HHS Public Access

Author manuscript

J Am Acad Child Adolesc Psychiatry. Author manuscript; available in PMC 2024 August 23.

Published in final edited form as:

J Am Acad Child Adolesc Psychiatry. 2023 November ; 62(11): 1171–1175. doi:10.1016/j.jaac.2023.07.994.

Dr. Johnstone et al. Reply to Dr. Elmrayed

Dr. Jeanette M. Johnstone, PhD,
Oregon Health & Science University, Portland, Oregon, National University of Natural Medicine, Helfgott Research Institute, Portland, Oregon

Dr. L. Eugene Arnold, MD,
The Ohio State University, Columbus, Ohio

Dr. Amelia Villagomez, MD,
University of Arizona College of Medicine, Tucson, Arizona

Dr. Lisa M. Robinette, MS,
The Ohio State University, Columbus, Ohio

Dr. Barbara L. Gracious, MD,
HCA Florida Orange Park Hospital, Orange Park, Florida, Edward Via College of Osteopathic Medicine, Spartanburg, South Carolina

Dr. Hayleigh K. Ast, ND,
Oregon Health & Science University, Portland, Oregon

Dr. Alisha M. Bruton, ND, MS,
Oregon Health & Science University, Portland, Oregon

Dr. Irene E. Hatsu, PhD, RD
The Ohio State University, Columbus, Ohio

We thank Dr. Elmrayed and colleagues[1] for highlighting clinical cautions in using broad-spectrum micronutrients to treat attention-deficit/hyperactivity disorder (ADHD) in children, in particular manganese (Mn) levels. We appreciate the opportunity to provide additional information and rationale for the vitamin and mineral doses contained in the studied formula.

Correspondence to Jeanette Johnstone, PhD, Oregon Health & Science University, 3818 SW Sam Jackson Park Road, Portland, OR 97239; jojeanet@ohsu.edu.

Author Contributions

Conceptualization: Johnstone, Arnold

Data curation: Johnstone, Arnold

Writing — original draft: Johnstone, Arnold, Villagomez, Robinette, Gracious, Ast, Hatsu

Writing — review and editing: Johnstone, Arnold, Villagomez, Robinette, Gracious, Ast, Bruton, Hatsu

The research was performed with permission from the Institutional Review Board at OHSU #16870 and The Ohio State University (OSU) (#2017H0188), the Health Research Ethics Board at University of Calgary (#17–0325) for the University of Lethbridge, and FDA IND#127832 Health Canada (Control #207742).

Disclosure: Please see the disclosure statement in the original article published May 2022.

All statements expressed in this column are those of the authors and do not reflect the opinions of the *Journal of the American Academy of Child and Adolescent Psychiatry*. See the Instructions for Authors for information about the preparation and submission of Letters to the Editor.

We agree that dose is important; as Paracelsus said, "The dose makes the poison."[2] All minerals and fat-soluble vitamins have a toxic level. Prior to starting this study, we obtained oversight and consultation from 2 government agencies: the US Food and Drug Administration (IND#127832) and Health Canada (Control #207742). Risk information was reviewed by institutional review boards at 3 institutions.

Although Table 3 in the original paper by Johnstone *et al.*[3] reports the ingredient amounts from a single capsule, we also provide ingredient doses for 9 and 12 capsules, along with Recommended Dietary Allowance/Adequate Intake (RDA/AI) and Lowest Observed Adverse Effect Level (LOAEL), in Table S2, available online.[3] The published paper stated that doses were between RDA and Tolerable Upper Intake Level (UL), an oversight for which we apologize. More accurately, doses of most nutrients were between RDA/AI and LOAEL, except for magnesium and niacin, which were above LOAEL for participants taking the maximum dose (9 capsules for 6- to 8-year-olds, 12 capsules for 9- to 13-year-olds), as noted in the published protocol.[4] Seven others (copper, manganese, selenium, zinc, vitamin A [retinyl palmitate], vitamin B_6 [pyridoxine], and vitamin B_9 [folate]) were above UL, but below LOAEL. These data are clarified in Table 1[5–8] showing doses for these 9 nutrients and their ULs and LOAELs, and also documented as a correction.[11]

Although 9 of the 36 nutrients in the researched formula were dosed at levels above the UL, only 4 were listed in Supplement 1, available online,[3] along with the following rationale:

> Dietary intake guidelines from the US Institute of Medicine state, "Although members of the general population should be advised not to routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged … as long as these trials employ appropriate safety monitoring of trial subjects. In addition, the UL is not meant to apply to individuals who are receiving a high dose of a nutrient under medical supervision. The UL is typically derived to apply to the most sensitive members of the general population. For this reason, many members of the population may regularly consume nutrients at or even above the UL without experiencing adverse effects."[12]

Dr. Elmrayed raised the concern of manganese being consumed in a "likely-toxic dose range." For participants 6 to 8 years old consuming 9 capsules, the dose equals 7.2 mg/d (UL: 3 mg), and for those 9 to 13 years old taking 12 capsules, 9.6 mg/d (UL: 6 mg). Although these doses are above the ULs, they are below the LOAEL of 15 mg/d and even the No Observed Adverse Effect Level (NOAEL) of 11 mg/d.[9]

Manganese is an essential mineral and necessary as a cofactor for many enzymes, for example, in metabolism, gluconeogenesis, and the antioxidant defense network.[10,13] Several factors affect Mn absorption and/or excretion, including interactions with calcium, magnesium, and iron. High intakes of these minerals (contained in the micro-nutrient formula) decrease absorption of Mn.[14] Manganese absorption also depends on exposure method: inhaled or by contaminated water source differs from ingestion, with toxicity typically related to environmental exposures.[13] Furthermore, as a guard against Mn's

potential toxicity, the body maintains tight homeostasis through intestinal absorption control and biliary excretion.[9]

Dr. Elmrayed cited the O'Neal and Zheng paper[15] regarding concern for a "known association" between dietary Mn and ADHD. Albeit comprehensive, that reference confines potential associations between ADHD and Mn to infant formula, not child dietary intake. To our knowledge, there is no established association between higher dietary Mn intake and risk of developing ADHD. Preliminary evidence from 4 studies of blood and hair Mn showed slightly higher Mn in children with ADHD than in healthy controls,[16] but was contradicted by a more recent study showing the opposite.[17]

Regarding "blood safety measures," to monitor potential toxicities, all US participants had a comprehensive metabolic panel before enrollment and at week 8 to check liver functioning, among other values, as poor liver metabolism may impair elimination of manganese. Comprehensive metabolic panel results were not clinically significant by physician review. We also investigated changes in plasma mineral levels following 8 weeks of supplementation in 77 US participants. Data showed a baseline average manganese concentration of 0.68 mg/L (range, 0–2.10 mg/L). The average change after 8 weeks in the micronutrient group was not significantly different from the change in the placebo group (data presented at AACAP 2022). However, plasma Mn levels may not be an ideal biomarker, as Mn has a 2-hour half-life in blood.[15] Reassuringly, adverse events were not significantly greater with micronutrients than with placebo, even in the corrected table.[18]

Regarding the potential for "serious long-term health effects," safety data for up to 5 years of micronutrient use, including blood values, have been published for children and adults.[19] In addition, a systematic review of micro-nutrient safety, including blood values (n = 144) and adverse event reports (n = 157), found only mild, transitory AEs not attributable to toxicity.[20]

As with any treatment, risks and benefits exist that clinicians consider for each patient. Individuals should consult with their doctor and should be monitored during treatment. Given current data, the benefit–risk ratio continues to appear favorable for micronutrients. Further research is needed on longer-term safety and optimal long-term doses in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was funded by the Foundation for Excellence in Mental Health Care (Dr. Johnstone), the National Center for Complementary and Integrative Health (NCCIH) (K2390281846; 5R90AT00892403, Dr. Johnstone), and NCCIH T32AT002688 (Drs. Johnstone and Bruton), the Gratis Foundation (Dr. Johnstone), the National Center for Advancing Translational Sciences (UL1TR000128; UL1TR002369; 8UL1TR000090-05, OHSU and Ohio State), the Jeffrey Fellowship (Dr. Gracious), and the Calgary Foundation (Dr. Johnstone).

REFERENCES

1. Elmrayed A Dosages of nutrient supplements and potential long-term toxicity in attention-deficit/hyperactivity disorder micronutrient study. J Am Acad Child Adolesc Psychiatry. Published online August 3, 2023. 10.1016/j.jaac.2023.01.027
2. Paracelsus T Die dritte Defension wegen des Schreibens der neuen Rezepte. Septem Defensiones. 1965;1538:508–513.
3. Johnstone JM, Hatsu I, Tost G. Micronutrients for Attention-Deficit/Hyperactivity Disorder in Youths: a placebo-controlled randomized clinical trial. J Am Acad Child Adolesc Psychiatry. 2022;61(5):647–661. 10.1016/j.jaac.2021.07.005 [PubMed: 34303786]
4. Johnstone JM, Leung B, Gracious B, et al. Rationale and design of an international randomized placebo-controlled trial of a 36-ingredient micronutrient supplement for children with ADHD and irritable mood: the Micronutrients for ADHD in Youth (MADDY) study. Contemp Clin Trials Commun 2019;16:100478. 10.1016/j.conctc.2019.100478 [PubMed: 31763491]
5. Huang YH, Zeng BY, Li DJ, et al. Significantly lower serum and hair magnesium levels in children with attention deficit hyperactivity disorder than controls: a systematic review and meta-analysis. Prog Neuro-psychopharmacol Biol Psychiatry. 2019;90:134–141. 10.1016/j.pnpbp.2018.11.012
6. Institute of Medicine, National Academy of Sciences. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. National Academy Press; 1997.
7. Institute of Medicine, National Academy of Sciences. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academy Press; 2000.
8. Institute of Medicine, National Academy of Sciences. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. National Academy Press; 1998.
9. Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academies Press; 2001.
10. Institute of Medicine (US). Panel on Micronutrients. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academies Press; 2002.
11. Correction. J Am Acad Child Adolesc Psychiatry. 2023. 10.1016/j.jaac.2023.07.995. in press.
12. Institute of Medicine (US) Subcommittee on Interpretation and Uses of Dietary Reference Intakes; Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. DRI Dietary Reference Intakes: Applications in Dietary Assessment, Using the Tolerable Upper Intake Level for Nutrient Assessment of Groups 6. Washington (DC): National Academies Press (US); 2000.
13. Buchman AL. Manganese. In: Ross C, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, eds. Modern Nutrition in Health and Disease. 11 ed. Jones & Bartlett Learning; 2014: 238–244.
14. Pauling L Orthomolecular psychiatry: varying the concentrations of substances normally present in the human body may control mental disease. J Nutr Envir Med 1995;5(2): 187–198. 10.1126/science.160.3825.265
15. O'Neal SL, Zheng W. Manganese toxicity upon overexposure: a decade in review. Curr Envir Health Rep 2015;2(3):315–328. 10.1007/s40572-015-0056-x
16. Shih J-H, Zeng B-Y, Lin P-Y, et al. Association between peripheral manganese levels and attention-deficit/hyperactivity disorder: a preliminary meta-analysis. Neuropsychiatr Dis Treat. 2018;1831–1842. 10.2147/NDT.S165378 [PubMed: 30140155]
17. Hawari I, Eskandar MB, Alzeer S. The role of lead, manganese, and zinc in autism spectrum disorders (ASDS) and attention-deficient hyperactivity disorder (ADHD): a case-control study on Syrian children affected by the Syrian crisis. Biol Trace Elem Res 2020;197(1):107–114. 10.1007/s12011-020-02146-3 [PubMed: 32347445]
18. Correction. J Am Acad Child Adolesc Psychiatry. 2022;61:1066. [PubMed: 35533797]
19. Rucklidge JJ, Eggleston MJ, Ealam B, Beaglehole B, Mulder RT. An observational preliminary study on the safety of long-term consumption of micronutrients for the treatment of psychiatric

symptoms. J Altern Complement Med 2019;25(6):613–622. 10.1089/acm.2018.0352 [PubMed: 31081672]

20. Simpson JS, Crawford S, Goldstein E, Field C, Burgess E, Kaplan B. Systematic review of safety and tolerability of a complex micronutrient formula used in mental health. BMC Psychiatry. 2011;11(1):62. 10.1186/1471-244X-11-62 [PubMed: 21501484]

J Am Acad Child Adolesc Psychiatry. Author manuscript; available in PMC 2024 August 23.

TABLE 1

Tolerable Upper Intake Level (UL) and Lowest Observed Adverse Effect Level (LOAEL) of Vitamins and Minerals Dosed Above UL for Children 4 to 13 Years Old, and Safety Rationale

Nutrient	Dose in 9 capsules	UL in children 4 to 8 years	Dose in 12 capsules	UL in children 9 to 13 years	LOAEL	Safety rationale for use under supervision in a clinical trial
Minerals						
Copper	5.4 mg	3 mg	7.2 mg	5 mg	10 mg[a]	Copper is above the UL, but below the No-Observed-Adverse Effect-Level (NOAEL) for adults of 10 mg.[9] The formula also contains zinc, which competes with copper for absorption.
Magnesium[b]	450 mg	110 mg	600 mg	350 mg	360 mg	UL is set because of concerns regarding diarrhea. A 2019 meta-analysis found that children with ADHD had lower Mg levels than those without.[5]
Manganese	7.2 mg	3 mg	9.6 mg	6 mg	15 mg	The LOAEL was not based on actual clinical adverse effects, but on "increases in serum manganese concentrations after 25 days of supplementation." There are no reports of manganese toxicity in children and adolescents.[10]
Selenium	0.15 mg	0.15 mg	0.20 mg	0.28 mg	0.91 mg	"The most frequently reported features of selenosis (chronic toxicity) are hair and nail brittleness and loss…. Intake above the UL may be appropriate for investigation within well-controlled clinical trials … the UL is not meant to apply to individuals who are receiving selenium under medical supervision."[7]
Zinc	36 mg	12 mg	48 mg	23 mg	60 mg	The primary safety concern is that higher levels may result in an imbalance with copper. As the formula also contains copper, this concern is reduced.[9] The formula includes zinc and copper in an accepted ratio (range, 5–10:1).[9]
Vitamins						
B_3 (niacin)[a]	67.5 mg	15 mg	90 mg	20 mg	50 mg	The 2 forms of niacin are grouped together (nicotinic acid and niacinamide [also called nicotinamide]) and UL set low to prevent skin flushing from nicotinic acid. No reports of skin flushing to date with this formula, which contains niacinamide. The IOM acknowledges that the 2 forms are clearly different.[8]
B_6 (pyridoxine)	52.5 mg	40 mg	70 mg	60 mg	500 mg	Neurological issues were reported in 1 adult study at a dose of 500 mg/d.[8] No cases of toxicity have been found with B_6 administration in children.
B_9 (folate)	0.60 mg	0.4 mg	0.80 mg	0.6 mg	5 mg	The UL was set to prevent masking a B_{12} deficiency; the formula contains B_{12}, so the risk of masking B_{12} deficiency is low.[8]
Vitamin A (as retinyl palmitate)	1.27 mg[c]	0.9 mg	1.73 mg	1.73 mg[c]	6.46 mg	There are limited case reports of hypervitaminosis (symptoms related to cerebrospinal fluid pressure: headache vertigo, double vision) above 6 mg/d in young children; the risk of exceeding UL appears to be small. The IOM acknowledges vitamin A intake above UL can be appropriate in controlled clinical trials.[9]

IOM = Institute of Medicine.

[a] Magnesium and niacin doses were above the LOAEL; the others were above the UL, but below the LOAEL.

[b] Copper has a NOAEL for adults; no LOAEL reported.

[c] Dosages for Vitamin A are calculated in milligrams of Retinol Activity Equivalents.