PATIENT-LED RESEARCH COLLABORATIVE

Repurposed Drug Recommendations for Clinical Trials for Long Covid
April 2024: [Regularly Updated]

Table of Contents

Assumptions Made in this Document

- These are suggested drugs for the **treatment** of Long Covid, not the **prevention** of LC.
- We believe a large subset of Long Covid patients have ME/CFS, dysautonomia/POTS, or both, and therefore utilized recommendations from these scientific and patient communities.
- We prioritized recommending treatments that aren't easily able to be tried by patients at home.
- We prioritized treatments that would act closer to cures than bandaids.
- Overall: we want to see antihistamines, anticoagulants, antivirals (including for reactivated herpesviruses like EBV and HHV-6), IVIG, JAK-STAT inhibitors, and other immunomodulators.
- Higher risk therapies we would like to see trialed include peritoneal cell transfusion, plasma B1 cell therapies, CAR-T, and similar therapies.

Overall Top Prioritized Drugs to Trial

*Please note: there are some that are on this list that we believe are effective clinically, but that already have multiple trials underway (for example, Low Dose Naltrexone). If a drug is not on this list, that does not mean we don't value it; it may mean there are already enough trials underway on it.

1. IVIG
2. JAK-STAT inhibitors
3. Anticoagulants and antithrombotics
4. Antivirals against COVID
5. Antivirals against latent viruses & reactivations (EBV, HHV-6, CMV)
6. Prescription mast cell stabilizers (Ketotifen, Cromolyn Sodium)
7. Ivabradine
8. Beta blockers
9. High quality probiotics + wide range of microbiome experiments
    a. Particular strains; butyrate producing bacteria like F. Prau; Low F. prausnitzii abundance correlates with more severe fatigue symptoms in ME/CFS:

i. https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(23)00029-X?_returnURL=https://linkinghub.elsevier.com/retrieve/pii/S193131282300029X%3Fshowall%3Dtrue
ii. https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(23)00021-5
iii. https://www.biogaia.com/pressrelease/metabogen-has-reached-a-new-crucial-milestone-in-its-development-of-novel-probiotic-products/

b. Particularly for those early in illness; some people in later illness can't tolerate probiotics as well

10.

Recommended Drugs To Trial

- Immunomodulators (drugs that interact with the immune system)
  - JAK-STAT inhibitors, esp JAK1 inhibitors (IFNa-itaconate shunt hypothesis)
    - Dinaciclib, Filgotinib, Barcitinib, Ruxolitinib
    - Efgartigimod
      - One clinical trial enrolling for treatment of POTS: https://www.argenx.com/patients/clinical-trials
    - Experts:
      - Dr. Ron Davis
      - Dr. Rob Phair
  - Cyclophosphamide
    - Studies of note:
      - https://www.frontiersin.org/articles/10.3389/fmed.2020.00162/full
  - Inspiritol
    - Studies of note:
      - https://www.biospace.com/article/releases/inspiritol-effective-in-covid-19-long-covid-and-me-cfs-patients/
    - Experts:
      - Dr. Liisa Selin
      - Dr. Anna Gil
  - Ampligen
    - Studies of note:
      - https://clinicaltrials.gov/ct2/show/NCT00215813
  - Imunovir/Isoprinosine
    - To improve natural killer cell function
    - https://www.tandfonline.com/doi/abs/10.1300/J092v11n02_06

- Antivirals for viral reactivations, including herpesviruses like EBV, HHV-6, CMV, VZV
    - Antivirals
        - Valcyte/Valganciclovir
        - Famvir
        - Valtrex/Valacyclovir
        - Artemisinin
    - EBV vaccine
    - Studies of note:
        - https://pubmed.ncbi.nlm.nih.gov/23959519/
        - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8233978/
        - https://pubmed.ncbi.nlm.nih.gov/24445302/
        - https://www.dovepress.com/getfile.php?fileID=6394
        - https://pubmed.ncbi.nlm.nih.gov/12582420/
            - Improved left ventricular function
        - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5328426/
        - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6036560/
    - Considerations:
        - Target the titre level of the reactivation (i.e. EBV, HHV-6)
        - Patients often feel worse as they adjust to taking these; trial teams need to be familiar with that
    - Experts to talk to:
        - Dr. Steven Deeks
        - Dr. Michael Peluso
        - Dr. Susan Levine
        - Dr. Skip Pridgen
- Antivirals for COVID
    - Remdesivir
    - Molnupiravir
    - Other monoclonal antibodies
- Mast cell stabilizers
    - Cromolyn sodium (oral and nasal)
        - Oral cromolyn sodium is particularly for gastrointestinal symptoms
    - Ketotifen
    - Considerations:
        - Consider multi arm design to evaluate with different combinations/dosages
            - Could include over the counter H1 and H2 antihistamines, low histamine probiotics, quercetin, and DAO enzyme
- Drugs that regulate microglial activation
    - Recommendations:
        - Low Dose Naltrexone (LDN)

                - Must start at very low doses (0.5mg) and work up to higher dose, up to 4.5mg
                - Takes months, even years to reach full benefit
                - Studies of note:
                    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3962576/
                    - https://casereports.bmj.com/content/13/1/e232502
                - Experts:
                    - Dr. Jarred Younger
            - Low Dose Aripiprazole
                - Studies of note:
                    - https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-021-02721-9
                - Ability to block serotonin (associated with infectious response) and block dopamine in some places while boosting others is interesting.
                - Experts:
                    - Dr. Hector Bonilla
                    - Dr. Ron Davis
                    - Dr. Laurel Crosby
- Anti-CGRP medications
    - For migraines
    - E.g. Emgality, Ajovy, Aimovig, Nurtec, Qulipta
- Beta blockers
    - For those with POTS
    - Propranolol, atenolol
- Midodrine
    - For those with POTS
- IVIG
    - For those with nerve damage or small fiber neuropathy
    - Studies of note:
        - https://nn.neurology.org/content/9/3/e1146
        - https://www.healthrising.org/treating-chronic-fatigue-syndrome/drugs/ivig-intravenous-gamma-globulin-therapy/
        - https://pubmed.ncbi.nlm.nih.gov/29403541/
- CAR-T
    - https://www.nature.com/articles/s41591-022-02017-5
- Anticoagulants, vascular functioning
    - Nattokinase/serrapeptase
    - Pycnogenol
    - Sulodexide
        - Studies of note:
            - https://www.frontiersin.org/articles/10.3389/fcvm.2022.866113/full
    - Triple Therapy
        - Studies of note:

- https://assets.researchsquare.com/files/rs-1205453/v1_covered.pdf?c=1640805028
    - proton pump inhibitor (PPI) pantoprazole 40 mg/day was also prescribed for gastric protection
- Considered top priority clinical trial by Dr. Pretorius — specifically notes single anticoagulant will fail according to their research. Need anticoagulants to act on both pathways.
- Reports from Dr. Jaco Laubscher https://www.youtube.com/watch?v=vWisaTFp4KI Notes that patients treated at less than six months of illness need 4-6 weeks of therapy, and patients at more than 6 illness may need 4-6 months of therapy.

- Statins
    - Studies of note:
        - https://www.researchsquare.com/article/rs-1344323/v1
    - Experts:
        - Dr. Resia Pretorius
        - Dr. Caroline Dalton
        - Dr. Jaco Laubscher
- Sildenafil
    - Studies of note:
        - https://pubmed.ncbi.nlm.nih.gov/34980198/
        - https://clinicaltrials.gov/ct2/show/NCT00598585
        - https://journals.lww.com/americantherapeutics/Fulltext/2022/08000/Drug_Therapy_for_Unexplained_Dyspnea_in.8.aspx
    - Tadalafil may be even better since it's longer acting (matters in this population which is highly sensitive)

- Mestinon (Pyridostigmine)
    - For exercise/exertion intolerance; is an acetylcholinesterase inhibitor that raises the amount of acetylcholine between nerve cells and muscles
    - Studies of note:
        - https://pubmed.ncbi.nlm.nih.gov/35526605/
        - https://endmecfs.mgh.harvard.edu/heartpreload/
    - Experts:
        - Dr. David Systrom
- Heart medications
    - For those with POTS
    - Ivabradine
    - Colchicine
    - Spironolactone
    - Studies of note:
        - https://onlinelibrary.wiley.com/doi/10.1111/imj.23_15766
        - https://clinicaltrials.gov/ct2/show/NCT05481177

- GI therapies
    - To improve gut permeability
        - Lactoferrin (also an immunomodulator and anti-viral)
            - Studies of note:
                - https://www.eurekaselect.com/article/116899
                - https://www.mdpi.com/2305-6320/8/9/47
                - https://www.mdpi.com/2072-6643/14/15/3090
                - https://www.mdpi.com/2227-9067/9/10/1446
                - https://www.mdpi.com/2072-6643/14/5/1000
            - Experts:
                - Dr. Nancy Klimas
                - uses/ recommends: https://www.nova.edu/nim/2022-inim-conference-presenters-slides.pdf
    - Microbiome
    - Studies of note:
        - https://polybio.org/projects/sars-cov-2-gut-persistence-intestinal-permeability-and-spike-protein-in-pediatric-long-covid-mis-c/
- Therapies targeting glymphatic/lymphatic dysfunction
    - **Lymph drainage massage**, including **Perrin technique**
        - Studies of note:
            - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2991935/
            - https://pubmed.ncbi.nlm.nih.gov/32982905/
- Therapies targeting cervical spine abnormalities
    - Note: this is experimental and for the subset of patients with craniocervical issues
    - **Peptides**
        - **Copper collagen peptide therapy.**
        - Possibly for patients with Long Covid and comorbid connective tissue diseases and related craniocervical instability
        - Studies of note:
            - https://clinicalpeptidesociety.com/wp-content/uploads/2019/08/HoltorfKentPeptideLyme2019.pdf
            - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6073405/
    - Experts:
        - Dr. David Kaufman (peptides)
        - Dr. Ilene Ruhoy (peptides)
        - Bragee Center (spinal structural abnormalities)
        - Dr. Bolognese (spinal structural abnormalities)
        - Jeff Wood
- Mitochondrial medications and supplements
    - **Ubiquinone (Coenzyme Q10)**
        - Studies of note:
            - https://pubmed.ncbi.nlm.nih.gov/34444817/
            - https://europepmc.org/article/med/20010505

                - https://www.eurekaselect.com/article/116899
                - https://onlinelibrary.wiley.com/doi/full/10.1002/mco2.196
                - Note: dosage in neuroinflammatory conditions higher than “heart healthy” CV dose of 250mg/day https://www.tandfonline.com/doi/abs/10.1179/1476830513Y.0000000106 and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4225059/.
            - Experts:
                - Jaime Seltzer
        - **Acetyl-L-Carnitine**
            - Studies of note:
                - https://clinicaltrials.gov/ct2/show/NCT04623619
                - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8667465/
            - Experts:
                - Dr. David Kaufman
                - Dr. Susan Levine
        - **Palmitoylethanolamide (PEA)**
            - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9326613/
            - https://www.sciencedirect.com/science/article/pii/S1388245722009385?dgcid=rss_sd_all
            - Note: often given with Luteolin, may have MAOI activity
- Treatments for COVID-triggered obstructive sleep apnea
    - CPAP and BiPap machines
        - Studies of note:
            - https://openres.ersjournals.com/content/7/suppl_7/24
            - https://clinicaltrials.gov/ct2/show/NCT05290350
            - https://www.frontiersin.org/articles/10.3389/fmed.2022.884218/full
            - https://jmedicalcasereports.biomedcentral.com/articles/10.1186/s13256-021-02819-0
            - https://academic.oup.com/sleep/article/44/Supplement_2/A336/6260701
            - https://amjcaserep.com/abstract/full/idArt/937427
- DRP-1 Inhibitors
    - For mitochondrial dysfunction, heart disease, and brain injury
    - Studies of note:
        - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5398851/
- GLP-1 medications
- Others of note
    - Maraviroc
        - For memory loss
        - Relevant studies:
            - https://www.nature.com/articles/s41586-022-04783-1
            - https://www.researchsquare.com/article/rs-1344323/v1
    - Truvada

        - Similar to maraviroc
        - https://www.researchgate.net/publication/366412536_FIRST_PROTOCOL_AND_THERAPEUTIC_TEST_WITH_EMTRICITABINETENOFOVIR_DISOPROXIL_PrEP_Truvada_or_generic_TO_ASSIST_THE_DIAGNOSIS_OF_VIRAL_PERSISTENCE_IN_POST-ACUTE_COVID_SYNDROME_PACS_OR_LONG_COVID_AND_IN_M
    - Glutathione infusions:
        - Studies of note:
            - https://clinicaltrials.gov/ct2/show/NCT05371288
            - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9589528/
            - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7172740/
        - Experts:
            - Dr. David Systrom
            - Brigham and Women's Long COVID clinic
            - Mount Auburn Marino Center
    - Perispinal etanercept
            - Studies of note:
                - https://www.tandfonline.com/doi/abs/10.1080/03007995.2022.2096351?journalCode=icmo20
                - https://pubmed.ncbi.nlm.nih.gov/35174650/
    - Modafinil
        - For cognition, nerve issues, and POTS, Cognitive and Physical Fatigue

Suggested Endpoints

- We suggest:
    - Biological markers whenever possible
        - Natural Killer Cell function
        - Cerebral blood flow
        - Blood lactate levels
        - Endothelial dysfunction
        - Blood total extracellular vesicle levels of mitochondrial proteins
            - MOTS-c, VDAC-1, Humanin and ⬆ SARM-1
            - https://www.amjmed.com/article/S0002-9343(23)00258-9/fulltext
        - Levels of reactivated viruses (i.e. EBV, HHV-6)
        - *Spike & S1 (Simoa assay)*
            - *Blood is Simoa*
        - *Gut biopsies for viral persistence*
        - *Stool PCR*
        - Oct-A/corneal confocal microscopy
    - Questionnaires
        - MFIS for fatigue
        - FUNCAP

    - Exploratory outcomes:
- Be careful if using:
    - Cytokines
        - Can decrease over time without corresponding improvement in symptoms
        - Each have different trajectories https://pubmed.ncbi.nlm.nih.gov/26079000/
        - Recommend as secondary exploration

Trial Design Considerations

- We recommend primarily trialing treatments in patients who have been ill a year or longer, as those sick earlier do sometimes recover which can bias studies or undermine their generalizability.
    - Unless the trial is specifically looking at preventing Long Covid.
- Disease duration needs to be a core feature of analysis, as there is a likely immune change between year 2 and 3 in the subset of Long Covid patients who have ME/CFS
    - https://pubmed.ncbi.nlm.nih.gov/26079000/
- In trials that ask about anxiety and depression:
    - Tools that include somatic symptoms in the questions *cannot* be used for chronic illnesses like Long Covid. The presence of somatic symptom questions artificially increases the depression and anxiety scores, especially questions like fatigue, difficulty concentrating, difficulty sleeping, and heart palpitations.
    - Tools that can't be used include the PHQ-9, Beck Anxiety Inventory, and Beck Depression Inventory
    - Tools that work include the PHQ-2, GAD-7, and HADS, or subscales of PROMIS-29
    - If you've already collected PHQ-9, you can get PHQ-2 from that.
- We recommend never using mental health outcomes as primary endpoints
    - Unless if the trial is targeting a mental health symptom (i.e. PMDD)
- We recommend adhering to clinical trial design principles that minimize bias in estimates of efficacy and safety. These principles' importance is magnified when endpoints are patient reported outcomes rather than biomarkers. Such design principles include:
    - Comparing treatment groups to control groups either via parallel or crossover designs (avoiding uncontrolled trials)
    - Randomized treatment assignment
    - Double- or triple- blinded assignment
    - Placebo controls

- We recommend against designs with greater treatment group vs control group size. This is because symmetry in treatment and control group size (1:1 randomization) provides greater statistical power to detect treatment efficacy.
- We recommend using crossover designs so patients always receive the drug and not only placebo; this will help recruitment as well.

Acknowledgments

Thanks to the Patient-Led Research Collaborative research team, and to external contributors Dr. Amy Proal, Dr. Steven Deeks, Dr. Michael Peluso, Jaime Seltzer, Siebe Rozendal, Lauren Nichols, Angela Meriquez Vázquez, and Dr. Ruth Ann Crystal.