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PSYCHIATRY ACADEMY

Treatment With Nutraceuticals in Pediatric Psychopharmacology

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Disclosures



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Dr. Janet Wozniak has recently received consultation fees from Bristol Myers Squibb and Otsuka.

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She is the author of the book, “Is Your Child Bipolar” published May 2008, Bantam Books.

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FDA Approved Treatments for Pediatric Psychiatric Disorders are Fraught With Annoying and Serious Side Effects, Which May Fuel Reluctance to Diagnose



ADVERSE EVENTS

weight gain

dyslipidemia

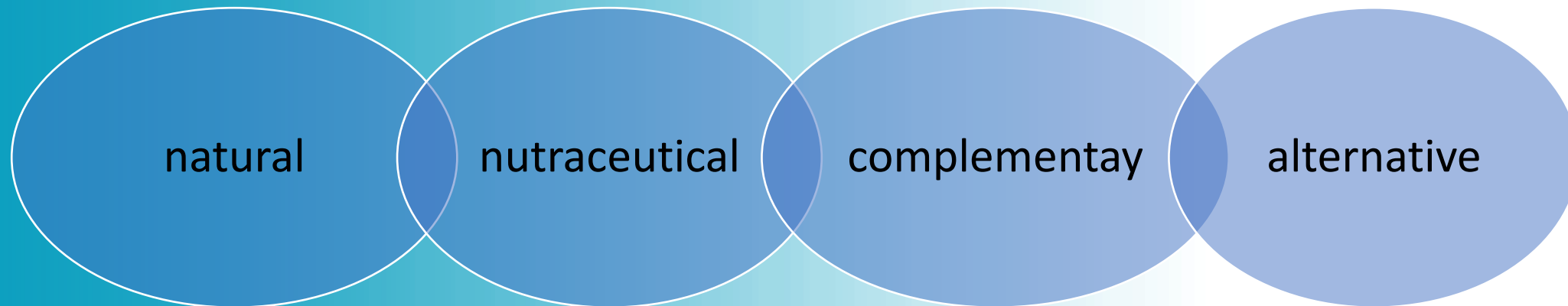
glycemic dyscontrol

risk for tardive dyskinesia



Over-the Counter Dietary Supplements Marketed for Health are not Approved by the FDA

- intended to supplement diet
- not represented as a food or sole item of a meal/diet
- contains vitamins, minerals, amino acids, herbs, natural substances
- could be a concentrate, metabolite, constituent, extract



A fortified food or dietary supplement that provides some health benefit

Clinician Guidelines for the Treatment of Psychiatric Disorders With Nutraceuticals in Adults



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PSYCHIATRY ACADEMY

Disorder	Treatment
Bipolar Depression	Omega-3 (+)
OCD-related disorders	NAC (+)
Schizophrenia Negative Sx	NAC (++) Methylfolate (++) Ginko (+) Vitamin D (+)
ADHD	Micronutrients (+) Vitamin D (+)
Unipolar Depression	St John's wort (+++) Curcumin (++) Saffron (++) Lavender (+)
Anxiety Related Disorders	Ashwagandha (++) Lavender (++) Galphimia (+)

Literature Search

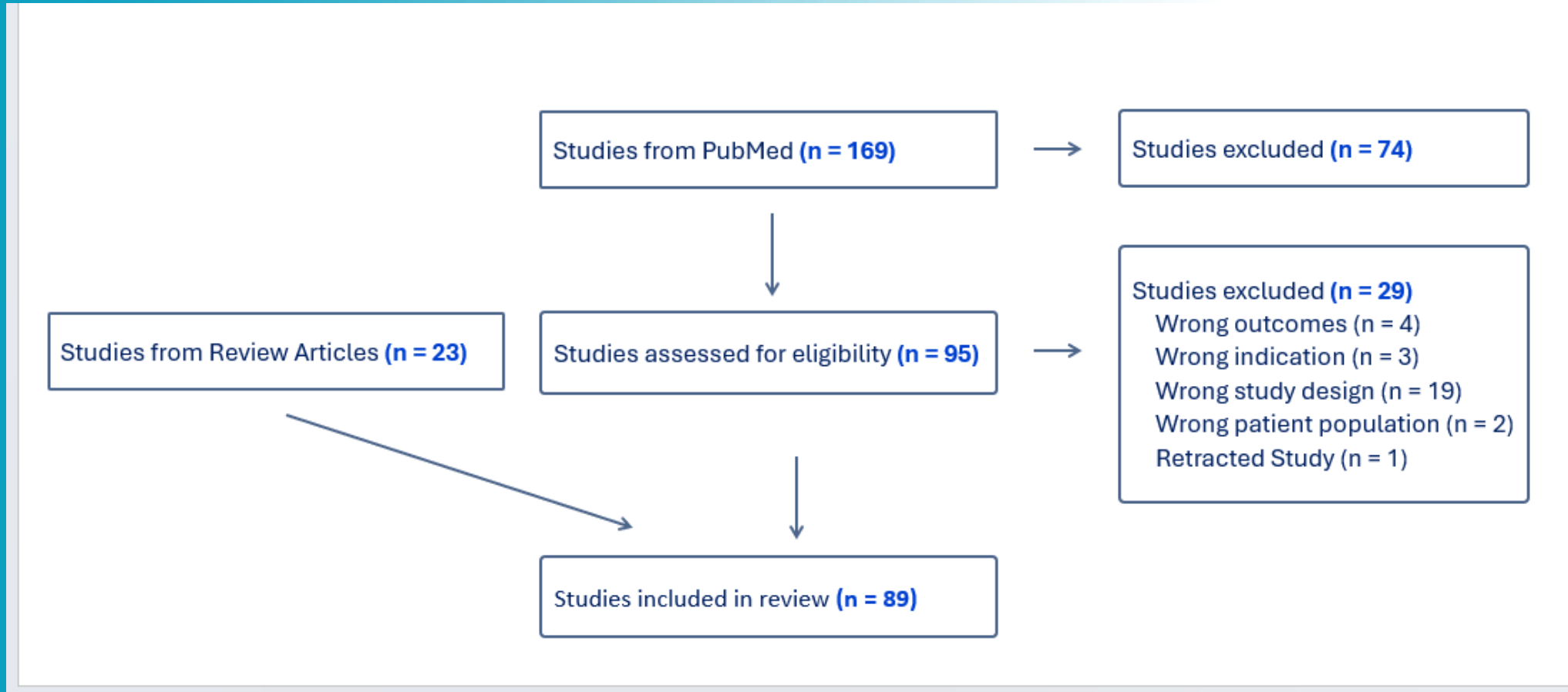
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Criteria: Clinical Trial and Randomized Controlled Trial

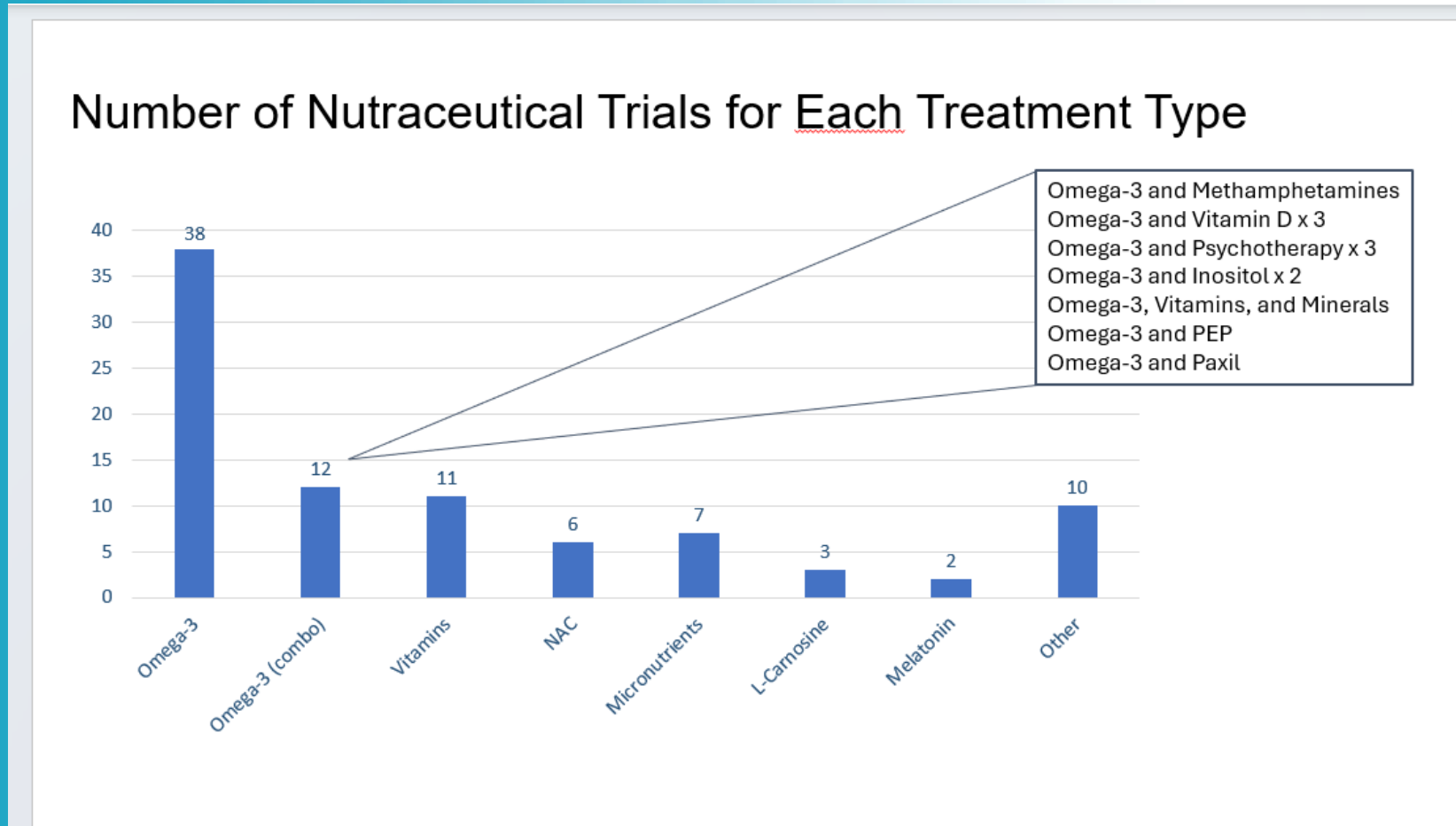


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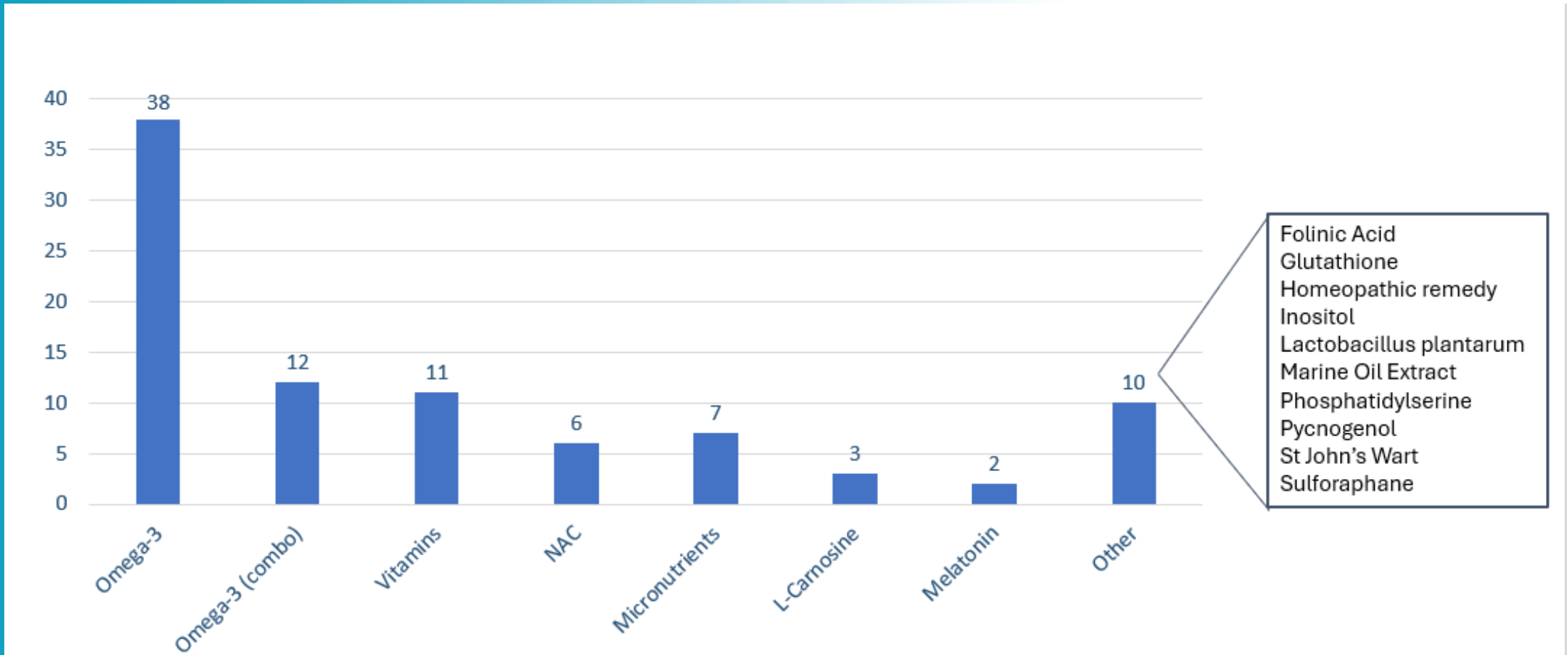
PSYCHIATRY ACADEMY



Number of Nutraceutical Trials for Each Treatment Type

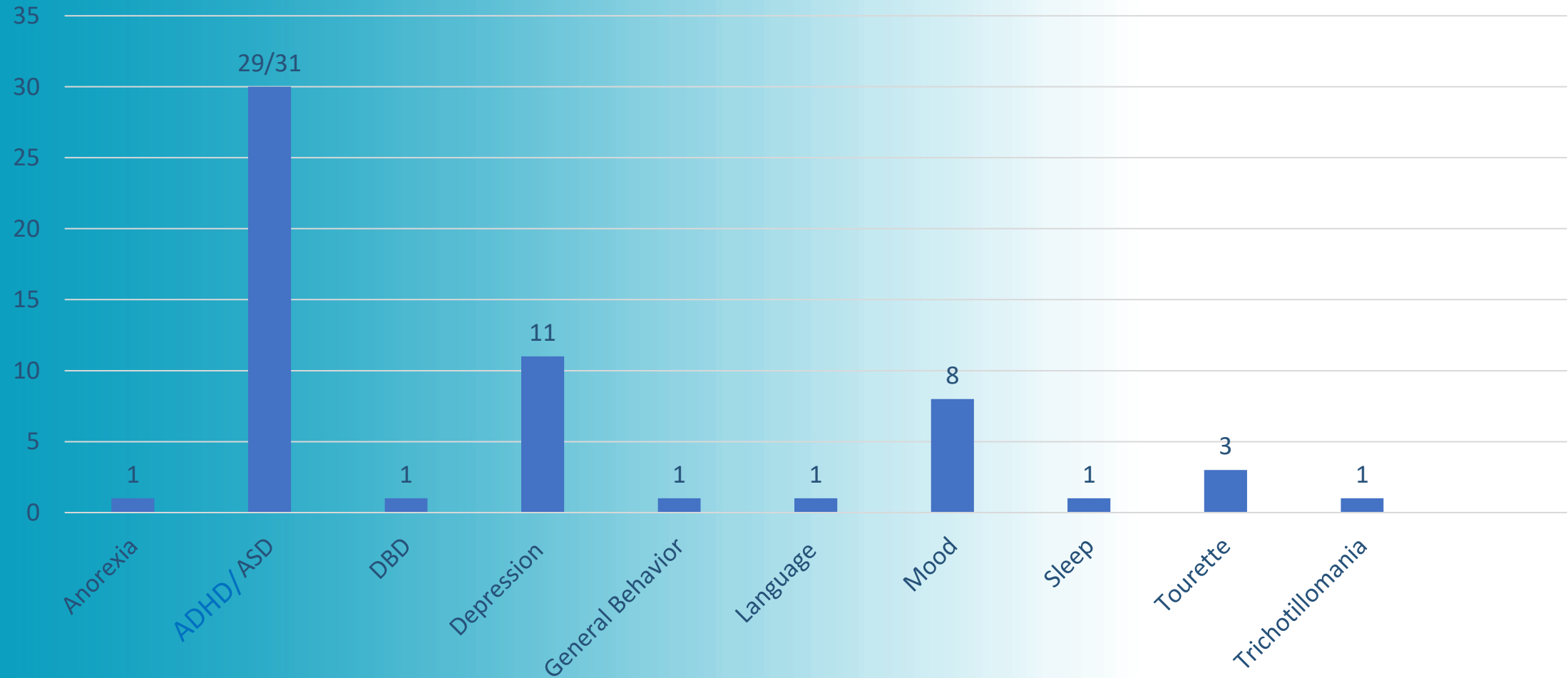


Number of Nutraceutical Trials for Each Treatment Type





Number of Nutraceutical Trials by Targets





Treatment Positive trials/Total trials (percent +)

Folinic Acid	1/1 (100%)
Glutathione	0/1 (0%)
Homeopathic remedy	1/1 (100%)
Inositol	0/1 (0%)
Lactobacillus plantarum	1/1 (100%)
L-Carnosine	3/3 (100%)
Marine Oil Extract	0/1 (0%)
Melatonin	2/2 (100%)
Micronutrients	7/7 (100%)
NAC	3/6 (50%)
Omega-3	24/38 (63%)
Omega-3 (combo)	12/12 (100%)
Phosphatidylserine	1/1 (100%)
Pycnogenol	1/1 (100%)
St John's Wart	0/1 (0%)
Sulforaphane	1/1 (100%)
Vitamins	10/11 (91%)

Dark Green- 2+ positive trials (none negative)

Light Green- >50% positive trials

Orange- replication required

Red- pursue additional trials if warranted

Treatment	Positive trials/Total trials (percent +)
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L-Carnosine	3/3 (100%)
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Melatonin	2/2 (100%)
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Micronutrients	7/7 (100%)
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NAC	3/6 (50%)
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Omega-3	24/38 (63%)
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Omega-3 (combo)	12/12 (100%)
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Vitamins	10/11 (91%)
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Dark Green- 2+ positive trials (none negative)

Light Green- >50% positive trials

Omega-3s 24/38 (63%) 12/12 (100%)

Vitamins 10/11 (91%)

Micronutrients 7/7 (100%)

Melatonin 2/2 (100%)

NAC 3/6 (50%)

L-Carnosine 3/3 (100%)



Omega-3 – Cell Membrane Component

- Types:

- ALA (found in plants)
- DHA
- EPA (found in seafood)

Sources:

fatty fish (salmon,
mackerel)

Flaxseed

Chia seeds

Fish oil supplements



Omega-3 (ADHD-Positive trials)

Trial	Target	Effective	N	Age (years)	Time	Treatment
Stevens 2003	ADHD + DBD	Yes	50	6-13	4 months	EPA (80 mg) + DHA (480 mg) + AA (40 mg) + GLA (96mg) + alpha-tocopheryl acetate (24mg) or placebo
Johnson 2009	ADHD	Yes	75	8-18	3 months	EPA (558 mg) + DHA (174 mg) + gamma linoleic acid (60 mg) + Vitamin E (10.8 mg) or placebo
Gustafsson 2010	ADHD	Yes	92	7-12	15 weeks	EPA (500 mg) or placebo
Hariri 2012	ADHD	Yes	103	6-12	8 weeks	EPA (635 mg) + DHA (195mg) or placebo
Johnson 2012	ADHD	Yes	75	8-18	3 months	EPA (558 mg) + DHA (174 mg) + gamma linoleic acid (60 mg) and Vitamin E (10.8 mg) or placebo
Richardson 2012	ADHD	Yes	74	7-9	16 weeks	DHA (600 mg) or placebo
Bos 2015	ADHD	Yes	89	8-14	16 weeks	EPA (650 mg) + DHA (650 mg) or placebo
Milte 2015	ADHD	Yes	90	6-13	4 months each tx	EPA (1,109 mg) + DHA (108 mg) or EPA (264 mg) + DHA (1,032 mg) or placebo
Chang 2019	ADHD	Yes	92	6-18	12 weeks	EPA (1200 mg) or placebo
Dopfner 2021	ADHD	Yes	40	3-6	4 months	EPA (372 mg) + DHA (116 mg) + GLA (40 mg) or placebo

Ranges

Sample Size



40 to 103

Age



3 to 18

Dose



EPA=80-1200mg
DHA=108-480mg

Time



3-4 months

Omega-3 (ADHD- Negative trials)

Trial	Target	Effective	N	Age (years)	Time	Treatment
Hirayama 2004	ADHD	No	40	6-12	2 months	DHA (3.6g/week) in foods or control foods
Raz 2009	ADHD	No	73	7-13	7 week	linoleic acid (480 mg) + alpha-linolenic acid (120 mg) or vitamin C placebo
<u>Matsudaira 2015</u>	ADHD	No	76	12-16	12 weeks	EPA (558 mg) + DHA (174 mg) + γ-linoleic acid (60 mg) + and vitamin E (9.6 mg) or placebo
Cornu 2018	ADHD	No	162	6-15	3 months	EPA (336-672 mg) + DHA (84-168 mg) + vitamin A (100 µg) + vitamin D (1.25 µg) and vitamin E (3.5 mg) or placebo
<u>Crippa 2019</u>	ADHD	No	50	7-14	6 months	DHA (500 mg) or placebo
Carucci 2022	ADHD	No	160	6-12	6 months	EPA (558 mg) + DHA (174 mg) or placebo

Ranges

Sample Size



40 to 162

Age



6 to 16

Dose



EPA=336-558mg
DHA=84-174mg

Time



2-6 months



Omega-3 (ASD)

Trial	Target	Effective	N	Age (years)	Time	Treatment
<u>Amminger 2007</u>	ASD (core)	Yes	13	5-17	6 week	EPA (840 mg) + DHA (700 mg) or placebo
<u>Parellada 2017</u>	ASD (core)	Yes	68	5-17	8 weeks	EPA (577.5 mg) + DHA (385 mg) + vitamin E (385 mg) for ages 5-11 or EPA (385 mg) + DHA (462 mg) + vitamin E (2.01mg) for ages 12-17 or placebo
<u>Keim 2018</u>	ASD (core)	Yes	31	18-38 months	90 days	EPA (338 mg) + DHA (225 mg) + GLA (83 mg) or placebo
<u>Doaei, 2021</u>	ASD (core)	Yes	54	5-15	8 weeks	EPA (180 mg) + DHA (120 mg) or placebo
Boone 2022	ASD (behavior and sleep)	Yes	31	18-38 months	90 days	EPA (338 mg) + DHA (225 mg) or placebo
Bent 2011	ASD (hyperactivity)	No	27	3-8	12 weeks	EPA (700 mg) + DHA (460 mg) or placebo
Bent 2014	ASD (hyperactivity)	No	57	5-8	6 weeks	EPA (700 mg) + DHA (460 mg) or placebo

Ranges

Sample Size



13-68

Age



3-17

Dose



EPA=180-840 mg
DHA=120-700 mg

Time



6-12 months



Omega-3 (Depression)

Trial	Target	Effective	N	Age (years)	Time	Treatment
Nemets 2006	Depression	Yes	20	6-12	16 weeks	EPA (400 mg) + DHA (200 mg) or placebo
Trebaticka 2020	Depression	Yes	60	7-18	12 weeks	EPA (1000 mg) + DHA (750 mg) or placebo
McNamara 2022	Depression	Yes	39	9-21	12 week	EPA (1350 mg) + DHA (780 mg) or placebo
Gabbay 2018	Depression	No	51	12-19	10 weeks	EPA (2400 mg) + DHA (1200 mg) or placebo
McNamara 2020	Depression	No	56	9-21	12 week	EPA (450 mg) + DHA (260 mg) or placebo
Amminger 2024	Depression	No	233	15-25	12 weeks	EPA (840 mg) + DHA (560 mg) or placebo

Ranges

Sample Size



20-233

Age



6-25

Dose



EPA=400-2400 mg
DHA=200-1200 mg

Time



10-16 months



Omega-3 (Mood)

Trial	Target	Effective	N	Age (years)	Time	Treatment
Gracious 2010	Bipolar	Yes	51	6-17	16 weeks	flax oil capsules α -LNA (6.6 grams) or placebo
Arnold 2017	Mood disorders	Yes	95	7-14	12 weeks	EPA (1400 mg) + DHA (200 mg), psychoeducation, both, or placebo

Ranges

Sample Size



51-96

Age



6-17

Time



12-16 weeks



Omega-3 (other)

Trial	Target	Effective	N	Age (years)	Time	Treatment
<u>Amminger 2013</u> <u>Amminger 2015</u>	Psychosis	Yes	15	13-25	12 weeks f/u 6.7 years	EPA (700 mg) + DHA (480 mg) + vitamin E (7.6 mg) or placebo
Montgomery 2014	Sleep	Yes	395	7-9	16 weeks	DHA (600 mg) or placebo
Sheppard 2017	Language (ASD risk)	Yes	31	18-38 months	3 months	EPA (338 mg) + DHA (225 mg) or placebo
<u>Gabbay 2012</u>	Tourette	No	33	6-18	20 weeks	O3FA (6000 mg) or placebo
Dean 2014	DBD (aggression)	No	21	7-14	6 weeks	EPA (400 mg) + DHA (2000 mg) or placebo
Manos 2018	Anxiety (anorexia)	No	24	12-16 female	12 weeks	EPA (2120 mg) + DHA (600 mg) or placebo



Omega-3 Combination

Trial	Target	Effective	N	Age (years)	Time	Treatment
Barragan 2017	ADHD	Yes	90	6-12	12 weeks	MPH (0.5mg-1mg/kg) or EPA (558 mg) + DHA (174 mg) or both
Mazahery 2019, 2020	ASD (core)	Yes	73	2.5-8	12 month	Vit D (2000 IU/day), DHA (722 mg), both or placebo
Mazahery 2019	ASD (irritability + hyperactivity)	Yes	111	2.5-8	12 month	Vit D (2000 IU/day), DHA (722mg), both or placebo
Wozniak 2015, 2022	BPD	Yes	24, 52	5-12	12 week	Inositol (722 mg) + placebo, EPA (975 mg) + DHA (675 mg) + placebo, or inositol and Omega-3
Fristad 2015	BPD	Yes	23	7-14	12 weeks	Psychoed psychotherapy or EPA (1400 mg) + DHA (200 mg), or both
Fristad 2019	BPD/MDD		72	7-14	12 weeks	
Fristad 2021			39	9-19	f/u 2-5 yrs	
Li 2024	Depression	Yes	71	13-24	12 weeks	Paxil (20 mg) +/- EPA (1941 mg) + DHA (759 mg)
Young 2017	Depression	Yes	72	7-14	12 weeks	PEP + omega-3 (1400 mg EPA, 200 mg DHA, 400 mg other), PEP monotherapy, omega-3 monotherapy, or placebo
Tammam 2016	TD	Yes	196	13-16	12 week	Multivitamins/minerals + EPA (165 mg) + DHA (116 mg) or placebo

Ranges

Sample Size



24-196

Age



2.5-24

Time



12 weeks-
2 months



Omega-3 Grade

Targets	Grade	Explanation
ADHD	1B	10/ 16 trials positive 1 positive trial in combination with MPH
ASD (core)	2B	4 positive trials 1 large positive trial adjunct with Vit D
ASD (behavior and sleep)	2C	1 small trial
ASD (hyperactivity)	2C	2 negative trials hyperactivity (small and medium Ns) 1 large positive trial adjunct with Vit D
Anxiety (anorexia)	Do not recommend	1 negative trial
DBD (aggression)	Do not recommend	1 negative trial
Depression	2A	3/6 trials positive, the largest sample studied was negative 1 pos trial adjunct with PEP; 1 pos trial adjunct with Paxil
Language (ASD risk)	2C	1 trial positive N=31 18-38 months
Mood/bipolar	1B	2 positive trials large Ns 3 positive trials adjunct with PEP; 1 positive trial adjunct with inositol, 1 negative trial DBD/ aggression small N and short length 6 weeks
Psychosis	2C	1 positive trial small N
Sleep	2C	1 positive trial DHA small improvements only in the small subsample narrow age range 7-9
Tourette	Do not recommend	1 negative
TD	Do not recommend	1 negative



Vitamins- Varied Mechanisms of Action

- 13 types:
 - Vitamin A
 - Vitamin B complex (B1, B2, B3, B5, B6, B7, B9, B12)
 - Vitamin C
 - Vitamin D
 - Vitamin E
 - Vitamin K



Vitamins- ADHD

Trial	Target	Effective	N	Age (years)	Time	Treatment
<u>Mohammadpour 2018</u>	ADHD	Yes	62	5-12	8 weeks	Vitamin D (2000 IU) or placebo and methylphenidate
<u>Elshorbagy 2018</u>	ADHD	Yes	90	6-14	12 weeks	Vitamin D3 (3000 IU) or placebo and methylphenidate
<u>Dehbokri 2019</u>	ADHD	Yes	96	2 - 18	6 weeks	Vitamin D3 (50,000 IU/week) or placebo
<u>Honarvar 2022</u>	ADHD	Yes	75	6 - 12	3 months	Vitamin D3 (2,000 IU/day) or placebo
<u>Rahmani 2022</u>	ADHD	Yes	120	6 -15	12 weeks	Vitamin D3 pearl (50,000 IU/ week) neurofeedback, both, or none
<u>Mirhosseini 2024</u>	ADHD	Yes	42	7 -13	2 months	Vitamin D3 (50,000 IU/week) or placebo

Ranges

Sample Size



42 to 120

Age



2 to 18

Dose



2000-7000
IU/day

Time



6 weeks-
3 months



Vitamins- Depression

Trial	Target	Effective	N	Age (years)	Time	Treatment
Amr 2013	Depression	Yes	24	7 - 14	6 months	Vitamin C (1000 mg/day) or placebo
<u>Libuda 2020</u>	Depression	Yes	113	11 - 19	4 weeks	Vitamin D3 and TAU (2640 IU/day) or placebo

Ranges

Sample Size



23 to 113

Age



7 to 19

Time



4 weeks-
6 months



Vitamins- ASD

Trial	Target	Effective	N	Age (years)	Time	Treatment
Hendren 2016	ASD (core)	Yes	57	3-7	8 weeks	Vitamin Methyl B12 (75 µg/kg) or placebo (every 3 days)
<u>Javadfar 2020</u>	ASD (core)	No	43	3 - 13	15 weeks	Vitamin D drop (300 IU/kg up to a maximum of 6000 IU daily) or placebo

Ranges

Sample Size



43 to 57

Age



3 to 13

Time



8-15 weeks



Vitamins- Tourette

Trial	Target	Effective	N	Age (years)	Time	Treatment
Rizzo 2022	Tourette	Yes	34	4-17	2 months	Vitamin B6 (2.8 mg/day) and L-Theanine (200 mg/day) or placebo

Ranges

Sample Size



34

Age



4 to 17

Time



2 months



Vitamins - Grade

Target	Grade Score	Explanation
ADHD	1C	6 trials for D vitamins, large N, 2 as adjunct to MPH, small improvements in most trials
ASD (core)	Vit D Not recommended 2C for <u>Vit B12</u>	Vit D one negative trial Vit B12 one pos trial
Depression	2C for <u>Vit C</u> 2B for <u>Vit D</u>	One small trial for Vit C One large trial for Vit D
Tourette	2C	One small trial Vitamin B6 and L-Theanine



Vitamins and Minerals Micronutrients

- Essential micronutrients (vitamins & minerals) needed in small amounts for healthy development and function
- Given small improvements, combinations of natural treatments with synergistic mechanisms of action are promising
- Easy to take just one supplement
- Child friendly formats (gummies, drops)



Vitamin & Minerals Micronutrients- ASD

Trial	Target	Effective	N	Age (years)	Time	Treatment
Adams 2004	ASD (core)	Yes	20	3-8	3 months	Multivitamin/ mineral supplement (details unavailable)
Adams 2011	ASD (core)	Yes	141	3-60	3 months	vitamin/mineral supplement
Adams 2018	ASD (core)	Yes	117	3-58	12 months	vitamin/mineral supplement, g essential fatty acids, Epsom salt baths, carnitine, digestive enzymes, and a healthy gluten-free, casein-free, soy-free (HGCSF) diet
Adams 2022	ASD (core)	Yes	161	1-74	NA (Survey)	ANRC-EP vitamin/mineral supplement

Ranges

Sample Size



20-161

Age



3 to 60

Time



3 to 12 months



Vitamin & Minerals Micronutrients- ADHD

Trial	Target	Effective	N	Age (years)	Time	Treatment
Darling 2019	ADHD	Yes	93	7 - 12	12 months	Broad-spectrum micronutrient (details unavailable)
Johnstone 2022	ADHD	Yes	135	6-12	8 weeks	Micronutrients
<u>Rucklidge 2018</u>	ADHD	Yes	93	7-12	10 weeks	Micronutrients

Ranges

Sample Size



93-135

Age



6 to 12

Time



8 weeks to 12 months



Vitamin & Minerals Micronutrients: Vitamins Dose

Vitamin	Adams 2011	Adams 2018	Adams 2022	Darling 2019	Johnstone 2022	Rucklidge 2018	Range
A	2000 IU	975 IU	2000 IU	4608 IU	1738 mcg	4608 IU	975 – 4608 IU
C	600 mg	500 mg	300 mg	480 mg	600 mg	480 mg	300 – 1000 mg
D	300 IU	1000 IU	2500 IU	2400 IU	72 mcg	2400 IU	300 – 2400 IU, 73 mcg
E	150 IU	150 IU	67 IU	288 IU	234 mg	288 IU	67 – 288 IU, 234 mg
Mixed Tocopherol	0	0	55 mg	0	0	0	55 mg
K	0	55 mcg	300 mcg	24 mcg	120 mcg	24 mcg	24 – 300 mcg
B1 Thiamin	20 mg	20 mg	30 mg	48 mg	60 mg	48 mg	20 – 60 mg
B2 Riboflavin	20 mg	40 mg	40 mg	14.4 mg	18 mg	14.4 mg	14.4 – 40 mg
B3 Niacin	25 mg	35 mg	60 mg	72 mg	90 mg	72 mg	25 – 90 mg
B5 (pantothenic acid)	15 mg	30 mg	30 mg	24 mg	30 mg	24 mg	15 – 30 mg
B6	40 mg	40 mg	40 mg	56.4 mg	69.9 mg	56.4 mg	40 – 69.9 mg
B9 (Folate)	550 mcg	600 mcg	300 mcg	1200 mcg	1332 mcg	639.6 mcg	300 – 1332 mcg
B12	500 mcg	500 mcg	600 mcg	720 mcg	900 mcg	720 mcg	500 – 900 mcg
Biotin	150 mcg	225 mcg	500 mcg	864 mcg	1080 mcg	864 mcg	150 – 1080 mcg

Vitamin & Minerals

Micronutrients: Minerals Dose



Ingredient	Adams 2011	Adams 2018	Adams 2022	Darling 2019	Johnstone 2022	Rucklidge 2018	Range
Calcium	100 mg	70 mg	200 mg	1056 mg	1320 mg	1056 mg	70 – 1320 mg
Chromium	70 mcg	70 mcg	70 mcg	499.2 mcg	624 mcg	504 mcg	70 – 624 mcg
Copper	0	0	0	6 mg	7.2 mg	5.8 mg	5.8 – 7.2 mg
Iodine	100 mcg	100 mcg	100 mcg	163.2 mcg	204 mcg	163.2 mcg	100 – 163.2 mcg
Iron	0	0	0	10.8 mg	12.8 mg	10.8 mg	10.8 – 12.8 mg
Lithium	500 mcg	350 mcg	350 mcg	0	0	0.8 mg	350 mcg – 0.8 mg
Magnesium	100 mg	100 mg	200 mg	480 mg	600 mg	480 mg	100 – 600 mg
Manganese	3 mg	1 mg	0.5 mg	7.2 mg	9.6 mg	7.7 mg	0.5 – 9.6 mg
Molybdenum	150 mcg	100 mcg	100 mcg	155.2 mcg	144 mcg	120 mcg	100 – 150 mcg
Phosphorus	0	0	0	672 mg	840 mg	672 mg	672 – 840 mg
Potassium	50 mg	50 mg	50 mg	192 mg	240 mg	192 mg	50 – 240 mg
Selenium	22 mcg	40 mcg	50 mcg	163.2 mcg	204 mcg	168 mcg	22 – 204 mcg
Sulfur	500 mcg	0	0	0	0	0	500 mcg
Zinc	12 mg	15 mg	15 mg	38.4 mg	48 mg	38.4 mg	12 – 48 mg

Vitamin & Minerals Micronutrients: Other Nutrients Dose



Ingredient	Adams 2011	Adams 2018	Adams 2022	Darling 2019	Johnstone 2022	Rucklidge 2018	Range
Carnitine	0	200 mg	300 mg	0	0	48 mg	48 – 300 mg
Methylsulfonylmethane	500 mg	500 mg	500 mg	0	0	0	500 mg
Taurine	0	0	514mg	0	0	0	514 mg
Vanadium	0	25 mcg	0	0	0	1.0 mg	1 – 25 mg
Boron	0	250 mcg	0	0	0	1.9 mg	250 mcg – 1.9 mg
Choline	250 mcg	250 mg	250 mg	0	192 mg	432 mg	192 – 432 mg
Inositol	100 mg	100 mg	100 mg	0	0	144 mg	100 – 144 mg
Mixed Carotenoids	3.6 mg	5525 IU	6000 IU	0	0	0	5525 – 600 IU, 3.6 mg
CoQ10	50 mg	50 mg	100 mg	0	0	0	50 – 100 mg
NAC	50 mg	45 mg	100 mg	0	0	24 mg	24 – 100 mg
Riboflavin	0	0	0	0	18 mg	14.4 mg	14.4 – 18 mg
Alpha-Lipoic Acid	0	0	0	0	0	399.6 mg	399.6 mg
Mineral Wax	0	0	0	0	0	150 mg	150 mg
Grape Seed Extract	0	0	0	0	0	36 mg	36 mg
Ginkgo Biloba Leaf Extract	0	0	0	0	0	28.8 mg	28.8 mg
Methionine	0	0	0	0	0	24 mg	24 mg
Lithium Orotate	0	0	0	0	0	0.8 mg	0.8 mg
Nickel	0	0	0	0	0	0.024 mg	0.024 mg

Vitamin & Minerals Micronutrients- Grade



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Targets	Grade	Explanation
ASD (core)	1C	4 large trials, complicated combination of nutrients, unclear which are active and at what dose
ADHD	1C	3 large trials, complicated combination of nutrients, unclear which are active and at what dose



Melatonin

Trial	Target	Effective	N	Age (years)	Time	Treatment
Maras 2018	ASD (insomnia)	Yes	95	2-17	13 weeks <u>39 week</u> f/u	Prolonged release melatonin (2/5 mg) or placebo
Schroder 2019	ASD or SMS (insomnia)	Yes	125	2-17	13 weeks	Prolonged release melatonin (2/5 mg) or placebo

Ranges

Sample Size



31-70

Age



2-17

Dose



2/5 mg/day

Time

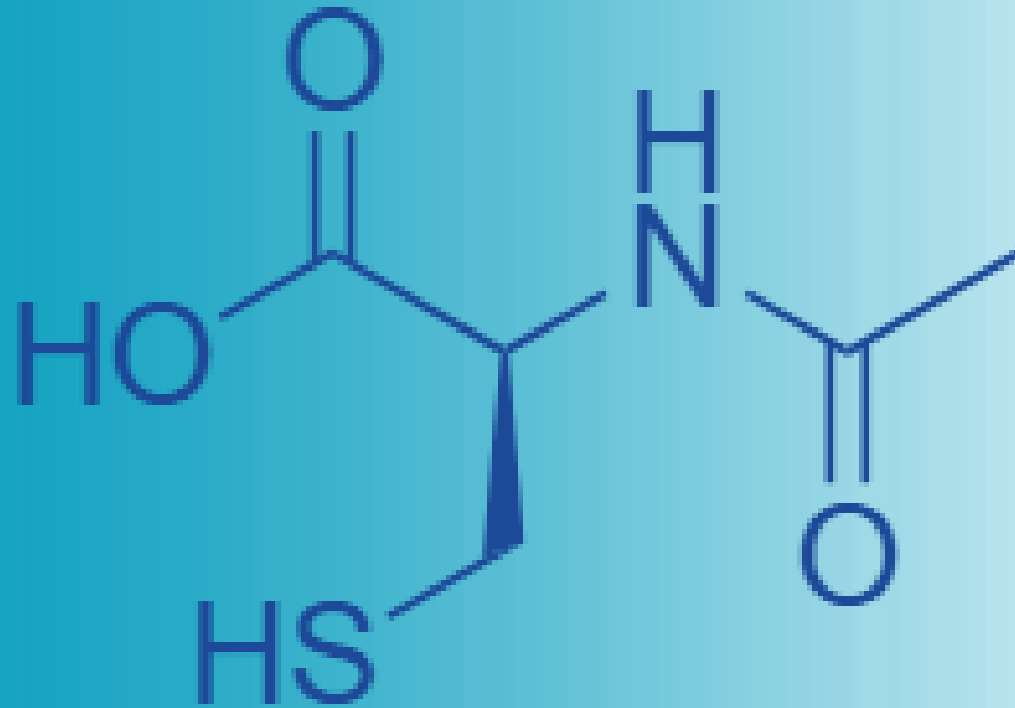


13 weeks

Targets	Grade	Explanation
ASD (insomnia)	2B	2 large positive trials



N-Acetylcysteine (NAC)



- Synthetic L-cysteine
- Precursor for GSH
- Modulates oxidative stress, mitochondrial dysfunction, apoptosis, and inflammation



NAC- ASD

Trial	Target	Effective	N	Age (years)	Time	Treatment
Hardan 2012	ASD (behavior disturbance)	Yes	33	3- 12	12 weeks	NAC (900 - 1800 mg/day) or placebo
<u>Ghanizadeh 2013</u>	ASD (irritability)	Yes	40	3.5-16	8 weeks	NAC (1200 mg/day) + risperidone or placebo + risperidone
<u>Nikoo 2015</u>	ASD (irritability)	Yes	40	4-12	10 weeks	NAC (900 mg/day)+ risperidone or placebo + risperidone
Wink 2016	ASD (core)	No	31	4 - 12	12 weeks	NAC (60 mg/kg/day) or placebo

Ranges

Sample Size



31 to 40

Age



3 to 16

Dose



900-1800
mg/day

Time



8-12 weeks



NAC- Other

Trial	Target	Effective	N	Age (years)	Time	Treatment
Bloch 2016	Tourette	No	31	8 - 17	12 weeks	NAC (1200 - 2400 mg/day) or placebo
Bloch 2013	Trichotillomania	No	39	8 - 17	12 weeks	NAC (up to 2400 mg/day) or placebo

Ranges

Sample Size



31 to 39

Age



8 to 17

Dose



1200-2400
mg/day

Time



12 weeks



NAC- Grade

Trial	Grade Score	Explanation
ASD (core)	Not recommended	1 negative study
ASD (irritability)	1B	Positive in 2 Larger samples as adjunct to risperidone
ASD (behavior disturbance)	1C	Small N positive RCT, and positive trials for 'irritability
Tourette	Not recommended	Only 1 RCT, negative
Trichotillomania	Not recommended	Only 1 RCT, negative



L-Carnosine

Trial	Target	Effective	N	Age (years)	Time	Treatment
Chez 2002	ASD (core)	Yes	31	3-12	8 weeks	L-carnosine (800 mg) or placebo
<u>Mehrazad-Saber 2018</u>	ASD (sleep)	Yes	43	4-16	2 months	Carnosine (500 mg) or placebo
<u>Hajizadeh-Zaker 2018</u>	ASD (core)	Yes	70	4-12	10 weeks	L-carnosine (800 mg) or placebo and Risperidone (2 mg/day)

Target	Grade	Explanation
ASD (core)	2C	2 positive trials one adjunct with risperidone
ASD (sleep)	Not recommended	1 small positive trial

Ranges

Sample Size



31-70

Age



3-16

Dose



500-800 mg/day

Time



8-10 weeks

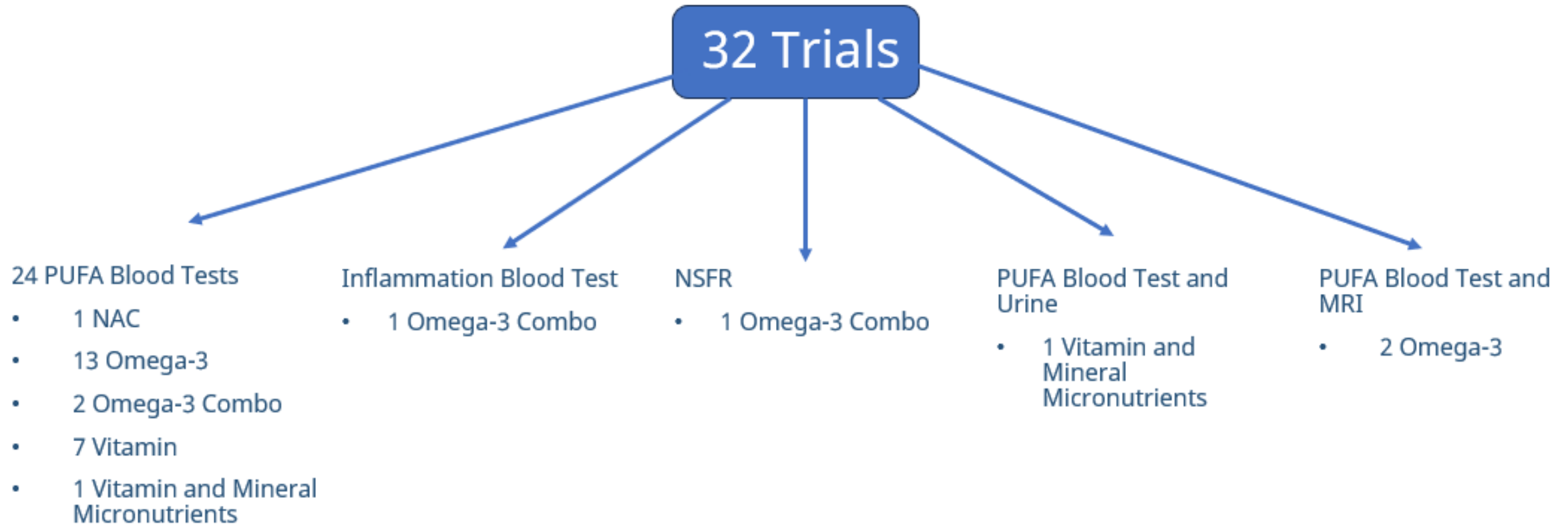
Others—One Trial



Trial	Target	Effective	N	Age (years)	Time	Treatment
<u>Trebaticka 2006</u>	ADHD	Yes	61	6-14	1 month	Pycnogenol (1 mg/kg/day)
Hirayama 2014	ADHD	Yes	36	4-14	2 months	Soy-derived phosphatidylserine (200 mg/day)
Singh 2014	ASD (core)	Yes	44	13-27	18 weeks	Sulforaphane (50 μmol for <100 lb, 100 μmol for 101-199 lb, and 150 μmol for >200 lb)
Frye 2018	ASD (language)	Yes	48	3-14	12 weeks	Folinic Acid (2 mg kg ⁻¹ per day, maximum 50 mg per day)
Liu 2019	ASD (core)	Yes	80	7-15	4 weeks	Lactobacillus plantarum PS128 (3 × 10 ¹⁰ CFU/capsule)
Brule 2024	ADHD	Yes	151	6-16	28 weeks	Homeopathic remedy (potencies 6CH to 10M)
Weber 2008	ADHD	No	54	6-17	8 weeks	St John's Wart (300 mg of H. perforatum/ 3 times/day)
Levine 1997	ASD (core)	No	10	4-7	8 weeks	Inositol (400 mg/k)
Kean 2017	ADHD	No	144	6-14	14 weeks	Marine oil extract PCSO-524 (260 mg)
Williams 2025	ASD (core)	No	24	5-16	8 weeks	Weekly glutathione 600 mg; or TRIO dose 600 mg glutathione, 2000 mg vitamin C, and N-acetylcysteine 29 mg/kg to a maximum dose of 600 mg in normal saline



Studies With Biomarkers





Long Term Effects

- Outcomes of Vitamin and Mineral micronutrient supplement for ADHD 52 weeks post baseline
 - **84% of participants who stayed on supplement reported “much” or “very much” improved**
 - Those who stayed were more likely to have a history of failed medication trials
 - Most common reason for stopping was cost and number of pills to swallow

Darling, K. A., Eggleston, M. J. F., Retallick-Brown, H., & Rucklidge, J. J. (2019). Mineral-vitamin treatment associated with remission in attention-deficit/hyperactivity disorder symptoms and related problems: 1-year naturalistic outcomes of a 10-week randomized placebo-controlled trial. *Journal of Child and Adolescent Psychopharmacology*, 29(9), 688–704. <https://doi.org/10.1089/cap.2019.0036>



Long Term Effects

- Outcomes of Omega-3 for pediatric bipolar or depression 2 to 5 years after RCT
 - **50% of youth commenced or continued Ω 3**
 - Suggests some degree of consumer satisfaction
 - Majority of parents and youth reported improved youth emotion regulation skills and family communication

Fristad, M. A., Roley-Roberts, M. E., Black, S. R., & Arnold, L. E. (2021). Moody kids years later: Long-term outcomes of youth from the omega-3 and therapy (OATS) studies. *Journal of Affective Disorders*, 281, 24–32.

<https://doi.org/10.1016/j.jad.2020.11.115>



Summary

- There are challenges in applying the GRADE system to natural treatments
- Risks associated with natural treatments are very low, hence even for treatments with weak recommendation with low quality or quantity evidence, it is frequently true that: *[potential] benefits clearly outweigh risks and can apply to most patients without reservations*
- Studies with small improvements are considered 'positive'
- We have difficulty measuring the risk associated with discouraging, delaying or neglecting the use of an FDA approved treatment with known robust efficacy in an individual patient



Summary

- We need more studies of promising products
- *Omega-3 Fatty Acids (EPA, DHA)* is the natural treatment that has the most RCT evidence for use in pediatric psychiatry?
- We need study for more indications
- *Autism* is the most common indication for RCTs for natural treatments in pediatric psychiatry studied is autism.
- We need study of biomarkers to guide treatment and understand mechanisms of action
- *Polyunsaturated fatty acid blood levels* is the most commonly reported biomarker outcome measure reported in RCTs of natural treatments in pediatric psychiatry