Long COVID and Impact on Mental Health

ECHO IDAHO

Behavioral Health in Primary Care

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Learning Objectives

- **Identify the major mental health symptoms associated with Long COVID**—including mood, anxiety, sleep, and cognitive impairments—and understand their underlying biological and psychosocial mechanisms.

- **Describe common recovery trajectories in Long COVID**, recognizing the variability in symptom course, including gradual improvement, relapsing-remitting patterns, and prolonged functional impairment.

- **Apply a multimodal, evidence-informed treatment framework** incorporating CBT-based strategies, cognitive rehabilitation approaches, and appropriate pharmacologic interventions to support mental health recovery in Long COVID patients.

Emergence of COVID-19 and Long COVID

- **SARS-CoV-2 identified in Wuhan, China (Nov 2019).**
- Persistent post-infection symptoms were reported by **May 2020**, later termed **Long COVID**.
- By **early 2021**, the condition gained formal scientific and clinical recognition

Definition of Long COVID

- **Long COVID** is a chronic, infection-associated condition that:
    - Begins within 3 months of the initial COVID-19 illness.
    - Persists for at least 2 months, with some cases reported up to 3 years post-infection.
    - Cannot be explained by an alternative diagnosis.
- the most widely used **definition** - Describes Long COVID as persistent, fluctuating, multi-system symptoms that continue 4–12 weeks or longer after a COVID-19 infection.

Prevalence & Symptom Profile of Long COVID

- Late 2022: 77.5% of people in the U.S. had experienced COVID at least once. With over 1.2 million COVID-related deaths.

- **Prevalence** estimates have declined over time:

  ~7.6% in summer 2023

  ~5.3% by August–September 2024

- Global economic impact is substantial, with estimated costs of ~$1 trillion annually (≈ 1% of global GDP).

The burden affects individuals, healthcare systems, and national economies.

- Long COVID is associated with more than 200 reported **symptoms**, most commonly:

  - Fatigue, Post-exertional malaise

  - Cognitive impairment ("brain fog"); Memory and concentration   difficulties

  - Dyspnea, Myalgias, Headaches

  - Mental health symptoms: anxiety, depression, mood disturbances, PTSD-like features

Clinical Course

- Long COVID - shared trigger of a COVID-19 infection

- **Clinical patterns** may be:

  - Persistent

  - Fluctuating

  - Relapsing–remitting

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Risk factors

- **Demographic**: female individuals and older adults.

- **Disease severity**: severe acute COVID-19, ICU admission.

- **Socioeconomic factors:** financial deprivation and ethnic minority status.

- **Medical risk factors** Psychiatric disorders, Asthma, Diabetes, Obesity, Immunosuppression, Cardiovascular disease, Chronic kidney disease, History of post-viral fatigue

- **Lifestyle contributors:** Smoking and Low physical activity levels

Protective Factors

- **Protective factors:**
  - Vaccination—two doses, with mRNA vaccines even when given after infection.
  - Omicron variant infections- lower risk of Long COVID.

Risk Factors Are Not Deterministic

- Long COVID has been observed even in individuals who were:
  - Young and previously healthy
  - Fully vaccinated
  - Had mild or asymptomatic acute infection
  - Were never hospitalized
  - Had no pre-existing medical conditions

- **Risk factors represent statistical associations**, not certainties:
  - They increase likelihood but do not predict who will or will not develop Long COVID.

Pathogenesis & Diagnostic Challenges

- **Pathogenesis is multifactorial,**

  - Viral persistence triggering downstream cellular disruption
  - Elevated inflammatory markers
  - Immune dysregulation
  - Autoimmune responses
  - Coagulation abnormalities

- **No validated biomarker nor diagnostic imaging currently exists** that reliably identifies Long COVID or guides targeted therapy.

Recovery & Prognosis in Long COVID

- **Overall Duration & Persistence**
  - Long COVID may last months to years.
  - ~25% remain symptomatic at 3+ years.
  - 17–23% remain unrecovered at 12–24 months.
  - When symptoms persist beyond 2 years, the chance of complete recovery declines significantly.

- **Recovery Patterns**

Recovery is generally gradual with highly variable trajectories:
  - 68% experience steady, continuous improvement
  - 14% improve with a fluctuating course
  - 4% show a relapsing–remitting pattern
  - 5% worsen over time
  - 19% report apparent full recovery.

Factors Associated With Better Recovery

- Vaccination (before and after infection)
- Milder acute illness
- Shorter symptom duration, especially improvement within the first 6 months
- Younger age
- Male gender
- Hispanic ethnicity

Factors Linked to Delayed or Poor Recovery

- Severe fatigue (strongest predictor of non-recovery)
- Myalgias
- Dysautonomia
- Severe/critical acute illness
- Early-pandemic infection (2020)
- Prolonged hospitalization
- Obesity
- Female gender

Mental Health Impact of Long COVID

- Long COVID is associated with new onset psychiatric conditions as well as worsening of pre-existing mental health disorders.

- 1 in 4 individuals with long covid experiences MH mental health symptoms

  - Anxiety disorders
    - Depression
    - Cognitive impairments
    - Insomnia
    - Substance use disorders
    - Psychotic disorders
    - PTSD

- **Duration and risk patterns:**
  - Cognitive deficits, dementia, and psychotic disorders may remain elevated for up to two years after acute infection.
  - Anxiety and depressive disorders typically begin to decline by about six months post-infection.
  - These mental health risks are higher than those seen after influenza or other respiratory infections, suggesting COVID-specific mechanisms.

Stigma & Barriers to Care

- Stigma and misunderstanding surrounding Long COVID remain common.

- Many patients report dismissive or invalidating experiences within healthcare settings.

- Such stigma can be emotionally distressing and may:
  - Reduce engagement with healthcare services
  - Increase the risk of untreated or worsening mental health conditions

APA Guidance on Mental Health Care in Long COVID

- low threshold for screening for pre- and post-Covid symptoms and treating mental health conditions in individuals with Long COVID.

- Failure to address untreated psychiatric symptoms can:
  - Increase overall disease burden
  - Elevate healthcare costs
  - Widen existing disparities in access to care

Management of Symptoms in Long COVID

- **Multimodal,** Collaborative treatment approach

- **PHYSICAL therapy:** Breathing exercises, Symptom-guided activity modification, Gradual functional restoration, Carefully structured, graded activity

- **Additional Supportive Interventions:** Acupuncture, Massage, Yoga, Tai chi, Chiropractic care

- **Lifestyle interventions:** Sleep management, Nutritional support, Stress-reduction strategies

- **Functional support**: Olfactory training and Workplace or academic accommodations

- **COGNITIVE REHABILITATION** strategies**:**
  - Compensatory tools: planners, reminders, apps
  - Cognitive strategies for attention, memory, executive function
  - Energy conservation & pacing techniques
  - Gradual aerobic activity as tolerated
  - Reduced screen time
  - Optimizing sleep quality

- **PHARMACOLOGIC Interventions** should be **individualized** based on each patient's symptom profile.

    Recognizing symptoms early and initiating treatment promptly as well as periodic reassessment may reduce long-term disability and decrease the overall symptom burden.

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Psychotherapy/Cognitive Behavioral Therapy (CBT) in Long COVID

- The APA recommends **CBT** for patients experiencing:
  - Somatic preoccupation
  - Depression and anxiety
  - Trauma-related symptoms
  - Cognitive impairment
  - Maladaptive coping patterns
  - Stress

- **CBT targets**:
  - Catastrophic thinking
  - Activity avoidance
  - Symptom-perpetuating behaviors
  - Other maladaptive coping strategies

- **Benefits in Long COVID**:
  - Reduces psychological contributors to fatigue and cognitive difficulties
  - Helps mitigate functional decline
  - Strengthens therapeutic alliance, validation, reassurance
  - Enhances engagement in treatment and shared decision-making

- **Key Point**:
  - CBT is one of the few therapeutic modalities with emerging **evidence of benefit** in Long COVID and should be included in a multimodal treatment plan.

Antidepressants in Long COVID

- Serotonin depletion may occur in Long COVID and contribute to:
    - Anxiety
    - Depression
    - Mood disturbances
    - PTSD-like symptoms

- Observational data early in the pandemic showed that several SSRIs (fluoxetine, paroxetine, escitalopram, mirtazapine, venlafaxine, fluvoxamine) were associated with reduced severity of acute COVID-19 when patients were already taking them.
    - Proposed mechanisms:
    - Anti-inflammatory effects
    - Cytokine modulation
    - Fluvoxamine: in vitro antiviral activity (sigma-1 receptor interaction → reduced cellular stress and viral replication)

- Clinical response:
    - Post-COVID depression: ~92% response rate to SSRIs within 4 weeks
    - Two-thirds of patients are experiencing improvement in: Brain fog, Fatigue and Dysautonomia symptoms (tachycardia, orthostatic dizziness, syncope, etc.)

- Treatment considerations:
    - SSRIs effective in both first-episode and recurrent presentations
    - Antidepressants should be paired with psychotherapy to address mood, anxiety, and sleep disturbances

Guanfacine

- Guanfacine is a selective alpha-2A adrenergic agonist that enhances prefrontal cortex (PFC) network connectivity, relevant because Long COVID may impair PFC circuits involved in:
  - Attention
  - Working memory
  - Executive functioning
- Treatment targets: hyperarousal, enhanced cognitive performance, decreased autonomic activation and potential benefit for trauma patients
- Proposed mechanism: reduced overactivity (locus coeruleus and amygdala); weakens maladaptive amygdala plasticity; lower norepinephrine levels; anti-inflammatory effects,

- Currently used off-label for Long COVID.

- Practical considerations:
  - Hypotension
  - Sedation
  - Gradual tapering is required when discontinuing to prevent rebound hypertension.

Stimulants in Long COVID

- Stimulants are under investigation for Long COVID–related fatigue and cognitive dysfunction, but evidence is limited and no formal guideline recommendations exist yet.

- Medications being explored include:
  - Methylphenidate
  - Amphetamine/dextroamphetamine
  - Lisdexamfetamine
  - Modafinil
  - Amantadine

- Proposed Mechanisms
  - Frontal cortex hypometabolism
  - Reduced activity in anterior cingulate, insula, caudate
  - Possible reduction of CNS inflammation and microglial activation

- Clinical Observation
  - Methylphenidate: may help post-COVID central hypersomnia and fatigue.
  - Modafinil, amphetamine/dextroamphetamine, lisdexamfetamine: explored for cognitive symptoms ("brain fog").
  - Amantadine: early studies show improvement in fatigue scales.

- Cautions & Clinical Considerations

- Stimulants may increase alertness but also risk post-exertional symptom exacerbation if patients overexert during periods of enhanced energy.

- Use should be:
  - Individualized
  - Cautious
  - Aligned with standard prescribing guidelines

Low-Dose Naltrexone (LDN)

- Low-dose naltrexone (LDN) is an **emerging therapy** with early evidence suggesting benefit for:
  - Fatigue
  - Post-exertional malaise
  - Sleep disturbances
  - Chronic pain
  - Overlapping conditions (e.g., chronic fatigue syndrome, fibromyalgia)
- Proposed mechanisms:
  - Immunomodulatory effects
  - Anti-inflammatory activity
  - Reduction in neuroinflammation
- Clinical response:
  - About two-thirds of patients report good to strong improvement.
  - Most benefit observed at 4.5 mg daily.
- Practical considerations:
  - Used off-label and requires compounding.
  - Often involves out-of-pocket costs for patients.

Systematic reviews show no increased risk of serious adverse effects compared with placebo across multiple conditions studied

Antipsychotics in Long COVID

- Antipsychotics should be used only when psychosis or severe agitation is present, such as in:
  - Agitated delirium
  - COVID-related psychosis
  - Mania
  - Schizophrenia
  - Significant behavioral disturbances

- Not recommended for core Long COVID symptoms (e.g., fatigue, dyspnea, cognitive difficulties).

Clinical Context

- Delirium and COVID-related psychosis are most commonly encountered in acute care settings.

- Preferred agents: Olanzapine, Aripiprazole, due to lower risk of precipitating catatonia.

Special Safety Consideration

- During acute COVID-19, Clozapine serum levels may rise significantly, requiring: Close monitoring and possible dose reduction.

General Prescribing Considerations

- Monitor for potential antipsychotic side effects:
  - QT prolongation, Sedation, Metabolic disturbances, Extrapyramidal symptoms (EPS), Increased mortality risk (for certain populations groups).

Low-Dose Aripiprazole (Theoretical Use)

- Very low dose aripiprazole **(0.5–2 mg)** has been proposed based on theoretical mechanisms, not clinical evidence.

- Rationale includes:
  - Possible anti-inflammatory and immunomodulatory effects
  - Genomic studies – reverse expression of 94 genes altered by COVID-19 infection

  There is no proven clinical benefit for using Aripiprazole for Long COVID at this time.

Anxiolytics & Benzodiazepines in Long COVID

- **Benzodiazepines**
  - May be helpful for short-term management of acute anxiety.
  - Benzodiazepines may be appropriate in mania associated with Long COVID, but only when used with mood stabilizers and antipsychotics.
  - Generally avoided in patients with cognitive impairment or PTSD, as they can worsen:
    - Cognitive dysfunction
    - PTSD symptoms (due to anterograde memory-impairing effects)
- **Gabapentin**
  - May help with anxiety and neuropathic pain.
  - Can worsen cognitive symptoms, so use requires careful individualized assessment.
- **General Principles**
  - Both benzodiazepines and gabapentin should be prescribed after thoughtful, personalized evaluation.
  - Avoid medications that may exacerbate cognition, fatigue, or post-exertional symptom flares.
  - Choose agents that minimize risks such as:
    - Respiratory depression
  - Review comorbidities, contraindications, and drug interactions thoroughly.

Hypnotics & Sleep Management in Long COVID

- **Sleep disturbances** in Long COVID are **multifactorial**, driven by physiological, psychological, and neurological factors.

- APA recommendations:
  - **First-line:** Sleep hygiene
  - **Refer to sleep medicine** if obstructive sleep apnea is suspected

- Both pharmacologic and non-pharmacologic approaches may help, but non-pharmacologic treatments are especially promising.

- Caution With Hypnotics as they may worsen cognitive symptoms (e.g., brain fog, cognitive dysfunction).

- Use must align with standard insomnia treatment guidelines and be applied carefully in Long COVID.

When to Use Specific Hypnotics

- **Sleep-onset insomnia:**
  - Short-term use of **benzodiazepines** may be considered.

- **Sleep-maintenance insomnia:**
  - Orexin receptor antagonists
  - Low-dose doxepin

- **Adults ≥ 65 years:** Preferred options include:
  - Trazodone
  - Low-dose doxepin
  - Orexin antagonists (daridorexant/Quviviq, lemborexant/Dayvigo, suvorexant/Belsomra)

Duration & Tapering Guidelines

- Typical regimen: Nightly use for 2–4 weeks, then reassess.

- If ongoing treatment is needed:
  - Use intermittent dosing (2–4 nights/week).

- Avoid nightly use beyond 3 months.

- Discontinuation:
  - Taper gradually—reduce dose by ~25% per week to avoid withdrawal or rebound insomnia.

Note: None are considered **standard therapy** for Long COVID insomnia.

Opioids in Long COVID

- First consider **Non-pharmacologic Interventions** and **Non-Opioid Pharmacologic Pain Options** (NSAID, TCA, SNRI, Gabapentinoids, topicals)

- **OPIATES** have a very limited role in Long COVID management.
- **ONLY** for severe, refractory pain and only after all non-opioid options have been exhausted.

    Risks of Opioid Use in Long COVID

- Sedation that interferes with rehabilitation and daily functioning
- Worsening brain fog, impaired attention, and memory problems
- Dependence, tolerance, and misuse potential

    Alternative Long Covid pain treatment approach- Emerging Research

- Low-dose naltrexone (LDN)
- Stellate ganglion block
- Enhanced External Counter pulsation (EECP)
- Neuromodulation techniques

Mood Stabilizers in Long COVID

- **Limited role** in Long COVID management.
- Primarily used to treat mania, often alongside antipsychotics and benzodiazepines when indicated.
- Use should remain restricted to traditional indications such as:
  - Bipolar disorder
  - Acute manic episodes
- Bipolar disorder appears far less common among individuals with Long COVID, reducing the overall need for mood stabilizers in this population.

Bottom Line

- Long COVID treatment must be patient-centered and multimodal, addressing both psychiatric and medical symptoms.

- Care plans should be individualized, tailored to each patient's specific symptoms, functional limitations, and personal goals.

- Empathic, validating, patient-centered communication to reduce stigma, enhance engagement, and support functional recovery in individuals experiencing Long COVID–related mental health challenges.

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