An Overview of Pharmacologic Treatments Under Investigation for Long COVID

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Disclosure Statement

The speaker has no conflicts of interest or relationships with commercial entities that may be referenced in this presentation.

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Learning Objective

- Discuss pharmacologic treatment options under investigation in various clinical trials for Long COVID

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Definition of Long COVID

- AKA: 'post-COVID-19', 'long-haul covid', 'post-acute sequelae of COVID-19 (PASC)', 'ongoing COVID-19', 'chronic Covid syndrome'
- Prolonged/ residual COVID-19 symptoms lasting more than 4 weeks OR
- Relapsing/ new symptoms ≥ 30 days after acute infection

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Prevalence of Long COVID

- 45% of individuals with ≥ 1 unresolved symptom (at ~ 4 months)
  - Hospitalized patients: 52.6%
  - Non-hospitalized patients: 34.5%
- Few people have full recovery
  - 85% of those w/ symptoms 2 months after acute infection, had symptoms 1 year after symptom onset

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Symptoms of Long COVID

- ≥ 60 physical & psychological symptoms
  - Fatigue, brain fog, postexertional malaise, dizziness
  - Palpitations, chest pain
  - Breathlessness, chronic cough
  - Loss of or change in smell or taste
- Others: sleep disturbance, GI symptoms, changes in sexual desire, thirst, abnormal movements

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Pathogenesis of Long COVID

- Persisting viral reservoirs in tissues
- Immune dysregulation
- Autoimmunity
- Changes in gut microbiota
- Microvascular blood clotting with endothelial dysfunction
- Signaling dysfunction in brainstem/ vagal nerve

Davis HE, McCorkell L, et al. 2023 Mar;21(3):133-146. PMID: 36639608.

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Pharmacological Treatments Under Investigation in Clinical Trials

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Core Symptoms

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Nirmatrelvir/Ritonavir

- **Trial registration#** NCT05668091
- **Study design:** randomized, double-blind
- **Inclusion:** highly symptomatic adults with long COVID
- **Intervention:** Nirmatrelvir 2x150 mg tab Q12h + Ritonavir 1X100 mg cap Q12h for 15 days
- **Primary outcome:**
  - Physical Health Summary Score (depression, physical function, pain interference, fatigue, sleep disturbance, satisfaction with participation in social roles)

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05668091?cond=NCT05668091&draw=2&rank=1. Accessed August 3, 2023.

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Nirmatrelvir/Ritonavir (cont'd)

- **Trial registration#** NCT05576662
- **Study design:** randomized, double-Blind
- **Inclusion:**
  - ≥ 2 long COVID symptoms (fatigue, brain fog, shortness of breath, GI or CV symptoms) persisting > 3 months
- **Intervention:** Nirmatrelvir 2x150 mg tab Q12h + Ritonavir 1X100 mg cap Q12h for 15 days
- **Primary outcome:**
  - Core Symptoms Severity Scale Score (fatigue, brain fog, dyspnea, body aches, gastrointestinal symptoms, cardiovascular symptoms)

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05576662?cond=NCT05576662&draw=2&rank=1. Accessed August 3, 2023.

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Remdesivir

- **Trial registration#** NCT04978259
- **Study design:** randomized, open label
- **Inclusion:** alive patients who attended the SOLIDARITY Finland sub-study (w/ confirmed COVID infection + were admitted to hospital/ICU)
- **Intervention:** remdesivir IV during hospital stay up to 10 days
- **Primary outcome:** effect on long-COVID symptoms & quality of life at 1 and 2 years post-discharge

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04978259. Accessed August 4, 2023.

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Vitamin K2 & Vitamin D3

- **Trial registration#** NCT05356936
- **Study design:** randomized, open label
- **Inclusion:**
  - Diagnosed with COVID-19 ≥ 3 months ago
  - With persistent, recurrent or even new long COVID symptoms
- **Intervention:** Vitamin K2 and Vitamin D3 by mouth daily
- **Primary outcome:** Effects on Inflammatory Biomarkers

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05356936?term=vitamin+d&cond=long+covid+or+post+covid&draw=2&rank=6. Accessed August 7, 2023.

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Metformin

- **Trial registration#** NCT04510194
- **Study design:** randomized, quadruple-blind
- **Inclusion:**
  - Adults, overweight/ obese
  - Documented SARS-CoV-2 positive within 3 days before enrolment
- **Intervention:**
  - Metformin administered within 3 days of symptom onset
  - Dose was titrated over 6 days: 500 mg on day 1, 500 mg BID on days 2–5, then 500 mg in AM and 1000 mg in PM up to day 14
- **Primary outcome:** metformin reduced incidence of long COVID by ~ 41%

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Bramante CT, et al. Lancet Infect Dis. 2023 Jun 8:S1473-3099(23)00299-2. PMID: 37302406.

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Neurocognitive Impairment

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Baricitinib

- **Trial registration#** NCT05858515
- **Study design:** randomized, double blind
- **Inclusion:** documented COVID infection + neurocognitive symptoms for ≥ 60 days prior to screening
- **Intervention:** baricitinib 4 mg tab daily for 12 weeks
  - Dose adjusted for renal dysfunction (to 2 mg or 1 mg)
- **Primary outcome:** Global Neuropsychological Function

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ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05858515. Accessed August 4, 2023.

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Fluvoxamine

- **Trial registration#** NCT05874037
- **Study design:** randomized, double blind
- **Inclusion:** COVID infection ≥ 3 months ago + long COVID neurocognitive symptoms (e.g., brain fog)
- **Intervention:**
  - One dose of fluvoxamine 25mg, then one dose of 50mg, then one dose of 100mg
  - Assessment of subjective reaction to these test doses then randomize to individually tailored course of fluvoxamine for 16 weeks
- **Primary outcome:** improvement in long COVID symptoms (cognitive performance)

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05874037?term=Fluvoxamine&cond=long+covid+or+post+covid&draw=2&rank=1. Accessed August 7, 2023.

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Vortioxetine

- **Trial registration#** NCT05047952
- **Study design:** randomized, double-blind
- **Inclusion:** COVID infection > 3 months ago + symptoms persisting for ≥ 2 months
- **Intervention:**
  - Adults 18-64 yrs old: vortioxetine 10 mg daily for 2 weeks, then dosed up to 20 mg daily for weeks 2-8
  - Adults 65+ years: vortioxetine 5 mg daily for 2 weeks, then dosed up to 10 mg daily for weeks 2-8
- **Primary outcome:** Changes in cognitive function

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05047952?term=Vortioxetine&cond=long+covid+or+post+covid&draw=2&rank=1. Accessed August 7, 2023.

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Lithium

- **Trial registration#** NCT05618587
- **Study design:** randomized, double-blind
- **Inclusion:** positive COVID test + symptoms of brain fog/fatigue
- **Intervention:** lithium 10mg PO daily for 3 weeks
- **Primary outcome:** effects on brain fog and fatigue

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05618587?term=lithium&cond=long+covid+or+post+covid&draw=2&rank=1. Accessed August 7, 2023.

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Atorvastatin

- **Trial registration#** NCT04904536
- **Study design:** randomized, open label
- **Inclusion:** adults, COVID diagnosis + persisting neurological symptoms (impairment in memory, concentration, mood)
- **Intervention:** atorvastatin 40mg daily for 18 months
- **Primary outcome:** improvement in neurocognitive function

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT04904536. Accessed August 7, 2023.

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Nicotinamide Riboside

- **Trial registration#** NCT04809974
- **Study design:** randomized, double-blind
- **Inclusion:** COVID infection ≥ 2 months ago + persisting brain fog (and other neurological/ physical symptoms)
- **Intervention:** Niagen (Nicotinamide Riboside, Vitamin B3) 2000mg capsules daily
- **Primary outcome:** improvement in cognitive function, mood, physical health

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT04809974?cond=NCT04809974&draw=2&rank=1. Accessed August 7, 2023.

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Chronic Fatigue Syndrome

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Naltrexone

- **Trial registration#** NCT05430152
- **Study design:** randomized, double-blind
- **Inclusion:** confirmed COVID infection + clinical diagnostic criteria for post-COVID fatigue syndrome
- **Intervention:** Low-Dose Naltrexone as a compounded capsule:
  - Week 1: 1 mg/day (1 mg cap)
  - Week 2: 2 mg/day
  - Week 3: 3 mg/day
  - Weeks 4-16: 4.5 mg/day
- **Primary outcome:** fatigue intensity, decline in levels of inflammatory markers

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05430152?term=naltrexone&cond=long+covid+or+post+covid&draw=2&rank=2. Accessed August 7, 2023.

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Pregabalin

- **Trial registration#** NCT05967052
- **Study design:** randomized, double-blind
- **Inclusion:** documented COVID infection ≥ 6 months ago + diagnosis criteria of post-COVID chronic fatigue syndrome
- **Intervention:** pregabalin 75 to 300 mg daily + comprehensive rehabilitation for 6 months
- **Primary outcome:** change in fatigue intensity, walking distance

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Probiotics

- **Trial registration#** : NCT05975034
- **Study design:** randomized, double-blind
- **Inclusion:** persistent long COVID symptoms ≥ 3months after COVID infection
- **Intervention**: Probiotic taken daily for 12 weeks
  - Participants will use app to track symptoms for 3 weeks before study + last 3 weeks of treatment
- **Primary outcome:** fatigue severity

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05975034?term=probiotic&cond=COVID-19&draw=2&rank=23 Accessed August 7, 2023.

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Respiratory Symptoms

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Montelukast

- **Trial registration#** NCT04695704
- **Study design:** randomized, double-blind
- **Inclusion:** documented COVID infection + persistent respiratory symptoms, mild-moderate dyspnea
- **Intervention:** montelukast 10 mg daily for 28 days
- **Primary outcome:** respiratory symptoms

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ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT04695704. Accessed August 7, 2023.

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Colchicine

- **Trial registration#** NCT04818489
- **Study design:** randomized, open label
- **Inclusion:** confirmed COVID infection
- **Intervention:** Colchicine 2x0.5 mg BID (loading dose), then 1x0.5mg BID for 3 weeks
- **Primary outcome:** Pulmonary fibrosis

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT04818489. Accessed August 7, 2023.

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Pirfenidone

- **Trial registration#** NCT04607928
- **Study design:** randomized, double blind
- **Inclusion:** recovered from severe COVID pneumonia + fibrotic lung sequelae
- **Intervention:** pirfenisone 2x267 mg cap Q8hr for 1 week, then if tolerated, increase to 3x267 mg cap Q8hr for 24 weeks
- **Primary outcome:** changes in pulmonary fibrosis

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT04607928?term=Pirfenidone&cond=covid&draw=2&rank=3. Accessed August 7, 2023.

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Cardiovascular Symptoms

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Metoprolol Succinate

- **Trial registration#** NCT05096884
- **Study design:** single group assignment, open label
- **Inclusion:** documented PCR positive COVID infection + tachycardia/dyspnea with minimal activity
- **Intervention:** metoprolol succinate 25 mg daily for 2 weeks, then if well tolerated every 2 weeks to a max dose of 400 mg daily for 8 weeks
- **Primary outcome:** Change in 6 minute walk test, cardiac function, quality of life

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05096884. Accessed August 7, 2023.

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Efgartigimod

- **Trial registration#** NCT05633407
- **Study design:** randomized, double blind
- **Inclusion:** new-onset postural orthostatic tachycardia syndrome post-COVID
- **Intervention:** efgartigimod IV infusion 10mg/kg weekly for 24 weeks
- **Primary outcome:** reduction in severity of long COVID postural orthostatic tachycardia syndrome

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05633407?term=Efgartigimod&cond=COVID-19&draw=2&rank=2. Accessed August 7, 2023.

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Coenzyme Q compound

- **Trial registration#** NCT05373043
- **Study design:** non-randomized, double blind
- **Inclusion:** positive COVID test ≥ 3 months ago + long COVID symptoms
- **Intervention:** Exercise + Mito-Q (Mitoquinone) vs. Exercise + Placebo
- **Primary outcome:** improvement in vascular endothelial function

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05373043?term=Mitoquinone&cond=covid&draw=2&rank=1. Accessed August 7, 2023.

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Sensory Symptoms

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Gabapentin

- **Trial registration#** NCT05184192
- **Study design:** randomized, double blind
- **Inclusion:** recovered from COVID infection + within 2 weeks, experienced post-COVID olfactory dysfunction for ≥ 3 months
- **Intervention:**
  - gabapentin, week 1: 300mg TID, week 2: 600mg TID, week 3: 900mg TID, week 4: 1200mg TID
  - then fixed dose (highest tolerable dose) for 8 weeks
  - then taper down for 2 weeks
- **Primary outcome:** improvement in olfactory function

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05184192?cond=NCT05184192&draw=2&rank=1. Accessed August 7, 2023.

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Pimozide

- **Trial registration#** NCT05507372
- **Study design:** randomized, double blind
- **Inclusion:** tinnitus after COVID infection, persisting for ≥ 4 weeks
- **Intervention:** pimozide 1mg
- **Primary outcome:** treatment of COVID induced tinnitus

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ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05507372?term=pimozide&cond=COVID-19&draw=2&rank=1. Accessed August 7, 2023.

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Polling Question!

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Polling Question 1

➢Which dietary supplement(s) is/are under investigation for management of long COVID symptoms?

a) Coenzyme Q
b) Vitamin B3
c) Vitamin D3
d) Vitamin K2
e) All of the above

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Key Takeaways

✓Symptoms ≥ 30 days after acute infection
- Fatigue, brain fog, palpitations, breathlessness
- Involves one or multiple organs

✓Pathogenesis/possible treatment options:
- Persisting viral reservoirs in tissues => antivirals
- Immune dysregulation => JAK inhibitors
- Changes in gut microbiota => probiotics
- Endothelial dysfunction => β-blockers
- Signaling dysfunction in brainstem/ vagal nerve => antidepressants

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Questions?

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