MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Nutraceuticals

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Disclosures

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For Janet Wozniak MD

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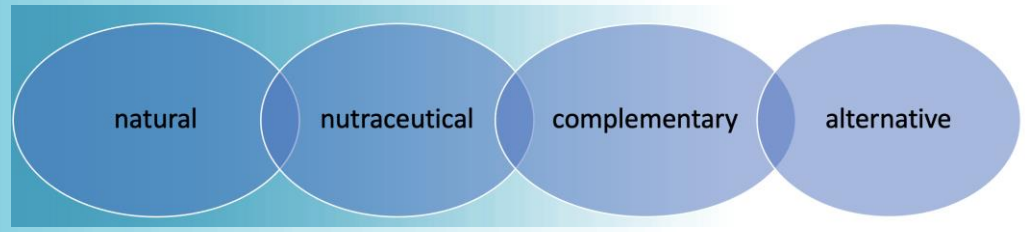
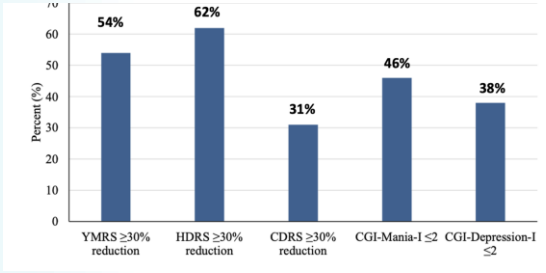
Overview:
Neutraceuticals are popular, but poorly studied, especially for bipolar disorder; omega-3 fatty acids, inositol and NAC have emerging data supporting use in pediatric bipolar disorder.

Over-the-counter dietary supplements marketed for health are not approved by the FDA



Omega-3s and Inositol have complementary mechanisms of action and can be mildly useful in youth with mild-moderate bipolar disorder

N-acetylcysteine has evidence for use in adult and pediatric bipolar disorder



12 week open label
N=26
Average age 10 years
46% male
73% caucasian

We have many FDA approved treatments for youth with emotional dysregulation

Lithium: manic or mixed states, patients age 13-17

Risperidone 2007: manic or mixed states, age 10-17
Aripiprazole 2008: manic or mixed states, age 10-17
Olanzapine 2008: manic or mixed states, age 13-17
Quetiapine 2009: monotherapy or adjunct to lithium or divalproex sodium, manic states, age 10-17
Asenapine Saphris 2015: manic or mixed episodes in BPD I, age 10-17

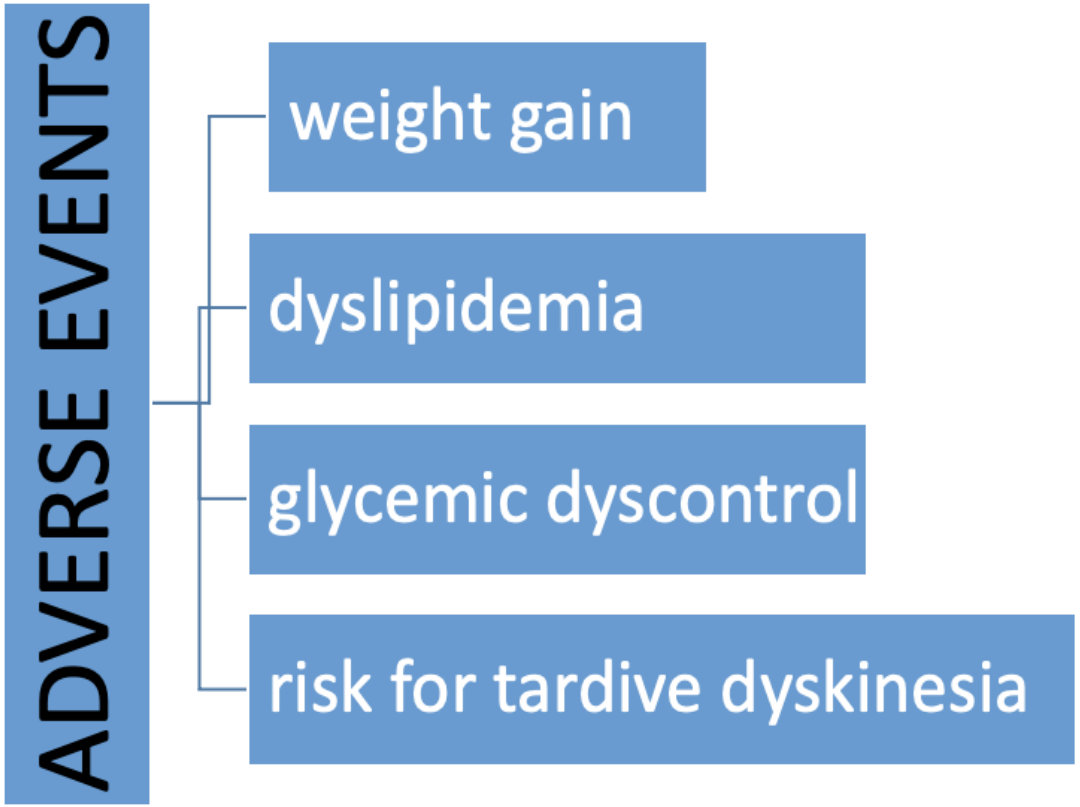
Lurasidone Latuda 2018: pediatric bipolar depression
Olanzapine-fluoxetine 2013: pediatric bipolar depression

Fluoxetine: depression and OCD age 8+
Escitalopram 2002: depression age 12+

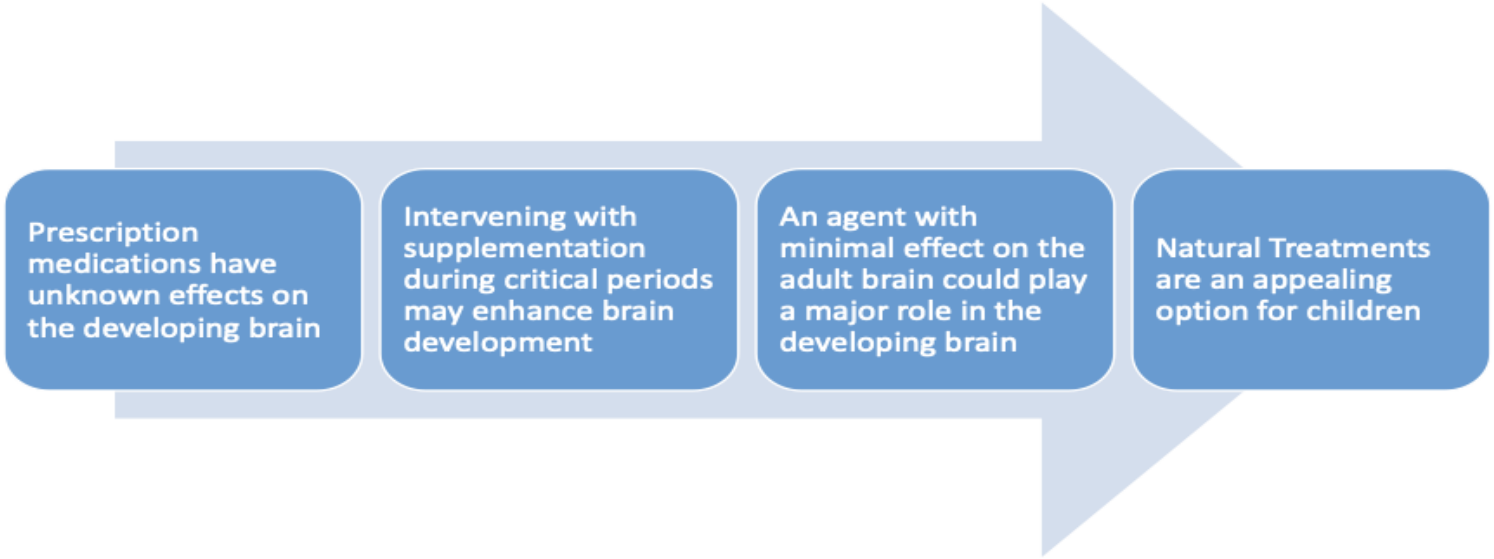
Sertraline, fluvoxamine, anfranil: pediatric OCD
Duloxetine Cymbalta: GAD 7+

Risperidone 2006: irritability associated with autism age 5-16
Aripiprazole 2009: irritability associated with autistic disorder age 6-17

FDA approved treatments for pediatric bipolar disorder are fraught with annoying and serious side effects, which may fuel reluctance to diagnose

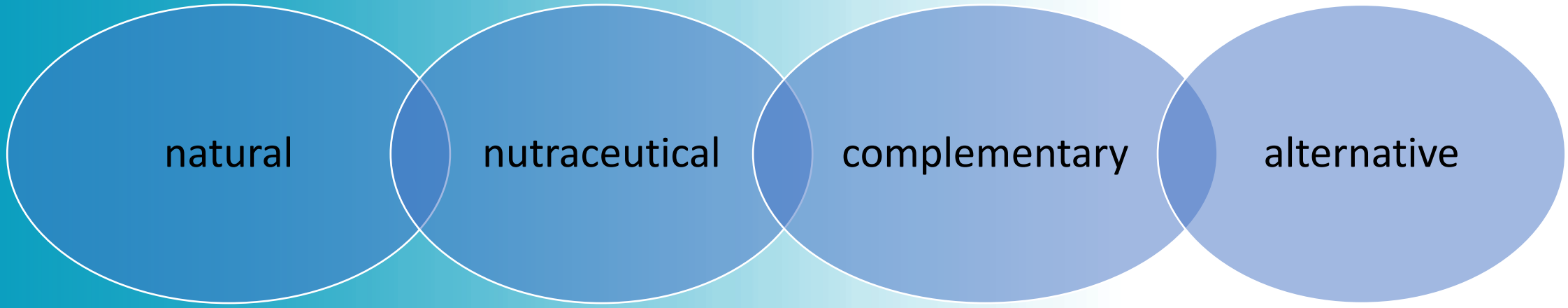


Natural treatments are an appealing option for the treatment of bipolar disorder in children



Over-the-counter dietary supplements marketed for health are not approved by the FDA

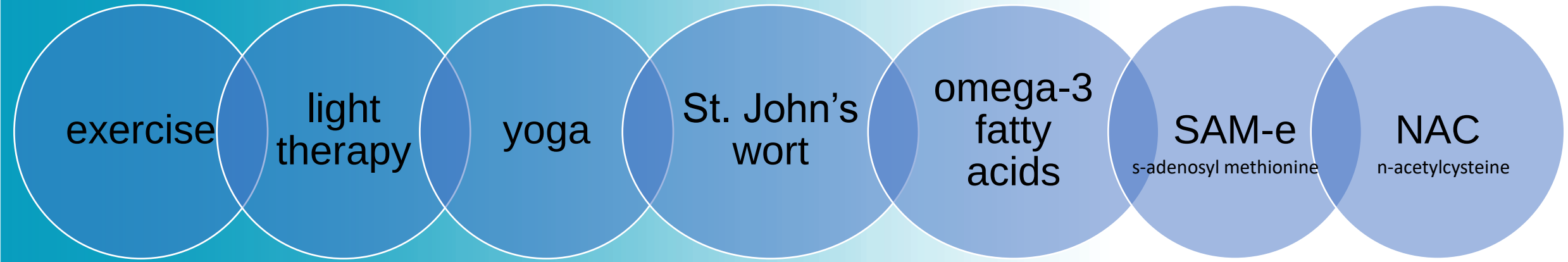
- intended to supplement diet
- not represented as a food or sole item of a meal/diet
- contains vitamins, minerals, amino acids, herbs, natural substances
- could be a concentrate, metabolite, constituent, extract



A fortified food or dietary supplement that provides some health benefit

Mischoulon 2019

Very few studies of CAM have involved patients with bipolar disorder; most available evidence is derived from trials conducted in patients with major depressive disorder

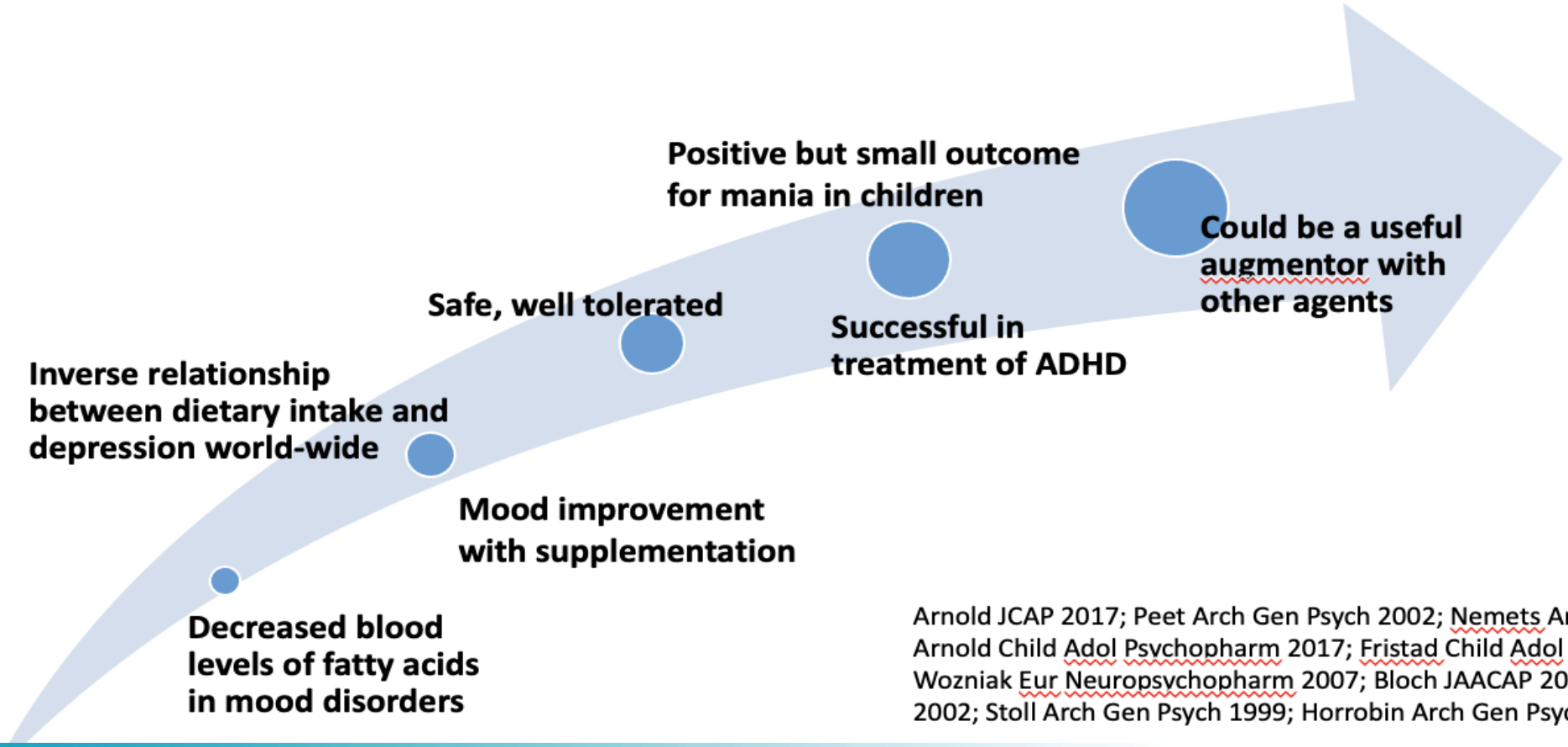


Other treatments and products have less evidence

Ravindran Canadian J Psych 2016

omega-3 fatty acids - Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

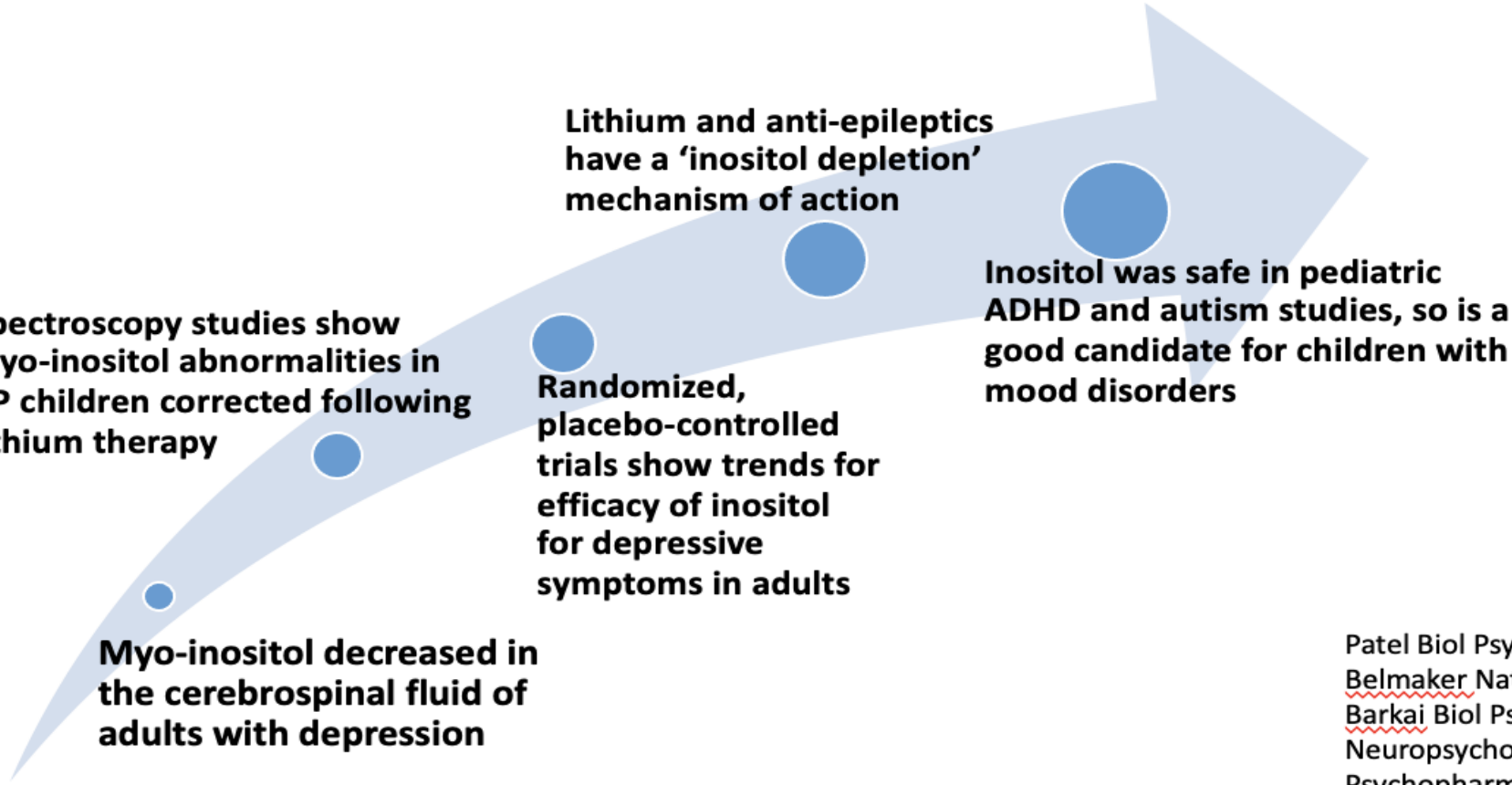
Found in fish such as mackerel, trout, herring, sardines and tuna (oily fish)



Arnold JCAP 2017; Peet Arch Gen Psych 2002; Nemets Am J Psych 2002; Arnold Child Adol Psychopharm 2017; Fristad Child Adol Psychopharm 2015 Wozniak Eur Neuropsychopharm 2007; Bloch JAACAP 2011; Hibbelyn 1998, 2002; Stoll Arch Gen Psych 1999; Horrobin Arch Gen Psych 2002; Puri 2002

Inositol - simple sugar, glucose isomer

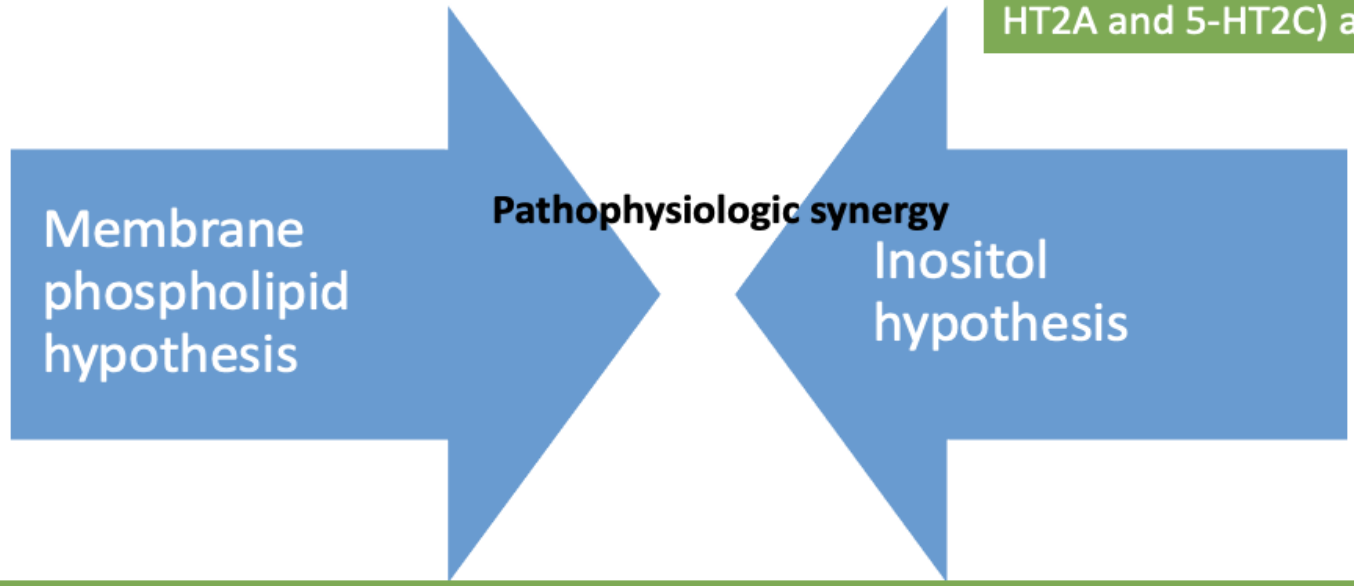
Found in beans, grains, nuts and many fruits



Patel Biol Psych 2006; Baraban Am J Psychiatry 198
Belmaker Natural Medications Psychiatry 2008;
Barkai Biol Psychiatry 1978; Davanzo
Neuropsychopharmacology 2001 ; Mukai Hum
Psychopharmacol 2014; Wei Cell Signal 2018

Omega-3 and inositol have complementary mechanisms of action, so the combination could have an additive effect in the treatment of Pediatric Bipolar Disorder

Phosphatidyl inositol cycle is the second messenger system for numerous neurotransmitter receptors, including cholinergic muscarinic, alpha 1 noradrenergic, serotonin (5-HT2A and 5-HT2C) and dopaminergic D1 receptors



PUFA double bonds in O3s aid in the fluidity and behavior of the brain cell membrane:

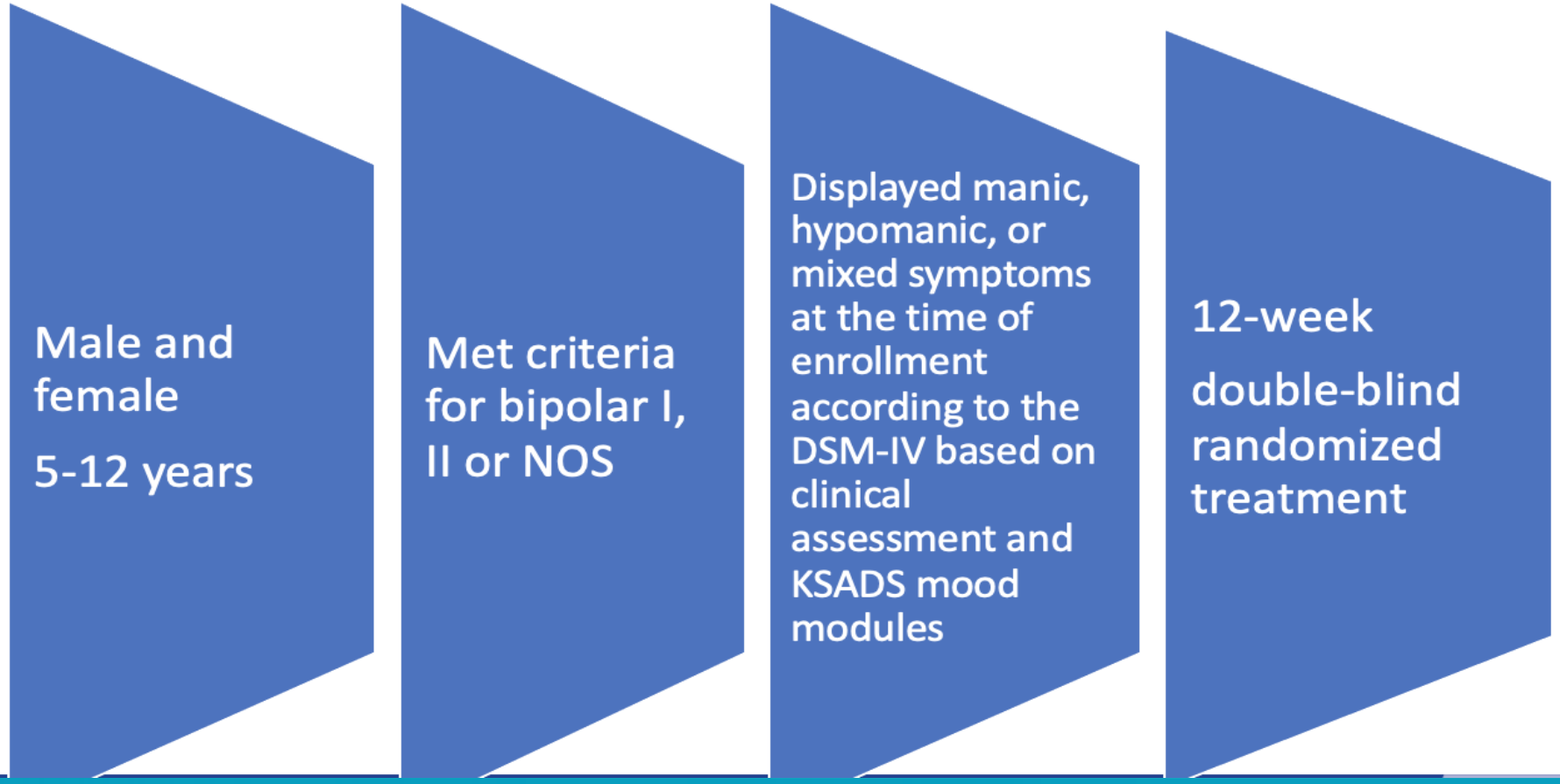
- modulate the function of the membrane bound proteins
- influence the release and reuptake of neurotransmitter, influence post-synaptic neurotransmitter actions
- affect nerve conduction

Assess the efficacy and tolerability of omega-3 fatty acids (FAs) and inositol alone and in combination for the treatment of pediatric bipolar (BP) spectrum disorder in young children

- Data supports use of omega-3s for children with bipolar spectrum disorder
- Inositol well tolerated and useful for mood disorders in adults
- Reported monotherapy effects are small, but omega3s + inositol could act via synergistic mechanisms of action
- We compared antimanic response of omega3s and inositol in youth with bipolar disorder, randomized to treatment with a potentially active treatment
- **Hypothesis:** omega-3 FAs and inositol in combination would be more effective than either supplement alone in the treatment of pediatric BP spectrum disorder

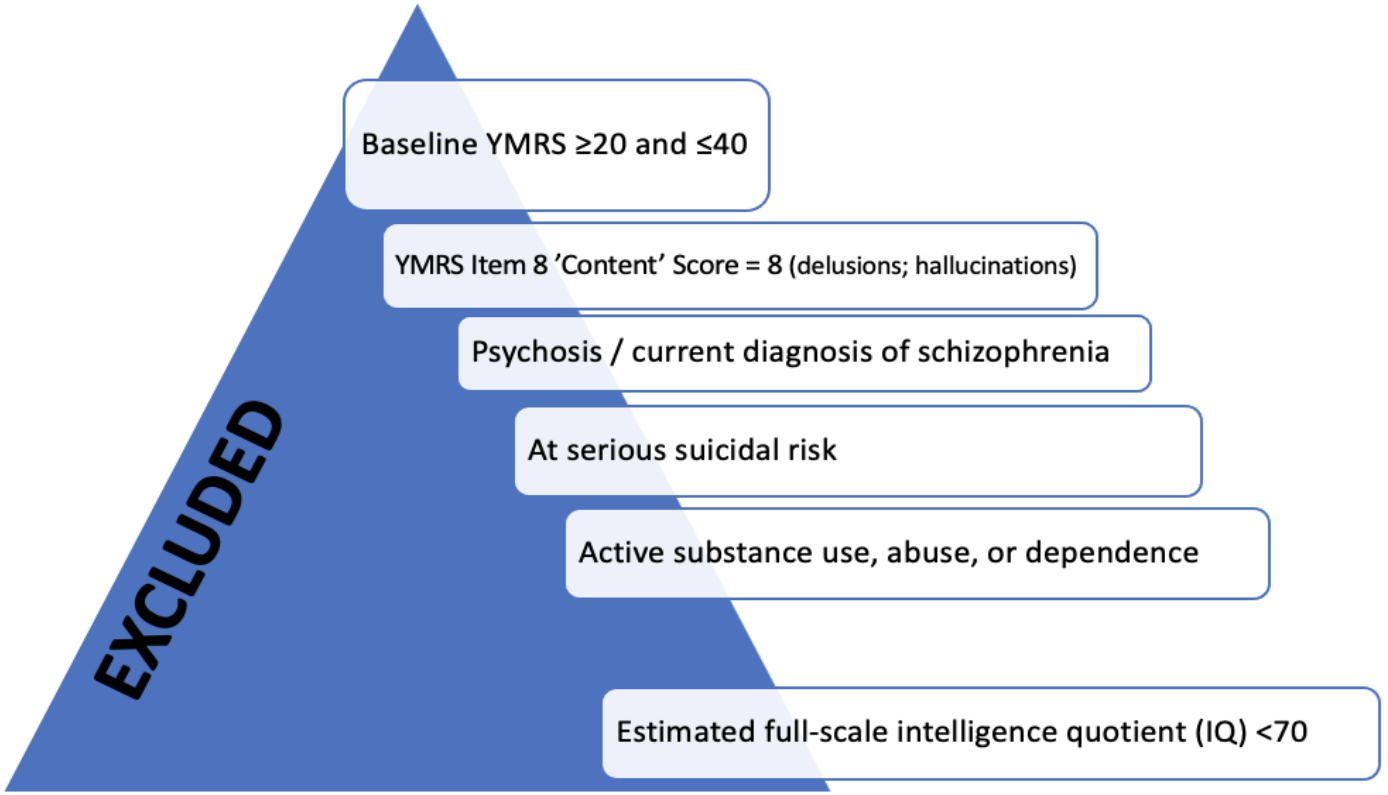
Randomized, double-blind, placebo-controlled pilot trial

All study procedures were reviewed and approved by the Partners Human Research Committee. All participants' parents or guardians signed written informed consent forms and all children older than 7 years of age signed written assent forms to participate.

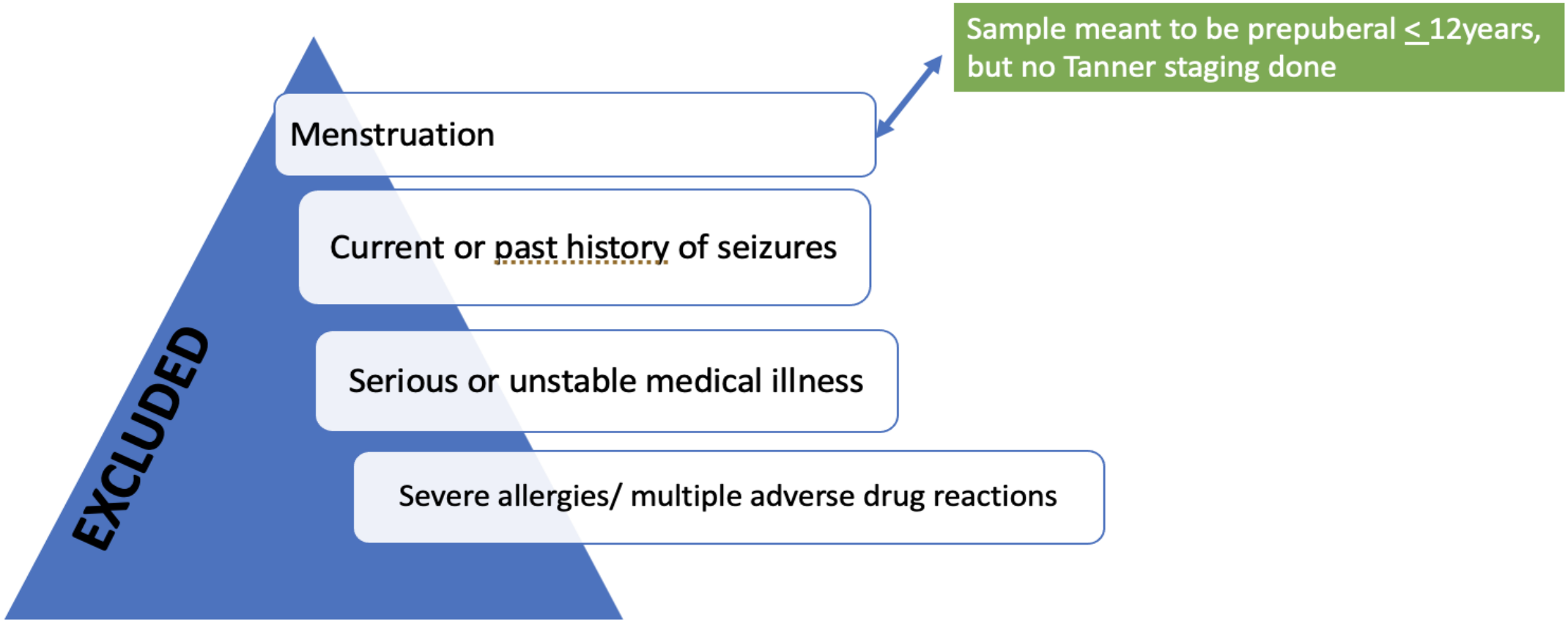


Exclusionary Criteria – severe psychiatric illness

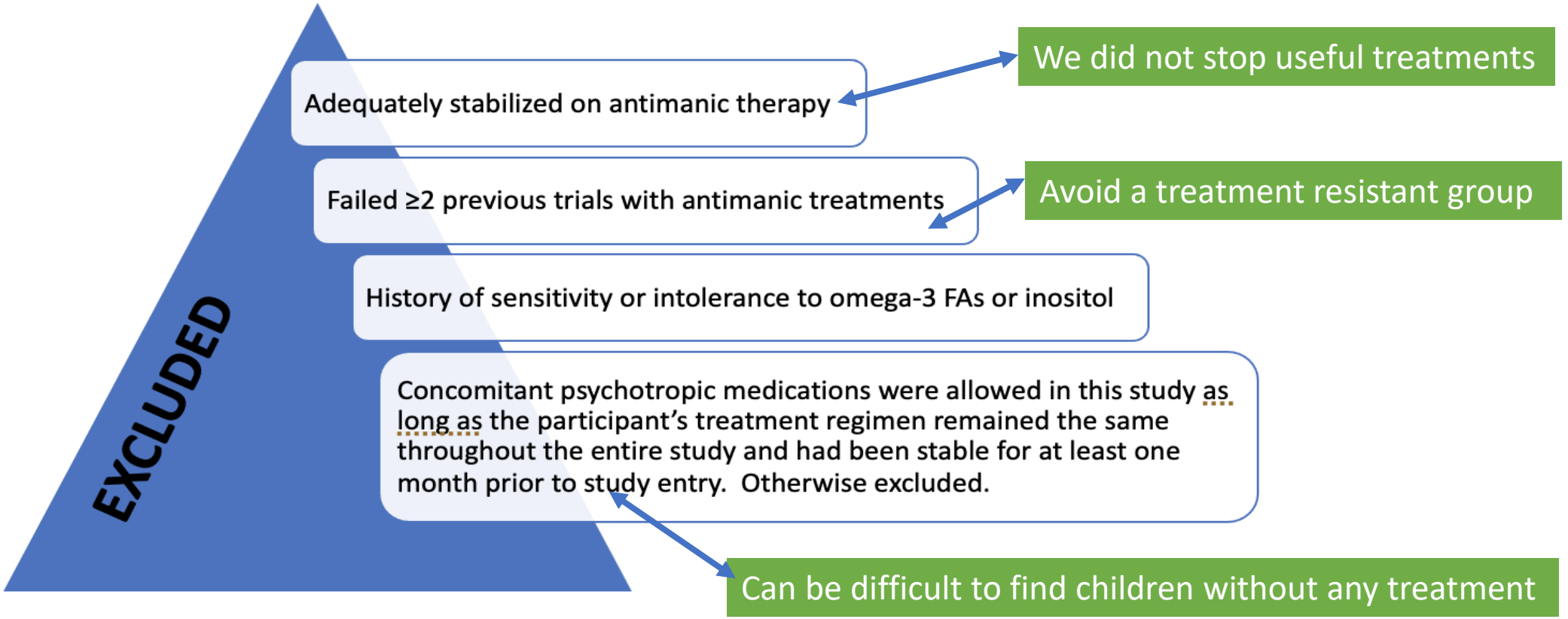
to protect children with severe illness who should be offered FDA approved treatments



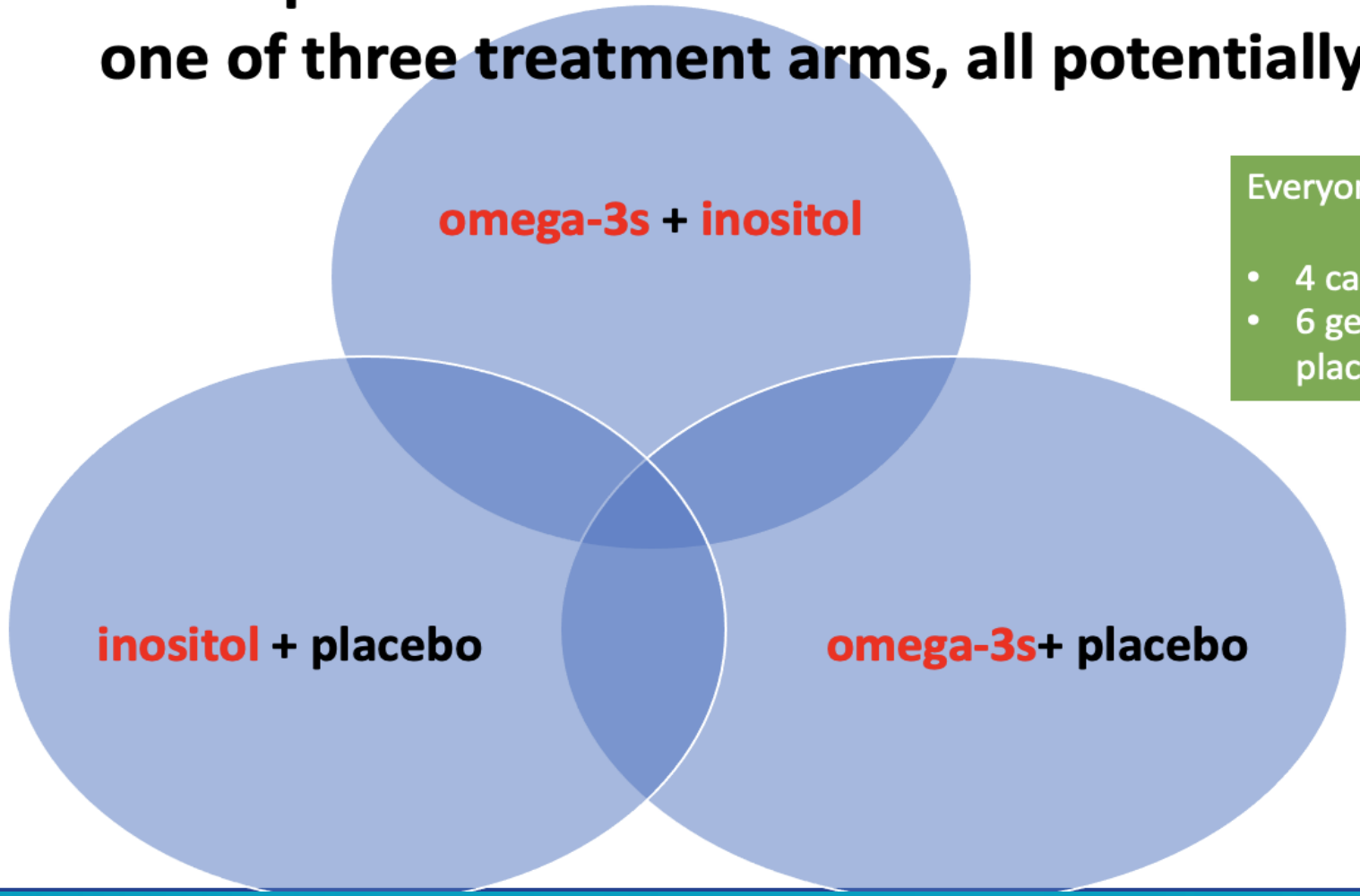
Exclusionary Criteria - medical



Exclusionary Criteria - medications



Participants were randomized in double-blind fashion into one of three treatment arms, all potentially active



Everyone received identical treatment with:

- 4 capsules (inositol or placebo inositol)
- 6 gel caps (omega-3 fatty acids or placebo omega-3 fatty acids)

Omega 3 Fatty Acids dose = 975mg EPA

Dose of 1000mg EPA chosen based on previous studies. Gel cap palatable for children potency led to 975mg as close enough

Nordic Naturals provided the omega-3 gel caps and placebo

Omega-3 fatty acid soft gels

325mg EPA and 225mg DHA

per 2 capsules

The placebo soft gels contained 500mg soybean oil each

Participants were dosed at

975mg EPA

(EPA+DHA=1650mg)

6 gel caps

Placebo Omega-3s:

- Same **strawberry** flavoring as the active soft gels
- A small amount of omega-3 FAs (approximately 55mg with 1.9mg EPA) was added to placebo soft gels to provide a **slightly fishy taste**

Inositol dose = 2000mg *

Inositol 2000mg tolerated in previous studies

Life Extension provided inositol powder

Inositol and matched placebo capsules created by the MGH Pharmacy

Inositol capsules contained 500mg inositol powder

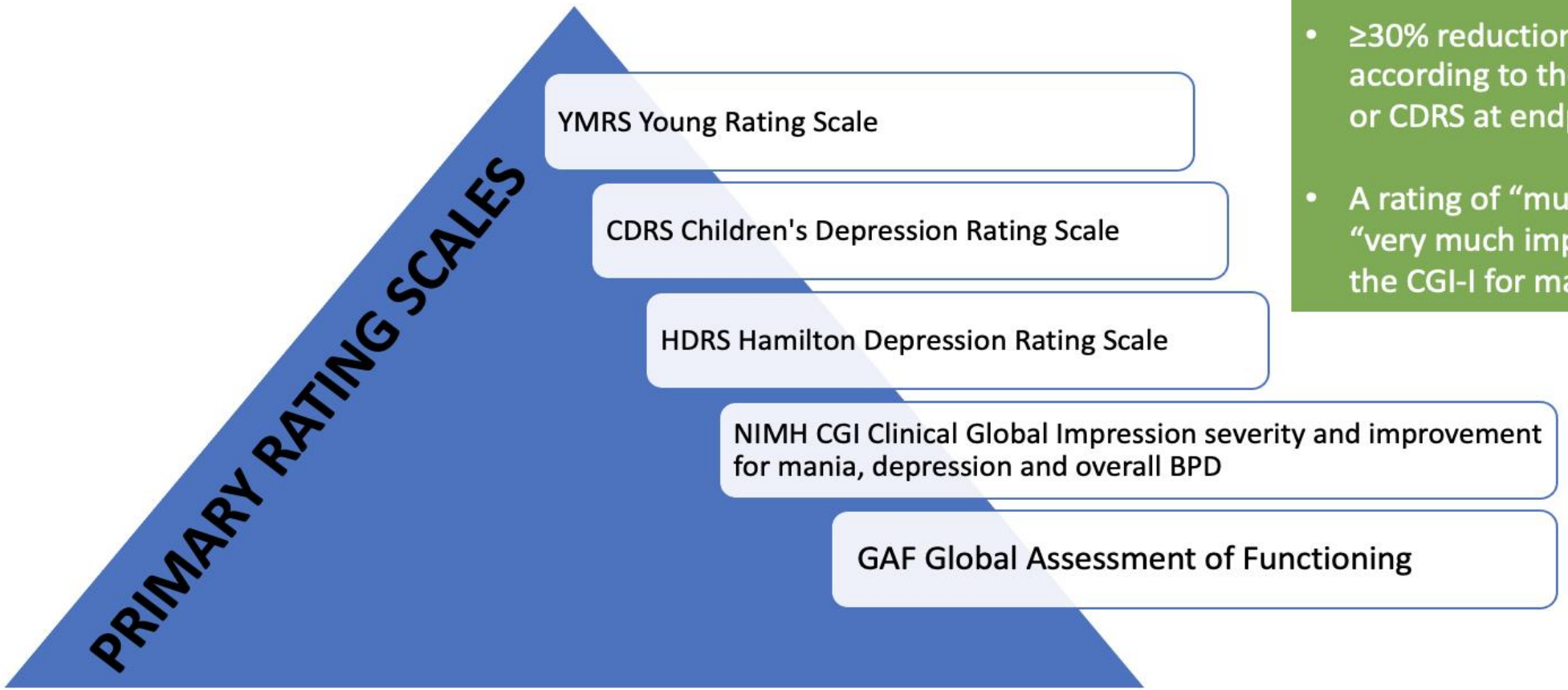
Placebo capsules contained 500mg lactose powder

Participants weighing ≥25kg* were dosed at 2,000mg of inositol or placebo daily

4 capsules

*Participants weighing <25kg were dosed at *80mg per kg* rounded down to the nearest 500mg capsule

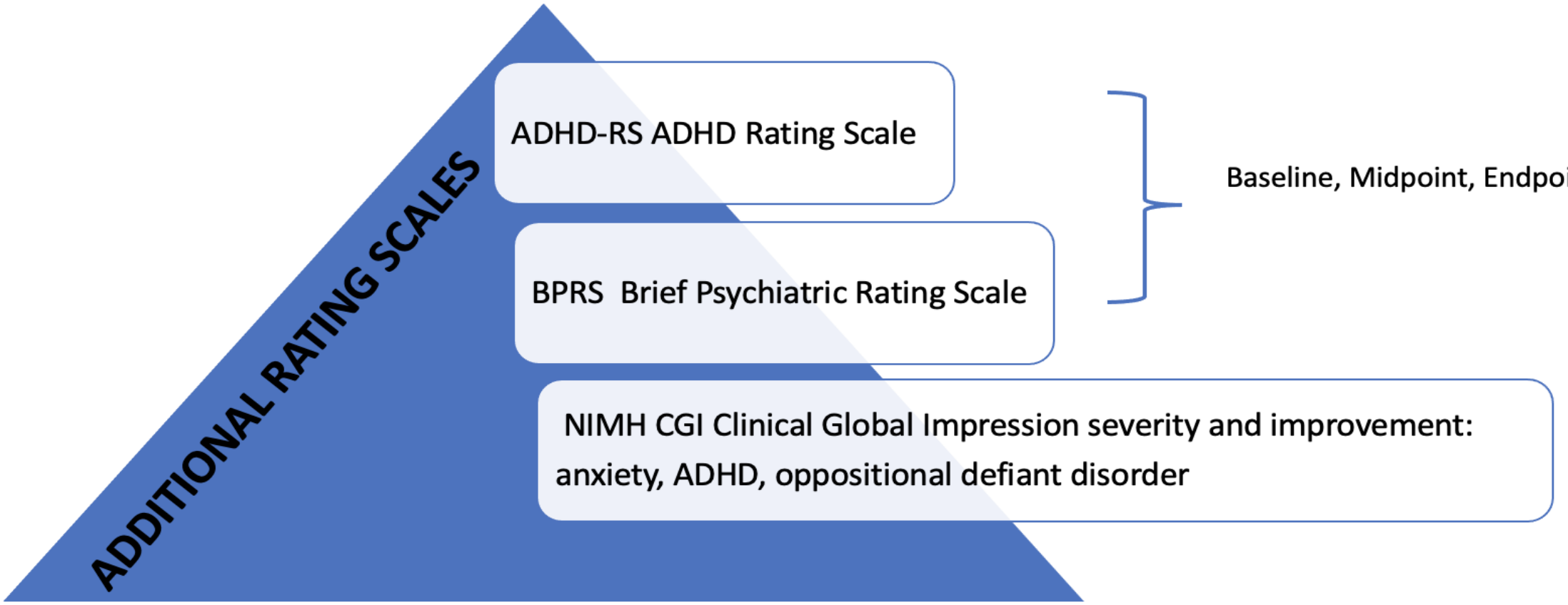
Main Outcome Measures



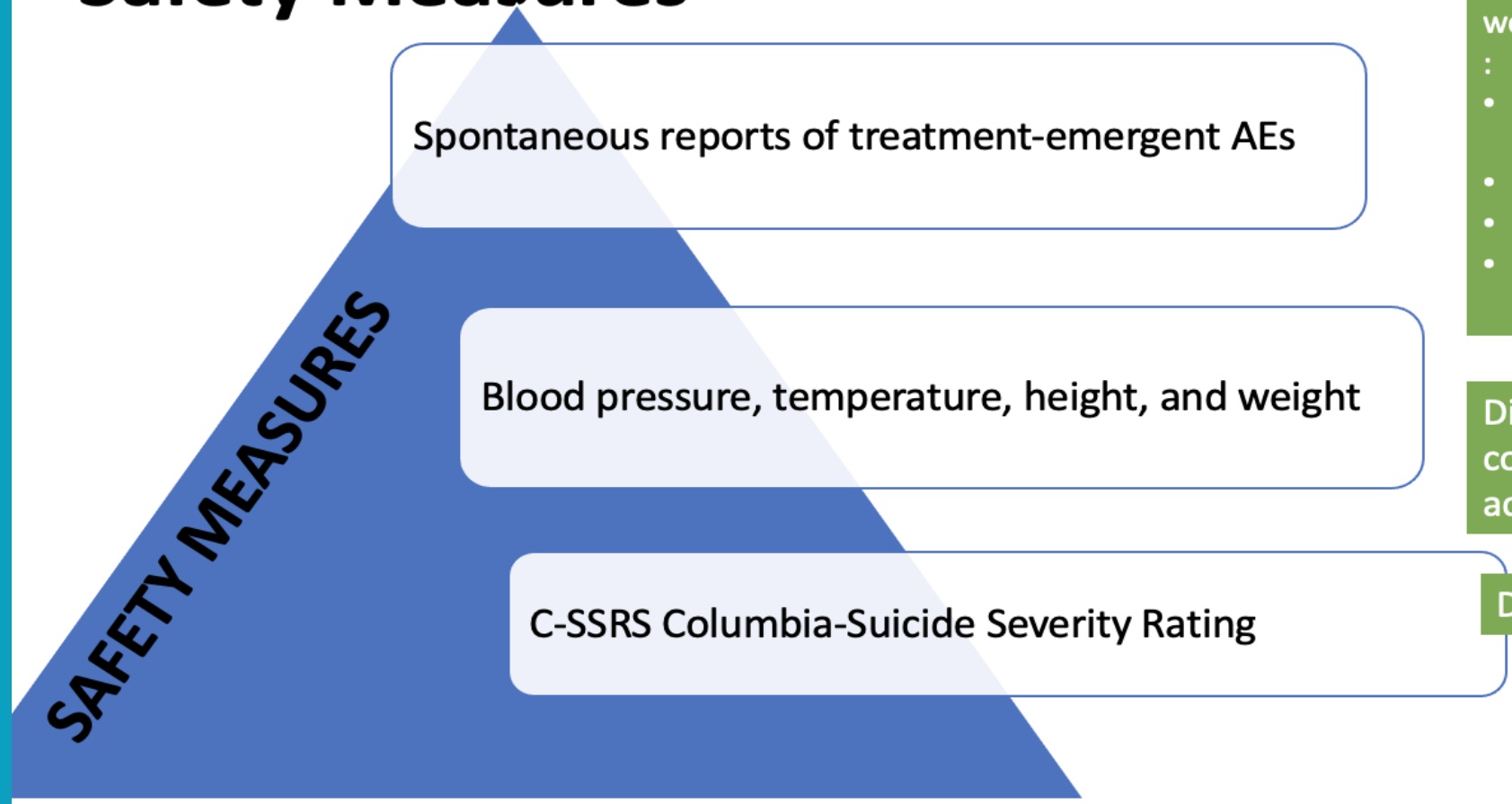
Response at endpoint defined as either

- ≥30% reduction in symptoms according to the YMRS (also HDRS, or CDRS at endpoint)
- A rating of "much improved" or "very much improved" (score ≤2) on the CGI-I for mania (or depression)

Additional Outcome Measures



Safety Measures



Discontinuation after 2 weeks in a row of worsening mania
:

- CGI-S overall BP 2 points higher than baseline
- YMRS score 30% higher than baseline
- YMRS item score of 8 on item 8 (content)
- YMRS item score of than 6 on item 9 (disruptive/aggressive behavior)

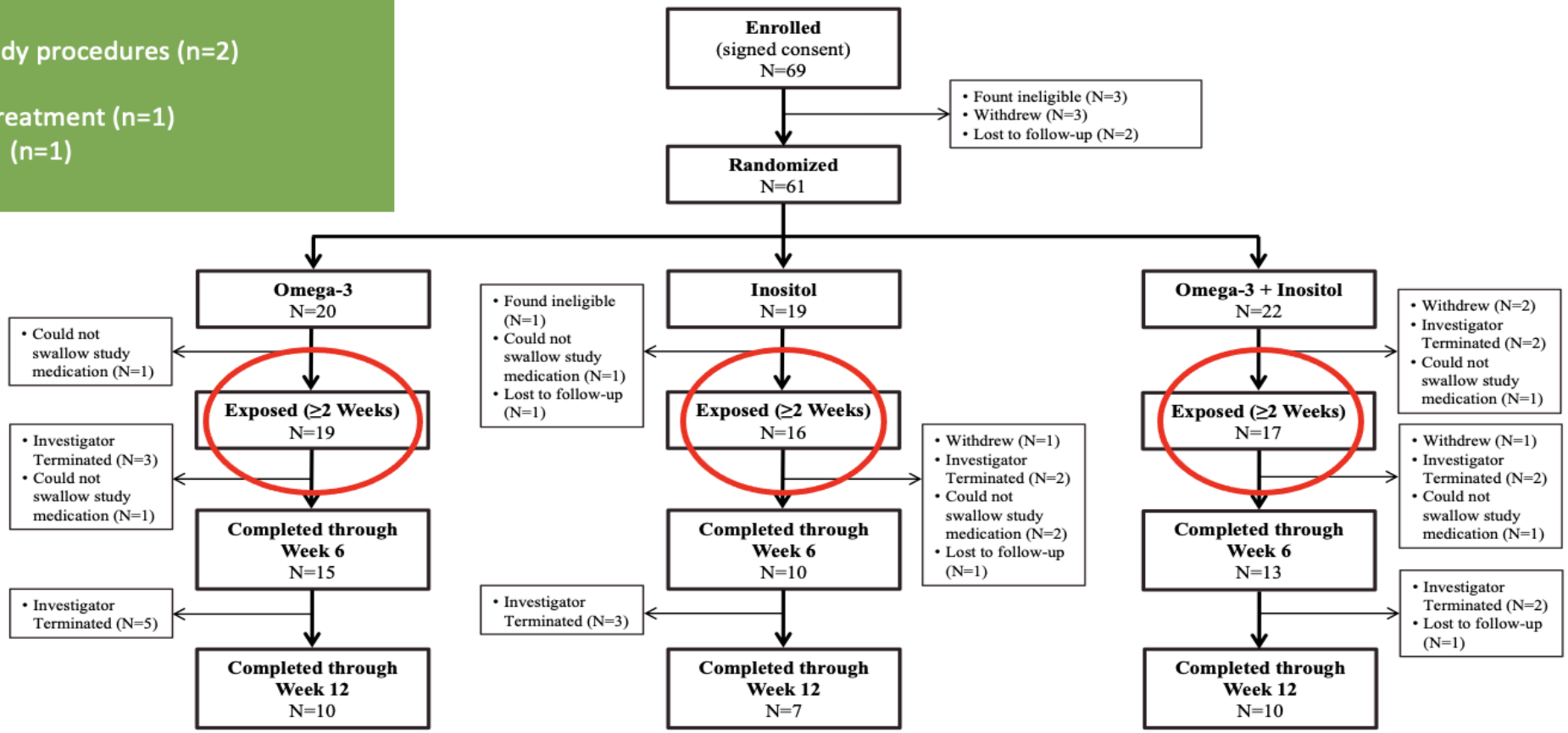
Discontinuation if less than 70% compliance for two weeks or longer according to pill counts

Discontinued for C-SSRS scores of ≥ 4

Reasons for not completing the study:

- lack of efficacy (n=15)
- participant could not swallow the study medication (n=7)
- lost to follow-up (n=3)
- non-compliant with the study procedures (n=2)
- worsening condition (n=1)
- need for more aggressive treatment (n=1)
- ineligible after randomized (n=1)
- participant withdrew (n=4)

Figure 1. CONSORT Flow Diagram



There were no significant differences between the groups in:

age

omega-3 FAs: 7.9 ± 1.6 years vs. inositol: 8.6 ± 2.4 years vs. combination: 8.2 ± 2.5 years; p=0.69

full-scale IQ

omega-3 FAs: 99.5 ± 17.6 vs. inositol: 104.6 ± 14.7 vs. combination: 113.3 ± 21.5; p=0.11

baseline GAF

omega-3 FAs: 52.0 ± 2.9 vs. inositol: 51.4 ± 2.7 vs. combination: 52.6 ± 1.8; p=0.47

proportion of male participants

omega-3 FAs: 59% [n=10/17] vs. inositol: 71% [10/14] vs. combination: 50% [n=8/16]; p=0.49

proportion of Caucasian participants

omega-3 FAs: 93% [n=14/15] vs. inositol: 93% [n=13/14] vs. combination: 94% [n=15/16]; p=1.00

Significant (p<0.05) decreases in scores for most measures for all 3 groups (exceptions highlighted

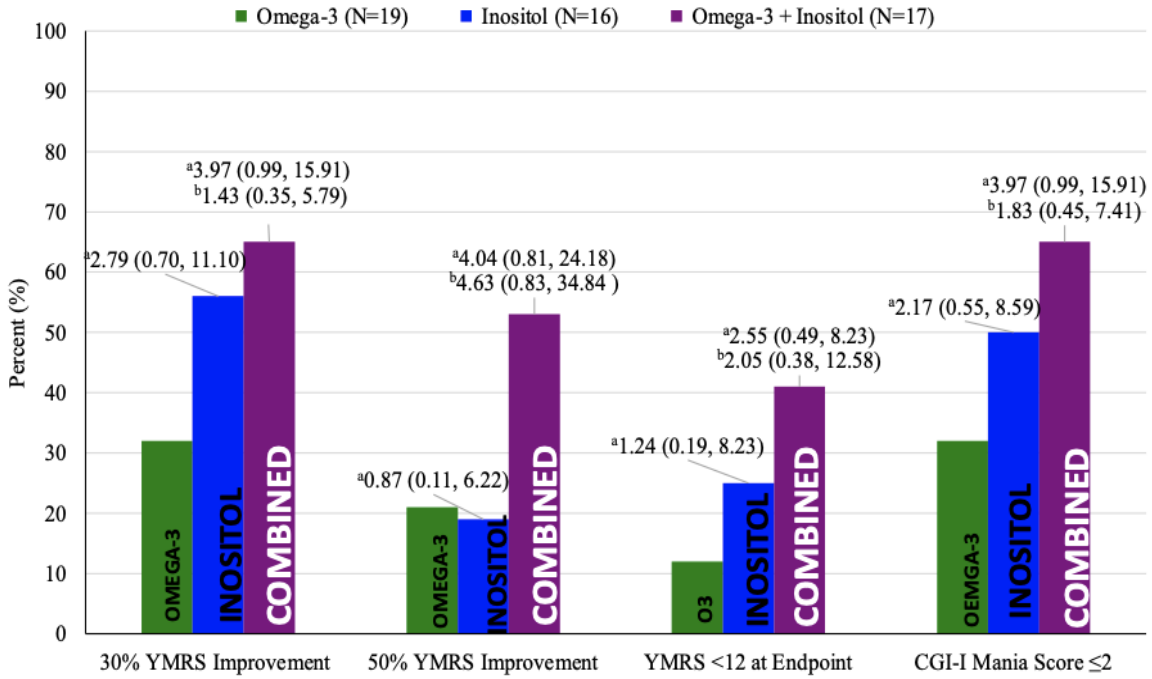
Table 1. Change in score from baseline to endpoint in measures of mania, depression, ADHD, and general psychopathology

Measure	N	Baseline Score	Endpoint Score†	Difference	Within Group		Between Group		
					Effect Size	P-value	Effect Size		P-Value
		Mean ± SD	Mean ± SD	Mean ± SD	SMD (95% CI)		SMD (95% CI)		
							Vs. Omega-3	Vs. Inositol	
YMRS									0.19
Omega-3	19	26.1 ± 7.2	21.3 ± 10.8	-4.8 ± 7.9	0.61 (0.12, 1.10)	0.01	-	-	
Inositol	16	25.8 ± 6.5	19.4 ± 10.1	-6.4 ± 6.4	0.99 (0.39, 1.59)	<0.001	0.22 (-0.45, 0.88)	-	
Omega-3 + Inositol	17	24.2 ± 5.8	14.1 ± 10.5	-10.2 ± 9.0	1.13 (0.52, 1.74)	<0.001	0.64 (-0.04, 1.31)	0.48 (-0.21, 1.17)	
HDRS									0.30
Omega-3	19	16.5 ± 5.3	12.2 ± 6.6	-4.3 ± 8.8	0.49 (0.01, 0.97)	0.009	-	-	
Inositol	16	18.2 ± 9.1	14.0 ± 8.4	-4.2 ± 9.0	0.46 (-0.06, 0.98)	0.04	-0.01 (-0.68, 0.65)	-	
Omega-3 + Inositol	17	17.1 ± 7.3	8.0 ± 3.8	-9.1 ± 8.4	1.08 (0.52, 1.74)	<0.001	0.56 (-0.11, 1.22)	0.56 (-0.14, 1.26)	
CDRS									0.11
Omega-3	19	39.4 ± 9.3	34.5 ± 11.1	-4.9 ± 10.6	0.46 (-0.01, 0.93)	0.04	-	-	
Inositol	16	40.7 ± 10.9	35.1 ± 11.4	-5.6 ± 10.1	0.55 (0.02, 1.08)	0.06	0.06 (-0.60, 0.73)	-	
Omega-3 + Inositol	17	38.8 ± 7.9	27.9 ± 6.8	-10.8 ± 7.4	1.46 (0.77, 2.14)	<0.001	0.64 (-0.03, 1.31)	0.60 (-0.11, 1.29)	
BPRS‡									0.12
Omega-3	17	48.6 ± 11.0	38.4 ± 12.3	-10.2 ± 11.4	0.89 (0.33, 1.45)	<0.001	-	-	
Inositol	13	48.9 ± 13.0	44.1 ± 12.2	-4.8 ± 12.0	0.40 (-0.16, 0.96)	0.002	-0.46 (-1.19, 0.27)		
Omega-3 + Inositol	14	47.1 ± 8.3	32.9 ± 7.9	-14.2 ± 11.2	1.26 (0.56, 1.96)	<0.001	0.35 (-0.36, 1.07)	0.81 (0.02, 1.59)	
ADHD RS‡									0.27
Omega-3	17	39.8 ± 13.1	30.5 ± 13.7	-9.3 ± 10.9	0.86 (0.30, 1.42)	<0.001	-	-	
Inositol	13	37.8 ± 15.1	32.4 ± 12.2	-5.4 ± 11.3	0.47 (-0.10, 1.04)	0.03	-0.36 (-1.09, 0.37)	-	
Omega-3 + Inositol	14	32.6 ± 15.4	30.7 ± 16.9	-1.9 ± 13.7	0.14 (-0.39, 0.67)	0.43	-0.61 (-1.33, 0.12)	-0.27 (-1.03, 0.49)	

† Endpoint score uses last observation carried forward for those who dropped prior to week 12.‡ Subjects were excluded from analysis if they were missing baseline data (N=1) or did not have any follow-up data (N=7).

Omega-3 + Inositol combined outperforms either used alone for mania (N=52)

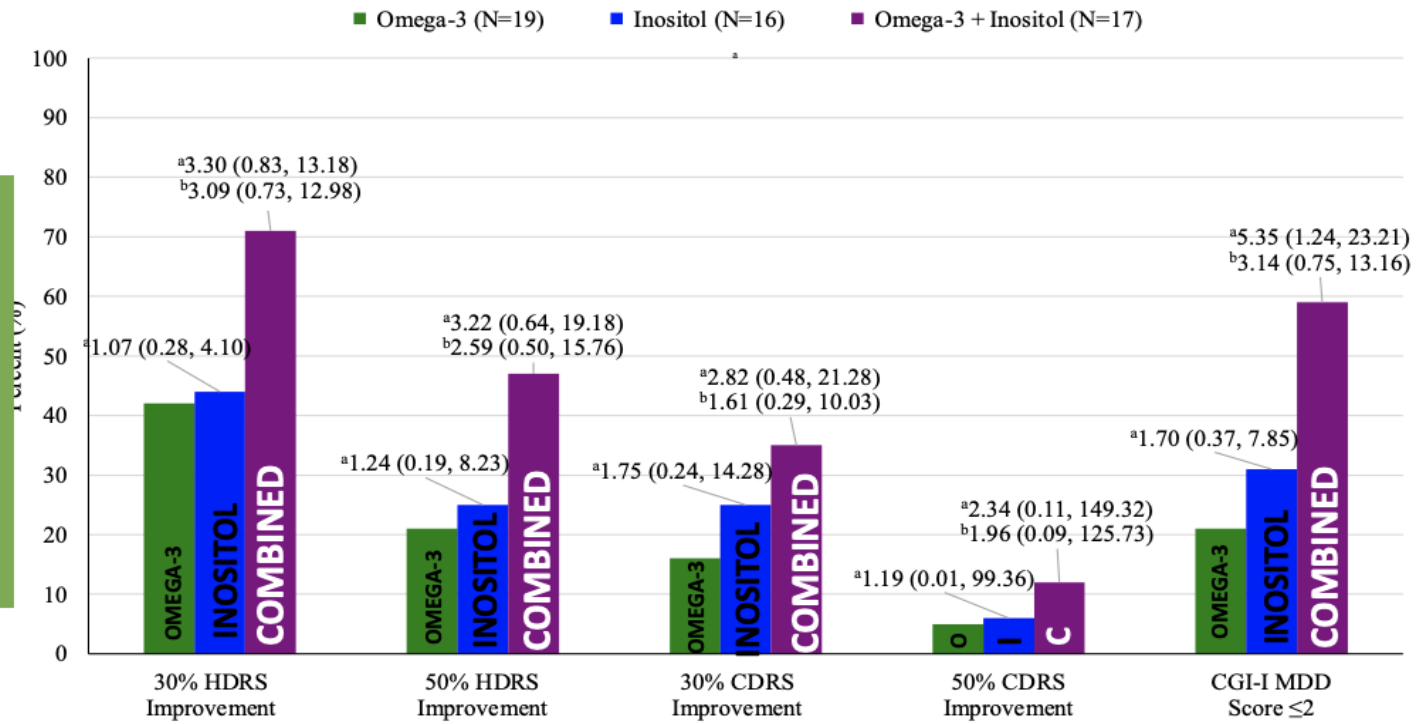
Percent improved according to different definitions was *always greater for the combined group* treatment than either used alone under blind conditions



SMDs (standardized mean differences) and ORs (odds ratios) for the combination group versus the omega-3 and inositol groups are clinically meaningful (SMDs ≥0.04, ORs ≥2)

Omega-3 + Inositol combined outperforms either used alone for depression (N=52)

Percent improved according to different definitions was *always greater for the combined group* treatment than either used alone under blind conditions

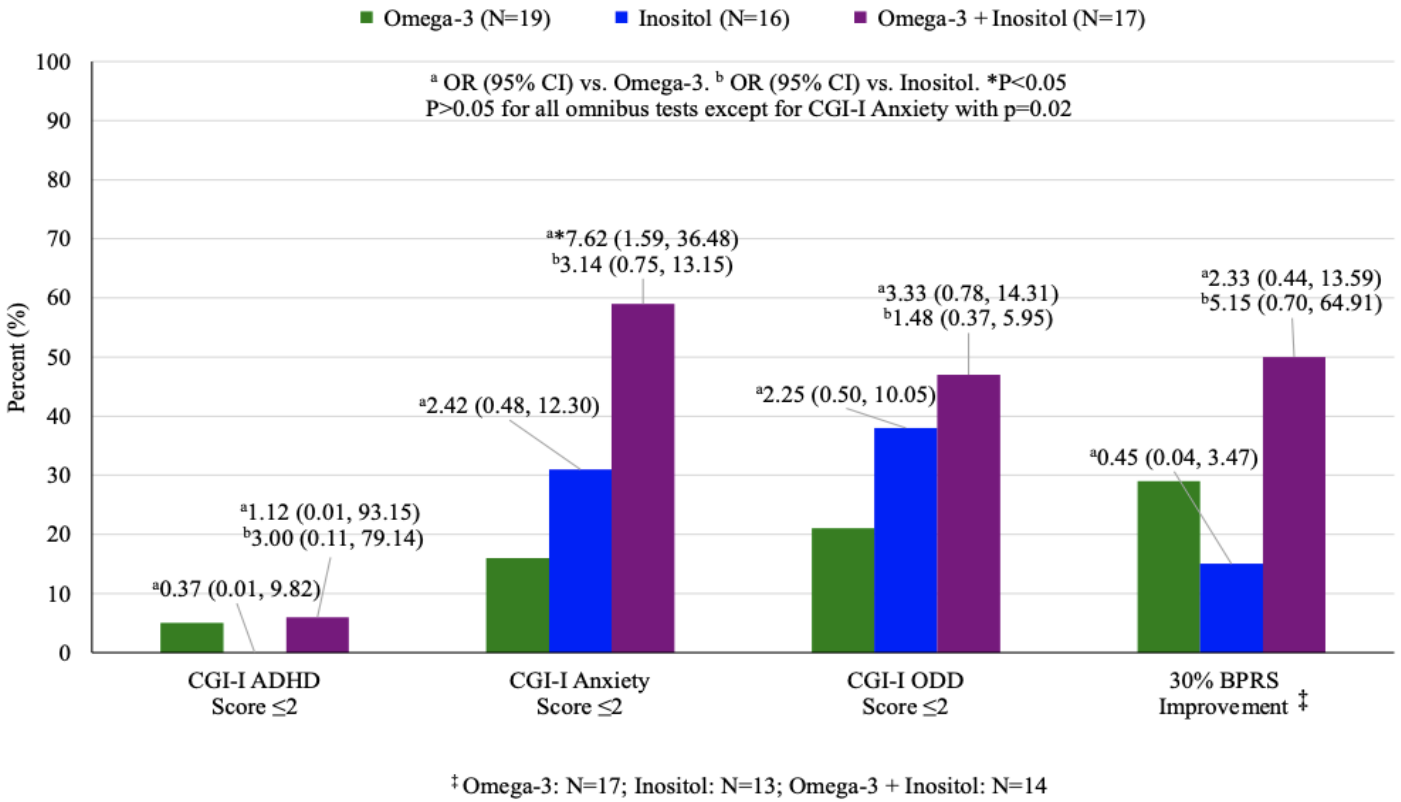


SMDs (standardized mean differences) and ORs (odd rations) for the combination group versus the omega-3 and inositol groups are clinically meaningful (SMDs ≥0.04, ORs ≥2)

Wozniak, 2021

Omega-3 + Inositol <u>combined</u> outperforms either used alone for symptoms of ADHD, Anxiety ODD, Psychosis (N=52)

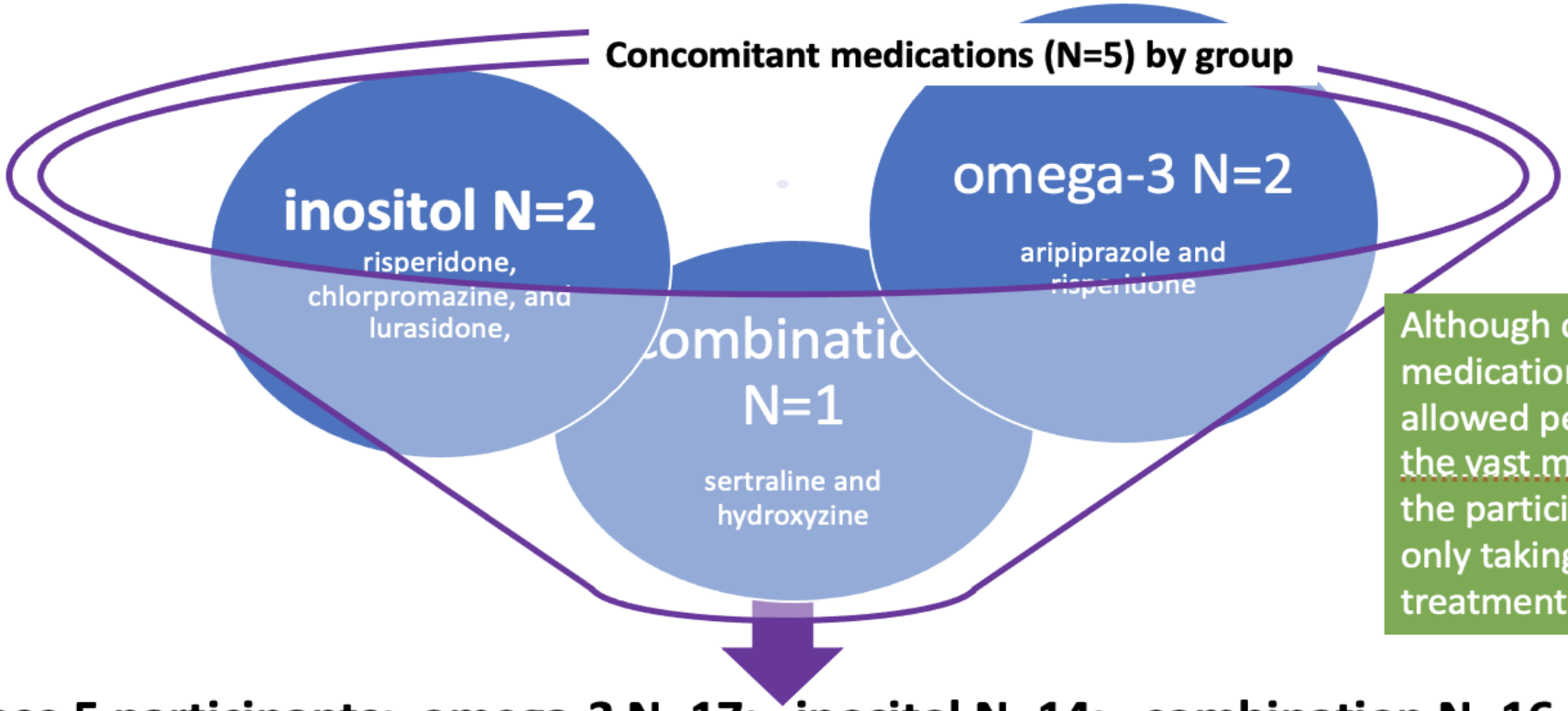
Percent improved according to different definitions was *always greater for the combined group* treatment than either used alone under blind conditions



‡ Omega-3: N=17; Inositol: N=13; Omega-3 + Inositol: N=14

SMDs (standardized mean differences) and ORs (odd rations) for the combination group versus the omega-3 and inositol groups are clinically meaningful (SMDs ≥0.04, ORs ≥2)

We excluded 5 participants who took concomitant medications from analysis to remove any possible positive effect from the concomitant medications

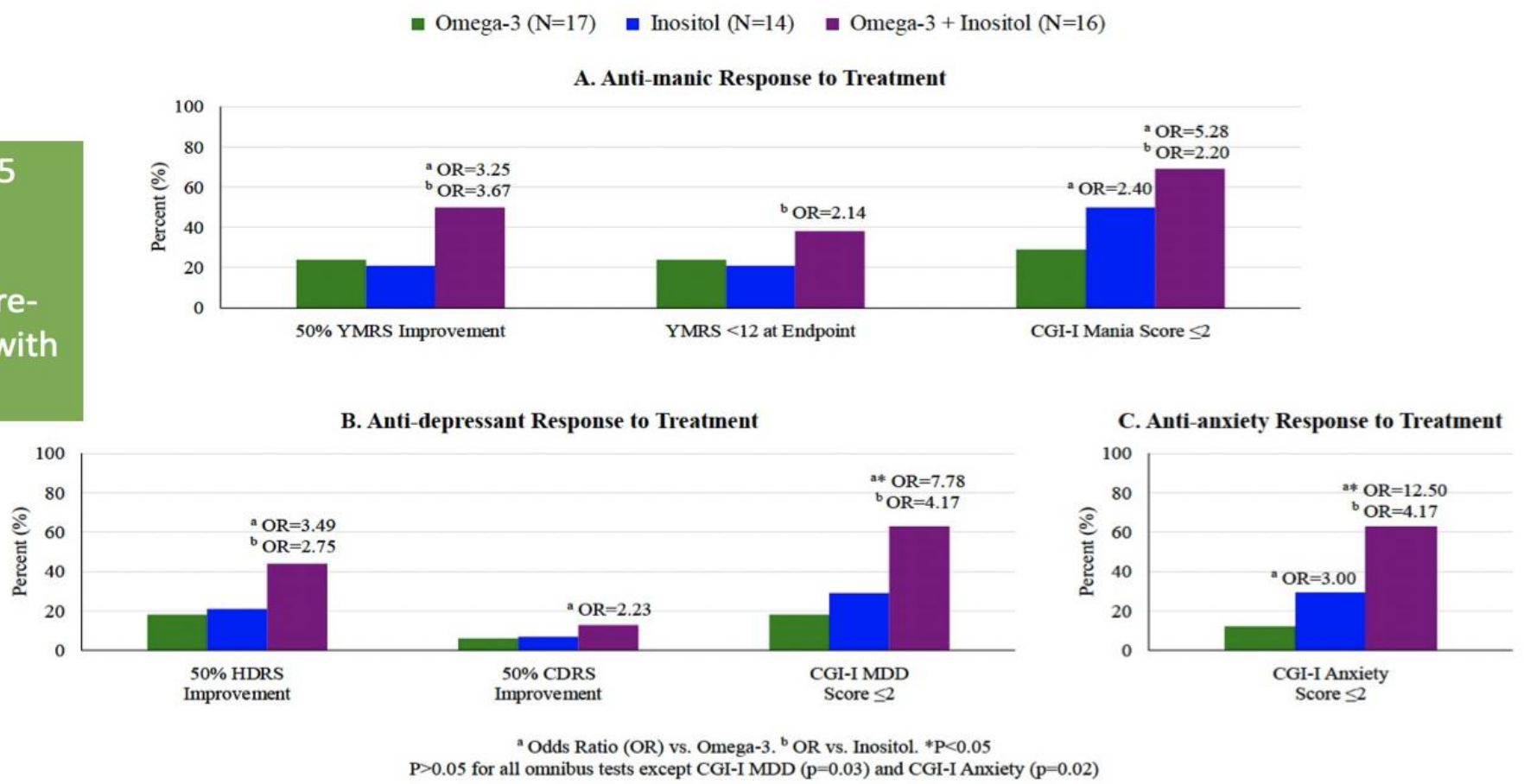


Although concomitant medications were allowed per protocol, the vast majority of the participants were only taking the study treatments

Without these 5 participants: omega-3 N=17; inositol N=14; combination N=16

Omega-3 + Inositol combined outperforms either used alone for mania or depression when use as montherapy (N=47, removing 5 subjects taking concomitant medications)

We removed the 5 subjects on concomitant medications and re-ran the analyses with similar findings

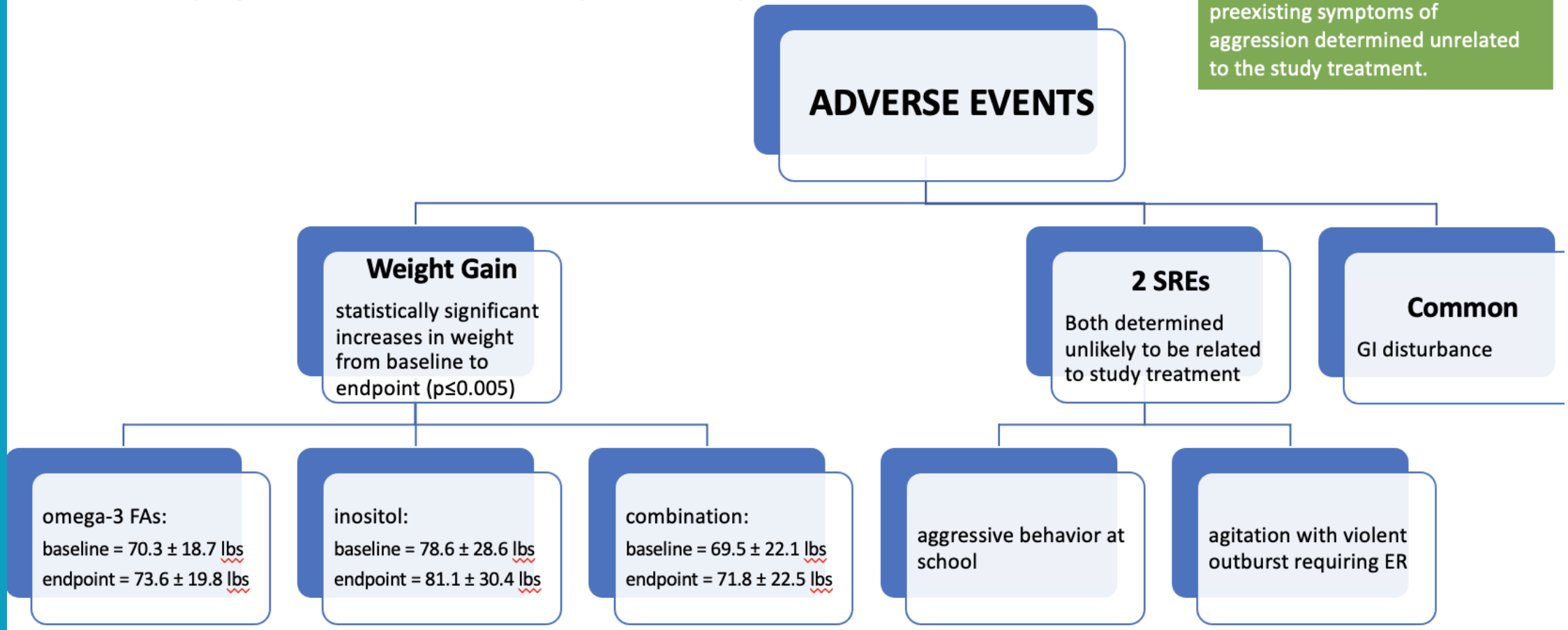


[a] Odds Ratio (OR) vs. Omega-3. [b] OR vs. Inositol. *P<0.05
P>0.05 for all omnibus tests except CGI-I MDD (p=0.03) and CGI-I Anxiety (p=0.02)

ADVERSE EVENTS

No clinically significant effects on blood pressure or pulse

One participant randomized to the combination group dropped at baseline, psychiatrically hospitalized due to exacerbation of preexisting symptoms of aggression determined unrelated to the study treatment.



Strengths:

- Pre-adolescent age 5-12 years
- All received an active treatment
- Only 5 participants on concomitant medications, so we could analyze the data without them for monotherapy results
- Use of combination natural treatments promising
- First study of inositol for mood disorders in children

Limitations:

- No Tanner staging, so can not say this was a prepubertal study
- High drop out rate and long recruitment period
- Predominantly Caucasian sample
- May not be generalizable to the general population, as our sample consisted only of referred children
- Due to exclusion safety measure our results apply only to children with YMRS scores of 40 or lower, limiting the generalizability of our findings to youth with more severe symptoms.
- There was no placebo only group so cannot assess if the increase in weight is due to the study treatments

Conclusion:

The antimanic and antidepressant effects of the combination treatment of omega-3 FAs and inositol were consistently superior to either treatment used alone.

This combination may offer a safe and effective alternative or augmenting treatment for youth with BP spectrum disorder, but more work is needed to confirm the statistical significance of this finding.

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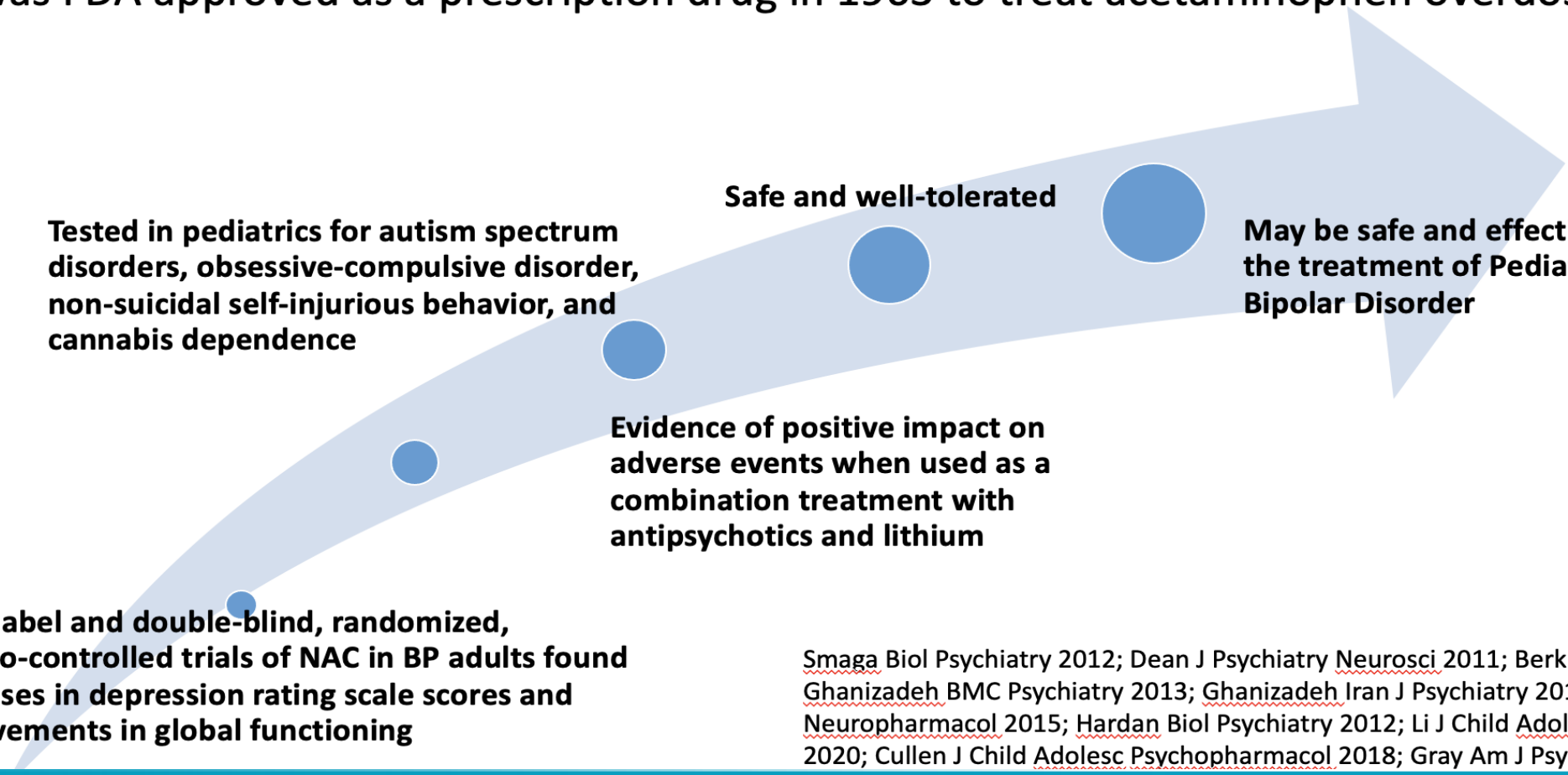
Gagan Joshi MD
Mai Uchida MD
Carrie Vaudreuil, MD

n-acetylcysteine (NAC) - acetylated amino acid and a precursor of glutathione

NAC was FDA approved as a prescription drug in 1963 to treat acetaminophen overdose



Smaga Biol Psychiatry 2012; Dean J Psychiatry Neurosci 2011; Berk Biol Psychiatry 2008 Ghanizadeh BMC Psychiatry 2013; Ghanizadeh Iran J Psychiatry 2017; Nikoo Clin Neuropharmacol 2015; Hardan Biol Psychiatry 2012; Li J Child Adolesc Psychopharmaco 2020; Cullen J Child Adolesc Psychopharmacol 2018; Gray Am J Psychiatry 2012

N-Acetyl Cysteine for Depressive Symptoms in Bipolar Disorder—A Double-Blind Randomized Placebo-Controlled Trial

Michael Berk, David L. Copolov, Olivia Dean, Kristy Lu, Sue Jeavons, Ian Schapkaitz, Murray Anderson-Hunt, and Ashley I. Bush

Background: Treatment-resistant subthreshold depression is a major problem in bipolar disorder. Both depression and bipolar disorder are complicated by glutathione depletion. We hypothesized that treatment with N-acetyl cysteine (NAC), a safe, orally bioavailable precursor of glutathione, may improve the depressive component of bipolar disorder.

Methods: A randomized, double-blind, multicenter, placebo-controlled study of individuals ($n = 75$) with bipolar disorder in the maintenance phase treated with NAC (1 g twice daily) adjunctive to usual medication over 24 weeks, with a 4-week washout. The two primary outcomes were the Montgomery Asberg Depression Rating Scale (MADRS) and time to a mood episode. Secondary outcomes included the Bipolar Depression Rating Scale and 11 other ratings of clinical status, quality of life, and functioning.

Results: NAC treatment caused a significant improvement on the MADRS (least squares mean difference [95% confidence interval]: −8.05 [−13.16, −2.95], $p = .002$) and most secondary scales at end point. Benefit was evident by 8 weeks on the Global Assessment of Functioning Scale and Social and Occupational Functioning Assessment Scale and at 20 weeks on the MADRS. Improvements were lost after washout. There was no effect of NAC on time to a mood episode (log-rank test: $p = .968$) and no significant between-group differences in adverse events. Effect sizes at end point were medium to high for improvements in MADRS and 9 of the 12 secondary readouts.

Conclusions: NAC appears a safe and effective augmentation strategy for depressive symptoms in bipolar disorder.

Key Words: Bipolar disorder, clinical trial, depression, glutathione, N-acetyl cysteine, neurochemistry

Glutathione is the main antioxidant substrate in all tissue. Increased oxidative stress with perturbed glutathione metabolism is increasingly described as a feature of major psychiatric disorders (1), including schizophrenia (2,3), bipolar disorder (4–7), and depression (8). Peripheral abnormalities of the glutathione and other antioxidant metabolic pathways associated with bipolar disorder and depression have been reported to improve with somatic and drug treatments (6–10), reducing oxidative stress (11–14).

Data are accumulating that mood stabilizers buffer oxidative defenses. Valproate may protect neuronal cells from damage related to oxidative stress (15). Chronic lithium and valproate treatment has been found to increase expression of cellular risk for schizophrenia, where there is a decrease in brain glutathione (18).

Glutathione production is rate-limited by its precursor, cysteine. Its acetylated derivative, N-acetyl cysteine (NAC) is more efficiently bioavailable and is deacetylated by the liver (19,20). N-acetyl cysteine is neuroprotective in a variety of neurodegenerative disease models (21–23). We recently found in a placebo-controlled, randomized, double-blind clinical trial that NAC treatment over 24 weeks significantly improved Clinical Global Impression (CGI) and Positive and Negative Syndrome Scale (PANSS) for schizophrenia scores in subjects with chronic schizophrenia (24). N-acetyl cysteine increases blood glutathione levels and improves auditory mismatch negativity in schizophrenia within 8 weeks (25).

We hypothesized that add-on NAC treatment may also be of clinical benefit in both the treatment and prevention of depres-

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Berk, Biol Psychiatry 2008

ORIGINAL ARTICLES

N-Acetylcysteine as an Adjunctive Therapy to Risperidone for Treatment of Irritability in Autism

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Efficacy and Safety

Nikoo, Mohammadali MD; Radnia, Hanieh MD; Farokhnia, Mehdi MD; Mohammadi, Mohammad-Reza MD; Akhondzadeh, Shahin PhD

Objectives

According to the proposed interference of *N*-acetylcysteine (NAC) with pathophysiologic processes of autistic disorders (ADs), we aimed to assess the effectiveness and safety of NAC as an adjunct to risperidone in the treatment of ADs in a randomized, double-blind, clinical trial.

Methods

The participants were referred outpatients between 4 and 12 years of age with the diagnosis of ADs and a score of more than 12 on Aberrant Behavior Checklist-Community (ABC-C) Irritability subscale score. The participants were randomized into 2 groups. One group received risperidone plus NAC, and the other group received risperidone plus placebo. The dose of risperidone was titrated between 1 and 2.0 mg/d, and the dose of NAC was 600 to 900 mg/d. The main outcome was mean decrease in the ABC-C irritability subscale score from baseline at 5 and 10 weeks. Changes in other subscales were considered as secondary outcome measures.

Results

Forty patients completed the 10-week trial. Baseline characteristics including age, sex and body weight, as well as baseline scores in 5 subscales did not demonstrate statistically significant difference between the 2 groups. Repeated-measures analysis showed significant effect for time × treatment interaction in irritability ($P = 0.01$) and hyperactivity/noncompliance ($P = 0.02$) subscales. By week 10, the NAC group showed significantly more reduction in irritability ($P = 0.02$) and hyperactivity/noncompliance ($P = 0.01$) subscales scores.

Conclusions

N-acetylcysteine can be considered as an adjuvant therapy for ADs with beneficial therapeutic outcomes.

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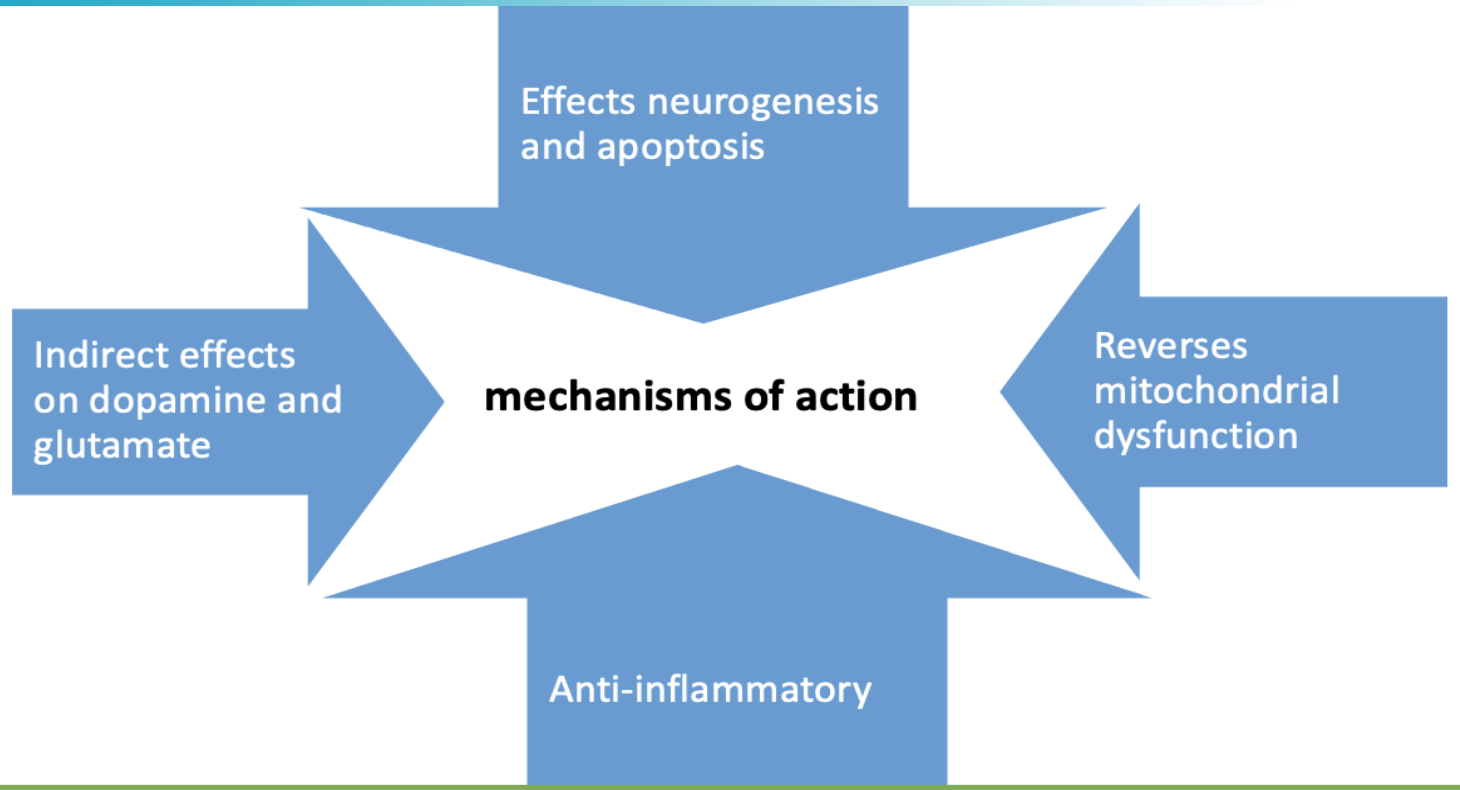
Nikoo, Clinical Neuropharmacology 2015

NAC



Increases cysteine levels and allows for the synthesis of more glutathione in the brain
Glutathione, an antioxidant, acts to reduce oxidative stress (implicated in BP disorder and major depression)
Glutathione is not a treatment options as it is is poorly absorbed and rapidly metabolized when ingested
NAC crosses the blood-brain barrier with ease to increase glutathione synthesis

Berk Neurosci Biobehav Rev 2011; Smaga Biol Psychiatry 2012; Witschi Eur J Clin Pharmacol 1992; Dean J Psychiatry Neurosci 2011

Assess the efficacy and tolerability of N-ACETYLCYSTEINE (NAC) for the treatment of pediatric bipolar (BP) spectrum disorder in young children

- NAC well tolerated and useful for depressive symptoms in bipolar spectrum disorder in adults
- May have protective effects
- Pediatric studies demonstrate safety for children, but never tested in pediatric bipolar disorder
- We assessed the safety, tolerability, and effectiveness of NAC in the treatment of Pediatric Bipolar Spectrum Disorder
- **Hypothesis:** NAC would be a safe, well-tolerated and effective treatment in the treatment of pediatric bipolar disorder

Open label clinical trial NAC

All study procedures were reviewed and approved by the Partners Human Research Committee. All participants' parents or guardians signed written informed consent forms and all children older than 7 years of age signed written assent forms to participate.

Male and female

5-17 years

Met criteria for

bipolar I, II or NOS

Displayed manic, hypomanic, or mixed symptoms at enrollment according to the DSM-V based on clinical assessment and KSADS mood modules

12-week

Open-label clinical trial

Weeks 1-4: office visits

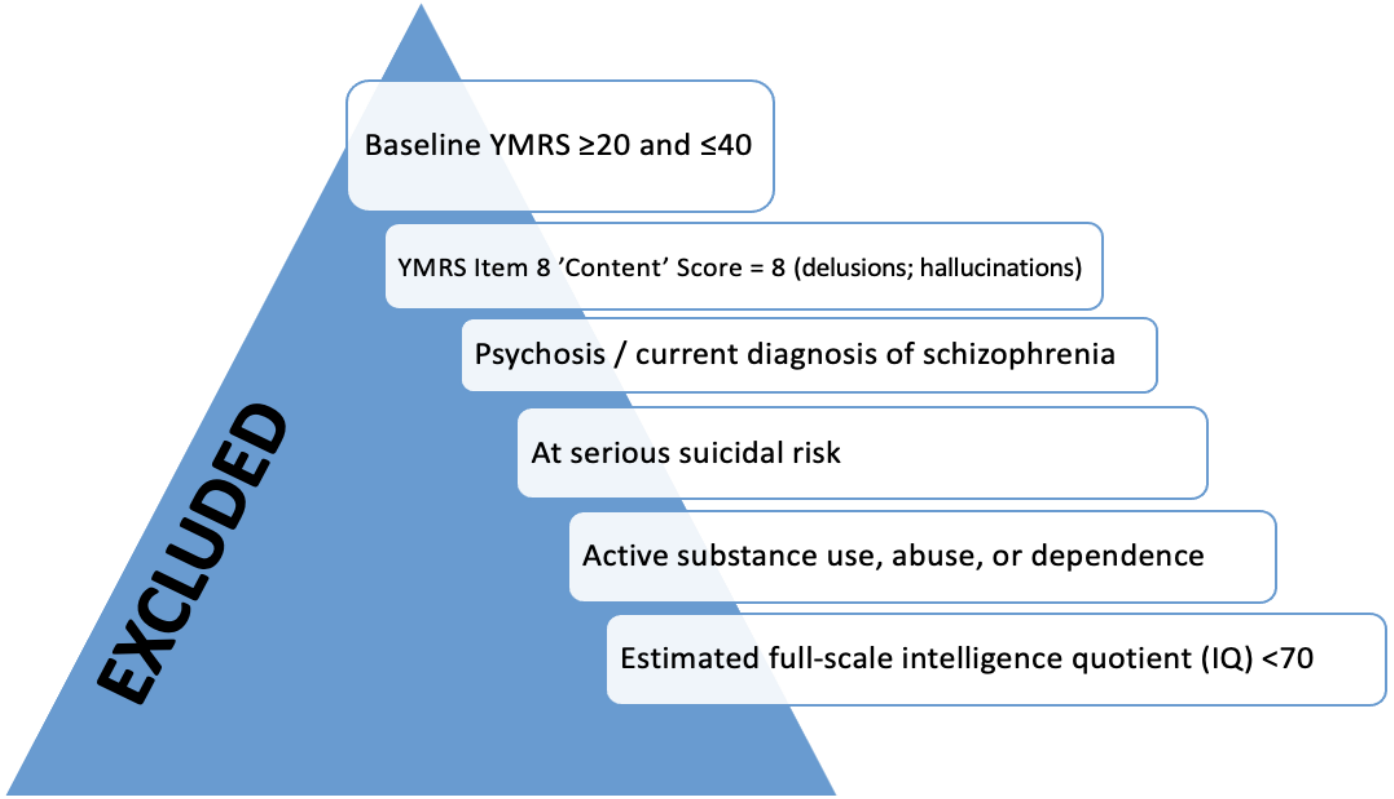
Weeks 4-12:

--Monthly office visits

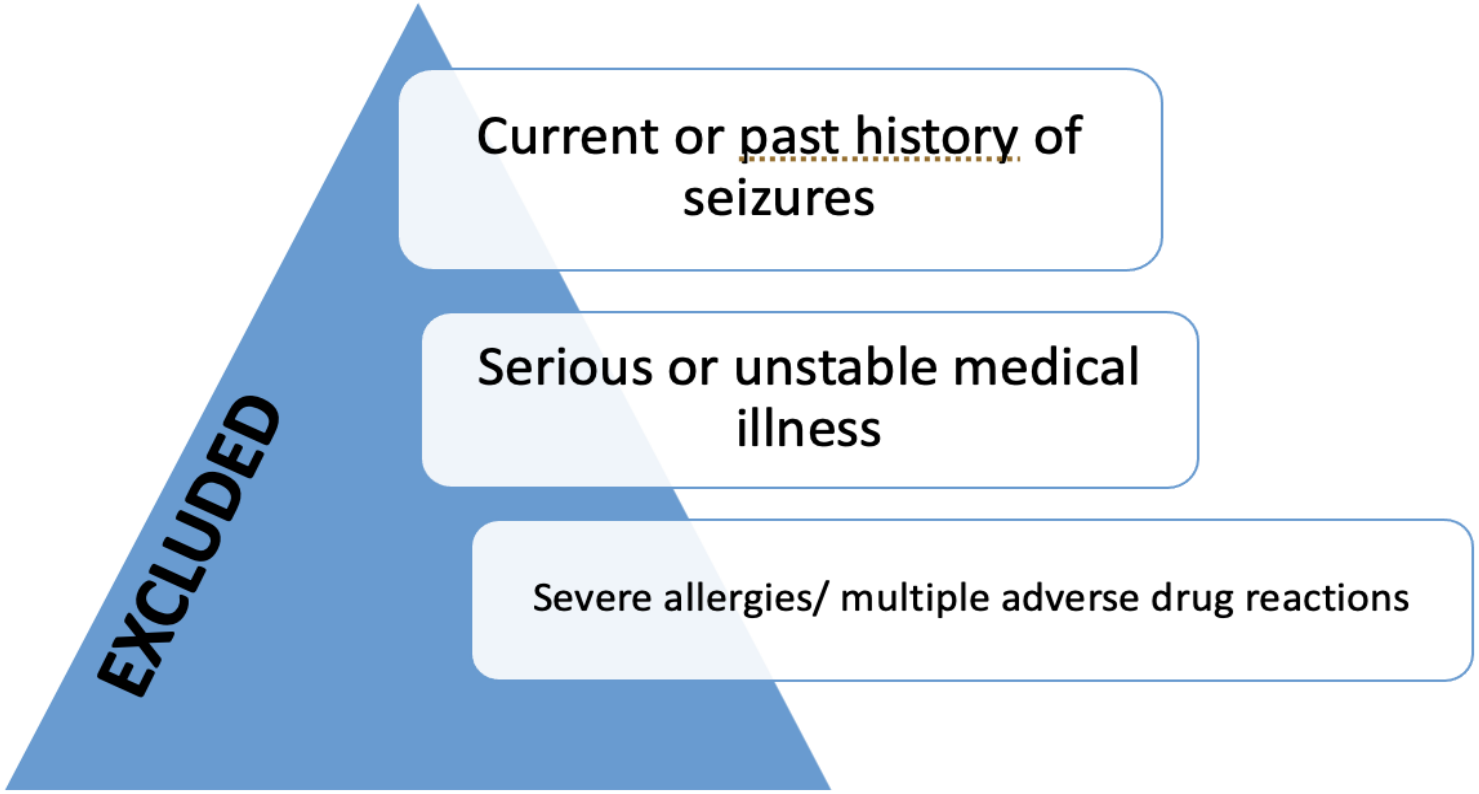
--Other weeks tele-visits

Exclusionary Criteria – severe psychiatric illness

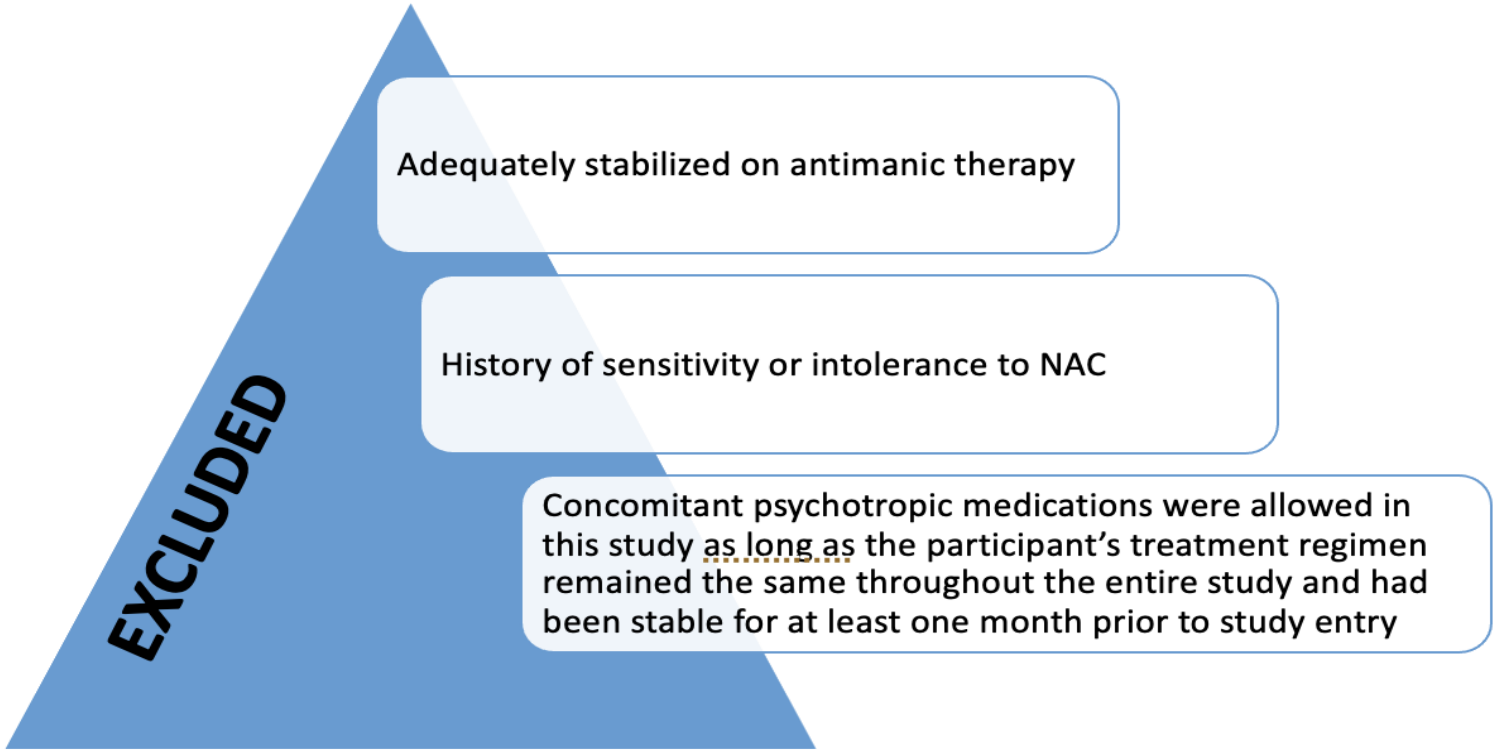
to protect children with severe illness who should be offered FDA approved treatments



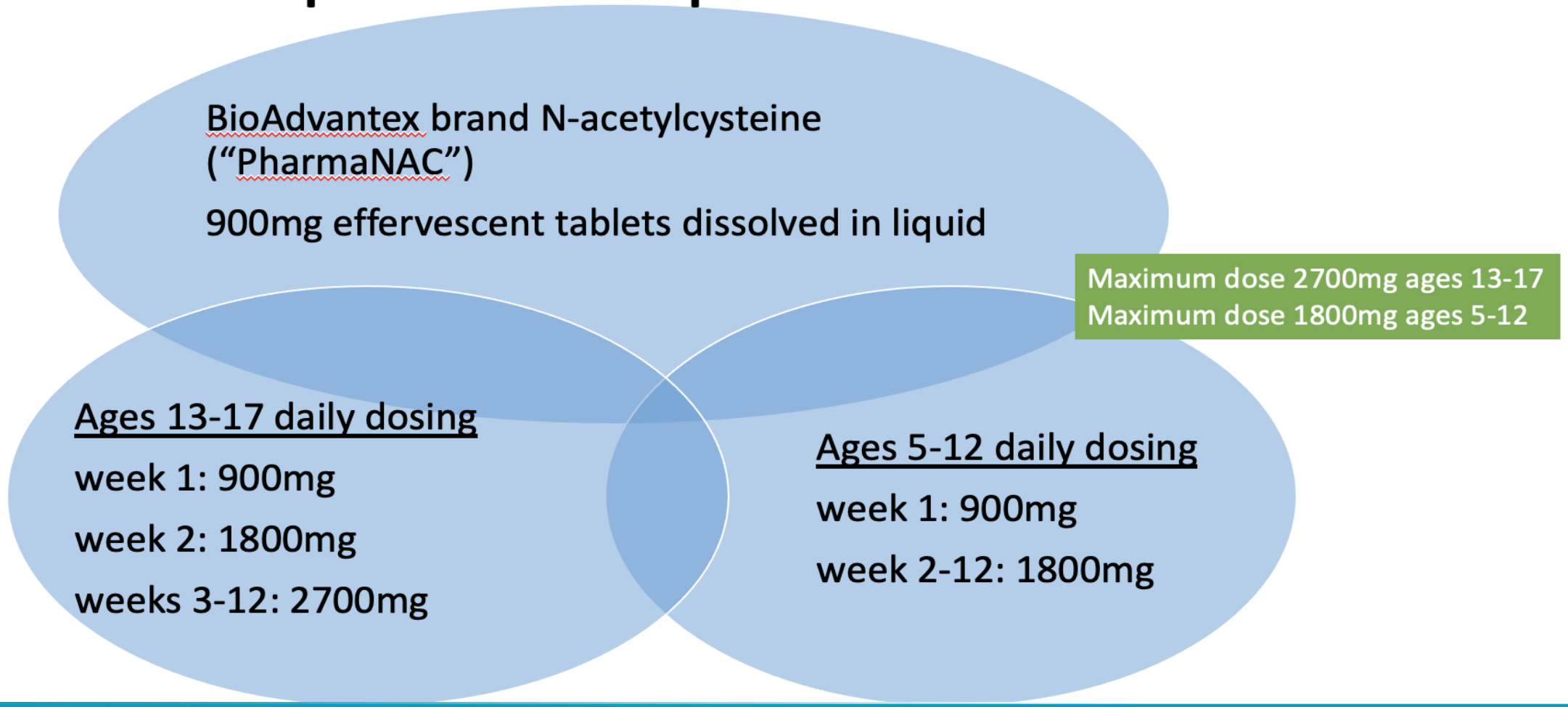
Exclusionary Criteria - medical



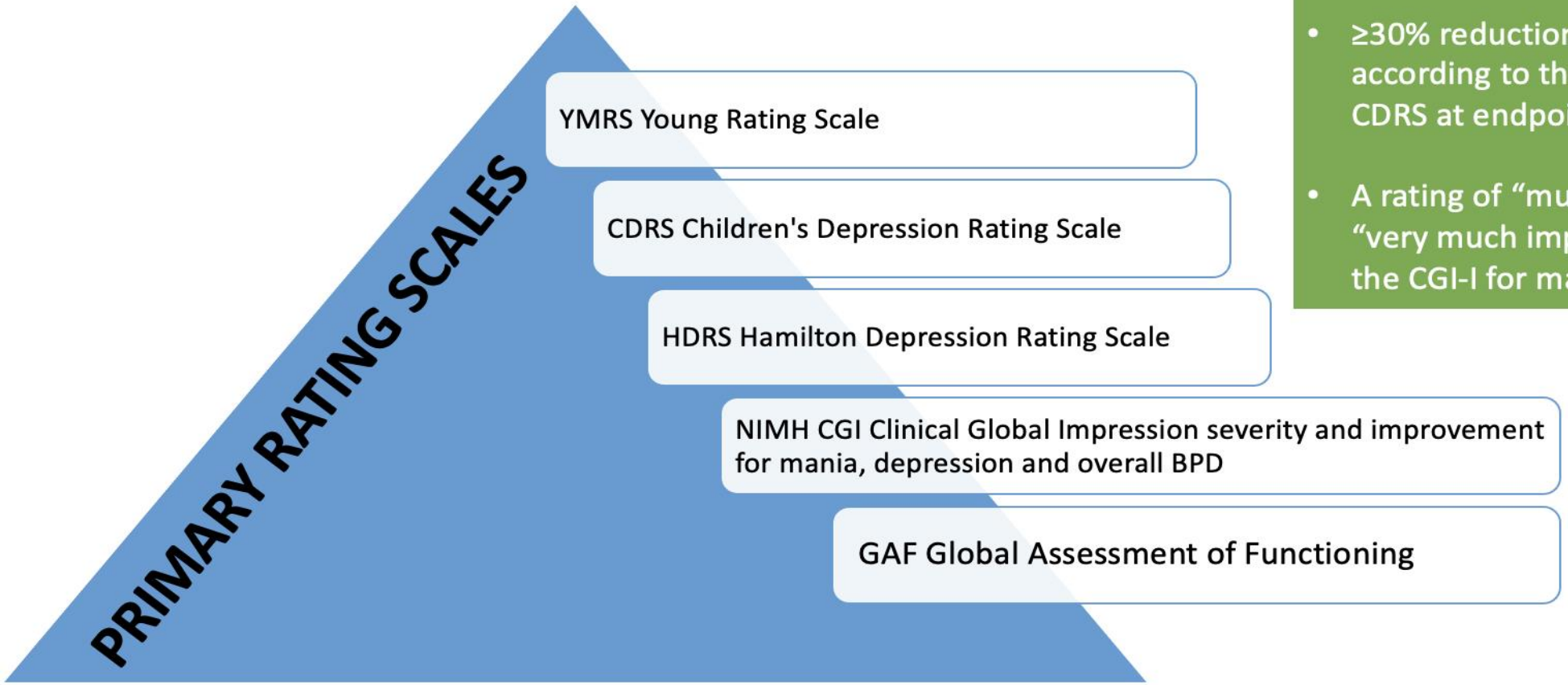
Exclusionary Criteria - medications



Participants received open label treatment with NAC



Main Outcome Measures

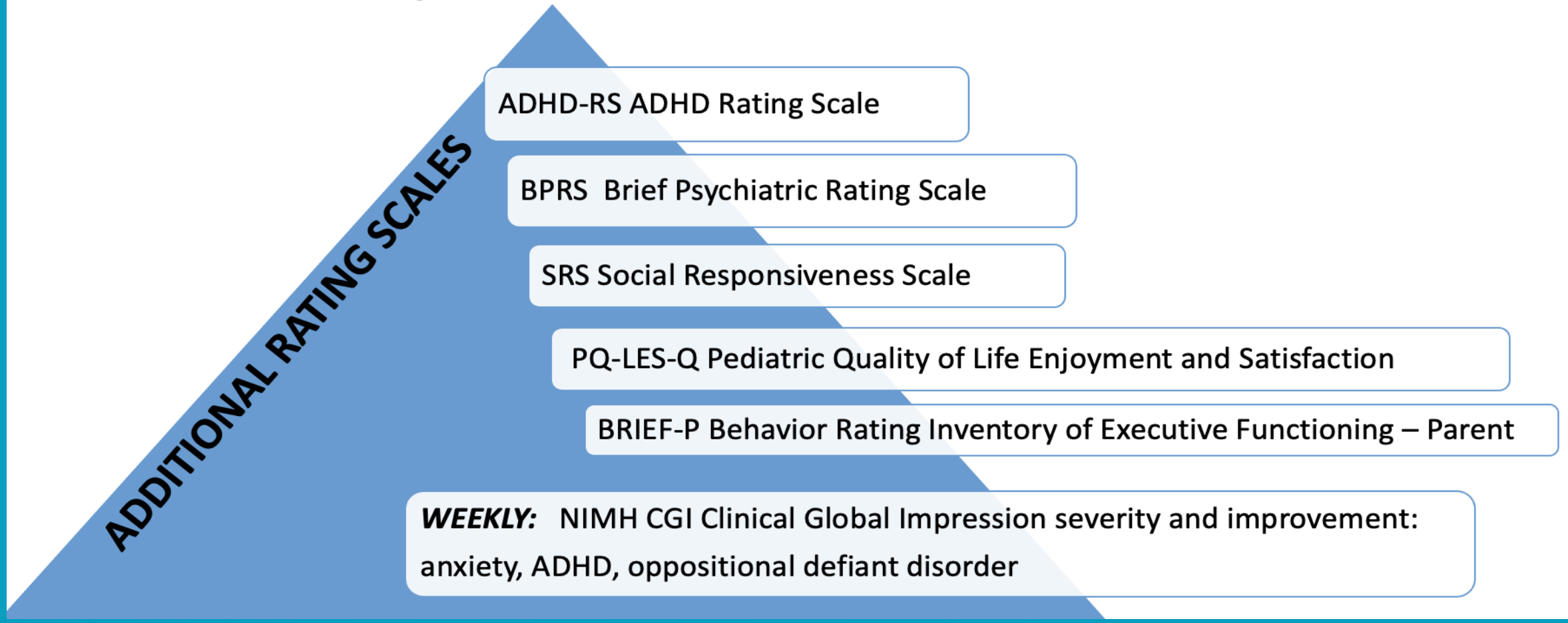


Response at endpoint defined as either

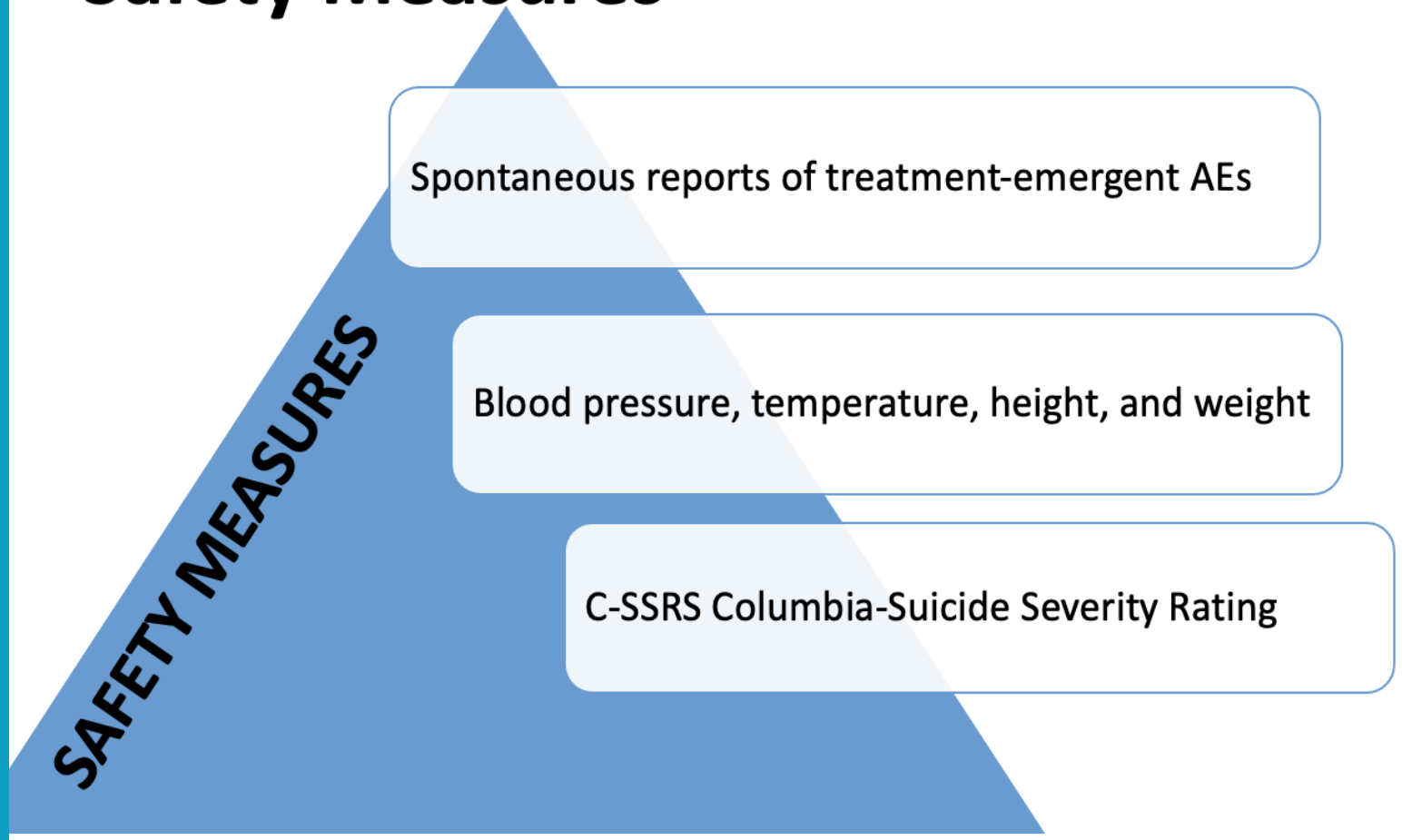
- ≥30% reduction in symptoms according to the YMRS, HDRS, or CDRS at endpoint
- A rating of "much improved" or "very much improved" (score ≤2) on the CGI-I for mania or depression.

Additional Outcome Measures-

Baseline and Endpoint



Safety Measures



Discontinuation after 2 weeks in a row:

- CGI-S overall BP 2 points higher than baseline
- YMRS score 30% higher than baseline
- YMRS item score of 8 on item 8 (content)
- YMRS item score of than 6 on item 9 (disruptive/aggressive behavior)

Discontinuation if less than 70% compliance for two weeks or longer according to pill counts

Discontinued for C-SSRS scores of ≥ 4

Open label NAC was useful for pediatric bipolar disorder with significant difference from baseline to endpoint YMRS, HDRS and CDRS

Table 1. Change in scores from baseline to endpoint on measures of mania and depression.

		Baseline	Endpoint†	Difference	Cohen's d (95% CI)	Test Statistic	P-Value
	N	Mean ± SD	Mean ± SD	Mean ± SD			
YMRS	26	23.8 ±5.7	15.7 ±10.1	-8.1 ±8.5	0.99 (0.41, 1.56)	z=-7.19	<0.001
CDRS	26	37.1 ±11.7	31.9 ± 14.7	-5.2 ±10.7	0.39 (-0.16, 0.94)	z=-3.90	<0.001
HDRS	26	15.3 ± 7.9	9.5 ±8.5	-5.8 ±7.2	0.70 (0.14, 1.26)	z=-3.95	<0.001

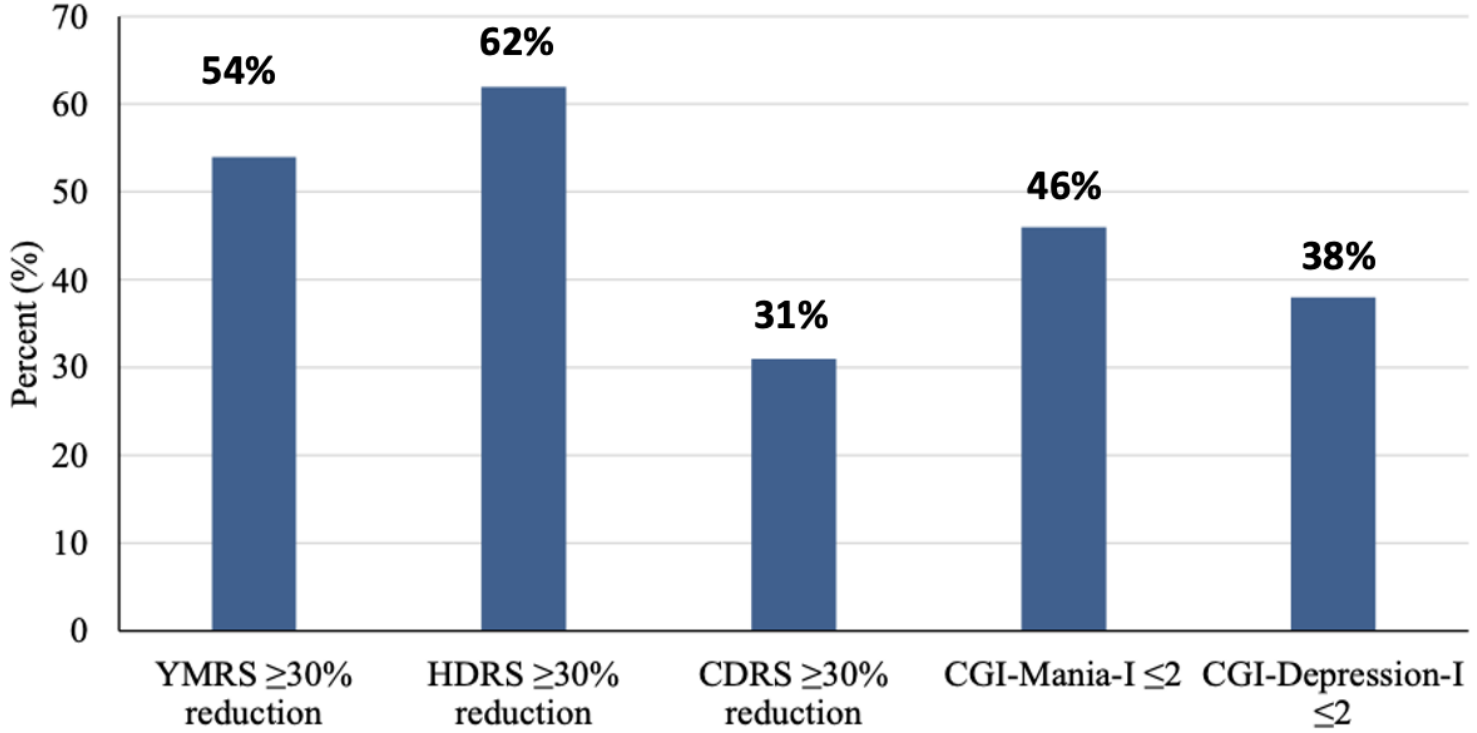
†Endpoint mean uses last observation carried forward for subjects who dropped prior to week 12.
SD=standard deviation; CI=confidence interval; YMRS=Young Mania Rating Scale; CDRS=Child Depression Rating Scale; HDRS=Hamilton Depression Rating Scale

Overall Functioning

There were significant improvements in overall functioning as measured by the clinician-rated GAF (Baseline: 53.8 ± 5.8, Endpoint: 58.2 ± 8.3, Mean Difference: 4.3 ± 6.1; SMD [95% CI]: 0.61 [0.05, 1.16]; p<.001)

Parents reported significant improvements in their children's quality of life as measured by the PQ-LES-Q (Baseline: 44.1 ± 7.0, Endpoint: 50.1 ± 7.9, Mean Difference: 6.0 ± 7.6; SMD [95% CI]: 0.81 [0.08, 1.52]; p=.002)

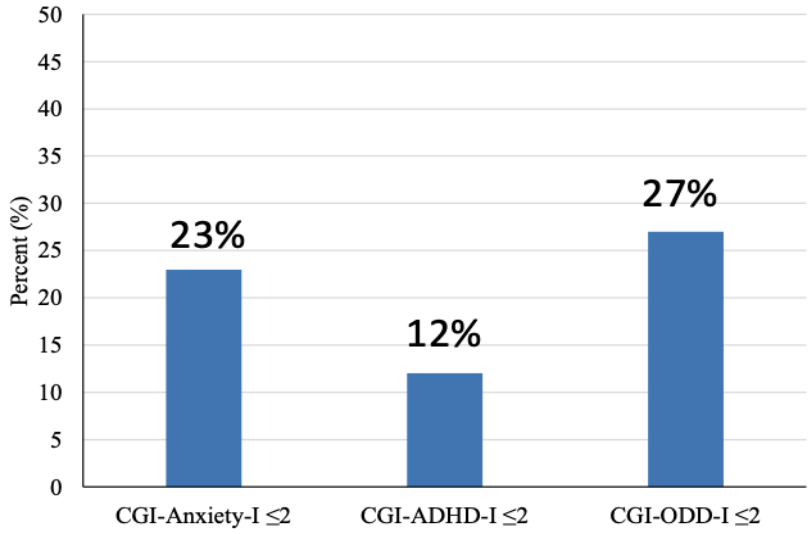
Percent with 30% reduction in YMRS, HDRS, CDRS and percent with CGI-Improvement ≤ 2 mania and depression



12 week open label
N=26
Average age 10 years
46% male
73% caucasian

Other domains: Percent with CGI-Improvement ≤ 2 Anxiety, ADHD and ODD

Figure 2. Response to treatment in other domains at endpoint (week 12 or last week completed for those who dropped)



CGI-I=Clinical Global Impressions-Improvement

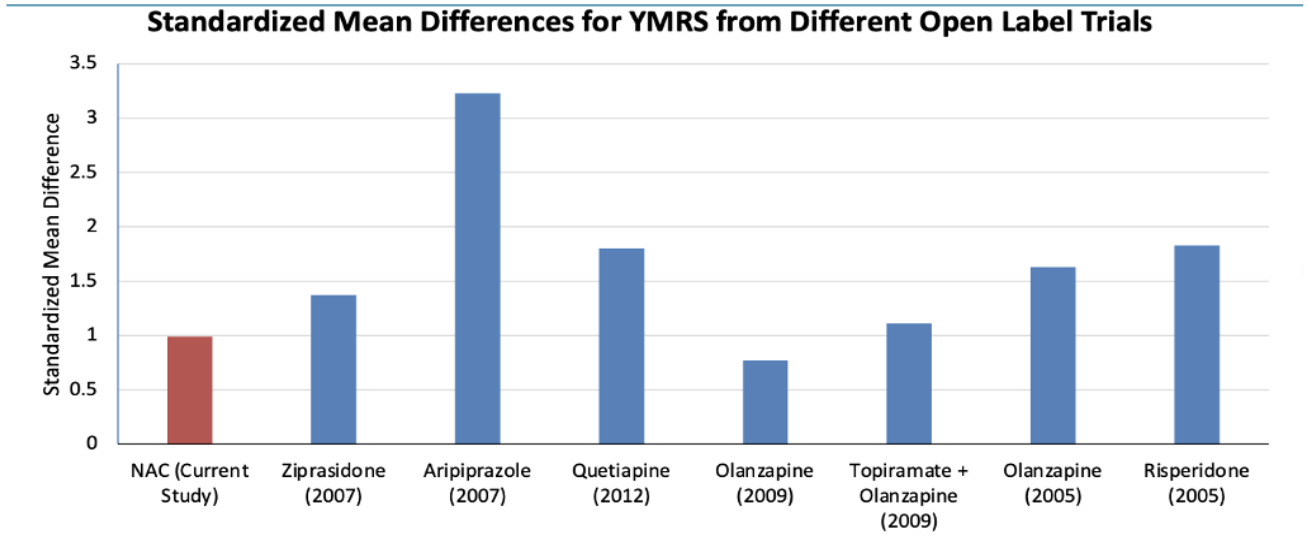
There was a statistically significant p=.03 improvement in ADHD symptoms on the clinician-rated ADHD-RS

Baseline: 34.2 ± 15.0
Endpoint: 27.2 ± 15.4

NAC and mania

NAC has an effect size generally lower, but in the ballpark of the effect size of SGAs for mania

$$SMD = \frac{\text{Difference in mean outcome between groups}}{\text{Standard deviation of outcome among participants}}$$



The **standardized mean difference** is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways (for example, all studies measure depression but they use different psychometric scales). In this circumstance it is necessary to standardize the results of the studies to a uniform scale before they can be combined. The standardized mean difference expresses the size of the intervention effect in each study relative to the variability observed in that study.

Studies for which the difference in means is the same proportion of the standard deviation will have the same SMD, regardless of the actual scales used to make the measurements.

NAC and depression

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NAC has an effect size generally lower, but in the ballpark of the effect size of SGAs for depression

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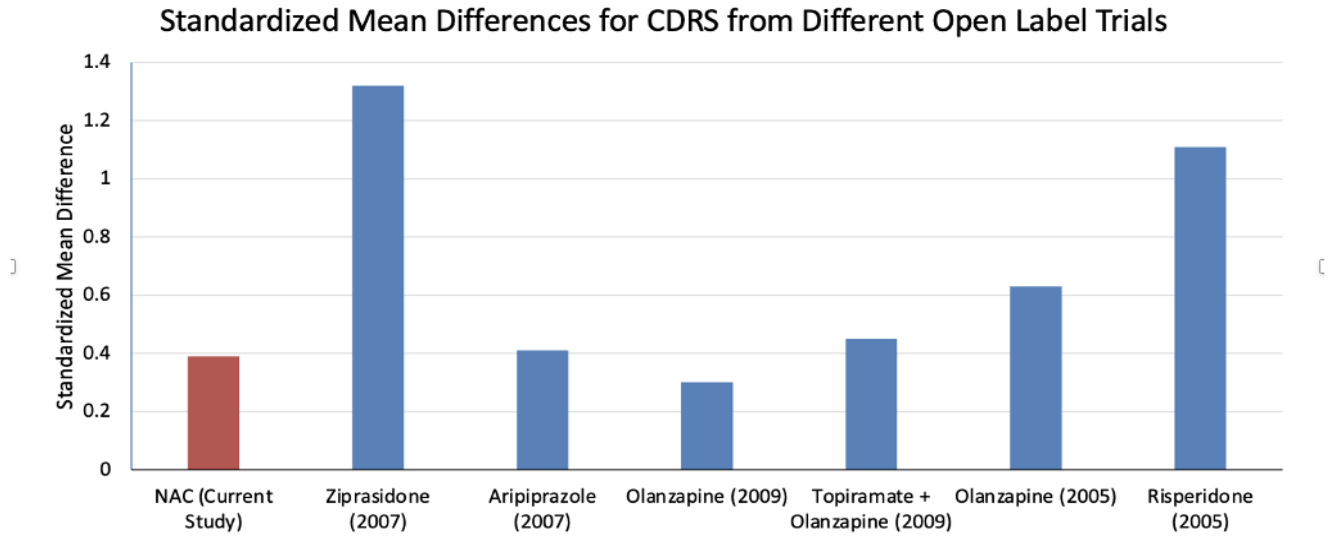

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Adverse Events

Adverse events in subjects who started study medication (≥1 week) (N=29)

Adverse Event	Occurred Only 1 Time	Occurred ≥2 Times
Nausea/Vomit/Diarrhea (Gastrointestinal)	5 (17)	2 (7)
Insomnia	4 (14)	0 (0)
Cold/Infection/Allergy	3 (10)	1 (3)
Headache	3 (10)	0 (0)
Anxious/Worried	2 (7)	0 (0)
Neurological	2 (7)	0 (0)
Dizzy/Lightheaded	1 (3)	0 (0)
Musculoskeletal	1 (3)	0 (0)
Increased Appetite	0 (0)	1 (3)
Dermatological	0 (0)	1 (3)
Other: Thirsty	0 (0)	1 (3)
Other: Bike injury with need for stitches	1 (3)	0 (0)
Other: Dissociation	1 (3)	0 (0)

17 (59%) at least one AE
GI complaints most common

No clinically or statistically significant (p>.05)changes in systolic blood pressure, diastolic blood pressure, HR or height

Two had outlying weight gains: 4.6 kg (taking concomitant medication olanzapine) and 5.4 kg (not taking any concomitant medications)

Sensitivity Analysis: NAC Monotherapy

21 exposed participants received NAC as monotherapy, without any concomitant medications

- Results largely remained the same when we performed a sensitivity analysis restricting the sample to the 21 exposed participants who were receiving NAC monotherapy.
- Significance stayed the same for all outcome measures except for the BRIEF Self Monitor and Initiate subscales, which lost significance.
- Most of the effect sizes saw minimal changes, with the exception of the YMRS, BPRS and MSC, which dropped from 0.99, 0.65, and 0.77, respectively, in the whole group to 0.91, 0.54, and 0.69, respectively, in the group receiving NAC monotherapy.
- Despite these decreases, the SMDs for the YMRS, BPRS, and MSC remained moderate to large in size.

Strengths:

- Pediatric participants
- First study of NAC for pediatric bipolar disorder
- Focus on improvement of mania and hypomania, not just depression

Limitations:

- Open label without a placebo group
- We were unable to report thoroughly on comorbid conditions
- Sample size relatively small
- This study had a high drop-out rate with only 53% completing all 12 weeks
- Predominantly Caucasian sample
- May not be generalizable to the general population, as our sample consisted only of referred children
- Due to exclusion safety measure our results apply only to children with YMRS scores of 40 or lower, limiting the generalizability of our findings to youth with more severe symptoms.

The high drop-out rate suggests the need to design future trials which place lower burden on participants, with fewer study visits, fewer study measures and study visits accomplished via telepsychiatry

Conclusion:
Our results provide pilot data suggesting the safety and tolerability of NAC used in a pediatric population with mixed, manic or hypomanic states.

In these pilot findings, with open-label conditions and small sample size, treatment with NAC led to significant improvements in our primary outcome measure of manic symptoms, but also depressive symptoms, and was very well tolerated.

These pilot open-label findings in a small sample provide preliminary data supporting the tolerability and safety of NAC in a pediatric population.

The findings of this pilot scale study indicating improvement in mania and depression are promising, but require replication with a monotherapy randomized placebo controlled clinical trial and larger sample.

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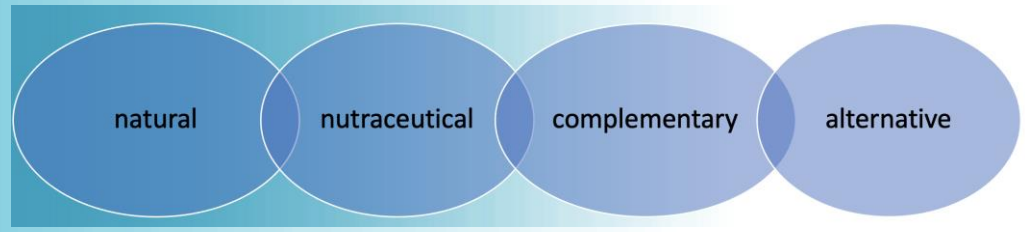
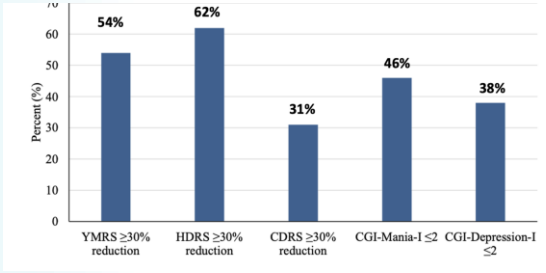
Overview:
Neutraceuticals are popular, but poorly studied, especially for bipolar disorder; omega-3 fatty acids, inositol and NAC have emerging data supporting use in pediatric bipolar disorder.

Over-the-counter dietary supplements marketed for health are not approved by the FDA



Omega-3s and Inositol have complementary mechanisms of action and can be mildly useful in youth with mild-moderate bipolar disorder

N-acetylcysteine has evidence for use in adult and pediatric bipolar disorder



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Average age 10 years
46% male
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QUESTIONS?