



Long COVID and supplements

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Disclosures or conflict of interest

- I have no relationship with any supplement or pharmaceutical companies
- No conflicts of interest

Goals of this presentation

- Build awareness of OTC supplements that patients are taking for long covid
- Discuss potential benefits and harms
- Review any monitoring for side effects if known

You don't know what you don't know

- When asking about medications it is important to ask about other supplements that the patient is taking
- Vitamins, minerals, plant and animal extracts, hormones and amino acids
- Other formulations – liquids, powders, teas, nutraceuticals, essential oils
- 4 out of 5 adults report having taken one



Supplement “regulation” in the US

- FDA generally does not approve dietary supplement claims or other labeling before use. Under the FD&C Act, a firm is responsible for ensuring that the dietary supplements it manufactures or distributes are not adulterated, misbranded, or otherwise in violation of federal law. – Food and Drug Administration Website

It's the wild west out here

- Hundreds of dietary supplements on the market have contained undeclared or banned pharmaceutical ingredients, including some that were the subject of FDA warnings
- Many products marketed for weight loss, muscle building, or sexual function have contained illegal substances that caused severe AEs, especially among young adults using them more frequently

USP verification

- The Verification Program helps protect and inform consumers by providing them assurances that the products with the USP Verified Mark will not contain harmful levels of contaminants, toxic botanical species, or greater amounts of active/marker compounds than that indicated on the product specification and label
- USP has been establishing standards since 1820, and today, USP standards are used by manufacturers and regulators in more than 140 countries. While others may provide testing and quality seals, USP is the only standards-setting organization recognized in U.S. federal law that offers third-party verification.



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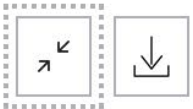


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So much out there!



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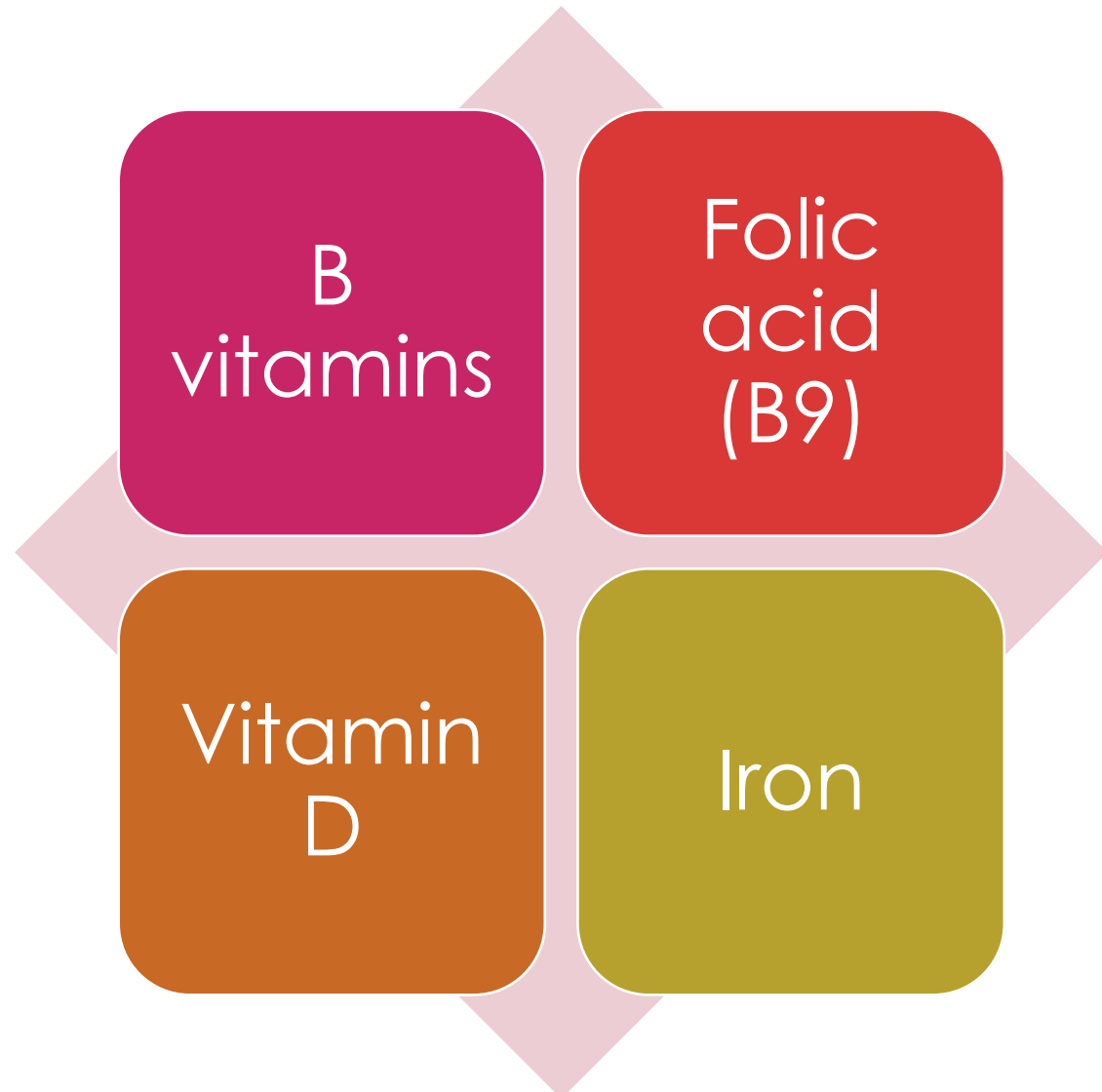
Pregnancy or Breast feeding

- Little is known about a number of these supplements in these populations
- Consults Maternal Fetal Medicine Specialist or OB/Gyn for specific information

Other considerations

- Allergies to ingredients
- Keeping track of symptoms to evaluate if the supplement is helping or making symptoms worse
- Drug induced liver injury

Fatigue workup



Restrictive diets: vegan, elimination diets etc

B vitamin supplements

- B12 levels can be measured
- Some may be combined with caffeine (energy drinks with B3 (aka Niacin), B6, B12, B5 (pantothenic acid))

Fat soluble vitamins

- A (congenital abnormalities, alopecia, ataxia, HL, liver toxicity)
- E (increased bleeding risk, possible increased cancer risk, increased all cause mortality)
- D (GI symptoms, elevated calcium, HTN, renal damage, bone demineralization)
- K (limited data, ? Abnormal bleeding/clotting)

- Overdose of these vitamins can lead to toxicity because excess is stored in fat
- Beyond RDA doses would measure levels

Vitamin D

- Frequently deficient (diet, sun exposure, melanin levels of skin)
- Deficiency associated with worse disease outcomes
- Recent death in the UK due to accidental supplement overdose, some cases with 60,000 IU per day!
- RDA is currently 4,000 IU
- D2 (RX version 50,000 IU per week), vegetarian
- D3 fish derived, made in our skin, raises levels more than D2
- BMI impact?, malabsorption
- Repeat measurement 3-4 months after supplementation

IRON

- RBC production, neurotransmitters (depression)
- High rates of deficiency in young women
- Optimal ferritin targets (above 25, although remember that ferritin is an acute phase reactant)
- IRONMAN “accidental” findings (heart failure study) less likely to develop severe effects from covid(thalassemia as well)
- Hanson et al, (Nat Immunol 2024, Iron dysregulation and inflammatory stress erythropoiesis associates with long term outcome of COVID-19) inflammation, low serum iron, altered iron homeostasis and iron dysregulation

IRON

- Iron deficiency was associated with elevated levels of inflammation markers, such as IL-6 and CRP
- low-iron levels could theoretically impair the efficacy of COVID-19 vaccination, underlining the importance of monitoring iron levels, especially in older adults with long COVID
- Iron supplementation with **325 Ferrous sulfate every other day on an empty stomach**. This dosing is more effective for uptake with reduced GI symptoms but may take 6 to 12 months for full iron store repletion. Avoid with coffee or tea
- Follow ferritin levels

Amino acids

- Branched chain amino acids (BCAA) leucine, isoleucine, and valine are essential amino acids with well-established effects on protein synthesis and glucose homeostasis
- Lymphocyte proliferation, protein synthesis, mitochondrial function, gut mucosal defense
- Often sold as a workout supplement
- Potential side effects – nausea, diarrhea, mood, fatigue, possible increased risk of cardiovascular disease, seems relatively safe in doses of 12 g per day

Beta-hydroxy-beta-methyl butyrate (HMB)

- Active metabolite of leucine
- Modulates several physiologic processes, including protein metabolism, insulin activity, skeletal muscle hypertrophy, cell apoptosis, and muscle stem cell proliferation and differentiation
- Oral supplementation of HMB (3 g/d) prevents decline in muscle mass and preserves muscle function in older adults and frail people, especially during hospital stay and recovery
- Short-term anti-inflammatory and anticatabolic effects and improved pulmonary function in COPD in the ICU

Selenium

- Involved in several physiologic processes, including neurologic, endocrinologic, cardiovascular, and immune functions, antioxidant properties
- Important for immune response to viral infections, especially respiratory viruses
- Low plasma concentration of selenium was also correlated with increased tissue damage and organ failure, prothrombotic activity, and overall mortality in patients in intensive care, which could explain a correlation with severity of symptoms in patients with COVID-19 and possible COVID-19 sequelae in long haulers
- Several studies have reported that circulating selenium concentrations were lower in patients with COVID-19 as compared with healthy controls and associated with COVID-19 severity and mortality
- Safe upper limits is 400 micrograms per day (food sources preferred), overdose symptoms include bad breath, hair loss, fever, fatigue, nausea

Zinc

- Essential for the maintenance of immune health, cell homeostasis, and reproduction
- Deficiency is quite common in the general population and is also associated with immune dysfunction, affecting both the innate and the adaptive immune systems
- Deficiency is associated with increased risk of upper- and lower-respiratory tract infections, especially in older adults, possibly related to anosmia and abnormal taste after COVID infection
- Zinc gluconate seems to reduce duration and severity of common cold symptoms
- Topical zinc nasal swabs have been associated with sometimes permanent anosmia
- Prospective randomized clinical trial, COVID A to Z study, evaluated the efficacy of a treatment with zinc gluconate, ascorbic acid, or their combination in shortening the duration of COVID-19 symptoms. The study failed to demonstrate a significant improvement in symptoms, and the study was stopped for futility

Magnesium

- Magnesium plays a role in modulating the innate and adaptive immune system.
- Subclinical magnesium deficiency is correlated with low-grade chronic inflammation, which can be crucial for the prognosis of COVID-19 and the persistence of COVID-19 symptoms
- Magnesium supplementation, especially in older adults, could help prevent the risk of thromboembolism in COVID-19 and long-term consequences in COVID-19 survivors but more research is needed
- Magnesium citrate - has a laxative function
- Magnesium glycinate
- Can monitor levels with blood testing

Probiotics

- Probiotics are “live microbes that, when administered in adequate amounts, confer health benefits on their hosts.”
- Probiotics (mainly Bifidobacteria and Lactobacilli) may exert relevant immunomodulatory functions on the gut-lung axis
- In COVID-19 outpatients, the administration of a mixture of *Lactiplantibacillus plantarum* and *Pediococcus acidilactici* strains improved viral clearance and reduced both respiratory and gastrointestinal symptoms compared with placebo
- Further studies are needed to assess the effects of specific probiotic formulations and/or the combination of probiotics with other bioactive compounds on long-term COVID-19 sequelae
- Avoid in patients with severe immune compromising conditions (active chemotherapy etc)

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PMID: [35868674](https://pubmed.ncbi.nlm.nih.gov/35868674/)

Nutraceuticals and Dietary Supplements for Older Adults with Long COVID-19

[Matteo Tosato](#), MD, PhD,^a [Francesca Ciciarello](#), MD,^a [Maria Beatrice Zazzara](#), MD,^a [Cristina Pais](#), MD,^a [Giulia Savera](#), MSc,^a [Anna Picca](#), PhD,^a [Vincenzo Galluzzo](#), MD,^a [Hélio José Coelho-Júnior](#), PhD,^b [Riccardo Calvani](#), PhD,^{a,*} [Emanuele Marzetti](#), MD, PhD,^{a,b} [Francesco Landi](#), MD, PhD,^{a,b} and , on behalf of Gemelli Against COVID-19 Post-Acute Care Team



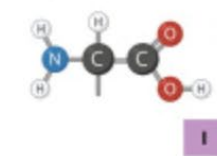
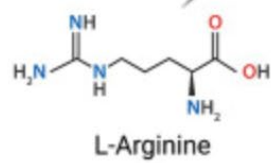
Amino acids, malic acid, succinic acid, and citric acid



Pollen-based herbal extract and Vitamin D



Beetroot juice



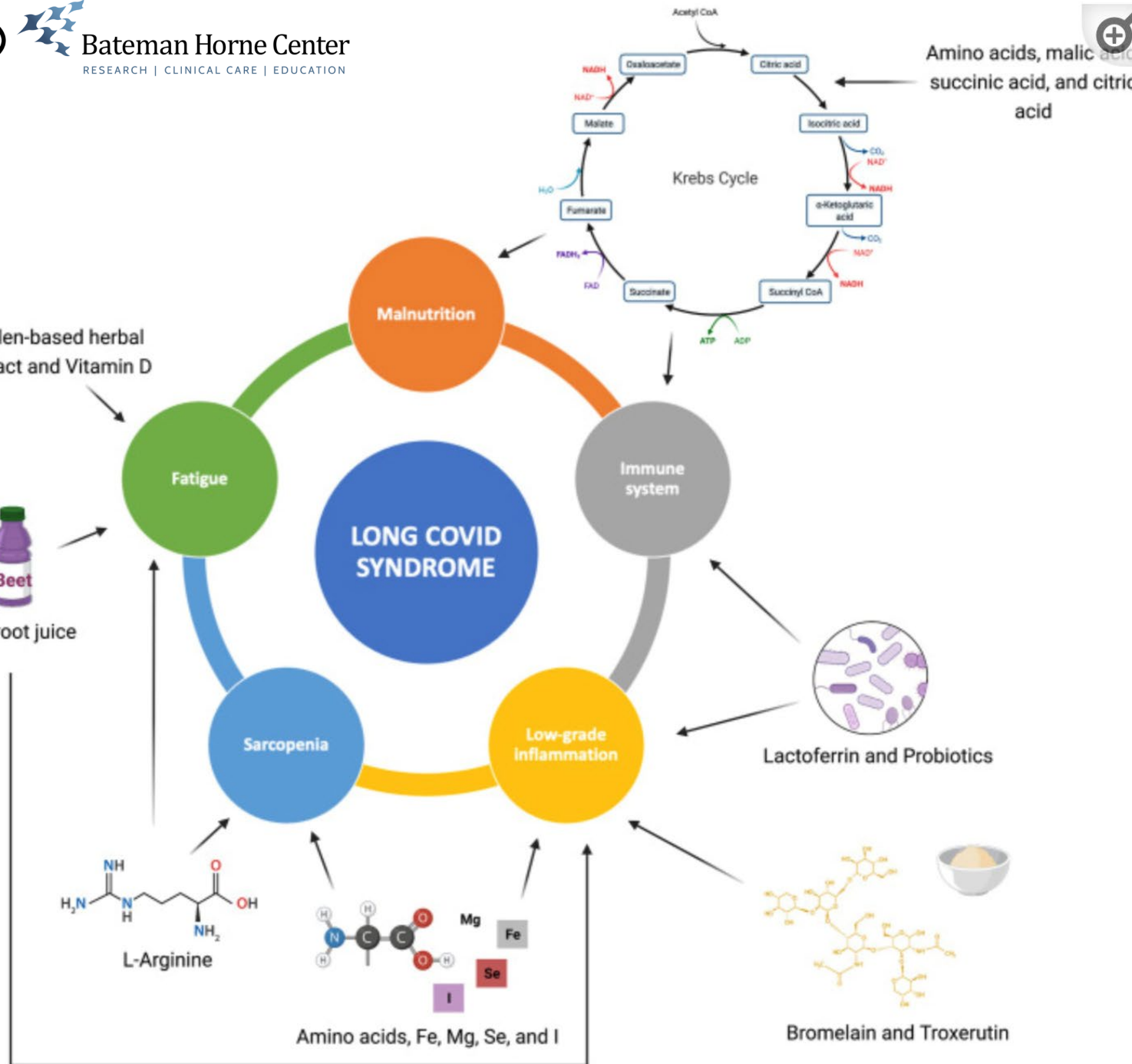
Amino acids, Fe, Mg, Se, and I

Mg

Fe

Se

I



N-acetyl cysteine (NAC)

- Anti-oxidant, anti-inflammatory
- Can have a bad taste
- 600 mg of NAC daily
- In the Yale protocol was combined with Guanfacine (assistance with prefrontal cortex, originally FDA cleared for ADHD) 1 mg then increase to 2 mg after one month. Taken at bedtime to help with brain fog symptoms. 8/12 patients in paper responded. Guanfacine needs an RX. Some stopped due to hypotension and dizziness
- Guanfacine and NAC still need placebo controlled trials

Acetylcarnitine

- Shortest metabolite of a class of fatty acid metabolites called acylcarnitines
- One of the most abundant blood metabolites in humans can be used as a dietary/nutritional supplement with proven clinical efficacy in the treatment of MDD, ME/CFS and other neuropsychiatric disorders

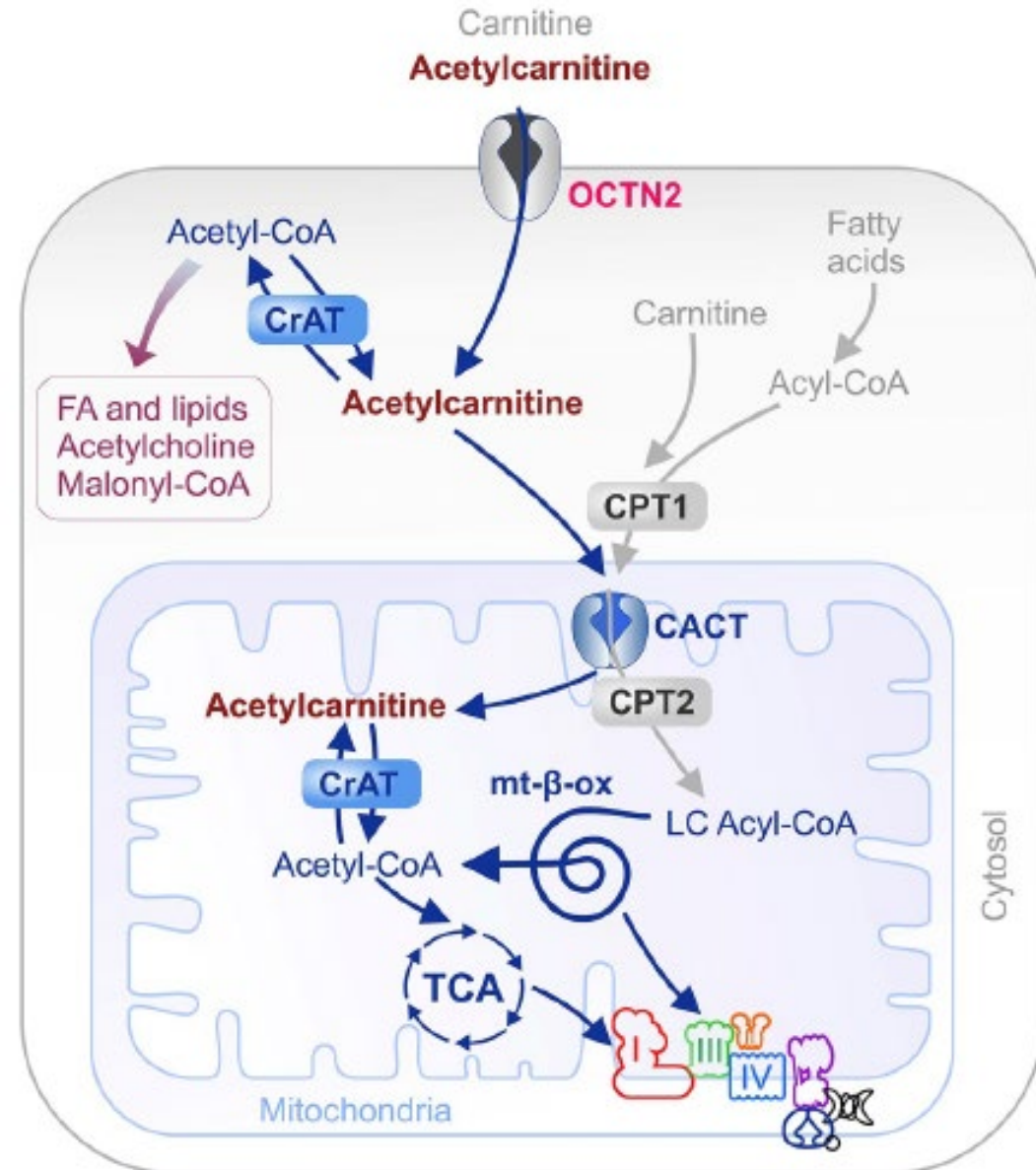


Fig. 3 Intracellular effects of acetylcarnitine supplementation

Acetylcarnitine

- In their meta-analysis (results of twelve randomized controlled trials), they reported a significant decrease in depression severity after acetylcarnitine supplementation as monotherapy compared with placebo intake or no intervention. The incidence of adverse effects with acetylcarnitine supplementation was comparable to that with placebo and lower than with antidepressants, in line with a previous meta-analysis. Acetylcarnitine supplementation has been reported to be as effective as antidepressants in meta-analyses
- A recent study of patients with long COVID syndrome reported a decrease in fatigue and an increase in subjective energy levels after 2 weeks of taking a supplement containing 150 mg of acetylcarnitine (pilot observational study)

Summary

- There are a lot of supplements being looked at to treat the symptoms of long COVID
- There are interesting candidates and many patients are trying them
- Talk with your patients and engage in shared decision making about the risks and benefits
- Monitor for potential side effects

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Journal Article

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Affiliations + expand

PMID: 38172332 DOI: [10.1007/s00406-023-01734-3](#)

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Clinical experience with the α 2A-adrenoceptor agonist, guanfacine, and N-acetylcysteine for the treatment of cognitive deficits in “Long-COVID19”

Arman Fesharaki-Zadeh^{a b}  , Naomi Lowe^a, Amy F.T. Arnsten^c

References

- Up to date for RDA for vitamins

Questions or comments

