Optimize clinical trial design to study nutraceutical correction of essential fatty acid ratio for weight restoration and maintenance in anorexia nervosa

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Introduction

How do we know when, what and how much to eat?

Preparatory/appetitive phase

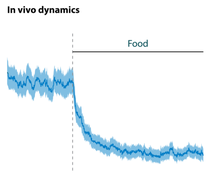
Consummatory phase

Satiety phase

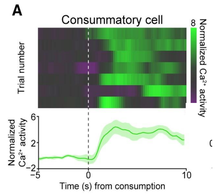
AGRP-expressing arcuate neurons are activated during hunger and rapidly inhibited by food and food-predicting cues

(A subset of) GABAergic neurons in the lateral hypothalamus are activated during consumption

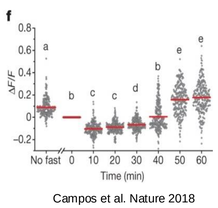
CGRP-expressing parabrachial neurons are activated as satiety develops



Betley et al. Nature 2015

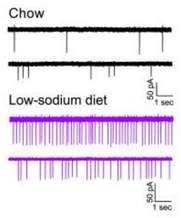


Jennings et al. Cell 2015



Campos et al. Nature 2018

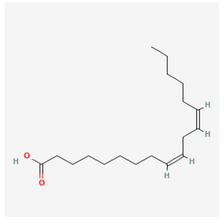
The brain enables adequate intake of total calories and essential nutrients, salt as an example:



Resch et al. Neuron 2017

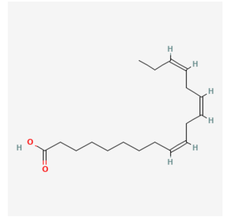
Did evolution leave out essential fatty acids?

Omega-6 (ω-6) **Pro**-inflammatory



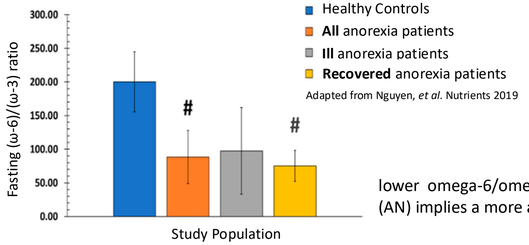
linoleic acid

Omega-3 (ω-3) **Anti**-inflammatory



alpha-linolenic acid

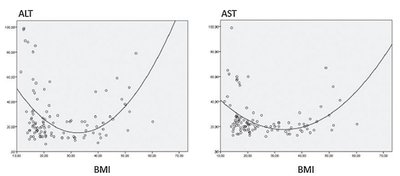
Why omega-6 and omega-3 matter?



Adapted from Nguyen, *et al.* Nutrients 2019

lower omega-6/omega-3 in anorexia nervosa (AN) implies a more **anti-inflammatory** state

But AN is a pro-inflammatory state by multiple systemic and end-organ measures



Quadratic line interaction: R^2 =0.19; p<0.001

Quadratic line interaction: R^2 =0.16; p<0.001

Lelli, et al. European Eating Disorders Review 2014

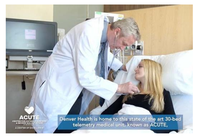
How do we reconcile this paradox?

Low omega-6/omega-3 ratio prevents those with genetic predisposition from responding appropriately to hunger cues thus **sustains the AN state**.

Methods - a pilot RCT

- **Based on neural circuitry principles governing feeding behavior**
- **Fits easily into the typical treatment course for AN**

Inpatient (IP) or residential → Partial hospitalization program (PHP) → Intensive outpatient program (IOP) → Outpatient (OP)



ACUTE at Denver Health

Johns Hopkins Day Hospital

Walden Middletown, CT

Eating Recovery Center

Hypothesis: compared with no nutraceutical intervention, increasing omega-6/omega-3 ratio via nutraceutical supplementation

- accelerates **weight restoration** during **IP/residential** treatment
- increases the likelihood of **long-term weight maintenance**

Inclusion criteria:

1. Age ≥ 14; meet DSM-V diagnostic criteria for AN, admitted to IP or residential treatment centers in Connecticut and other states
2. Follow up for at least 6 months after discharge, at their PHP, IOP, and OP visits

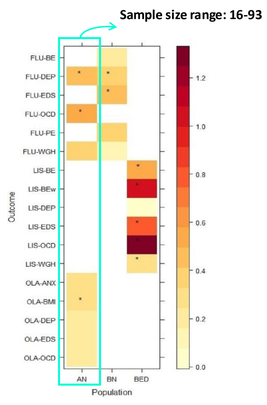
Exclusion criteria:

1. Metabolic disorders, including but not limited to type 1 diabetes and inborn errors of metabolism
2. Inability to complete the Eating Disorder Examination, Questionnaire Version (EDE-Q)[8], a validated eating disorder psychopathology assessment)
3. Newly been on antipsychotic medication or other medication known to affect weight for < 4 weeks, or plan to start these medications within the first 8 weeks of starting this trial
   - participants can be on a stable dosage of psychotropic medications if they had not consistently gained weight (>3 lb) over the 4 weeks prior to study participation.

Sample size = 60 patients, 30 in each group, determined by 5 factors:

1. Pooled effect sizes on weight gain from meta-analysis of psychopharmacological RCTs for AN till the Aug 2022[3]
2. Empirical sample sizes in recent psychopharmacological RCTs for AN in the U.S. – this represents recruitment feasibility[3]
3. Effect sizes on weight of approved treatment modalities for AN, irrespective of patients' age[6]
   - notice none is pharmacological
   - the most effective treatment for AN: family therapy for adolescents, effect size on weight = 0.44

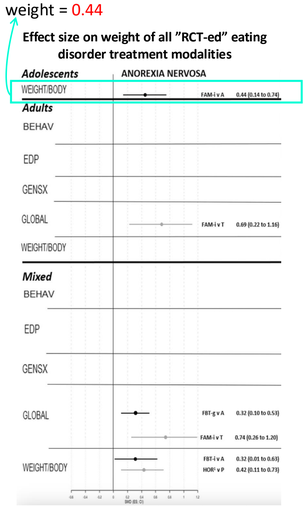
Pooled effect sizes



*denotes statistically significant Hedges'g values

Fornaro et al. Journal of Affective Disorders 2023

Effect size on weight of all "RCT-ed" eating disorder treatment modalities



Monteleone et al. Neuroscience & Biobehavioral Review, 2022

4. Effect size on weight of the most successful recent drug RCT for AN (olanzapine, by Attia, et al.) = 0.629[2]
   - Olanzapine not approved because failed in other trials
5. Dropout rate approximated to be 1/3 (33.3%) based on
   - most recent pharmacological RCTs for AN had/estimated dropout rates to be 30-38%[1, 2]
   - Non-pharmacological RCTs has lower dropout rates[3, 6]

Set significance level (alpha) = 0.05, desired statistical power = 0.8, sample size must >= 40 without dropout. Thus, sample size is set to be 60, 30 in each group.

Randomization strategy

Rolling randomization, aim for equal number to receive

- omega-6 (or omega-6 and omega--3 combo if patient is deficient at admission) that targets published fasting ω-6/ ω-3 ratio in healthy controls, or a placebo
  - Compound name and starting doses for omega-6: gamma LA (linoleic acid) 60 mg daily
  - For omega-3: EPA (eicosapentaenoic acid) 2,120 mg daily and DHA (docosahexaenoic acid) 600 mg daily
  - **How starting doses are determined:**
    1. have been used in published clinical trials on children and young adolescent for neuropsychiatric conditions
    2. Are at the low end of all published trials using these compounds, all age group included
  - Targeted ratio: [200, 250] (the upper bound 250 approximates mean in healthy control + one std)
- after discharge from IP or residential, patients to continue in **the same randomized group** for 6 months

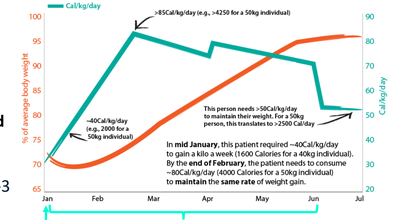
ω-6 (or ω-6 and ω-3 combo) placebo

Primary outcomes:

- **Rate of BMI increase** during IP/residential treatment: ΔBMI/days
- **% of patients** maintaining **BMI > 18.5** kg/m² in supplemented vs. placebo groups 6 months after discharge

Secondary outcomes:

- **Rate of BMI change** (gain, maintenance, loss) **when patient is "out and about"** (PHP, IOP, and OP)
- Safety and target engagement **Labs**
  - **Lab draw frequency:** every 2 days until targeted omega-6/omega-3 ratio is reached and maintained for 1 week, then space out to weekly draws
  - **What to measure:**
    - **Hemodynamic stability**: CBC, CMP, Ca, Mg, phosphorous
    - **Systemic and end-organ inflammation** markers: ESR, high-sensitivity CRP, AST, ALT
    - **Plasma omega-6, omega-3** and their respective metabolites in the soluble epoxide hydrolase pathway (**sEH, a novel anorexia susceptibility gene**[7])
- Severity of **eating disorder psychopathology** measured by EDE-Q[8]



- During these 6 months, AN patients need to **eat much more** to gain or just maintain weight, compared to healthy control of the same weight
  - **4250 kcal per day for a 50 kg AN patient**
- Thus, easy to transiently enter an energy deficit state
- Higher ω-6/ω-3 is expected to prevent AN patients from being stuck in energy deficit

Adapted from Marzola et al., BMC psychiatry 2013

Expected Results and Conclusion

1. Compared to no supplementation, omega-6 (or omega-6 and omega-3 combo) supplementation will
   - accelerate BMI increase during IP/residential course
     - supplemented patients will require shorter hospital stay for the same amount of weight gain
   - result in higher % of patients who maintain BMI > 18.5 kg/m² six months after discharge.
2. An RCT design based on neural circuity control of innate behavioral drives may lead to new treatment and recovery maintenance strategies for AN.

Reference and Acknowledgment

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