**842**		**Treated Patients:531** **Adverse events: 63 (12%)** **Serious Adverse Event: < 1%**

- Patients with ASD receive high-frequency in-depth medical supervision
- Patients require a multi-modal approach, involving behavioral therapy, pharmacotherapy, and more
- Core symptoms of autism include impairments in social interaction and communication

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

Cristan Farmer, PhD, **Audrey Thurm, PhD**, and **Paul Grant, MD**
Pediatrics and Developmental Neuroscience Branch, National Institute of Mental Health, Bethesda, MD, USA

There is no gold-standard for the measurement of change in autism symptoms in clinical trials (85). The gold-standard diagnostic instruments, the Autism Diagnostic Interview-Revised (86) and the Autism Diagnostic Observation Schedule (87) were not created to measure severity or improvement of the disorder. None of the measures used in the reviewed studies holistically and comprehensively measures change in core symptom domains, with adequately established reliability and validity across all subgroups of individuals with ASD (e.g., developmental and chronological age levels). While we recognize this as a limitation

Approved Therapies for Patients with ASD

Source: FDA Briefing Document; Pharmacy Compounding Advisory Committee (PCAC) Meeting; June 9, 2021, Tab 2c page 24

There are no drugs approved to treat the core symptoms of ASD. Two drugs—risperidone and aripiprazole—are approved for the treatment of irritability associated with autism. Labeled warnings associated with both of these drugs include metabolic changes, neuroleptic malignant syndrome, and tardive dyskinesia, among others. Common adverse reactions include akathisia, extrapyramidal symptoms, and weight gain.

Frequency of Use – Industry Survey

- 24 pharmacies in the US
- 27,565 patients in last 12 months
- 662,000 mL of compounded methylcobalamin dispensed in last 12 months
  - Typical dose is 0.1mL
  - Thousands of patients will be impacted by this decision

- Docket has received 1,167 comments as of June 2

- Medicaid data from JHU research is not informative. Prescription claims for compounded methylcobalamin are unlikely to be submitted to CMS.

May 4, 2017 FDA public meeting: Patient-focused drug development for Autism

- https://www.fda.gov/media/105399/download
- Parents testified directly to FDA about the impact of methylcobalamin injections on their children's autism symptoms
- Testimony addressed the various FDA-approved products and therapies they have attempted, and currently use
- Discussion included the inadequacies of current clinical trial process to measure certain outcomes in patients with ASD

BIO ENERGY MEDICAL CENTER
TREATING ILLNESS AT ITS SOURCE

May 23, 2021

Re: FDA-2021-N-0357

I am a licensed physician in the State of Michigan dually board certified in Emergency and Integrative Medicine with over 30 years of experience caring for chronically ill children and adults. I have had the honor of caring for children on the autism spectrum both through my ABA center and the therapies they provide (ABA, OT, SLT) as well as the bio-medical treatments I provide to address their health issues. Many of these children suffer from an impairment in their ability to detoxify resulting from a decreased ability to make reduced glutathione. This process is intimately linked with the methylation cycle for which both methylfolate and methylcobalamin (MB12) are essential. I have been using injectable MB12 for the children that are demonstrating these issues successfully since 2007, when I discovered its use. This is one of the interventions that has been a backbone of my biomedical treatment of these children. Unlike methylfolate, MB12 is much more difficult to absorb making the injectable form critical. In a survey of over 5000 parents done by the Autism Research Institute (ARI), MB12 was one of the top four interventions in terms of its positive response rate (over 70%) versus its negative response rate. I have personally witnessed recovery of language, eye contact, and extinction of stimming as a result of its administration. I, myself, have used it to manage some of my own symptoms and found it as useful as stimulants to manage my ADHD symptoms. MB12 has also lowered my homocysteine (a cardiac risk factor) from over 18 to around 7 (when injected or oral cyanocobalamin, oral MB12, and Mfolate were ineffective). Other than the possibility of increasing hyperactivity and local redness at the injection site, there are no dangerous side effects, something that cannot be said for the two drugs approved for kids on the spectrum (Abilify and Risperdal). Removing this valuable asset from the bulk compounding list would be a disaster for these kids that can benefit from its effects. I would beg this committee to leave MB12 on the compounding list so that its benefits can continue to be enjoyed by the children that need it the most.

I thank you for your consideration in this matter.

Yours in health

James R. Neuenschwander, M.D.

4201 VARSITY DRIVE • SUITE A • ANN ARBOR, MI 48108 • (734) 995-3200 • FAX (734) 995-4254
WWW.BIOENERGYMEDICALCENTER.COM

Source: https://www.regulations.gov/comment/FDA-2021-N-0357-0822

provide to address their health issues. Many of these children suffer from an impairment in their ability to detoxify resulting from a decreased ability to make reduced glutathione. This process is intimately linked with the methylation cycle for which both methylfolate and methylcobalamin (MB12) are essential. I have been using injectable MB12 for the children that are demonstrating these issues successfully since 2007, when I discovered its use. This is one of the interventions that has been a backbone of my biomedical treatment of these children. Unlike methylfolate, MB12 is much more difficult to absorb making the injectable form critical. In a survey of over 5000 parents done by the Autism Research Institute (ARI), MB12 was one of the top four interventions in terms of its positive response rate (over 70%) versus its negative response rate. I have personally witnessed recovery of language, eye contact, and extinction of stimming as a

Source: https://www.regulations.gov/comment/FDA-2021-N-0357-0822

Pediatric Partners of Ponte Vedra, P.A.
5270 PALM VALLEY ROAD, PONTE VEDRA, FLORIDA 32082
PHONE 904-543-1288 FAX 904-543-1289

May 25, 2021

Re: Docket Number FDA-2021-N-0357

To Whom It May Concern:

I have more than 15 years of clinical experience treating patients with autism, inborn errors of metabolism, vitamin B12 deficiency, and/or hyperhomocysteinemia.

I am writing with utmost concern over FDA's position leading into the Agency's scheduled review of methylcobalamin by the Pharmacy Compounding Advisory Committee (PCAC) on June 9, 2021. This compounded drug is essential for my patient's medical treatment, wellbeing and health. In fact, in the years of my practice of medicine, I have witnessed profound beneficial outcomes, such as dramatic measurable improvement in speech, resolution of anxiety, reduction in homocysteine levels, and improvement in multiple measurable outcomes in terms of health for those with inborn errors of metabolism or B-12 deficiency. It is also worth noting that I have never had, in the same 15 years, had no significant sustained side effects.

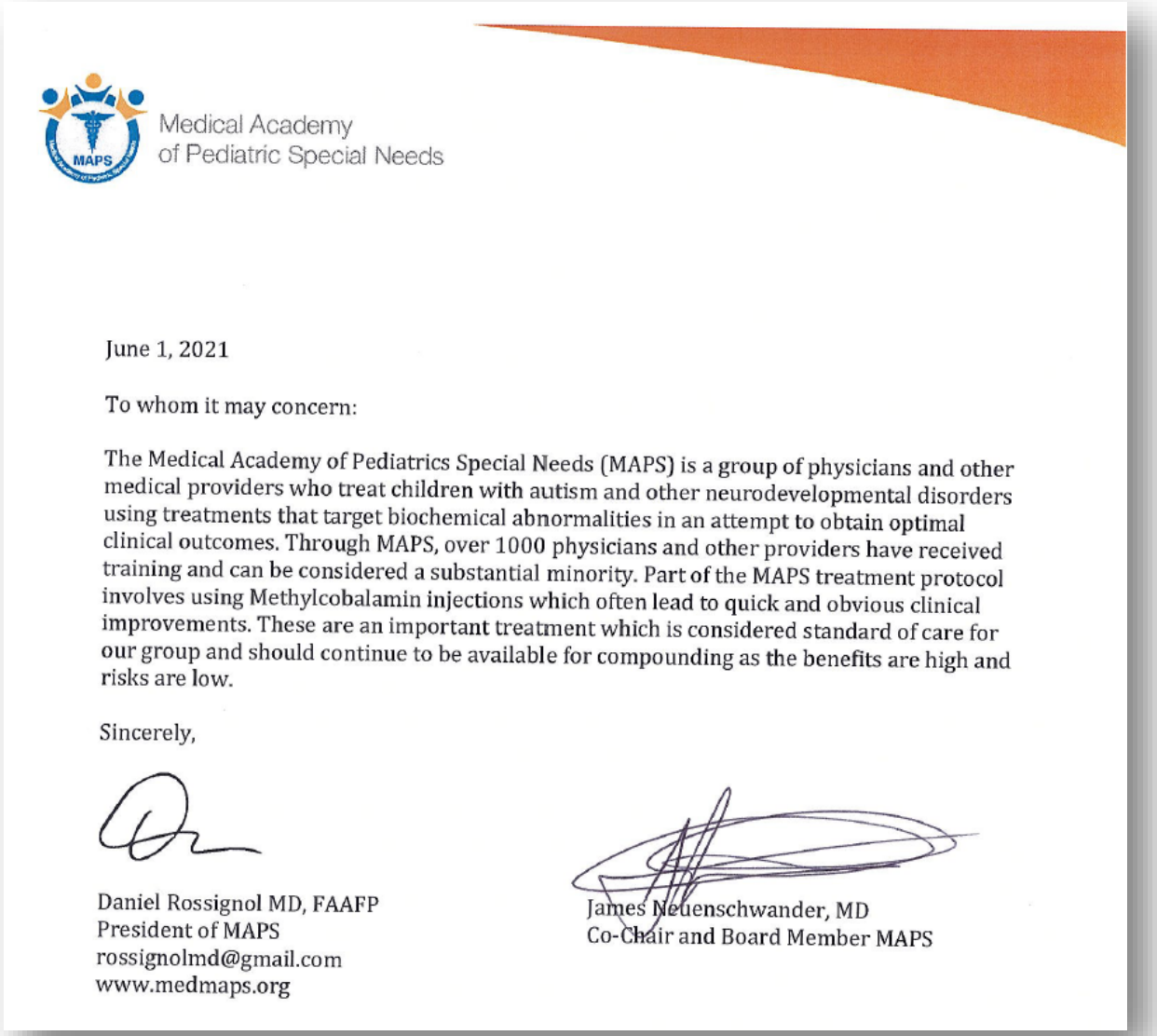
It is my professional position that methylcobalamin, in forms outside of a nutritional supplement, is a vital and key treatment for my patients.

Sincerely,

Julie A. Buckley, MD

Source: https://www.regulations.gov/comment/FDA-2021-N-0357-1011

Medical Academy of Pediatric Special Needs STANDARD OF CARE



Medical Academy
of Pediatric Special Needs

June 1, 2021

To whom it may concern:

The Medical Academy of Pediatrics Special Needs (MAPS) is a group of physicians and other medical providers who treat children with autism and other neurodevelopmental disorders using treatments that target biochemical abnormalities in an attempt to obtain optimal clinical outcomes. Through MAPS, over 1000 physicians and other providers have received training and can be considered a substantial minority. Part of the MAPS treatment protocol involves using Methylcobalamin injections which often lead to quick and obvious clinical improvements. These are an important treatment which is considered standard of care for our group and should continue to be available for compounding as the benefits are high and risks are low.

Sincerely,

Daniel Rossignol MD, FAAFP
President of MAPS
rossignolmd@gmail.com
www.medmaps.org

James Neuenschwander, MD
Co-Chair and Board Member MAPS

Conclusions

- Approved as injection in Japan and Australia
- No significant adverse event reports from all available literature, worldwide
  - **“Adverse events reported with methylcobalamin use are infrequent and non-serious.” – FDA**
- Has been compounded since at least 2005
- No alternative options for patients

- Dr. Frye to address clinical and biochemical assessment

THANK YOU

References

- FDA Briefing Document; Pharmacy Compounding Advisory Committee (PCAC) Meeting; June 9, 2021, Tab 2c. https://www.fda.gov/media/149084/download. Accessed May 21, 2021.
- Paul C, Brady DM. Comparative Bioavailability and Utilization of Particular Forms of B12 Supplements with Potential to Mitigate B12-Related Genetic Polymorphisms. *Integr Med (Encinitas). 2017;*16(1):42-49.
- Japanese Package Insert: https://pdf4pro.com/cdn/methycobal-e-search-ne-jp-fb32d.pdf. Accessed May 25, 2021.
- Australian Package Insert: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-PI-02378-1&d=202106011016933. Accessed May 25, 2021.
- Australian Government Department of Health, Therapeutic Goods Administration Database of Adverse Event Notifications – medicines: https://apps.tga.gov.au/PROD/DAEN/daen-report.aspx. Accessed June 1, 2021.
- Farmer C, Thurm A, Grant P. Pharmacotherapy for the Core Symptoms in Autistic Disorder: Current Status of the Research. *Drugs.* 2013;73(4):303-14.

References for Safety Chart

- Hendren RL, James SJ, Widjaja F, Lawton B, Rosenblatt A, Bent S. Randomized, Placebo-Controlled Trial of Methyl B12 for Children with Autism. *J Child Adolesc Psychopharmacol*. 2016;26(9):774-783. doi:10.1089/cap.2015.0159.
- Bertoglio K, James SJ, Deprey L, Brule N, Hendren DO. Pilot Study of the Effect of Methyl B12 Treatment on Behavioral and Biomarker Measures in Children with Autism. 2020; 16 (5):555-560. doi:10.1089/acm.2009.0177.
- Frye RE, Melnyk S, Fuchs G, et al. Effectiveness of methylcobalamin and folinic Acid treatment on adaptive behavior in children with autistic disorder is related to glutathione redox status. *Autism Res Treat*. 2013;2013:609705. doi:10.1155/2013/609705.
- James SJ, Cutler P, Melnyk S, et al. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. *Am J Clin Nutr*. 2004;80(6):1611-1617. doi:10.1093/ajcn/80.6.1611
- James SJ, Melnyk S, Fuchs G, et al. Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism. *Am J Clin Nutr*. 2009;89(1):425-430. doi:10.3945/ajcn.2008.26615
- Zhang LL, Wang YH, Shao ZH, Ma J. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2017;25(2):480-484. doi:10.7534/j.issn.1009-2137.2017.02.031
- Shibuya K, Misawa S, Nasu S, et al. Safety and efficacy of intravenous ultra-high dose methylcobalamin treatment for peripheral neuropathy: a phase I/II open label clinical trial. *Intern Med*. 2014;53(17):1927-1931. doi:10.2169/internalmedicine.53.1951
- Chiu CK, Low TH, Tey YS, Singh VA, Shong HK. The efficacy and safety of intramuscular injections of methylcobalamin in patients with chronic nonspecific low back pain: a randomised controlled trial. *Singapore Med J*. 2011;52(12):868-873.
- Kaji R, Imai T, Iwasaki Y, et al. Ultra-high-dose methylcobalamin in amyotrophic lateral sclerosis: a long-term phase II/III randomised controlled study. *J Neurol Neurosurg Psychiatry*. 2019;90(4):451-457. doi:10.1136/jnnp-2018-319294
- Kuwabara S, Nakazawa R, Azuma N, et al. Intravenous methylcobalamin treatment for uremic and diabetic neuropathy in chronic hemodialysis patients. *Intern Med*. 1999;38(6):472-475. doi:10.2169/internalmedicine.38.472
- Tamura J, Kubota K, Murakami H, et al. Immunomodulation by vitamin B12: augmentation of CD8+ T lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. *Clin Exp Immunol*. 1999;116(1):28-32. doi:10.1046/j.1365-2249.1999.00870.x
- Nakano K, Noda N, Tachikawa E, Urano M, Takazawa M, Nakayama KS, Osawa M. A preliminary study of methyLcobalamin therapy in Autism. J. Tokyo Wom Med Univ. 2005; 75(3.4):64-69.
- Dave H, Agarwal DH, Manseeh A, Patel KR. Novel methylcobalamin Nasal spray versus intramuscular injection: A randomized, crossover comparative bioavailability study. Int J. Endocrinol Metab Disord. 2021: 7(1):dx.doi.org/10.16966/2380-548X.171.

Methylcobalamin Treatment For Autism Spectrum Disorder

Richard E. Frye, M.D., Ph.D.
Chief, Neurodevelopmental Disorders
Director of Autism and Fragile X Programs,
Phoenix Children's Hospital, Phoenix AZ
Professor of Child Health
University of Arizona College of Medicine - Phoenix, Phoenix AZ

Presenting on Behalf of PCCA

Disclosures

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Industry Clinical Trials: Finch Therapeutics; Zynerba Pharma

Advisory Board: Iliad Neurosciences, NeuroNeeds Inc

Disclaimer

Every attempted has been made to make this presentation as accurate as possible. The information is provided without any expressed or implied warranty. This presentation should not be substituted for medical advice. Treatments discussed are considered off-label and are not FDA-approved.

Key Points

Biochemical Pathways Involving Cobalamin Are Disrupted in Autism

- Methylation
- Redox Metabolism

Methylcobalamin Supports Disrupted Biochemical Pathways in Autism

- Not Necessarily a Treatment of a Deficiency
- Treatment of an Insufficiency in Cofactors for Methylation and Redox Metabolism

Evidence for Effectiveness of mB12 SQ Therapy

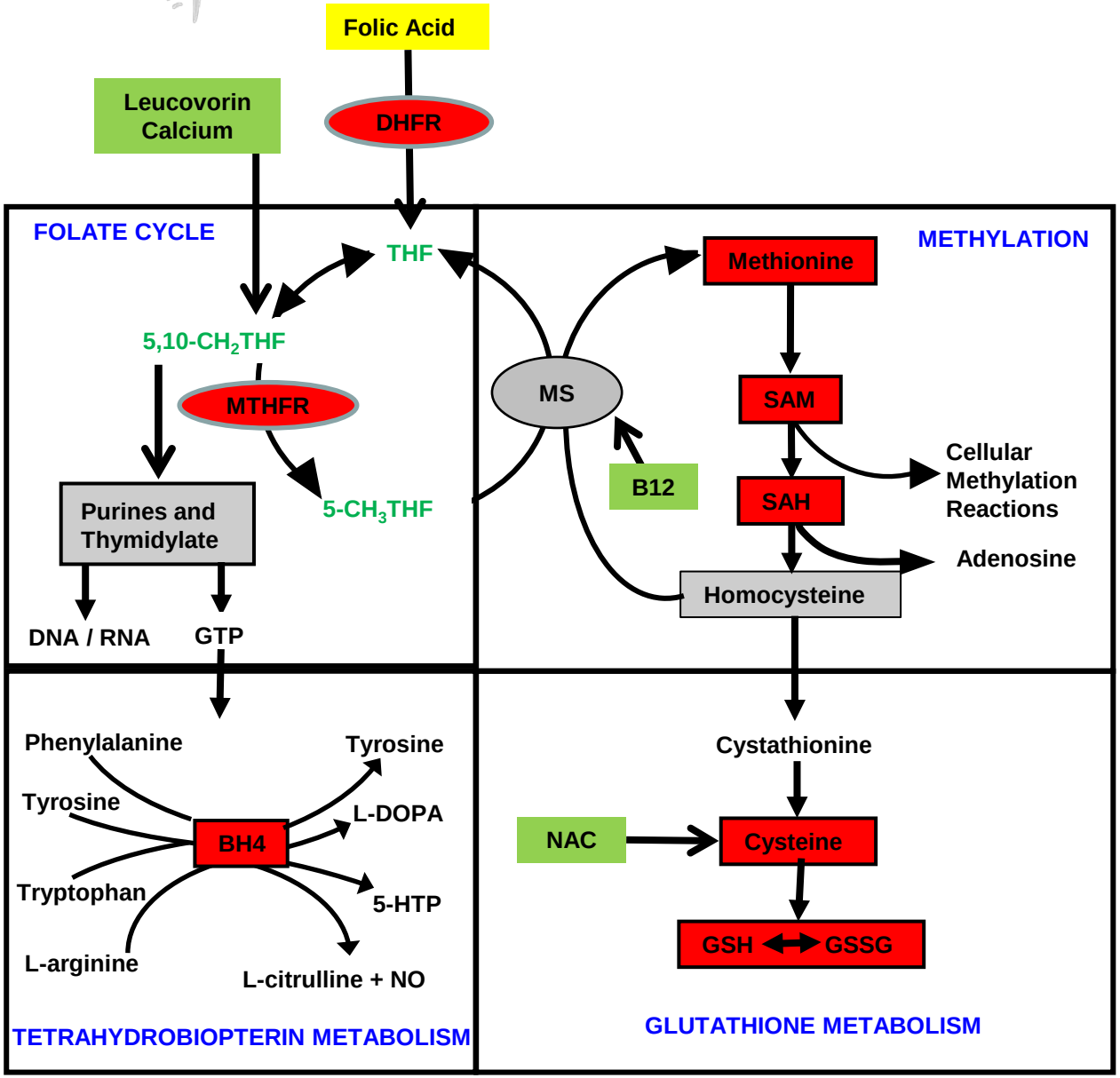
- Improves Redox and Methylation Biochemical Abnormalities
- Improves Autism Symptoms
- Improvement in Symptoms is Related to Improvement in Biochemical Abnormalities

Potential Biological Mechanisms in Autism

- Production of Glutathione Can Rebalance Glutamate Metabolism
- Polymorphism in Cobalamin Carrier Protein Could Reduce Cobalamin Transportation
- Cobalamin Concentrations Are Reduced in the Autism Brain
- Methionine Synthase mRNA Expression is Reduced in the Autism Brain
- Cobalamin Intake is Lower in Children with Autism

Subcutaneous Methylcobalamin is Standard of Care for Physicians Treating Autism

Methylcobalamin for Autism



Metabolites

THF	TetraHydroFolate
SAM	*S*-Adenosyl methionine
SAH	*S*-Adenosyl homocysteine
GSH	Reduced Glutathione
GSSG	Oxidized Glutathione
NO	Nitric Oxide
BH4	Tetrahydrobiopterin

Enzymes

DHFR	Dihydrofolate Reductase
MS	Methionine Synthase
MTHFR	Methylenetetrahydrofolate Reductase

Figure Key

Blue text outlines one of the four pathways related to folate metabolism
Ovals represent enzymes
Boxes represent metabolites
Red indicates metabolites and enzymes repeatedly noted to be abnormal in autism
Green highlights reduced folates
Yellow highlights oxidized folates

Methylcobalamin for Autism

American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 141B:947–956 (2006)

Metabolic Endophenotype and Related Genotypes are Associated With Oxidative Stress in Children With Autism

S. Jill James,[1]* Stepan Melnyk,[1] Stefanie Jernigan,[1] Mario A. Cleves,[1] Charles H. Halsted,[2]

[1]*Department of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital Research Institute, Little Rock, Arkansas*

TABLE II. Transmethylation and Transsulfuration Metabolites in Autistic Cases and Controls

	Control[a] (n = 73)	Autistic[a] (n = 80)	*P*-value
Methionine (μmol/L)	28.0 ± 6.5	20.6 ± 5.2	<0.0001
SAM (nmol/L)	93.8 ± 18	84.3 ± 11	<0.0001
SAH (nmol/L)	18.8 ± 4.5	23.3 ± 7.9	<0.0001
SAM/SAH ratio	5.5 ± 2.8	4.0 ± 1.7	<0.0001
Adenosine (μmol/L)	0.19 ± 0.13	0.28 ± .13	0.001
Homocysteine (μmol/L)	6.0 ± 1.3	5.7 ± 1.2	0.03v
Cystathionine (μmol/L)	0.19 ± 0.1	0.24 ± 0.1	<0.0001
Cysteine (μmol/L)	207 ± 22	165 ± 14	<0.0001
Cysteinylglycine (μmol/L)	39.4 ± 7.3	38.9 ± 11	0.78
Total GSH (μmol/L)	7.53 ± 1.7	5.1 ± 1.2	<0.0001
Free GSH (μmol/L)	2.2 ± 0.9	1.4 ± 0.5	<0.0001
GSSG (μmol/L)	0.24 ± 0.1	0.40 ± 0.2	<0.0001
Total GSH/GSSG ratio	28.2 ± 7.0	14.7 ± 6.2	<0.0001
Free GSH/GSSG ratio	7.9 ± 3.5	4.9 ± 2.2	<0.0001

SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; GSH, glutathione; GSSG, glutathione disulfide.
[a]Means ± SD.

Methylcobalamin for Autism

Oxidative stress-related biomarkers in autism: Systematic review and meta-analyses Frustaci et al. Free Radical Biology and Medicine 2012; 52:2128-41.

- Significant reduction in blood GSH, Methionine and Cysteine
- Significant elevation in blood GSSG
- Significant reduction in blood glutathione peroxidase
- Significant association of MTHFR homozygous C677T polymorphism with ASD

Glutathione Abnormalities are found in several tissues in children with ASD

Dr Jill James, Ph.D. and her group has demonstrated in case-control studies that glutathione antioxidant/detoxification capacity is decreased in lymphoblastoid cell lines, peripheral blood mononuclear cells and post-mortem brain from children with ASD (Rose et al. Autism Res Treat. 2012, 2012: 986519; Rose et al. Transl Psychiatry. 2012, 2:e134; James et al. FASEB J. 2009, 23:2374-83; James et al. Am J Med Genet. 2006, 141B:947, Zhang et al., PLoS One. 2016; 11(1): e0146797)

Redox Abnormalities can lead to DNA, protein and lipid oxidative damage in ASD

Studies have demonstrated oxidative damage in children with ASD (Melnyk et al., JADD 2012, 42:367; Rose et al. Transl Psychiatry. 2012, 2:e134; Napoli et al. Mol Autism. 2013, 4:2; Meguid et al. Biol Trace Elem Res 2011, 143:58; Damodaran et al. Redox Rep 2011 16:216)

Methylcobalamin for Autism

PLOS | COMPUTATIONAL BIOLOGY

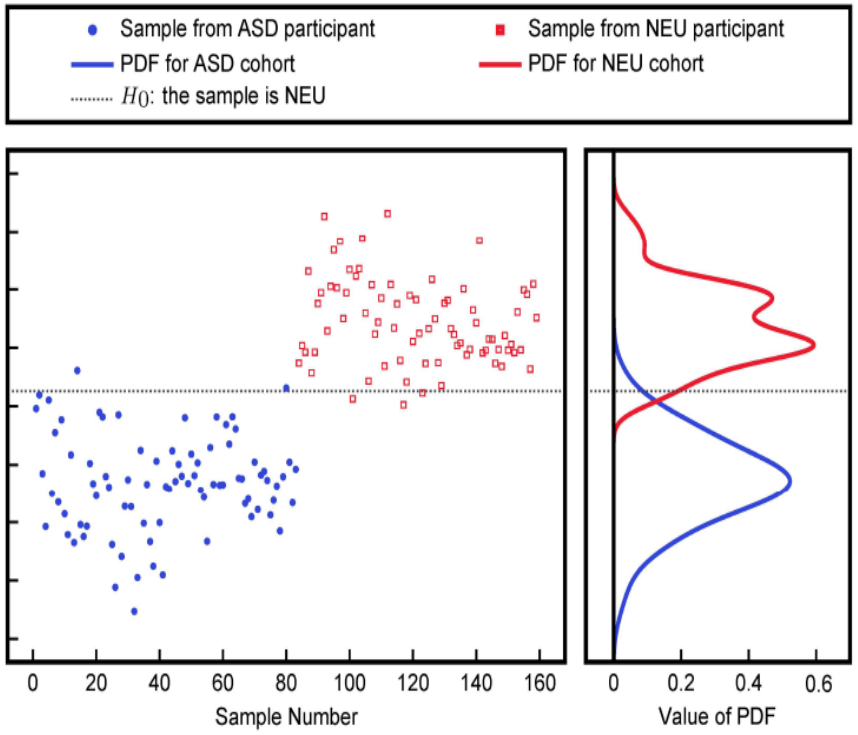
RESEARCH ARTICLE

Classification and adaptive behavior prediction of children with autism spectrum disorder based upon multivariate data analysis of markers of oxidative stress and DNA methylation

Daniel P. Howsmon[1,2], Uwe Kruger[3], Stepan Melnyk[4], S. Jill James[4], Juergen Hahn[1,2,3]*

1 Department of Chemical and Biological Engineering, Rensselaer Polytechnic Institute, Troy, New York, United States of America, **2** Center for Biotechnology and Interdisciplinary Studies, Rensselaer Polytechnic Institute, Troy, New York, United States of America, **3** Department of Biomedical Engineering, Rensselaer Polytechnic Institute, Troy, New York, United States of America, **4** Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, Arkansas, United States of America

Methylcobalamin for Autism



Predicted

Actual	ASD	NEU	
ASD	TP 81	FP 2	TPR 0.964
NEU	FN 3	TN 73	FPR 0.026
	PPV 0.976	NPV 0.961	

Metabolites Examined
(Highlighted Metabolites In Discriminant Fx)

Methionine	SAM
SAM/SAH	% DNA methylation
Adenosine	Homocysteine
Glu.-Cys.	Cys.-Gly.
fGSH	GSSG
tGSH/GSSG	Chlorotyrosine
Tyrosine	Tryptophane
fCysteine	fCystine/fCysteine
SAH	
8-OHG	
Cysteine	
tGSH	
fGSH/GSSG	
Nitrotyrosine	
fCystine	
% oxidized glutathione	

Metabolites

SAM	*S*-Adenosyl methionine
SAH	*S*-Adenosyl homocysteine
fGSH	Free Reduced Glutathione
tGSH	Total Reduced Glutathione
GSSG	Oxidized Glutathione
fGSH/GSSG	Glutathione Redox Ratio
8-OHG	8-hydroxy-2'-deoxyguanosine

Methylcobalamin for Autism

The American Journal of Clinical Nutrition

Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism[1–3]

S Jill James, Stepan Melnyk, George Fuchs, Tyra Reid, Stefanie Jernigan, Oleksandra Pavliv, Amanda Hubanks, and David W Gaylor

TABLE 1

Mean plasma metabolite concentrations (±SD) in age-matched control children, children who had autism at baseline before intervention, and children with autism after 3-mo intervention with methylcobalamin and folinic acid[1]

		Children with autism		
Plasma metabolite concentration	Control children ($n = 42$)	Pretreatment ($n = 40$)	Posttreatment ($n = 40$)	P value[2]
Methionine	24 ± 3	21 ± 4[3]	22 ± 3[4]	NS
SAM (nmol/L)	78 ± 22	66 ± 13[3]	69 ± 12[4]	NS
SAH (nmol/L)	14.3 ± 4.3	15.2 ± 5	14.8 ± 4	NS
SAM:SAH (μmol/L)	5.6 ± 2.0	4.7 ± 1.5[3]	5.0 ± 2.0	NS
Homocysteine (μmol/L)	5.0 ± 1.2	4.8 ± 1.8	5.3 ± 1.1	0.04
Cysteine (μmol/L)	210 ± 18	191 ± 24[3]	215 ± 19	0.001
Cysteinylglycine (μmol/L)	45 ± 6	40 ± 9[3]	46 ± 9	0.002
tGSH (μmol/L)	7.5 ± 1.8	5.4 ± 1.3[3]	6.2 ± 1.2[4]	0.001
fGSH (μmol/L)	2.8 ± 0.8	1.5 ± 0.4[3]	1.8 ± 0.4[4]	0.008
GSSG (μmol/L)	0.18 ± 0.07	0.28 ± 0.08[3]	0.22 ± 0.06[4]	0.001
tGSH:GSSG	47 ± 18	21 ± 6[3]	30 ± 9[4]	0.001
fGSH:GSSG	17 ± 6.8	6 ± 2[3]	9 ± 3[4]	0.001

[1] fGSH, free glutathione; SAH, *S*-adenosylhomocysteine; SAM, *S*-adenosylmethionine; tGSH, total glutathione; GSSG, oxidized glutathione disulfide. NS, $P > 0.05$.

[2] Pre- and posttreatment comparison.

[3] Significantly different from control children, $P < 0.005$.

[4] Significantly different from control children, $P < 0.01$.

Methylcobalamin for Autism

Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism[1–3]

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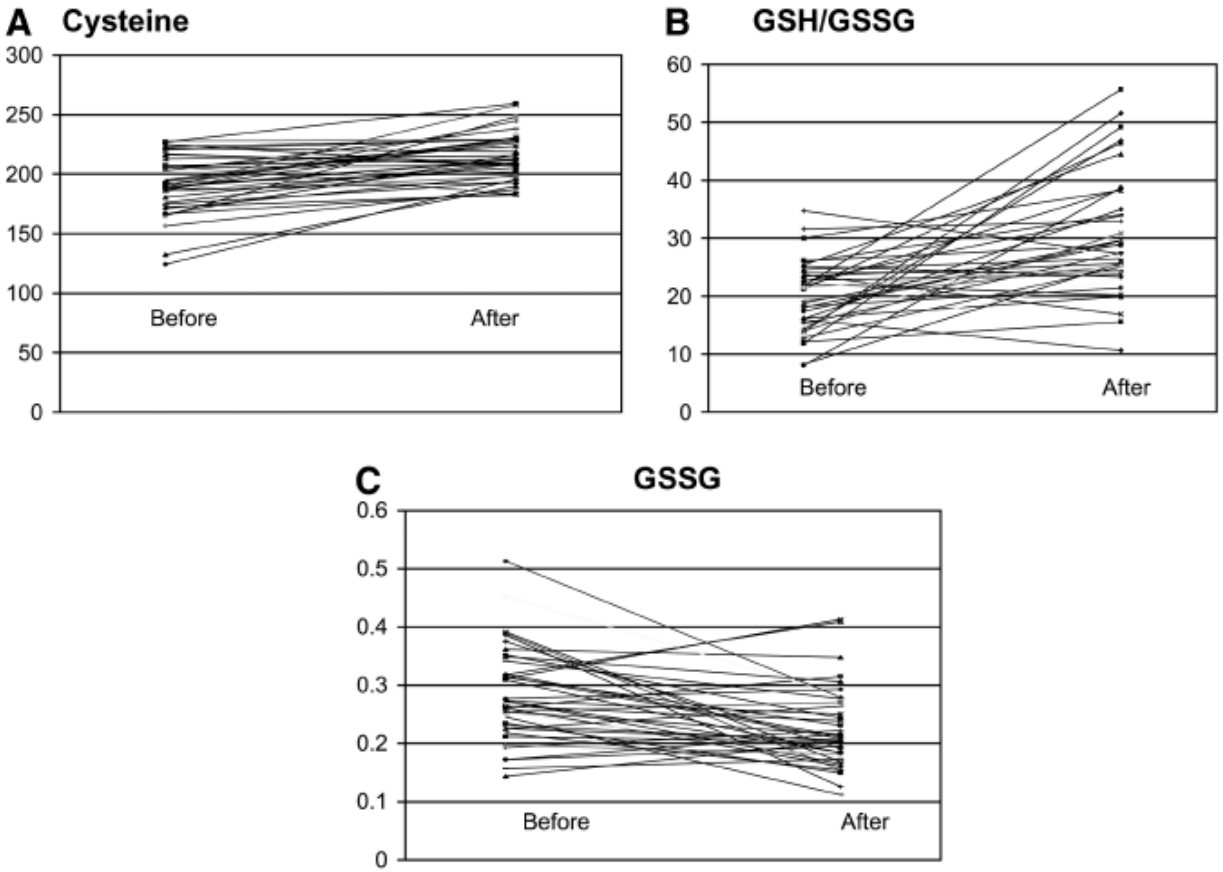

Methylcobalamin for Autism

Effectiveness of Methylcobalamin and Folinic Acid Treatment on Adaptive Behavior in Children with Autistic Disorder Is Related to Glutathione Redox Status

Autism Research and Treatment
Volume 2013, Article ID 609705, 9 pages
http://dx.doi.org/10.1155/2013/609705

Richard E. Frye,[1] Stepan Melnyk,[1] George Fuchs,[1] Tyra Reid,[1] Stefanie Jernigan,[1] Oleksandra Pavliv,[1] Amanda Hubanks,[1] David W. Gaylor,[2] Laura Walters,[1] and S. Jill James[1]

Vineland Subscale	Baseline Age Equivalent Months (mean ± SE)	Post-Intervention Age Equivalent Months (mean ± SE)	Change (months) (mean; 95% C I)
Receptive Language	23.1 ± 1.8	31.4 ± 3.4	**8.3 (2.9, 13.7)**
Expressive Language	20.6 ± 1.9	27.5 ± 2.9	**6.0 (3.3,9.4)**
Written Language	40.5 ± 3.8	46.7 ± 4.0	**6.2 (3.4, 9.0)**
Personal Skills	30.5 ± 2.3	40.5 ± 3.8	**10.0 (3.8, 16.2)**
Domestic Skills	30.3 ± 4.1	39.3 ± 5.9	9.0 (-1.4, 19.4)
Community Skills	32.9 ± 2.9	36.1 ± 3.8	2.0 (-3.0, 6.9)
Interpersonal Skills	18.7 ± 2.7	24.1 ± 3.9	5.4 (0.0, 10.9)
Play/Leisure Skills	22.0 ± 4.5	34.0 ± 4.1	**12.0 (4.1, 19.6)**
Coping Skills	25.8 ± 2.5	34.3 ± 4.0	**11.5 (4.9, 18.0)**

Methylcobalamin for Autism

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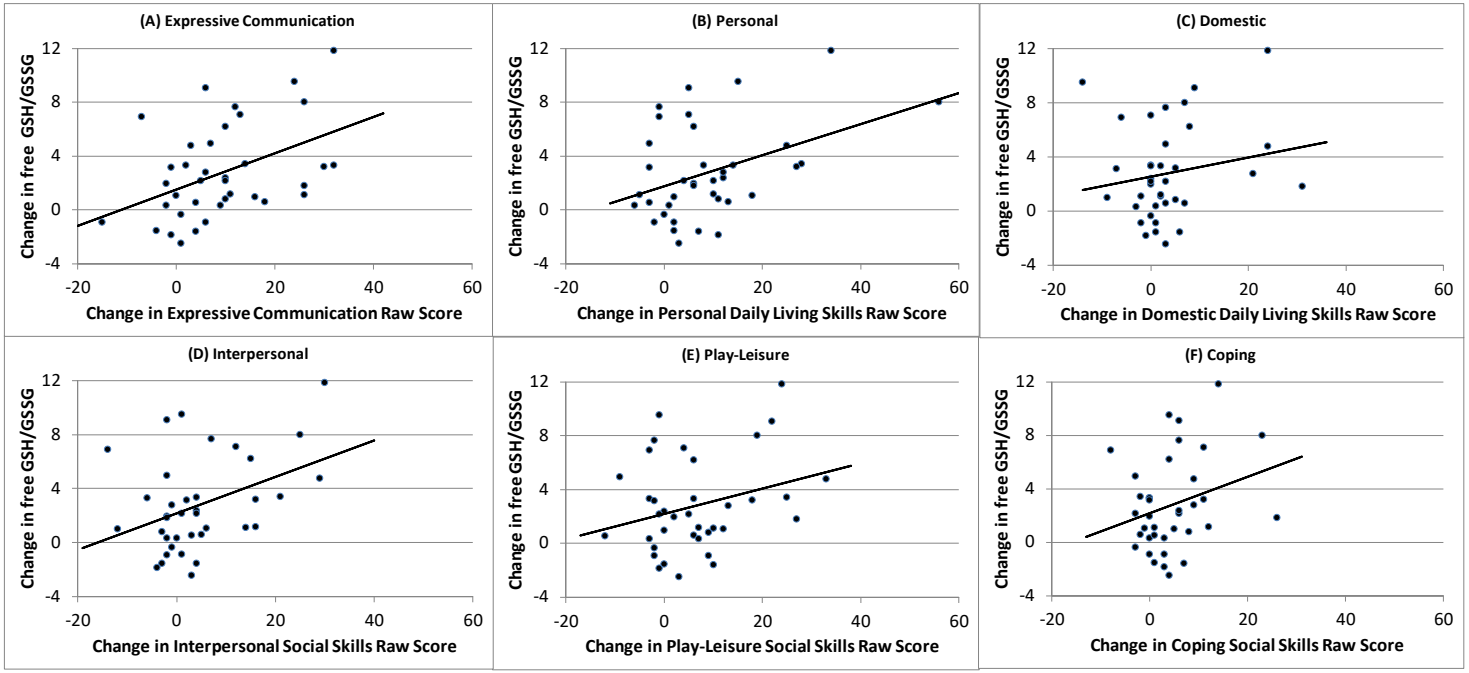


Methylcobalamin for Autism

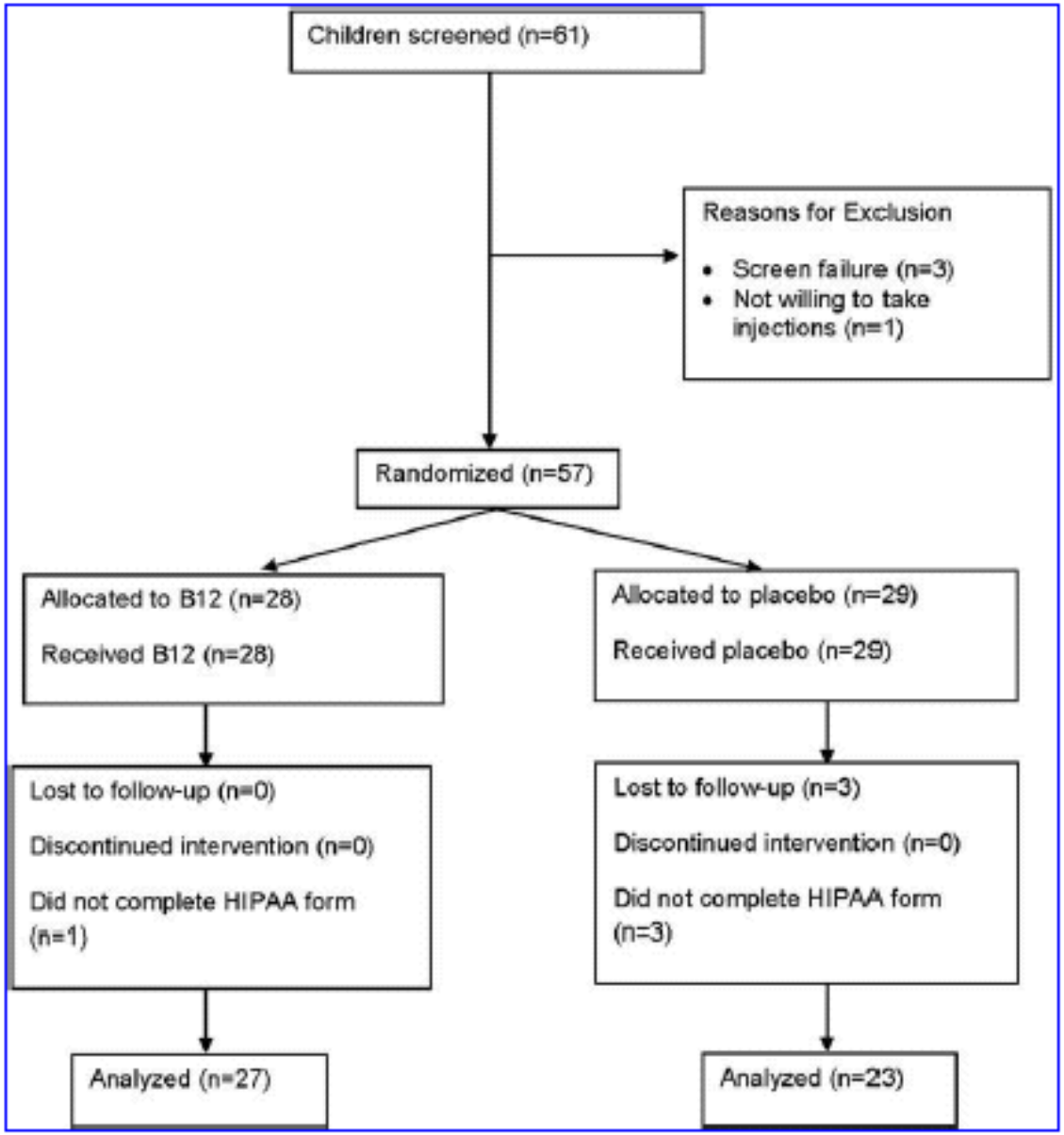
JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
2016 Nov;26(9):774-783

Randomized, Placebo-Controlled Trial of Methyl B12 for Children with Autism

Robert L. Hendren, DO,[1] S. Jill James, PhD,[2] Felicia Widjaja, MPH,[1] Brittany Lawton, BS,[1] Abram Rosenblatt, PhD,[1] and Stephen Bent, MD[1]

[1]Department of Psychiatry, University of California, San Francisco, California.
[2]Arkansas Children's Hospital Institute, Department of Pediatrics,

Methylcobalamin for Autism



Methylcobalamin for Autism

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Variable	*Mean change placebo (SD)*	*Mean change methyl B12 (SD)*	*Effect size*	*Difference in mean change*	*95% CI*	p *value*
CGI-Improvement	3.1 (0.8)	2.4 (0.8)	0.84	0.7 (0.8)	−1.2 to −0.2	0.005*
ABC Hyperactivity	−3.9 (7.1)	−0.9 (4.8)	−0.48	−3.0 (6.2)	−7.0 to 1.1	0.11
ABC Inappropriate Speech	−0.3 (1.6)	0.3 (1.4)	−0.43	−0.6 (1.5)	−1.6 to 0.3	0.17
ABC Irritability	−2.6 (4.3)	−0.1 (3.7)	−0.61	−2.5 (4.0)	−5.1 to 0.2	0.08
ABC Lethargy	−1.2 (7.1)	−1.9 (5.8)	0.12	0.8 (6.6)	−3.5 to 5.0	1.00
ABC Stereotypy	0.3 (3.2)	−0.3 (2.2)	0.23	0.6 (2.8)	−1.2 to 2.5	0.58
ABC Total Score	−7.6 (17.4)	−2.9 (12.1)	−0.30	−4.7 (15.4)	−14.6 to 5.3	0.23
SRS Social Awareness	0.0 (18.3)	−3.9 (10.0)	0.26	3.9 (15.0)	−5.9 to 13.7	0.18
SRS Social Cognition	−3.6 (10.5)	−2.7 (6.9)	−0.10	−0.9 (9.0)	−6.8 to 5.0	0.87
SRS Social Communication	−3.6 (8.8)	0.1 (15.0)	−0.30	−3.6 (12.1)	−11.5 to 4.2	0.22
SRS Social Mannerisms	−1.6 (14.3)	−0.8 (10.7)	−0.06	−0.8 (12.8)	−9.1 to 7.5	0.53
SRS Social Motivation	−6.1 (10.0)	0.2 (6.6)	−0.73	−6.3 (8.6)	−11.9 to −0.7	0.02*
SRS Total Score	−4.1 (7.7)	−1.6 (7.7)	−0.32	−2.5 (7.7)	−7.5 to 2.5	0.21

- Hendren Study did not use folate with mB12 Treatment
- The Clinical Global Impression (CGI) Scale is a Clinician Rated Instrument
- Both the Social Responsiveness Scale (SRS) and Aberrant Behavior Checklist (ABC) are Parent Reported Measures which are Notoriously Sensitive to Placebo Effects

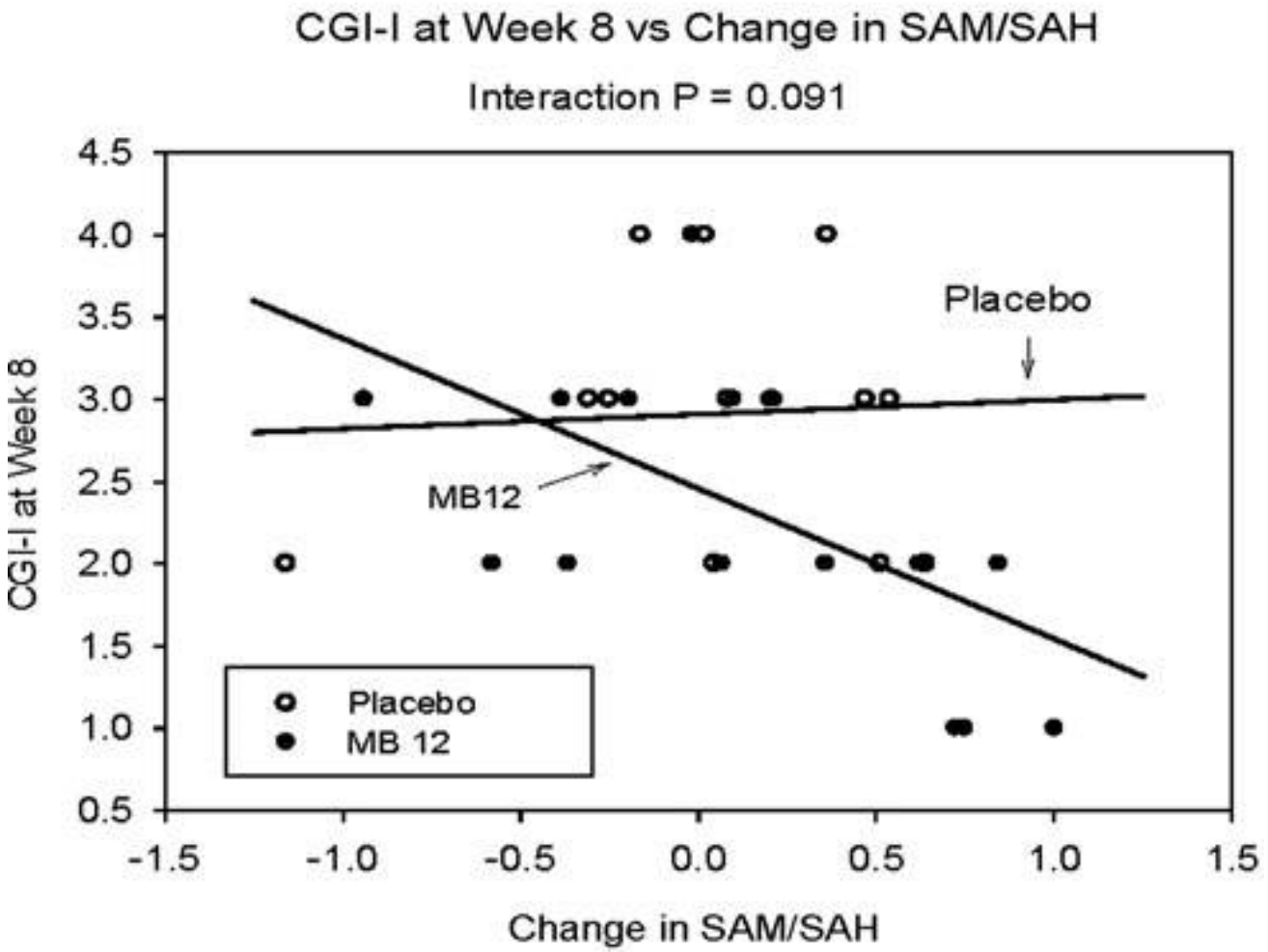
Methylcobalamin for Autism

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

Cristan Farmer, PhD, **Audrey Thurm, PhD**, and **Paul Grant, MD**
Pediatrics and Developmental Neuroscience Branch, National Institute of Mental Health, Bethesda, MD, USA

There is no gold-standard for the measurement of change in autism symptoms in clinical trials (85). The gold-standard diagnostic instruments, the Autism Diagnostic Interview-Revised (86) and the Autism Diagnostic Observation Schedule (87) were not created to measure severity or improvement of the disorder. None of the measures used in the reviewed studies holistically and comprehensively measures change in core symptom domains, with adequately established reliability and validity across all subgroups of individuals with ASD (e.g., developmental and chronological age levels). While we recognize this as a limitation

Methylcobalamin for Autism



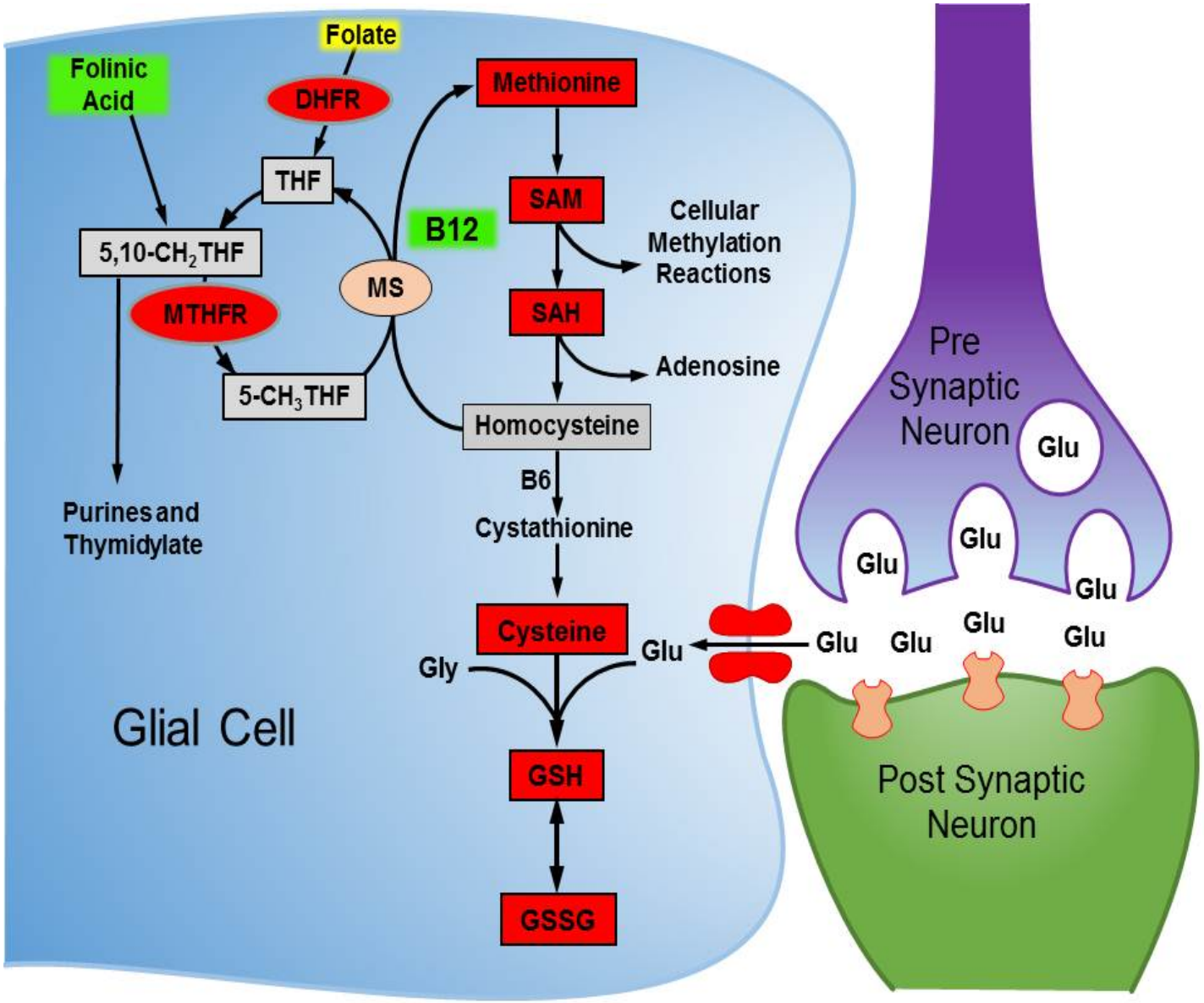
Methylcobalamin for Autism

Clinical Studies on Injected Methylcobalamin

Study Type	# of Studies	Total N	Dose	Outcome	Adverse Effects
Double Blind Placebo Controlled	2	87	MB12 64.5-75 µg/kg SQ q 3 days	• CGI Improved • Improvement Associated with Methylation Biomarkers	• Few, Mild • Hyperactivity • Mouthing Objects • No Serious
Open Label	3 (2 same group)	48	mB12 SQ 75 µg/kg 2-3 TIW	• Improved VABS • Improved Redox Metabolism • VABS Improvements Associated with Redox Biomarker	• Few, Mild • Hyperactivity • Insomnia • Impulsiveness • No Serious
Case Report/ Series	4	7	Various Doses SQ and IM	• Improved Vision • Improved ASD symptoms	None Reported

VABS = Vineland Adaptive Behavior Scale

Methylcobalamin for Autism



Methylcobalamin for Autism

Metabolic Endophenotype and Related Genotypes are Associated With Oxidative Stress in Children With Autism

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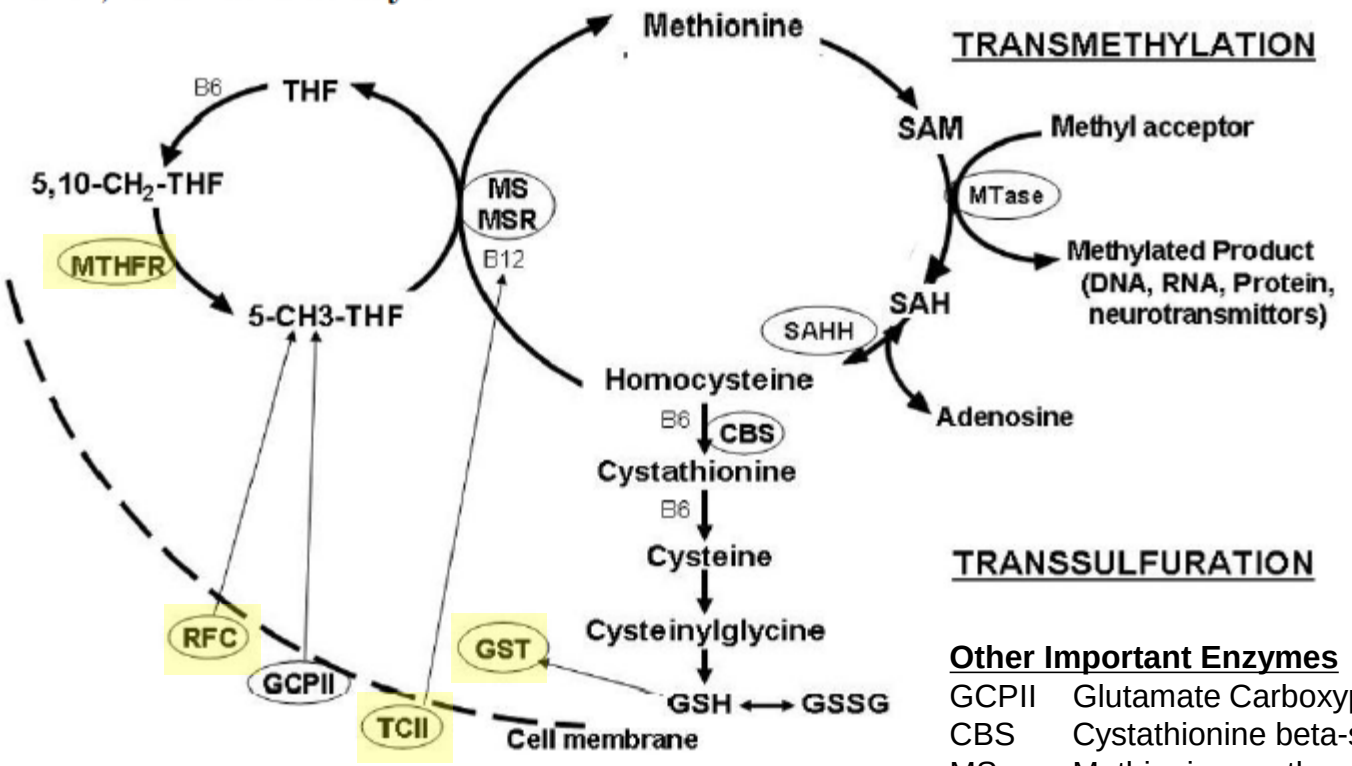

Other Important Enzymes

GCPII	Glutamate Carboxypepidase II
CBS	Cystathionine beta-synthase
MS	Methionine synthase
MSR	Methionine synthase reductase
MTase	Methyltransferase

Enzymes with Significant Polymorphisms (Yellow Highlight)

RFC	Reduced folate carrier
TCN2	Transcobalamin II (B12 binding protein)
MTHFR	Methylenetetrahydrofolate reductase
GST	Gluthathione S-Transferase

Am J Med Genet B Neuropsychiatr Genet. 2006 Dec 5;141B(8):947-56.

Methylcobalamin for Autism

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SNP	Genotype	OR (95% CI)
TCN2 776C > G/*COMT* 472G > A	CC/CC	Reference
	GG/GG	7.0 (2.32, 21.2)
RFC-1 80A > G/*MTHFR677C* > *T*	AA/CC	Reference
	GA/CT	3.24 (1.55, 6.78)
	GA/TT	4.40 (1.45, 14.0)
	GG/CT	3.10 (1.39, 6.84)
RFC-1 80A > G/*GSTM1* Null	AA/ ++	Reference
	GA/null	3.78 (1.80, 7.95)
	GG/null	2.67 (1.22, 5.89)
MTHFR 677 CT/*MTHFR* 1298AC	CT/AC	1.78 (0.97, 3.26)
MTHFR 677CT/1298AC/RFC 80G	(CT/AC)/GA	1.33 (1.33, 15.81)
	(CT/AC)/GG	3.57 (0.97, 13.49)

RFC Reduced folate carrier
TCN2 Transcobalamin II (B12 binding protein)
MTHFR Methylenetetrahydrofolate reductase
GST Gluthathione S-Transferase
COMT Catechol-O-methyltransferase

Am J Med Genet B Neuropsychiatr Genet. 2006 Dec 5;141B(8):947-56.

Methylcobalamin for Autism

J Pediatr Hematol Oncol 2017 Nov;39(8):e430-e436.

Long-term Outcome of 4 Patients With Transcobalamin Deficiency Caused by 2 Novel *TCN2* Mutations

Marwan Nashabat, MCR, Gustavo Maegawa, MD, PhD,† Peter H. Nissen, PhD,‡ Ebba Nexo, MD, PhD,‡ Hussain Al-Shamrani, MD,§ Mohammed Al-Owain, MD, FACMG,‖¶ and Majid Alfadhel, MD, FCCMG*#*

TABLE 1. Summary of the Patient's Clinical Findings

Autism Cases

	Patient 1	Patient 2	Patient 3	Patient 4
Molecular findings (*TCN2* gene mutation)	Splice mutation: intron 1 (c.64 + 4A > T)	Splice mutation: intron 1 (c.64 + 4A > T)	Nonsense mutation: exon 5 c.679C > T(p.R227X)	Nonsense mutation: exon 5 c.679C > T(p.R227X)
Laboratory findings on presentation. (reference intervals are indicated in parenthesis)	Mild macrocytic anemia Intractable metabolic acidosis P-MMA: 5.3 (< 0.28) µmol/L (GC-MS) and P-Hcy: 25.4 (≤15) µmol/L	Severe pancytopenia and macrocytic anemia.	Severe pancytopenia and macrocytic anemia Intractable metabolic acidosis P-MMA: 30.1 µmol/L (GC-MS) P-Hcy: 7 µmol/L	P-MMA: 29 µmol/L (GC-MS)
Follow-up (clinical)	No deterioration Speech delay Normal growth parameters	No deterioration Normal development Normal growth parameters	One deterioration at the age of 4 y Speech delay, social and communication impairment improving with behavioral therapy	One deterioration at the age of 2 y ASD, language delay, speech and responsivity deficit

Methylcobalamin for Autism

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Autism Cases

The management of TC deficiency is pharmacological doses of Cbl. Trakadis et al[27] conducted the largest retrospective observational cohort on TC deficiency. Their recommendation supported the aggressive treatment proposed previously[11] with parenteral hydroxo-Cbl 1 mg or cyano-Cbl 1 mg IM injection weekly. Patients 3 and 4 developed acute anemia while on cyano-Cbl injection every 4 weeks. The 2 patients were started on methyl-Cbl 1 mg injections weekly, and their condition was stabilized immediately until the date of this report. Obviously, we do not know whether this effect was related to change in treatment frequency or change in the form of Cbl administered. As methyl-Cbl is the active coenzyme, it could be considered to use this form of the vitamin. Follow-up and regular monitoring for these patients is an essential part to optimize the treatment regimen.[11,13,27]

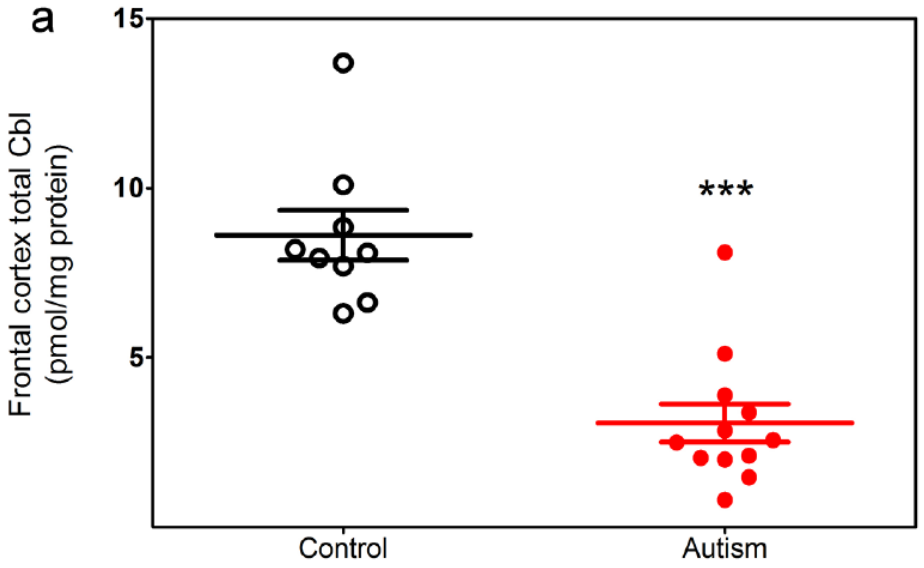
Methylcobalamin for Autism

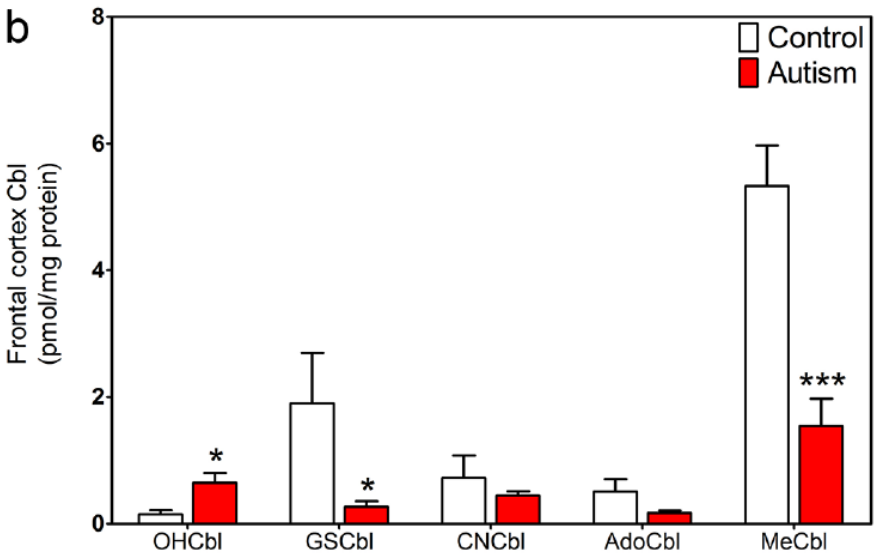
PLOS ONE | **PLoS One**. 2016; 11(1): e0146797.

RESEARCH ARTICLE

Decreased Brain Levels of Vitamin B12 in Aging, Autism and Schizophrenia

Yiting Zhang[1], Nathaniel W. Hodgson[1,2], Malav S. Trivedi[1,3], Hamid M. Abdolmaleky[4], Margot Fournier[5], Michel Cuenod[5], Kim Quang Do[5], Richard C. Deth[1,3]*





Methylcobalamin was 3.1 times lower in the ASD Brain

Methylcobalamin for Autism

PLOS ONE

PLoS One. 2016; 11(1): e0146797.

RESEARCH ARTICLE

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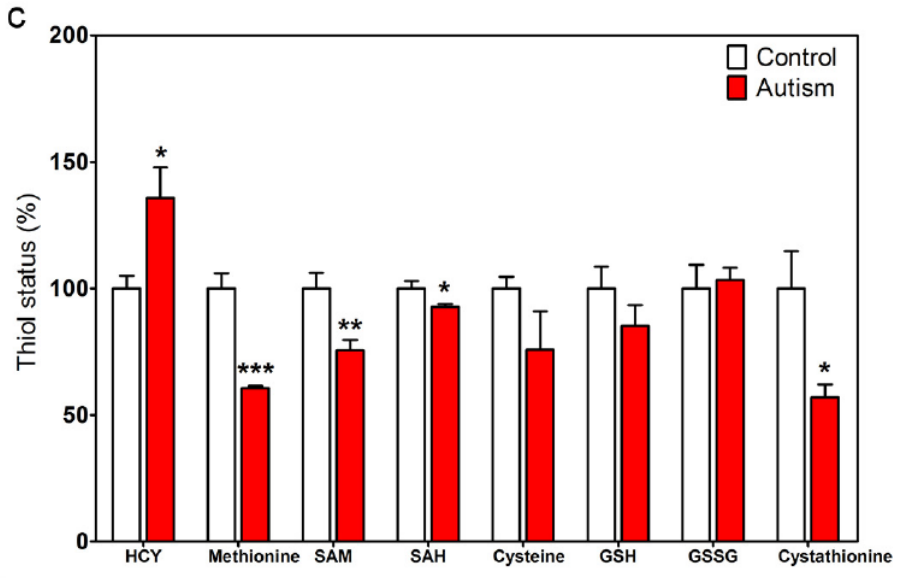

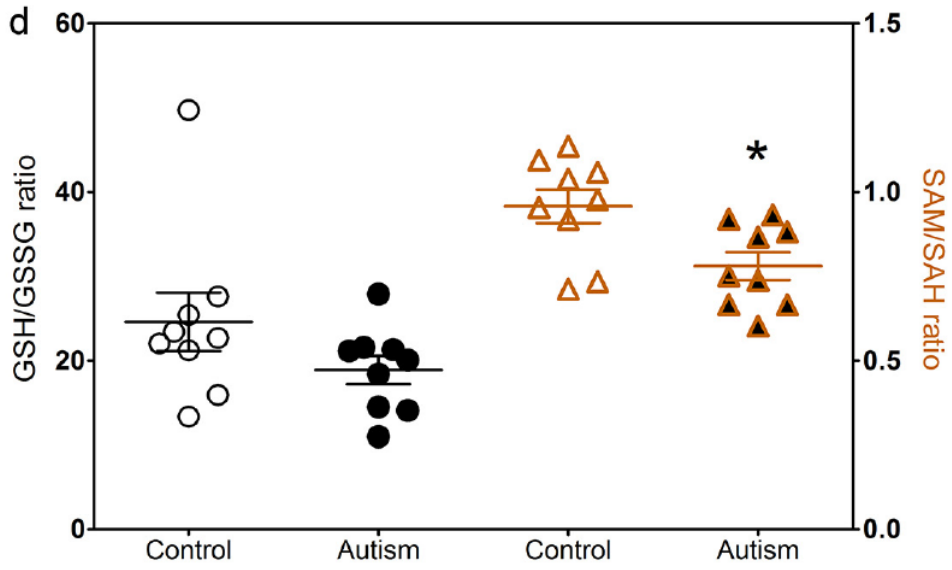

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PLoS One. 2013; 8(2): e56927

PLOS | ONE

Age-Dependent Decrease and Alternative Splicing of Methionine Synthase mRNA in Human Cerebral Cortex and an Accelerated Decrease in Autism

Christina R. Muratore[1], Nathaniel W. Hodgson[1], Malav S. Trivedi[1], Hamid M. Abdolmaleky[2], Antonio M. Persico[3], Carla Lintas[3], Suzanne De La Monte[4], Richard C. Deth[1]*

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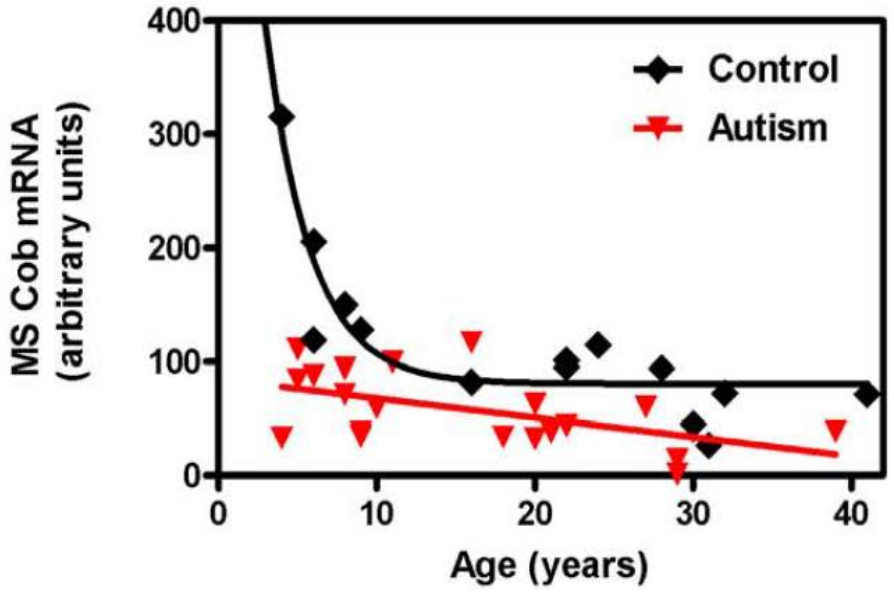

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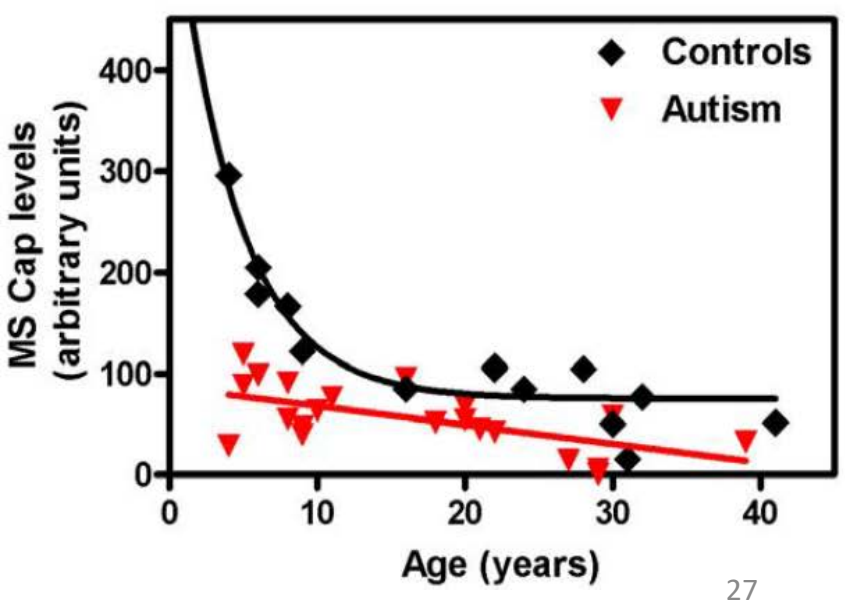

Methylcobalamin for Autism

B12 Intake is Lower in Children with Autism Spectrum Disorder

Review

autism

Autism
1–17
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Differences in food consumption and nutritional intake between children with autism spectrum disorders and typically developing children: A meta-analysis

Patricia Esteban-Figuerola[1,2,3], Josefa Canals[1,2,3], José Cándido Fernández-Cao[1,4] and Victoria Arija Val[1,3,5]

Study or Subgroup	ASD Children Mean	SD	Total	TD Children Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bandini et al., 2010	3.4	1.6	53	4.2	2.3	58	8.6%	-0.40 [-0.77, -0.02]
Castro et al., 2016	4	3.8	49	4.5	4.3	49	8.5%	-0.12 [-0.52, 0.27]
Emond et al., 2010	2.39	0.81	79	2.51	0.86	12901	8.9%	-0.14 [-0.36, 0.08]
Graf-Myles et al., 2013	3.7	2.19	69	4.37	1.76	37	8.5%	-0.32 [-0.73, 0.08]
Johnson et al., 2008	5.28	2.62	19	6.32	2.35	15	7.4%	-0.41 [-1.09, 0.28]
Malhi et al., 2017	0.51	0.24	63	0.51	0.3	50	8.6%	0.00 [-0.37, 0.37]
Marí-Bauset el al., 2014	4.81	3.74	40	5.43	3.26	113	8.6%	-0.18 [-0.54, 0.18]
Marí-Bauset et al., 2016b	5.38	3.95	105	5.36	3.46	495	9.0%	0.01 [-0.20, 0.22]
Meguid et al., 2017	0.39	0.12	80	0.85	0.15	80	8.2%	-3.37 [-3.86, -2.88]
Schmitt et al., 2008	3.3	1.9	20	3.1	2.2	18	7.6%	0.10 [-0.54, 0.73]
Shmaya et al., 2014	2.4	0.9	50	3.3	1.4	41	8.4%	-0.77 [-1.20, -0.35]
Zimmer et al., 2012	4.69	3.03	22	6.66	2.04	22	7.7%	-0.75 [-1.36, -0.14]
Total (95% CI)			649			13879	100.0%	-0.52 [-0.95, -0.09]

Heterogeneity: Tau² = 0.53; Chi² = 175.72, df = 11 (P < 0.00001); I² = 94%
Test for overall effect: Z = 2.38 (P = 0.02)

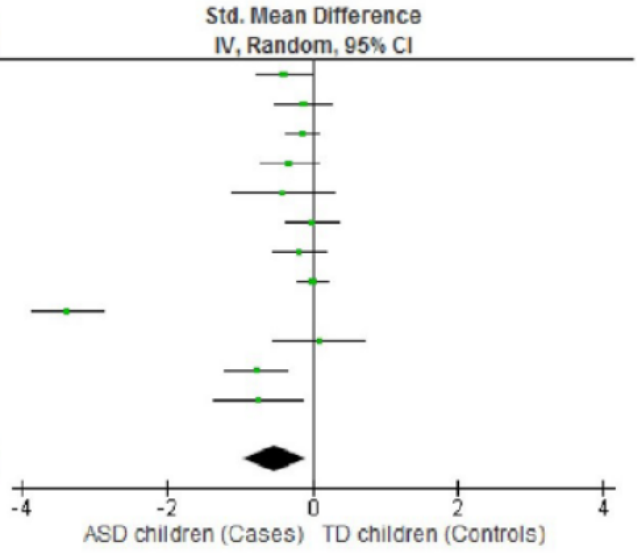

Figure 9. Forest plot of overall standardized mean difference in vitamin B12 intake between TD and ASD children.

Methylcobalamin for Autism

Letter from the President of The Medical Academy of Pediatric Special Needs (MAPS)

Medical Academy
of Pediatric Special Needs

June 1, 2021

To whom it may concern:

The Medical Academy of Pediatrics Special Needs (MAPS) is a group of physicians and other medical providers who treat children with autism and other neurodevelopmental disorders using treatments that target biochemical abnormalities in an attempt to obtain optimal clinical outcomes. Through MAPS, over 1000 physicians and other providers have received training and can be considered a substantial minority. Part of the MAPS treatment protocol involves using Methylcobalamin injections which often lead to quick and obvious clinical improvements. These are an important treatment which is considered standard of care for our group and should continue to be available for compounding as the benefits are high and risks are low.

Sincerely,

Daniel Rossignol MD, FAAFP
President of MAPS
rossignolmd@gmail.com
www.medmaps.org

James Neuenschwander, MD
Co-Chair and Board Member MAPS

MAPS considers Subcutaneous Methylcobalamin as Standard of Care For Children with Autism Spectrum Disorder

Methylcobalamin for Autism

Grants to Study Methylcobalamin in Autism are Not Easy to Get.
Methylcobalamin was seen as Standard of Care and Widely Available
So No Novelty or Need Was Seen for Further Clinical Research

Department of Defense
U.S. Army Medical Research and Materiel Command
Congressionally Directed Medical Research Programs
2016 Autism Research Program
Clinical Trial Award
Peer Review Summary Statement

CDMRP Log Number: AR160056
Grants.gov ID Number: GRANT12254348
Meeting Dates: 12/11/2016 - 12/13/2016
Review Panel: Clinical Trial

Project Duration: 48 months
Direct Costs: $994,595
Total Budget Requested: $1,254,373
Indirect Costs: $259,778

Title: A Safe and Effective Treatment for Children With Autism Targeting Core and Associated Symptoms Through Normalization of Redox, Methylation, and Folate Metabolism
Principal Investigator: Richard Frye

Department of Defense
U.S. Army Medical Research and Materiel Command
Congressionally Directed Medical Research Programs
Fiscal Year 2017 Autism Research Program
Clinical Trial Award
Peer Review Summary Statement

CDMRP Log Number: AR170139
Grants.gov ID Number: GRANT12520280
Meeting Dates: 01/07/2018-01/09/2018
Review Panel: Clinical Trial - Clinical Translation Research

Project Duration: 48 months
Total Budget Requested: $1,142,396
Direct Costs: $998,822
Indirect Costs: $143,574

Title: A Safe and Effective Treatment for Autism Targeting Core Symptoms Through Normalizing Metabolism
Principal Investigator: Richard Frye

Choline Chloride

Nomination for section 503A of the Federal Food, Drug, and Cosmetic Act, to the Pharmacy Compounding Advisory Committee (PCAC)

Paul S. Anderson, ND

for the Nominator,

American Association of Naturopathic Physicians (AANP)

Dietary Requirements:

"Current dietary recommendations for choline are likely too low for some men. In addition, these recommendations did not consider genetic variation as a modulator of dietary requirement because it was assumed that functional polymorphisms would be too rare (<5% of population) to be considered. It is clear that this assumption is not true for SNPs in folate metabolism (where 63% of subjects had at least one allele for the MTHFD1 SNP) or for SNPs in choline metabolism (where 74% of subjects had at least one allele for the PEMT promoter SNP). As discussed above, women with **low dietary choline** intake have a markedly increased risk of **having a baby with neural tube defects** (112). There is solid science in animal models that suggests choline is critical for normal brain development (31). **Choline deficiency** has other health consequences—it is associated with **liver and muscle damage** and with an exaggerated **plasma homocysteine** rise after a methionine load (34). Elevated plasma homocysteine is an independent risk factor for cardiovascular disease and stroke in humans (44,45,77)"
Quote from reference-11

Preterm Birth Nutritional Requirement:

According to the CDC website, there are approximately 374,754 babies born preterm and approximately 1% of all births of babies in the USA have fetal alcohol syndrome. This represents a large amount of new births in the USA that have special nutritional requirements.

There are no FDA approved Choline drugs available for physicians to prescribe. (One exception being parenteral egg-based lipid product)

These infants with special nutritional requirements can go under served in the medical community. Studies are providing valuable insight into the need for available treatment options.

Preterm Infant Need

One study done in preterm infants found that **choline deficiency can be present in preterm infants**.

Breast feeding **does not supply** enough choline to correct deficiency.1 Preterm babies will have higher levels of phosphatidyl choline leading to rapid turnover of choline levels. Decreased choline levels can result in hepatic damage and lung damage over time.1

Choline supplementation can be vital for normal development of preterm births.2,3

Preterm Infant Need

In another study in infants with preterm births Choline was seen increase docosahexaenoic acid (DHA) in preterm infants.4

Levels of these two essential nutrients can fall rapidly after birth in preterm infants and can lead to impaired lean body mass growth of the preterm infants.4

Choline deficiency results in the death of cells. This can lead to poor cellular repair and regeneration.5

Eventually the body can develop fragmented hepatocytes.

Fetal Alcohol Syndrome

In studies with babies with fetal alcohol syndrome, **Choline supplementation is well tolerated and showed improvement in cognitive charateristics**.6,7,8

Choline levels have been shown to be decreased by alcohol exposure to adults. The net result of high demand from infant and mother's exposure to alcohol during the pregnancy, can result in deficiency for the child.9

Fetal Alcohol Syndrome

Choline **supplementation can be beneficial when given during early developmental stages in preterm and fetal alcohol syndrome babies.**[8]

It is needed because of lack of any FDA approved drug treatments currently available.

Choline should be considered for addition to the FDA positive list.

Prenatal Requirements:

"Choline is critical for a number of physiological processes during the prenatal period with roles in membrane biosynthesis and tissue expansion, neurotransmission and brain development, and methyl group donation and gene expression. **Studies in animals and humans have shown that supplementing the maternal diet with additional choline improves several pregnancy outcomes and protects against certain neural and metabolic insults. Most pregnant women in the U.S. are not achieving choline intake recommendations** of 450 mg/day and would likely benefit from boosting their choline intakes through dietary and/or supplemental approaches." 10

Prenatal Continued:

“Choline may be especially important during pregnancy when it modulates proliferation of stem cells needed to form a normal fetus. Furthermore, it may influence brain development throughout gestation, and these influences may continue throughout the life span. Choline deficiency has been associated with liver and muscle damage and increases in homocysteine” 12

“Shaw and colleagues [Am J Epidemiol 2004;160:102–109. PubMed:

15234930] **found an increased incidence of neural tube defects in women consuming less than 300 mg choline per day during pregnancy** compared with women consuming more than 500 mg/d” 12

Meeting Requirements?

Choline was officially recognized as an essential nutrient by the Institute of Medicine (IOM) in 1998. There is a significant variation in the dietary requirement for choline that can be explained by common genetic polymorphisms.

Because of its wide-ranging roles in human metabolism, from cell structure to neurotransmitter synthesis, **choline-deficiency is now thought to have an impact on diseases such as liver disease, atherosclerosis and possibly neurological disorders.**

Meeting Requirements?

Choline is found in a wide variety of foods. Egg yolks are the most concentrated source of choline in the American diet, providing 680 milligrams per 100 grams.

Mean **choline intakes for older children, men, women and pregnant women are far below the Adequate Intake established by the IOM.** 13

“the recommendation remains the same—to **increase choline intake by diet or supplementation to attenuate de novo synthesis and reduce homocysteine levels. [Am J Clin Nutr 2005;82:836–842. PubMed: 16210714] These findings may indicate a need for intervention to ensure optimal choline intakes during pregnancy.”** 13

ASPEN Call for Parenteral Choline Availability

"Although choline and carnitine are not technically vitamins or trace elements, choline is an essential nutrient in all age groups, and carnitine is an essential nutrient in infants, according to the Food and Nutrition Board of the Institute of Medicine. **A parenteral choline product needs to be developed and available**."

Vanek VW, Borum P, Buchman A, Fessler TA, Howard L, Shenkin A, Valentine CJ; Novel Nutrient Task Force, Parenteral Vitamin and Trace Element Working Group; and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.); Novel Nutrient Task Force Parenteral Vitamin and Trace Element Working Group and the American Society for Parenteral and Enteral Nutrition A S P E N. A Call to Action to Bring Safer Parenteral Micronutrient Products to the U.S. Market. Nutr Clin Pract. 2015 Aug;30(4):559-69. doi: 10.1177/0884533615589992. Epub 2015 Jun 25. PMID: 26113560.

Current FDA Approved Product:

"Current parenteral nutrition sources of choline are available as egg phospholipid **in approved lipid products**." [06-09-PCAC-20210609-FDA_Backgrounder.pdf]

Compounding need:

Egg allergy: Adjusted mean incidence of HEA was 1.23% (95% CI 0.98-1.51) considering possible cases among eligible children who were not challenged. Centre-specific incidence ranged from United Kingdom (2.18%, 95% CI 1.27-3.47) 14

References:

1. Bernhard W, Poets CF, Franz AR. Choline and choline-related nutrients in regular and preterm infant growth. Eur J Nutr. 2019;58(3):931-945. doi:10.1007/s00394-018-1834-7.

2. Institute of Medicine, National Academy of Sciences USA(1998) Dietary reference intakes for folate, thiamin, riboflavin,niacin, vitamin B12, panthothenic acid, biotin, and choline, volNational Academies Press, Washington, DC

3. Crawford MA (2000) Placental delivery of arachidonic and docosahexaenoic acids: implications for the lipid nutrition of preterm infants. Am J Clin Nutr 71(suppl):275S–284S

4. Bernhard W, Böckmann K, Maas C, et al. Combined choline and DHA supplementation: a randomized controlled trial. Eur J Nutr. 2020;59(2):729-739. doi:10.1007/s00394-019-01940

5. Buchman AL. The Addition of Choline to Parenteral Nutrition. Gastroenterology. 2009;137(5 SUPPL). doi:10.1053/j.gastro.2009.08.010.

6. Wozniak JR, Fuglestad AJ, Eckerle JK, Kroupina MG, Miller NC, BoysCJ, Brearley AM, Fink BA, Hoecker HL, Zeisel SH, GeorgieffMK (2013) Choline supplementation in children with fetal alcohol spectrum disorders has high feasibility and tolerability. Nutr Res 33:897–904

7. Akison LK, Kuo J, Reid N, Boyd RN, Moritz KM. Effect of Choline Supplementation on Neurological, Cognitive, and Behavioral Outcomes in Offspring Arising from Alcohol Exposure During

8. Development: A Quantitative Systematic Review of Clinical and Preclinical Studies. Alcohol Clin Exp Res. 2018;42(9):1591-1611. doi:10.1111/acer.13817.

9. Zeisel SH (2011) What choline metabolism can tell us about the underlying mechanisms of fetal alcohol spectrum disorders. Mol Neurobiol 44:185–191.

10. Korsmo HW, Jiang X, Caudill MA. Choline: Exploring the Growing Science on Its Benefits for Moms and Babies. Nutrients. 2019;11(8):1823. Published 2019 Aug 7. doi:10.3390/nu11081823

11. Zeisel SH. Choline: critical role during fetal development and dietary requirements in adults. Annu Rev Nutr. 2006;26:229-250. doi:10.1146/annurev.nutr.26.061505.111156

12. Sanders LM, Zeisel SH. Choline: Dietary Requirements and Role in Brain Development. Nutr Today. 2007;42(4):181-186. doi:10.1097/01.NT.0000286155.55343.fa

13. Zeisel SH, da Costa KA. Choline: an essential nutrient for public health. Nutr Rev. 2009;67(11):615-623. doi:10.1111/j.1753-4887.2009.00246.x

14. Xepapadaki P, Fiocchi A, Grabenhenrich L, Roberts G, Grimshaw KE, Fiandor A, Larco JI, Sigurdardottir S, Clausen M, Papadopoulos NG, Dahdah L, Mackie A, Sprikkelman AB, Schoemaker AA, Dubakiene R, Butiene I, Kowalski ML, Zeman K, Gavrili S, Keil T, Beyer K. Incidence and natural history of hen's egg allergy in the first 2 years of life-the EuroPrevall birth cohort study. Allergy. 2016 Mar;71(3):350-7. doi: 10.1111/all.12801. Epub 2015 Dec 22. PMID: 26514330.