Whole Health System Approach

to Long COVID

Long COVID Clinic Guide

Nervous System

U.S. Department of Veterans Affairs

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EXECUTIVE SUMMARY

Long COVID is a multisystem illness estimated to affect as many as 5% of Veterans seeking care in the U.S. Department of Veterans Affairs (VA). There is no single diagnostic test for Long COVID, making its diagnosis and treatment complex. In addition, Long COVID is defined differently by a variety of healthcare entities. The scope of the VA Long COVID Clinic Guide is consistent with key aspects of the National Academies of Science, Engineering, and Medicine (NASEM) consensus definition. This Long COVID Nervous System Clinic Guide is anticipated to be the first of several symptom-focused clinical guides and covers pain, orthostatic intolerance, cognitive impairment, fatigue, and activity intolerance. Anosmia and dysgeusia will be discussed in the forthcoming Long COVID GI guide. The Guide has been developed using an evidence-informed Whole Health System (WHS) approach. The initiative involves stakeholders in VHA's Office of Specialty Care, Office of Research & Development, the Long COVID Community of Practice, the Long COVID Care Field Advisory Board (FAB), the Evidence Synthesis Program Coordinating Center (ESPCC), and the Veterans Experience Office. The evidence-informed information in this Guide was developed to support clinical decisions in the diagnosis, treatment, and creation of a personalized health plan for Veterans with Long COVID and nervous system symptoms.

To make effective use of existing evidence, we developed a set of just-in-time guidance at the midpoint between formal treatment guidelines and "expert opinion." A multidisciplinary writing group was convened. The group identified a list of clinically relevant questions and commissioned an independent review and synthesis of existing evidence. The group evaluated the strength of available evidence and used this evidence base to make clinical recommendations for the evaluation and treatment of Long COVID ("Evidence-informed Long COVID Guidance"). For history-taking, physical exam, and some commonly used, noninvasive diagnostic tests, recommendations are based on consensus determinations of useful and safe care ("Good Practice Statements"). Feedback was solicited from Veterans and other stakeholders.

QUALIFYING STATEMENTS

In developing this Guide, we adapted methods and principles used by other guideline development groups to make rapid, evidence-informed guides for clinical practice. Our starting point for evidence-informed recommendations was a rapid, systematic review of clinical and epidemiological evidence. For some aspects of everyday care that lack hypothesis-confirming data, such as history-taking, clinical examination, and initial laboratory testing, we applied recommended procedures for making "Good Practice Statements" in the context of an evidence-informed guide. In the recommendation tables, Good Practice Statements are marked in tan-colored boxes, Evidence-informed recommendations are marked in blue-colored boxes.

This Guide is not intended to replace clinical judgment but rather to supplement it. It is designed to provide suggestions for healthcare professionals during shared decision-making with Veterans who are being evaluated for or have been diagnosed with Long COVID. This document will be periodically updated and republished. General comments and questions about this Guide may be sent to VHALongCOVIDStrategiesandBestPractices@va.gov.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of clinical practice. Clinicians using this Guide should evaluate its appropriateness to their specific clinical setting.

This guidance is not intended to represent formal Department of Veterans Affairs policy.

WHO IS THIS GUIDE FOR?

This Nervous System Guide is written for Long COVID clinicians, specifically specialists, to support the creation of personalized healthcare management plans for Veterans.

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INTRODUCTION

The COVID/SARS-CoV-2 pandemic has led to a population of individuals who have symptoms that persist beyond acute infection or develop in the weeks or months following infection. (1) The National Academies of Science, Engineering, and Medicine (NASEM) proposed a consensus definition of Long COVID. (2) NASEM chose a broad definition of Long COVID that includes any "continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems", is present for 3 months, and occurs after a SARS-CoV-2 infection. This definition has been adopted by the VA's Long COVID FAB, the Centers for Disease Control and Prevention (CDC) (3), and other Federal agencies. Like NASEM, we endorse the idea that a wide variety of new or persistent symptoms could be related to recent COVID. Long COVID continues to affect Veteran populations. In a December 2023 analysis, clinical documentation of Long COVID was present in 5% of Veterans in the 12 months after testing positive for SARS-CoV-2 (4) (cumulative incidence 5.28% [95% CI, 5.21%-5.36%]). Nervous system related symptoms of Long COVID include orthostatic intolerance and autonomic dysfunction, cognitive impairment, fatigue and activity intolerance, and pain. In a cohort of randomly selected Veterans with Long COVID documentation (n=350), 12% presented symptoms involving the nervous system. (4)

Reliable evidence for an effective diagnostic testing and therapeutic approach to Long COVID is limited. To make effective use of existing evidence, we conceived a set of just-in-time guidance at the midpoint between formal treatment guidelines and “expert opinion.” A writing group with expertise in epidemiology, family medicine, integrative medicine, internal medicine, neurology, neuropsychology, occupational therapy, physical medicine and rehabilitation, pulmonary/critical care, and rheumatology was convened. The group developed a list of clinically relevant questions and commissioned a rapid review and synthesis of existing evidence. The review was conducted by the VA Evidence-based Synthesis Program Coordinating Center (ESPCC). The writing group evaluated the strength of available evidence and used this evidence base to make clinical recommendations for the evaluation and treatment of Long COVID. For recommendations concerning treatment, we relied primarily on insights from the ESPCC rapid review and from published evidence-informed recommendations. Elements of established processes for making recommendations were incorporated that consider the certainty of the evidence, the magnitude of possible effects, and the balance of benefits and harms. (e.g., the threshold for evidence of effectiveness was lower if harms were low). In the tables, these “Evidence-Informed Recommendations” are shown in blue boxes.

When an evidence synthesis was lacking, recommendations were based on consensus determinations of useful and safe care (“Good Practice Statements”). For each of these statements, published Long COVID guidance statements were reviewed and consensus was sought on their value in the care of Veteran populations. Good Practice Statements (5) were only used for recommendations about history-taking, physical examination, commonly used diagnostic tests, and the overall clinical approach, and not for invasive tests or treatments. In the tables, Good Practice Statements are shown in tan-colored boxes. Good Practice Statements that apply to the care of all Veterans with nervous system manifestations of Long COVID are provided in Table B. A summary of treatment recommendations is provided in Table C.

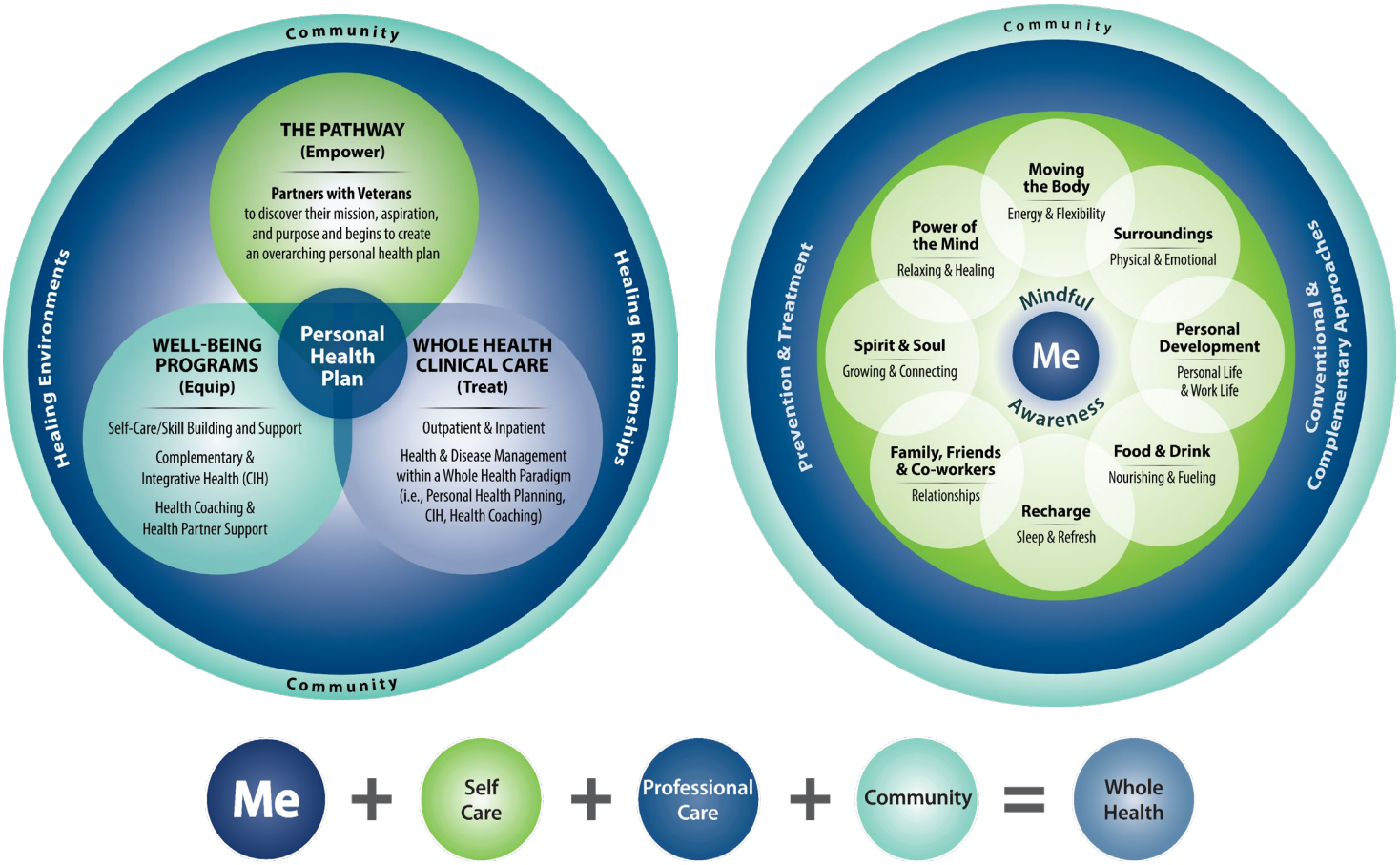
To provide Long COVID care to Veterans, two important approaches are recommended. First, we advocate an evidence-informed Whole Health System approach for clinicians providing Long COVID care to Veterans with nervous system-related symptoms. Importantly, the Whole Health System of care is not solely a separate and standalone consult service or program, but rather a system-wide approach. Second, we recommend clinicians use the VA Long COVID Questionnaire Batch to support a consistent approach to Long COVID care across VA.

WHOLE HEALTH SYSTEM APPROACH TO LONG COVID CARE

The Whole Health System approach is an evidence-informed, multi-disciplinary, personalized, Veteran-driven approach that equips Veterans to take charge of their health and well-being. The VA has adopted the Whole Health System approach across many health sectors.

The Whole Health System approach consists of three components: The Pathway, Well-Being Programs, and Whole Health Clinical Care. Included in the Whole Health System are health coaching, Complementary and Integrative Health approaches such as acupuncture and yoga, alongside conventional care.

Figure 1: Whole Health System Approach to Health Care



WHAT IS MOST IMPORTANT TO YOU TO DISCUSS IN THE VISIT TODAY?

Discussing what is most important to the Veteran ensures that the Veteran and the Veteran's unique circumstance are at the center of health care, not just signs and symptoms. This encourages and emphasizes the Veteran's ability to shape their health and well-being through self-care and self-management.

As part of this care, Veterans conclude their visit with a Personalized Health Plan that typically includes at least one specific, measurable, attainable, realistic, and time-bound (SMART) goal. Building a SMART goal with a clinician injects the care and expertise of professional care for prevention and treatment aligned with the Veteran's personal health plan. A SMART goal considers a Veteran's needs and environment, the community of support a Veteran has, as well as those who rely on the Veteran for support, Social Determinants/Drivers of Health (SDOH), and other important factors that affect a Veteran's everyday life. These and other Whole Health System tools help to ensure a Veteran-focused visit that empowers the Veteran to be an active participant in their health goals.

We recommend that Long COVID clinicians assess Social Determinants/Drivers of Health (SDOH), as they may affect symptom manifestation and ability to access healthcare. In treating patients with Long COVID, keep in mind that marginalized groups face socioeconomic and access-to-care barriers, though these may or may not be barriers for a specific individual patient. Note additionally that those identifying with more than one underrepresented or marginalized group (intersectional identities) often face enhanced levels of bias and discrimination. Also consider that employed Veterans may be experiencing limited job security, limited flexibility in their roles, and limited entitlement to sick pay and occupational health services as a result of illness. Awareness of these challenges is important in guiding diagnostic testing and treatment decisions, with the goal of minimizing time away from work. Additionally, knowledge of SDOH is important in the assessment and management of life stressors and mental health conditions that are common in Veterans. We recommend acknowledging Veterans for their psychological resilience in spite of their health concerns and encouraging Veterans with Long COVID to maintain social engagement and lean on support systems, which may include patient advocacy groups.

VA LONG COVID QUESTIONNAIRE BATCH

The Long COVID Community of Practice and the Field Advisory Board developed a recommended list of instruments for assessing and monitoring Long COVID symptoms. Called the VA Long COVID Questionnaire Batch, these include the Modified Yorkshire COVID-19 Rehabilitation Survey, the VA Whole Health Well-Being Signs (WBS), the Exercise Vital Signs (EVS) Questionnaire, the 2-Minute Step Test, and Whole Health questions such as 1) what do you want your health for; 2) and what is most important for you to discuss in the Long COVID Clinic during your medical appointment? VA clinicians caring for Veterans with Long COVID should consider this battery of instruments when feasible, especially in the initial assessment of Veterans with lingering symptoms after COVID. The VA Long COVID Questionnaire Batch has been incorporated into a note template available to all VA clinicians. Information about accessing the Questionnaire Batch template is available on the National Clinical Reminders SharePoint site.

LONG COVID CLINIC CONSULTATION AND CONSULTATION RESPONSE

The Long COVID Clinic Consultation template was developed to allow clinicians from a variety of settings to solicit input in the care of a Veteran with known or suspected Long COVID. The template can be used as a one-time consult or for continued care in a Long COVID Clinic. The referring clinician indicates symptom(s) of concern and may request further evaluation or treatment. Referring clinicians are also asked to identify what is most important to the Veteran to discuss with the Long COVID clinician.

The Long COVID Clinic team may review the request and determine a treatment plan using the Long COVID Clinic Consultation Response reminder dialog template. The consult response includes evaluation, management, and treatment using a WHS approach to Long COVID care and may incorporate information from the VA Long COVID Questionnaire Batch. The responding clinician may provide feedback for treatment outside of the Long COVID Clinic or develop a treatment plan within the Long COVID Clinic. Information collected using this template can be used as

the baseline assessment of symptoms to track Veteran response to a treatment plan. This reminder dialog consultation response template can be attached to a consult note title to respond to or close the Long COVID consult, or the facility can add it to the shared template folder or other note title.

Clinician education on the Long COVID Clinic Consults can be found on the VHA internal site: Consult Request; Consult Response

CODING LONG COVID

Long COVID coding is dynamic. Updates are available on the Centers for Medicare & Medicaid Services ICD-10 Code website.

Coding for diagnoses that may be related to Long COVID is important for clinical, operations, and research purposes. A partial list of International Classification of Diseases (ICD)-10 codes that may be useful in Long COVID is provided below. In general, the primary diagnosis code should be the specific condition or conditions that exist due to prior SARS-CoV-2 infection. U09.9 should be listed as secondary and signifies that a symptom or diagnosis may be a sequela of COVID. For example, in a patient with myalgic encephalomyelitis/chronic fatigue syndrome, a primary diagnosis code would be G93.32 (Myalgic encephalomyelitis/chronic fatigue syndrome) and a secondary code would be U09.9 to indicate it is a sequela of COVID. If a patient has a persistent symptom such as dyspnea, fatigue, or cognitive impairment that started after COVID but no specific associated diagnosis, appropriate codes might include R06.02 (shortness of breath), R53.83 (fatigue), or R41.89 (other symptom involving cognitive function and awareness). U09.9 would be a secondary diagnosis to indicate that the symptom is attributed to COVID.

If a patient has a condition(s) associated with a previous COVID-19 infection and develops a new active (current) COVID-19 infection, code U09.9 may be assigned in conjunction with code U07.1, COVID-19, to identify that the patient also has a condition(s) associated with a previous COVID-19 infection. Code(s) for the specific condition(s) associated with the previous COVID-19 infection and code(s) for manifestation(s) of the new active (current) COVID-19 infection should also be assigned.

TABLE A. Coding Long COVID – partial list of ICD-10 codes.

Please note: The codes are current as of 6/25/2024.

ICD-10	Description
F06.70	Mild neurocognitive disorder due to known
F06.71	Mild neurocognitive disorder due to known physiological condition with behavioral disturbance
G62.81	Critical illness polyneuropathy
G72.81	Critical illness myopathy
G90.A	Postural orthostatic tachycardia syndrome
G93.3	Postviral and related fatigue syndromes
G93.31	Postviral fatigue syndrome
G93.32	Myalgic encephalomyelitis/chronic fatigue syndrome
G99.0	Autonomic neuropathy in diseases classified
H93.19	Tinnitus, unspecified ear
H93.90	Unspecified disorder of ear, unspecified ear
M35.81	Multisystem inflammatory syndrome
M35.89	Other specified systemic involvement of

ICD-10	Description
M62.81	Muscle weakness (generalized)
M79.7	Fibromyalgia
R00.2	Palpitations
R07.9	Chest pain, unspecified
R13.10	Dysphagia, unspecified
R41.841	Cognitive communication deficit
R41.89	Other symptoms and signs involving cognitive functions and awareness for brain fog
R43.0	Anosmia
R43.9	Unspecified disturbances of smell and taste
R47.82	Fluency disorder in conditions classified elsewhere
R47.89	Other speech disturbances
R47.9	Unspecified speech disturbances
R53.1	Weakness

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TABLE B. GOOD PRACTICE STATEMENTS FOR THE CARE OF ALL VETERANS WITH LONG COVID PRESENTING WITH NEUROLOGIC SYMPTOMS

Good practice statements
Tan boxes Good practice statements for history-taking, physical exam, and commonly used noninvasive diagnostic tests are based on consensus determinations of useful and safe care.

History
Consider social drivers/determinants of health, marginalized groups, and intersectional identities in evaluation and management (6),(7).

Obtain a full patient history, including:
• Current symptoms
  ○ Timing in onset compared to acute COVID illness (if known)
  ○ Trajectory over time (new, improving, worsening, or unchanged)
  ○ How symptoms may correlate/cluster with each other
  ○ Triggers (including food, medications, activity, and positional changes)
  ○ Concerning symptoms or exam findings that warrant evaluation for an alternative process
• Symptoms that may be neurologic in nature, including:
  ○ Autonomic symptoms (including dizziness, lightheadedness, presyncope, syncope, orthostatic intolerance)
  ○ Headaches including migraine
  ○ Exercise intolerance
  ○ Cognitive dysfunction (including brain fog, slowed processing rate, and memory impairment)
  ○ Cognitive fatigue
  ○ Changes in gait/walking
  ○ Pain
• Relevant hospitalizations, time course and severity of acute COVID illness(es), treatments, vaccines/boosters
• Possible manifestations of post-intensive care syndrome (PICS) among Veterans who experienced critical illness, including prolonged new or worsening cognitive, physical, and mental health problems
• Review of pertinent prior medical comorbidities, and any changes since contracting COVID, including:
  ○ Pain or psychiatric conditions
  ○ Renal/endocrine conditions
  ○ Cardiovascular conditions
  ○ Neurologic conditions
  ○ Respiratory conditions
• Social history and functional history, including:
  ○ Previous and/or current alcohol and substance use
  ○ Diet and exercise
  ○ Physical and cognitive activity
  ○ Social drivers/determinants of health (including, housing, employment, family, insurance, access to community resources, and social stressors)

History

Changes in basic activities of daily living (including grooming, eating, dressing) and instrumental activities of daily living (participation in work, school, community avocational activities, such as hobbies (6),(8),(9).

Laboratory

Consider the following laboratory studies on initial evaluation if not obtained in the prior 3 months (8),(10):

- Complete blood count with differential
- Complete metabolic panel including blood glucose, creatinine, magnesium, and liver studies (bilirubin, alanine aminotransferase, aspartate amino transferase, and alkaline phosphatase)
- Thyroid stimulating hormone
- C-reactive protein (CRP) (consider high-sensitivity CRP if available)
- Erythrocyte sedimentation rate
- Vitamin B6 (pyridoxine), vitamin B9 (folate), vitamin B12 (cobalamin), vitamin D3 (cholecalciferol)
- Hemoglobin A1c

Personalized health plan: management and treatment

- Address life stressors and mental health conditions that may exacerbate Long COVID symptoms (7).
- Acknowledge Veterans for their psychological resilience. Encourage Veterans with Long COVID to maintain social engagement and lean on support systems, which may include Veteran peer support specialists (7).
- Consider a multimodal approach to support Veterans with Long COVID in their recovery. This often entails rehabilitation programs, pharmacological therapies for specific symptoms, and referrals to appropriate multidisciplinary clinicians (9).
- Address potential contributing factors such as nutritional status, physical activity, sleep, and stress (9).

TABLE C. SUMMARY OF EVIDENCE-INFORMED TREATMENT RECOMMENDATIONS[1]

Table C-1. Non-pharmacologic and pharmacologic interventions for autonomic dysfunction

Category	Topic	Autonomic dysfunction
Non-pharmacologic	Salt and Water by mouth[2]	No recommendation
	Physical activity[3]	Consider use
Pharmacologic	Low-dose β blockers (e.g., propranolol)	Consider use
	Pyridostigmine, Ivabradine	Consider use
	Midodrine, Fludrocortisone[2]	No recommendation
	Clonidine	No recommendation

2. In the VA, use of these interventions is limited because a high proportion of patients have conditions such as heart failure or renal disease. For this reason, we considered the evidence to be inadequate for a VA Long COVID population. In other populations, midodrine has adequate evidence; salt and water and fludrocortisone have minimally adequate evidence.

3. Many Veterans with Long COVID and postural tachycardia are already physically active. For those who are not active and do not have post-exertional malaise, most protocols begin with recumbent exercise (e.g., rowing machines, recumbent cycles, or swimming) 30 minutes 3-4 times a week.

Table C-2. Non-pharmacologic and pharmacologic interventions for cognitive impairment

Category	Topic	Cognitive impairment
Non-pharmacologic	Cognitive Rehabilitation[4]	Consider use
Pharmacologic	Amantadine	Consider not using
	Coenzyme Q10	No recommendation
	Donepezil	Consider not using
	Low-dose naltrexone (LDN)	No recommendation
	Methylphenidate	No recommendation

4. Attention to Long COVID-specific issues like post-exertional malaise and posture may be needed, which may require rehabilitation clinicians with appropriate training.

[1] For recommendations concerning treatment, we relied primarily on insights from the ESPCC rapid review and from published evidence-informed recommendations. Elements of established processes for making recommendations were incorporated that consider the certainty of the evidence, the magnitude of possible effects, and the balance of benefits and harms (e.g., the threshold for evidence of effectiveness was lower if harms were low). In Tables D-F, these "Evidence-Informed Recommendations" are shown in blue boxes.

Table C-3. Non-pharmacologic and pharmacologic interventions for fatigue

Category	Topic	Fatigue
Non-pharmacologic	Cognitive Behavioral Therapy[5] (CBT)	Consider use
	Graded Exercise Therapy	Consider not using
	Paced activity and energy conservation	Consider use
	Pulmonary rehabilitation	Consider not using
Pharmacologic	Amantadine	No recommendation
	Coenzyme Q10	No recommendation
	Low-dose naltrexone (LDN)	Consider use
	Modafinil	No recommendation

5. CBT may be considered for fatigue in Long COVID, with an important caveat, CBT should be delivered by a healthcare professional with appropriate training and experience working with Long COVID or similar conditions (e.g., Myalgic encephalomyelitis/chronic fatigue syndrome), and/or an understanding of evidence-based behavioral management of post-exertional malaise (PEM). Finally, clinicians should note that CBT is a multi-visit process. As part of a Whole Health Systems approach to Long COVID care, it is important to minimize appointment fatigue, which may cause excessive stress and worsen fatigue.

ORTHOSTATIC INTOLERANCE AND AUTONOMIC DYSFUNCTION

Description of condition

Orthostatic intolerance (OI) is recognized as a frequent early and late complication of COVID. (11) OI can be defined as "the inability to tolerate upright posture because of symptoms of cerebral hypoperfusion or sympathetic activation, or both, which are relieved with recumbency." (12) Orthostatic hypotension (OH) is a form of low blood pressure that happens when standing from a seated or supine position. Clinicians may be less familiar with postural orthostatic tachycardia syndrome (POTS), the major phenotype of autonomic dysfunction in patients with Long COVID. POTS is defined as a sustained increase in heart rate of 30 beats per minute after standing in the absence of OH. (13)

Prevalence and course

Infection with SARS-CoV-2 increases the risk of developing POTS. (14) Among people with persistent symptoms after COVID, the prevalence of POTS ranged from 2% to 14%. (15) Orthostatic symptoms and tachycardia often resolve in the first 3–6 months after COVID. After 6 months, the course of symptoms in general and of autonomic dysfunction specifically is less clear. Studies that have tried to assess the prognosis of autonomic dysfunction in patients with Long COVID have serious limitations and discrepant results, but do indicate clearly that some patients recover, while others continue to have significant disability after a year. (15),(16) The duration or severity of autonomic dysfunction have not been shown to be associated with the severity of the initial COVID illness. Vaccination against SARS-CoV-2 may also increase the risk of developing POTS, (14) although this association is disputed. (17),(18)

Etiology of Long COVID autonomic dysfunction

Possible etiologies for Long-COVID POTS include autoimmunity, viral persistence, activation of other viruses, persistent inflammation, mitochondrial dysfunction and brainstem swelling, and renin-angiotensin-aldosterone system imbalance, which also promotes the development of autoantibodies. (19) Autoimmunity is currently the most popular hypothesis for the etiology of Long COVID-POTS. (20) This hypothesis asserts that autonomic dysfunction

arises from direct injury to neurons or vessels from neuroinflammation provoked by autoimmune disease. The evidence for this hypothesis is indirect, but compelling. First, autoimmune diseases such as Sjogren's, celiac disease, rheumatoid arthritis, or inflammatory bowel disease commonly precede (or may be diagnosed after) a patient presents with POTS. (21),(22) Second, many antibodies have been associated with autonomic disorders in POTS patients with or without a history of COVID. (23),(24) Third, POTS is often associated with constitutional features that may signify immune dysregulation, such as fatigue, malaise, or skin rashes.

Cause of symptoms

Reduced cardiac output and cerebral blood flow are believed to cause many of the symptoms of POTS and OH. (16) Symptoms of cerebral hypoperfusion include lightheadedness, weakness, blurred vision, and brain fog, that is, difficulties with concentration, mental fatigue, and slowed information processing. Symptoms of sympathetic activation can include nausea, chest pain, palpitations, and tremulousness. Some experts believe decreased vagal tone also contributes to symptoms.

Bedrest deconditioning is in the differential diagnosis of tachycardia with activity or with standing. However, experts have abandoned the view that, in all or most POTS patients, symptoms are caused by deconditioning. (25),(13) For Long COVID-POTS, "the early-onset of orthostatic intolerance symptoms and high pre-illness physical activity levels of many Long COVID POTS patients make it unlikely that POTS in this group is due to deconditioning." (16)

Clinical considerations and recommendations

Evidence-informed guidance and Good Practice Statements for Long COVID autonomic intolerance are summarized in Table D. Because the ESPCC report did not address all of the relevant questions about management of POTS, our starting point was a literature review incorporated into guidelines for POTS diagnosis and management. (26),(27) Most treatments for POTS have not been studied in Long COVID-POTS patients. (28)

History

Dizziness, palpitations, chest and "coat-hanger" pain (i.e., "a charley horse kind of sensation, in the back of the neck and shoulder areas in the distribution that's like a coat hanger"), reduced exercise tolerance, palpitations, headaches, unrefreshing sleep, cognitive complaints, and many other symptoms associated with Long COVID are also part of the clinical picture of POTS. POTS symptoms can significantly impair functional status, mental health, and quality of life, making it difficult to work, socialize, and enjoy recreational activities.

POTS, and Long COVID-POTS, are closely associated with chronic fatigue syndrome (29), (30),(31) commonly called Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) or Systemic Exertion Intolerance Disease. (32) The hallmarks of ME/CFS are a prolonged, significant decrease in function that lasts at least six months and post-exertional malaise (PEM), which is "the worsening of [fatigue and other] symptoms following even minor physical or mental exertion, with symptoms typically worsening 12 to 48 hours after activity and lasting for days or even weeks." Further information can be found at this site: Strategies to Prevent Worsening of Symptoms | ME/CFS | CDC. In patients with Long-COVID POTS, the presence of PEM is associated with worse function and, often, a lower tolerance for activity. (15),(33)

Because orthostatic intolerance (OI) is common in Long COVID clinic patients (34) and has implications for management, all Veterans seen in a Long COVID clinic should be screened for OI using answers to relevant items on the VA Long COVID Questionnaire Batch, or by eliciting a history of palpitations, dizziness, breathlessness, postural or exertional tachycardia, chest tightness, and other relevant symptoms, such as cognitive dysfunction and fatigue. If the patient notes palpitations, tachycardia, dizziness, or lightheadedness, elicit the relationship to posture change. Some patients use a heart rate monitor and can provide a clear history of the degree of tachycardia, how long episodes last, and provocative factors. Others associate symptoms with standing or single out "sitting down" as an alleviating factor. Some may not have noticed that their symptoms are provoked by standing, especially those who

avoid activities that may provoke symptoms. Listen for provocative factors such as standing in line, showering, or shopping, and whether alcohol, environmental temperature, meals, or medications are related to symptoms. A functional assessment should also be done.

Ask about other autonomic symptoms, such as gastrointestinal or genitourinary dysfunction, abnormal sweating, acrocyanosis, dry mouth, and unexplained fever. (35) Structured assessment tools such as the COMPASS-31 or the Malmö POTS symptom score may be used to elicit symptoms of OI as well as autonomic symptoms related to secretomotor and vasomotor dysfunction, such as GI and bladder symptoms, sleep problems, and male erectile dysfunction.

Autoimmune disease is a risk factor for POTS. Ask specifically about migraine, rashes, and a past history of Sjogren's, Hashimoto's thyroiditis, celiac disease, or another autoimmune condition. In patients who do not have a history of an autoimmune condition, a thorough review of systems may uncover symptoms of (undiagnosed) celiac disease, Sjogren's, or another autoimmune condition. Mast cell disorders and Ehlers-Danlos syndrome were also associated with POTS in the pre-COVID era, although their relevance to Long COVID-POTS is not yet well-established.

Assess symptoms to help rule out other causes

Tachycardia, orthostatic intolerance, and dizziness have many causes. The differential diagnosis of tachycardia includes dehydration or over diuresis, thyrotoxicosis, cardiac arrhythmias, valvular heart disease, heart failure, anemia, lung disease, deconditioning, and use of medications, supplements, caffeine, and drugs.

Dizziness is the sensation of disturbed or impaired spatial orientation and can be due to any of these causes and a wide variety of others. (Vertigo is a specific type of dizziness defined as the sensation of self-motion when no self-motion is occurring.) Dizziness that is worse with head movement can be a sign of vestibular dysfunction. Explore if dizziness is worse with movement or when objects are moving around the patient (e.g., watching TV or scrolling on computer while sitting). Dizziness associated with

Basics of stand test for POTS

1. Have the patient remove shoes and socks and lie down quietly for 5 minutes. Obtain the blood pressure and heart rate using a sphygmomanometer on the upper arm.
2. With the patient standing quietly without moving or talking, obtain blood pressure and heart rate using a sphygmomanometer on the upper arm within (for example) 3, 5, 7, and 10 minutes of standing.
3. Record patient-reported symptoms and clinical observations throughout the test. Ask about dizziness, brain fog, and other symptoms and observe for flushing, tremor, and discoloration or discomfort in the feet. Some clinicians might be able to detect other signs of autonomic dysregulation, such as heart rate variability with deep breathing and briskness of pupillary reactions.
4. Caution should be exercised for highly symptomatic patients who are unable to safely stand for 10 minutes due to orthostatic intolerance or neuromuscular disorders with impaired mobility. If the test is stopped because of symptoms, have the patient lie down and continue to check heart rates for the remainder of the 10 minutes.
5. POTS can be diagnosed if blood pressure remains stable and there is a heart rate increase of 30 beats per minute from lying down to standing within 10 minutes of standing for at least 2 consecutive readings. An abrupt drop in blood pressure, often with relative bradycardia and presyncopal symptoms, suggests the same physiology as vasovagal syncope. (This has been called neurally mediated hypotension or neurocardiogenic syndrome.)
6. In practice, if the patient is taking medications for heart failure, arrhythmia, or hypertension that cannot be held safely, the test can be attempted but may be less likely to be diagnostic. In particular, β blockers prescribed for other reasons may blunt the increase in heart rate, in effect treating POTS. Not all protocols require that medications be held prior to testing.

A single 10-minute stand test can miss orthostatic tachycardia. When a patient has tachycardia that does not meet the criteria for POTS, repeat testing or home testing can provide additional information.

headaches can be vestibular migraine. Dizziness that worsens with getting into bed, getting out of bed, rolling in bed, bending, or looking up suggests benign positional paroxysmal vertigo. Deconditioning is in the differential diagnosis of patients who had a prolonged period of inactivity due to COVID, or who have had lifelong OI and fatigue. (13),(25), (36)

Physical exam

If the physical exam is conducted in person, it should include routine orthostatic blood pressure measurements (HR and BP lying and 1 and 3 minutes standing), chest and heart auscultation, and examination for tremor and for peripheral neuropathy. A history of flexible joints should prompt an exam for findings of Ehlers-Danlos syndrome.

When the history suggests orthostatic intolerance or other symptoms of autonomic dysfunction, perform a NASA 10-minute Lean Test or an Active Stand Test. Observe the patient for symptoms and signs including brain fog, dizziness, and discoloration or discomfort in the feet. While standard "orthostatic vital signs" (3–5 minutes of standing) may identify OH, a 10-minute test is more sensitive for tachycardia, and helps identify patients who develop symptoms, tachycardia, or hypotension when standing is prolonged. Some protocols are designed for use at home. Clinician instructions for the 10-Minute NASA Lean Test are available online. The basic procedures for most 10-minute test protocols are also outlined in the sidebar above.

Evaluation

Laboratory testing

For new patients, or those without laboratory testing in the prior 3 months, a list of routine tests to consider for those with a new nervous system-related symptom is noted in Good Practice Statements (Table B). Additional diagnostic testing should be offered based on the history and physical examination. For example, celiac disease screening can be done if there is a history of diarrhea, or ferritin if there is evidence of an iron deficiency anemia.

Investigations for autoimmunity, mast cell disorders, or infection should be guided by the initial evaluation (e.g., testing for Sjögren syndrome if the patient complains of dry eyes). Serum histamine or tryptase, thyroid antibodies, Epstein-Barr virus titers, G protein coupled receptor assays, and other antibodies have been used in studies of Long COVID patients, but their role is still unclear.

Diagnostic testing

An electrocardiogram (EKG) should be obtained in all patients and ambulatory monitoring should be obtained if there is a significant burden of palpitations, lightheadedness, or dizziness. Echocardiography is not routinely indicated to evaluate suspected orthostatic intolerance or tachycardia. If there are concerns for a cardiac or pulmonary etiology contributing to tachycardia, chest imaging should be considered (chest x-ray or CT). Additional cardiac testing, autonomic function testing, or referral may be used but are also not routine.

Head-up tilt table testing (HUTT) is not routinely required to diagnose POTS. Indications for HUTT in patients with Long COVID are not well-established. (37) In the pre-pandemic era, the active stand test had similar sensitivity and greater specificity for POTS than did HUTT. (38)

Personalized health plan: management and treatment

Patients benefit from working with a multidisciplinary team that includes specialists with expertise in autonomic dysfunction. This may include expertise in physical medicine and rehabilitation (PM&R), physical therapy (PT), occupational therapy (OT) and nutrition counseling.

Non-pharmacologic measures

Non-pharmacologic treatment is first line. While evidence is sparse, routine management of POTS may include:

- A high salt and water diet (unless contraindicated by heart failure or hypertension). Aim for 3 liters of water and 10 grams of salt (NaCl) taken by mouth daily
- Review for medications that exacerbate tachycardia or hypotension
- Limit or avoid symptom triggers such as exertion in hot weather, alcohol consumption
- Lifestyle modification including slowly getting out of bed before standing and use of compression socks
- Frequent, small, balanced meals with whole foods, protein, vegetables, and fruits, and high in fiber

Physical activity

If post-exertional malaise is present, follow guidance for management of PEM (see the History heading in the section on Fatigue & Activity Intolerance below). If PEM is not present, and the patient has had a prolonged hospitalization or period of inactivity, consider an exercise program under the supervision of a therapist experienced in Long COVID. Exercise in POTS patients usually begins with recumbent exercise, advancing as tolerated. Reclined exercises like stretches, yoga and gentle weightlifting done from a seated or supine position, recumbent biking, rowing, and swimming are examples. Only after the patient has spent a substantial amount of time building up tolerance to these exercises should the patient attempt upright exercises like jogging or upright biking.

Pharmacologic measures

If nonpharmacological measures are insufficient, consider medications. As noted above, the ESP report did not address medications for POTS. Instead, our starting point was another review of POTS drugs (26), (27) which we supplemented with more recent Long COVID-POTS literature.

Veterans with conditions such as heart failure or renal disease may require consultation with pertinent specialists before starting certain medications. Within the VA, clinicians with specialized expertise in Parkinson's Disease, neuropathies, and traumatic brain injury typically have the most experience using some of these medications for autonomic dysfunction.

The choice of medication for POTS depends on the symptoms and on the patient's blood pressure. (26), (27)

For persistent POTS symptoms in the absence of hypotension, consider a heart rate inhibitor. The evidence is strongest for a β blocker (propranolol 10–20 milligrams up to 4 times a day). Start with a low dose, especially in patients who developed hypotension on an active standing or LEAN test, or other medication intolerances are present. Evidence for other drugs used to reduce heart rate in POTS is weaker. These include ivabradine 2.5 to 7.5 milligrams twice daily, pyridostigmine 30 to 60 milligrams 3 times daily, and clonidine 0.1 to 0.2 milligrams 3 times daily.

For patients with low blood pressure, treatments are midodrine (2.5 to 15 milligrams every 4 hours 2–3 times per day; moderate evidence) and fludrocortisone (0.1-0.3 milligrams daily; low evidence).

Many other medications are used in patients with POTS. These include modafanil, methylphenidate, duloxetine, bupropion, guanfacine plus n-acetylcysteine, and low dose naltrexone (see Fatigue section). These medications are used primarily for fatigue and cognitive symptoms in patients who also have POTS. Droxidopa and desmopressin have also been used in POTS. Some of these medications can exacerbate tachycardia, so patients should be monitored carefully.

Currently, there is interest in the use of immune-modulating therapy for Long-COVID POTS, particularly in patients who have an underlying autoimmune disease. However, evidence is preliminary. (20), (9)

Counseling/supportive care

When counseling about the natural history of POTS, inform the Veteran that: (1) before COVID, 70% to 80% of young adults and adolescents with POTS recovered in 1–4 years; most patients with Long COVID-POTS improve within a year; (3) the longer-term prognosis is unclear. (15)

Table D. Guidance for orthostatic intolerance (OI) and autonomic dysfunction in Long COVID

Evidence-informed recommendations	Good practice statements
Blue boxes For the evidence underlying these recommendations see: Anderson et al. 2023[2]; Raj et al. 2020[3]; Raj et al. 2022[4]	**Tan boxes** Good practice statements for history-taking, physical exam, and commonly used noninvasive diagnostic tests are based on consensus determinations of useful and safe care.

History

Table D-1. Good practice statements

Topic	Details
Assessment of symptoms that may be related to OI	Screen for orthostatic intolerance by: • Reviewing VA Long COVID Questionnaire Batch responses • Asking about palpitations, dizziness, "electric shock" sensation on standing, breathlessness, postural or exertional tachycardia, chest tightness, and other relevant symptoms. Keep in mind that cognitive dysfunction and fatigue can be caused by autonomic dysfunction (15),(39).
Assessment of symptoms that may be related to autoimmunity	Ask specifically about: • Migraine • Rashes • History of autoimmune disorders such as Sjogren's, Hashimoto's thyroiditis, or celiac disease. Keep in mind that a thorough review of systems may uncover symptoms of (undiagnosed) celiac disease, Sjogren's, or another autoimmune condition. In the pre-COVID era, mast cell disorders and Ehlers-Danlos syndrome were also associated with POTS, although their relevance to Long COVID-POTS is not well-established (26).
Assessment of symptoms that may be related to autonomic dysfunction	Ask about other autonomic symptoms such as: • Gastrointestinal or genitourinary dysfunction • Abnormal sweating • Acrocyanosis • Dry mouth • Unexplained fever (26)
Use of structured assessment tools	Use a structured assessment tool such as the COMPASS-31 or the Malmö POTS symptom score to assess the likelihood of POTS.

[2] Anderson, J., S. Young, and K. Mackey, *Brief Evidence Assessment Guidance for Long COVID Clinics: Nervous System*. 2023, Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs: Washington, DC.
[3] Raj SR, Guzman JC, Harvey P, Richer L, Schondorf R, Seifer C, et al. Canadian Cardiovascular Society Position Statement on Postural Orthostatic Tachycardia Syndrome (POTS) and Related Disorders of Chronic Orthostatic Intolerance. Can J Cardiol. 2020;36(3):357-72.
[4] Raj SR, Fedorowski A, Sheldon RS. Diagnosis and management of postural orthostatic tachycardia syndrome. Cmaj. 2022;194(10):E378-E85.

Physical exam

Table D-2. Evidence-informed recommendations

Topic	Recommendation	Details
Physical exam elements	Recommend use	When the history suggests flexible joints, use the Beighton scale to look for findings of Ehlers-Danlos syndrome (26),(40).
Physical exam elements	Recommend use	When the history suggests orthostatic intolerance or other symptoms of autonomic dysfunction, perform a NASA LEAN test or an active stand test. Observe the patient for symptoms and signs including brain fog, dizziness, and discoloration or discomfort in the feet (26),(41).

Evaluation

Laboratory testing

Table D-3. Good practice statements

Topic	Details
Routine laboratory testing	Consider the following laboratory studies on initial evaluation if not obtained in the prior 3 months (8),(10): • Complete blood count with differential • Complete metabolic panel including blood glucose, creatinine, magnesium, and liver studies (bilirubin, alanine aminotransferase, aspartate amino transferase, and alkaline phosphatase) • Thyroid stimulating hormone • C-reactive protein (CRP) (consider high-sensitivity CRP if available) • Erythrocyte sedimentation rate • Vitamin B6 (pyridoxine), vitamin B9 (folate), vitamin B12 (cobalamin), vitamin D3 (cholecalciferol) • Hemoglobin A1c
Additional laboratory testing	Additional laboratory testing should be offered based on the history and physical examination findings.

Table D-4. Evidence-informed recommendations

Topic	Recommendation	Details
Specialized laboratory testing	Consider use	Use the initial evaluation to guide further laboratory testing for autoimmunity, mast cell disorders, or infection (for example, testing for Sjögren syndrome if the patient complains of dry eyes) (15).
Specialized laboratory testing	Consider not using	Thyroid antibodies, GAchR ab, FGFR3 Ab, TS-HDS, G protein coupled receptors, and reactivation of EBV have all been seen in Long COVID patients, but their role in clinical evaluation is still unclear (15),(42).

Diagnostic testing

Table D-5. Good practice statements

Topic	Details
Chest imaging	Obtain chest imaging. This might include plain radiographs or computed tomography of the chest.
Additional testing	Additional cardiac testing or referral to an autonomic medicine expert may be used per local practice but are not routine.

Table D-6. Evidence-informed recommendations

Topic	Recommendation	Details
Routine use of echocardiography	Consider not using	Echocardiography is not routinely indicated to evaluate suspected orthostatic intolerance or tachycardia (26),(41).
Routine use of head-up tilt table testing or autonomic function testing	Consider not using	Head-up tilt table testing and autonomic testing are not routinely required to diagnose POTS. Indications for heads-up tilt table testing in patients with Long COVID are not well established.

Personalized health plan: management and treatment

Table D-7. Good practice statements

Topic	Details
Multidisciplinary care	Patients benefit from working with a multidisciplinary team that includes specialists with expertise in autonomic dysfunction. This may include expertise in physical medicine and rehabilitation, physical therapy, and occupational therapy where available.
Nonpharmacologic interventions	While evidence is sparse, routine management of POTS may include (40),(43): • A high salt and water diet when not contraindicated. Aim for 3 liters of water and 10 grams of salt (NaCl) taken by mouth daily. • Stopping medications that exacerbate tachycardia or hypotension when possible • Limiting or avoiding symptom triggers such as exertion in hot weather, alcohol consumption • Lifestyle modification, including slowly getting out of bed before standing and use of compression stockings • Frequent small, balanced meals with whole foods, protein, vegetables, and fruits, and high in fiber

Table D-8. Evidence-informed recommendations

Topic	Recommendation	Details
Counseling	Consider use	When counseling about the natural history of POTS, inform the Veteran that: • Before COVID, 70% to 80% of young adults and adolescents with POTS recovered in 1–4 years • Most patients with Long COVID-POTS improve within a year • For those who do not improve within a year, the longer term prognosis is unclear (15),(44).
Physical activity	Consider use	If post-exertional malaise (PEM) is present, follow guidance for management of PEM (see Fatigue). If PEM is not present, and the patient has had a prolonged hospitalization or period of inactivity, consider an exercise program under the supervision of a therapist experienced in Long COVID. For most patients, exercise in POTS patients begins with recumbent exercise and advances as tolerated (15).
Pharmacologic treatment for POTS	Consider use	If nonpharmacological measures are insufficient, consider medications. The Canadian Cardiovascular Society (CCS) rated the evidence for various interventions. The choice of medication depends on the symptoms (see figure 4 in the CCS paper) (26).

Topic	Recommendation	Details
Treatment of orthostatic hypotension	No recommendation	For patients with low blood pressure, treatments are midodrine (2.5–15 milligrams by mouth every 4 hours 2–3 times per day; moderate evidence) and fludrocortisone (0.1–0.3 milligrams by mouth daily; low evidence). In the VA, however, use of these medications is limited because a high proportion of patients have conditions such as heart failure or renal disease. Within the VA, clinicians with expertise in Parkinson's disease, neuropathies, and traumatic brain injury may have the most experience using these medications (26),(40).
Heart rate inhibitors	Consider use	For persistent postural orthostatic tachycardia syndrome (POTS) symptoms in the absence of hypotension, use a heart rate inhibitor. The evidence is strongest for a β blocker (propranolol 10–20 milligrams up to 4 times a day). Start with a low dose, especially in patients who developed hypotension on an active standing or LEAN test. Evidence for other drugs used to reduce heart rate in POTS is weaker (including ivabradine 2.5–7.5 milligrams by mouth twice a day, pyridostigmine 30–60 milligrams by mouth 3 times a day, and clonidine 0.1–0.2 milligrams by mouth 3 times a day (26).

COGNITIVE IMPAIRMENT

Description of condition

Long COVID is associated with neurocognitive symptoms that may have a major impact on function and well-being. (45), (46) The term "neurocognitive" refers to the ability to think and reason, concentrate, remember things, process information, learn, speak, and understand. Among people with Long COVID, the most common neurocognitive complaints are difficulties with concentration or attention, poor memory, mental fatigue, and slowed information processing. (15) The term brain fog refers to any of these complaints (and others). (47)

Prevalence and course

In five systematic reviews, the proportion of adults reporting cognitive symptoms following COVID ranged from 0.6% to 22%. (15) Most studies followed up people who were severely ill with SARS-CoV-2 infection within the first year of the pandemic. In contrast, many people seen in a contemporary Long COVID clinic developed Long COVID after one or more recent episodes of milder acute infection.

The course of Long COVID cognitive symptoms is unclear. In a large proportion of patients, symptoms persist for 6 months, 12 months, or longer (48), but information about changes in severity over time is sparse. Studies of cognitive symptoms used inconsistent or unclear criteria for defining Long COVID, characterizing symptoms, and measuring severity.

Etiology of Long COVID cognitive impairment

Potential etiologies for cognitive impairment following COVID include ongoing neuroinflammation, alterations in immune pathways that can lead to neurologic diseases, hypoxic injury, microthrombosis, decreased cerebral perfusion, serotonin pathway dysregulation (49), persistent virus, or reactivation of latent herpesviruses. (50)

Cause of symptoms

Neuroimaging studies have not definitively linked different neurocognitive symptoms to specific regions of the brain. (51) ,(52) In other conditions, deficits in immediate (working) memory, speed of processing, and executive function implicate abnormal connections in the frontal/subcortical lobes of the brain. Short-term memory is housed in the mesial temporal lobes. Ongoing imaging studies in Long COVID patients are examining lesions and metabolism in different parts of the brain.

Clinical considerations and recommendations

Evidence-informed guidance for Long COVID cognitive impairment is summarized in Table E. For the evidence review underlying these statements, refer to the VA ESPCC's Brief Evidence Assessment. (15) Good Practice Statements for Long COVID cognitive impairment are summarized in Table E.

History

Clinicians should obtain a detailed history of cognitive symptoms. These may include deficits in (7):

- Attention (lost train of thought, concentration problems)
- Processing speed (slowed thoughts)
- Motor function (slowed movements)
- Language (word finding problems, reduced fluency)
- Memory (poor recall, forgetting tasks)
- Mental fatigue
- Executive function (poor multitasking or planning)
- Visuospatial domains (neglect)

Speed of processing information is manifested as slowness on timed tests (such as listing animals or words that start with a certain letter in 1 minute). Deficits of executive function can be manifested on the Stroop Color and Word Test (in which individuals must read a list of colors where the color of the words does not match the word). We did not specifically evaluate the performance of the Stroop Color and Word Test in Long COVID, so no recommendation is offered regarding its use over other instruments.

It is important to ascertain the onset of symptoms relative to the initial acute COVID illness and any subsequent reinfections, as well as how these symptoms are changing over time (whether they are improving, remaining stable, or worsening). Marked progression of symptoms over time may prompt elevated concern for a contributing cause, particularly in elderly patients. Pre-existing Alzheimer's disease, vascular white matter disease, traumatic brain injury, Parkinson's disease, multiple sclerosis, and normal pressure hydrocephalus are other causes of slow processing and other symptoms associated with Long COVID. Deficits in short-term memory are a common feature of early Alzheimer's disease. Mental fatigue can be exacerbated by polypharmacy, insomnia, or depression.

Ask patients about their ability to independently carry out instrumental activities of daily living (e.g., driving, medication management, clinical visits and appointment management, financial management, meal preparation, shopping, and cleaning), and if relevant, basic activities of daily living (e.g., bathing, grooming, eating, dressing, and toileting), which may be affected in patients with more severe cognitive impairment. Ascertaining the impact of cognition versus other causes (e.g., reduced mobility, fatigue) on functional abilities is important. Assessment across significant life roles should be conducted, including work, school, and social role functioning (e.g., managing a household, parenting, and impact on relationships).

Veterans should be asked about Nutrition (e.g., intake of plant-based foods), Exercise (e.g., activity level), Sleep, and Stress (NESS). To assess sleep, ask about sleep hygiene, insomnia, untreated or inadequately treated apnea, and whether sleep is refreshing. Symptoms of depression, anxiety, and post-traumatic symptoms (related to COVID or otherwise) should also be elicited. Because fatigue is common in Long COVID, (15) clinicians should ask about fatigue and fatigue severity when evaluating cognition and function. It is important to inquire about personality change, disinhibition, and social withdrawal. Finally, assess other factors unrelated to COVID that could be affecting cognitive functioning (e.g., vascular risk factors, history of traumatic brain injury, history of neurodevelopmental disorders such as Attention-Deficit/Hyperactivity Disorder (ADHD), movement disorders, other concurrent neurologic conditions, medications, and supplements). It is important to take health equity considerations into account, as well as social stressors associated with the pandemic.

If the Veteran is accompanied and with their concurrence, ask the companion about cognitive impairment warning signs such as asking the same questions over and over again; becoming lost in familiar places; not being able to follow directions; getting confused about time, people, and places; or having problems with self-care, nutrition, bathing, or safety.

Cognitive diagnoses are not made on the basis of screening tests. Patients with Long COVID and controls may score similarly on screening cognitive tests. (53),(54),(51) In addition, screening cognitive tests have low sensitivity and specificity when detecting mild deficits (55); thus, they may not be the ideal method to identify Long COVID-related cognitive impairment. (55)

The Montreal Cognitive Assessment (MoCA) should not be used alone to identify cognitive impairment. Because other conditions can cause a low MoCA score, the result may not reflect true cognitive impairment. Conversely, a patient with a "normal" score may still have cognitive impairment. In Veterans with known dementia and Long COVID symptoms, the MoCA may be used longitudinally to follow clinical trajectory.

Inadequate evidence was found to inform a recommendation for the use of the Mini-Mental State Examination (MMSE) or the Saint Louis University Mental Status Examinations (SLUMS).

Physical exam

Perform a screening neurologic exam (see sidebar). For clinicians providing virtual visits, sources have developed instructional guidance on the conduct of the virtual neurologic exam. (56) Assess orthostatic blood pressure, heart rate, cardiovascular assessment, cranial nerves, bradykinesia, sensation in extremities, reflexes, coordination, and gait. Bradykinesia can be evaluated using fast finger tapping between the thumb and the first finger.

Screening neurologic exam

Face-to-face visit

1. Vital signs
2. Gait:
    a. Walk independently?
    b. Romberg: any sway?
    c. Can they do tandem walking?
3. Muscle stretch reflexes (MSRs): knees
4. Motor: check drift (holds arms 10 sec)
5. Any abnormal movements?
6. Cranial nerves: symmetrical smile

Virtual visit

As above except:

1. MSR (knees): Ask the patient to cross one leg over the other and tap their knee with the edge of their hand.

Before testing gait, consider the safety of the environment and assess for symptoms that point to unsafe gait.

Evaluation

Laboratory testing

For new patients, or those without laboratory testing in the 3 months prior to their visit, a list of routine laboratory tests to consider for all Veterans presenting with a new nervous system-related symptom after COVID is offered in the Good Practice Statements (Table B). Additional diagnostic testing should be offered based on the history and physical examination findings.

Diagnostic testing

When there is concern for dementia or other cognitive etiologies, the evaluation should follow usual practice for these conditions. The decision to order computed tomography (CT) and brain magnetic resonance imaging (MRI) is based on usual practice. We did not review evidence about the diagnostic testing or therapeutic impact of neuroimaging in cognitive impairment in Long COVID.

In some cases, neuropsychological evaluation may be warranted. A neuropsychological evaluation typically includes evaluation of potential contribution from psychiatric/mood factors, fatigue, sleep, and pain. Neuropsychological

evaluation may pick up subtle deficits and provide a more nuanced assessment of cognitive deficits and relative strengths.

Personalized health plan: management and treatment

Referrals

Non-neurologists caring for a Veteran with Long COVID-related cognitive impairment should consider a consult to neurology when there is concern for other neurologic causes of cognitive decline due to the presence of other neurologic signs or symptoms, rapid progression, a complex or unclear presentation, or for older patients, who have a higher prevalence of major neurocognitive disorders than the general population. Refer to physical medicine and rehabilitation if the Veteran is experiencing impairment in physical or social role functioning. If mental health issues are present, develop a treatment plan or refer to psychiatry and psychology.

Speech-language pathology and occupational therapy may be appropriate consults for neuropsychological testing, though they may not assess all cognitive domains as fully as a complete neuropsychological evaluation. Physical therapy and occupational therapy may overlap in supporting activity pacing, sleep hygiene, stress management, and building self-efficacy. Clinicians may refer Veterans who are experiencing cognitive changes that are impairing function (e.g., performance of their basic or instrumental activities of daily living) to occupational therapy and to physical therapy for intervention in the context of musculoskeletal or neurologic comorbidities for balance. When therapies are needed in Veterans with post-exertional malaise, they should be delivered by therapists competent to address Long COVID or similar conditions (e.g., ME/CFS), and/or an understanding of evidence-based behavioral management of post-exertional malaise.

Non-pharmacologic measures

Cognitive rehabilitation: The effectiveness of cognitive rehabilitation for Long COVID is uncertain. Cognitive rehabilitation is thought to be effective for impairments after mild traumatic brain injury, but the applicability of this literature to patients with Long COVID is unclear. Like patients with Long COVID, patients with mild traumatic brain injury often have problems with attention, memory, executive function, and metacognitive skills. (15) Moreover the risk of adverse effects of cognitive rehabilitation is thought to be low. Thus, for patients with Long COVID-related cognitive impairment, we recommend that clinicians consider referral for rehabilitation interventions (commonly, speech therapy, neuropsychology, and/or occupational therapy) to address cognitive and/or functional problems. Attention to Long COVID-specific issues like PEM and posture may be needed, which may require rehabilitation clinicians with appropriate training.

Evidence is inadequate to recommend specific components of cognitive rehabilitation. For other conditions, commonly used approaches include psychoeducation on the impact of other factors such as sleep, mood, and pain on cognitive functioning; training or education on emotion regulation strategies to improve distress tolerance; modification of maladaptive self-messaging, diminish task and treatment avoidance; mindfulness practices to assist with attentional control; behavioral activation strategies to support cognitive function in the presence of fatigue; pacing strategies and activity scheduling; sleep hygiene strategies; and stress management. Cognitive rehabilitation may provide an avenue for patients to learn cognitive compensatory strategies regardless of whether neurocognitive evaluation reveals evidence for objective deficits.

Sleep interventions for sleep hygiene: Consider recommending sleep interventions as an option to patients with sleep concerns in patients with insomnia.

Soft belly breathing: Consider recommending soft belly breathing as an option to patients with reported high stress/mood/psychiatric symptoms.

Stress management: Consider recommending stress management as an option to patients with high stress/mood/psychiatric symptoms.

Nutrition: Consider nutrition counseling for patients with nutrition/dietary concerns.

When co-creating a personalized health plan, work with the patient and, if appropriate, other clinicians to optimize medications to balance therapeutic benefits with possible cognitive side effects. Address questions about supplement use, exercise, nutrition, sleep, and stress. Complementary modalities that may be of interest to Veterans with Long COVID-related cognitive impairment include:

- Mindfulness training, biofeedback, hypnotherapy, yoga, acupuncture, soft belly breathing, and/or autogenic training for improved stress management
- Sleep hygiene education for improving sleep/fatigue/post exertional malaise symptoms
- Nutrition education and/or coaching
- Exercise education and/or programming (e.g., use of local VA wellness center, tai chi, yoga, working with a Whole Health coach on developing an individualized plan); and
  pain management (e.g., CBT for chronic pain, acupuncture, chiropractic care, yoga, physical therapy).

For clinicians who offer these modalities, they may do so as per their usual practice. For clinicians who do not offer these modalities, they may refer to their local Whole Health service or team depending on local resources. In either case, remember that expertise in PEM in Long COVID is needed as this may affect the pacing of treatment.

Pharmacologic measures

Amantadine: We did not identify any completed trials of amantadine in Long COVID. Evidence in traumatic brain injury was inadequate, and applicability to Long COVID was unclear. Side effects such as orthostatic hypotension and syncope, dizziness, falls, impulse control and related disorders, livedo reticularis, neuropsychiatric symptoms (including confusion and disorientation), and withdrawal syndromes have been reported. Thus, we suggest not using amantadine for cognitive impairment in Long COVID until more evidence is available from randomized trials (see Amantadine Therapy for Cognitive Impairment in Long COVID).

Donepezil: No trials of donepezil in Long COVID were identified. No evidence for benefit has been demonstrated in relevant populations (e.g., mild traumatic brain injury). Harms of treatment in Long COVID are unknown. Thus, we suggest not using donepezil for cognitive impairment in Long COVID until more evidence is available.

Coenzyme Q: Inadequate evidence was found to inform a recommendation on cognitive symptoms.

Low-dose Naltrexone (LDN): There is uncertainty about the effectiveness of LDN in post-COVID cognitive impairment. Thus, no recommendation is currently offered. Other considerations for use of LDN appear in the Fatigue & Activity Intolerance and Pain sections below. In patients with concomitant pain or fatigue, cognitive impairment may improve with improvement in these symptoms.

Methylphenidate: Consider use in Veterans with deficits in processing speed and/or attention. Benefits may be similar to those seen in mild traumatic brain injury, but risks may be different (and potentially greater) due to sympathetic overdrive, which may occur in Long COVID. Individualized decision-making is needed. Before prescribing consider the risks of tachycardia, hypertension, diversion, irritability, sleep disturbances, especially in individuals with autonomic dysfunction or co-morbid cardiac disease. Collaborate closely with psychiatry if the Veteran has a diagnosis of bipolar disorder, anxiety disorder, or history of mania. We recommend against using methylphenidate to treat memory loss in the absence of deficits in processing speed or attention.

Table E. Guidance for cognitive impairment in Long COVID

Evidence-informed recommendations	Good practice statements
Blue boxes For the evidence underlying these recommendations see: Anderson et al. 2023[5].	**Tan boxes** Good practice statements for history-taking, physical exam, and commonly used noninvasive diagnostic tests are based on consensus determinations of useful and safe care.

History

Table E-1. Good practice statements

Topic	Details
Assessment of cognitive impairment symptoms	Obtain a detailed history of cognitive symptoms including: • Attention (brain fog, lost train of thought, concentration problems) • Processing speed (slowed thoughts) • Motor function (slowed movements) • Language (word finding problems, reduced fluency) • Memory (poor recall, forgetting tasks) • Mental fatigue (exhaustion, brain fog) • Executive function (poor multitasking or planning) Visuospatial domains (neglect) (7)

Table E-2. Evidence-informed recommendations

Topic	Recommendation	Details
Montreal Cognitive Assessment (MoCA) to identify cognitive impairment	Consider not using	The MoCA should not be used alone to identify cognitive impairment. In the presence of conditions such as sleep apnea, depression, and others, a low MoCA score may not reflect true cognitive impairment. A low MoCA score should prompt consideration of these other potential etiologies. Conversely, a patient with a "normal" score may still have cognitive impairment. In Veterans with known dementia and Long COVID symptoms, the MoCA may be used longitudinally to follow clinical trajectory.
Mini-Mental State Examination (MMSE)	No recommendation	Inadequate evidence was found to inform a recommendation.
Saint Louis University Mental Status (SLUMS)	No recommendation	Inadequate evidence was found to inform a recommendation.

[5] Anderson, J., S. Young, and K. Mackey, *Brief Evidence Assessment Guidance for Long COVID Clinics: Nervous System*. 2023, Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs: Washington, DC.

Physical exam

Table E-3. Good practice statements

Topic	Details

Components of the screening neurologic exam for face-to-face and virtual visits	*Face-to-face visit, assess:*
	• Vital signs
	• Gait:
	  ○ Test ability to walk independently
	  ○ Test tandem walking
	• Romberg
	• Muscle stretch reflexes (MSR): Knees
	• Motor: Check drift by holding arms up for 10 seconds
	• Any abnormal movements
	• Cranial nerves: Ask patient to smile, assess symmetry
	
	Virtual visit, assess:
	As above except
	• MSR (knees): Ask the patient to cross one leg over the other and tap their knee with the edge of their hand. Before testing gait, consider the safety of the environment and assess for symptoms that point to unsafe gait.

Evaluation

Laboratory testing

Table E-4. Good practice statements

Topic	Details
Routine laboratory testing	Consider the following laboratory studies on initial evaluation or if not obtained in the prior 3 months: • Complete blood count with differential • Complete metabolic panel including blood glucose, creatinine, magnesium, and liver studies (bilirubin, alanine aminotransferase, aspartate amino transferase, and alkaline phosphatase) • Thyroid stimulating hormone • C-reactive protein (CRP) (consider high-sensitivity CRP where available) • Erythrocyte sedimentation rate • Vitamin B1 (thiamine), vitamin B6 (pyridoxine), vitamin B9 (folate), vitamin B12 (cobalamin), vitamin D3 (cholecalciferol) • Hemoglobin A1c (35)
Additional laboratory testing	Additional laboratory testing should be offered based on the history and physical examination findings. For example, antinuclear antibody testing can be done if there is a history consistent with autoimmune symptoms.

Diagnostic testing

Table E-5. Good practice statements

Topic	Details
Computed tomography (CT) and magnetic resonance imaging (MRI)	The decision to order CT or brain MRI is based on usual practice. We did not review evidence about the diagnostic testing or therapeutic impact of neuroimaging in cognitive impairment in Long COVID (43).

Personalized health plan: management and treatment

Table E-6. Evidence-informed recommendations

Topic	Recommendation	Details
Cognitive rehabilitation	Consider use	Consider referral for rehabilitation interventions (commonly, speech therapy, neuropsychology, and/or occupational therapy) to address cognitive and/or functional problems. Attention to Long COVID-specific issues like pacing, post exertional malaise and posture may be needed, which may require rehabilitation clinicians to have additional training. No recommendation about specific cognitive rehabilitation interventions is offered due to inadequate evidence.

Topic	Recommendation	Details
Whole Health Systems interventions for sleep optimization, stress management, and nutrition optimization	Consider use	Sleep problems, high stress, mood symptom, and nutritional issues are common among patients with Long COVID. *Evidence was minimally adequate to inform specific recommendations. This recommendation was offered based on low risk of harm and because these interventions are commonly offered as part of the VA's Whole Health System program.*
Soft belly breathing	Consider use	Consider the use of soft belly breathing when high stress or affective symptoms are present. *Evidence was minimally adequate to inform a recommendation. This recommendation was offered based on low risk of harm and because this intervention is commonly offered as part of the VA's Whole Health System program.*
Amantadine	Consider not using	Evidence of effectiveness in traumatic brain injury was inadequate and applicability to Long COVID was unclear. Side effects such as orthostatic hypotension and syncope, dizziness, falls, impulse control and related disorders, livedo reticularis, neuropsychiatric symptoms (including confusion and disorientation), and withdrawal syndromes have been reported. Thus, we suggest not using amantadine for cognitive impairment in Long COVID until more evidence is available.
Donepezil	Consider not using	No evidence regarding the use of donepezil in Long COVID was identified. No evidence for benefit has been demonstrated in relevant populations such as mild traumatic brain injury. Harms of treatment in Long COVID are unknown. Thus, we suggest not using donepezil for cognitive impairment in Long COVID until more evidence is available.
Coenzyme Q10	No recommendation	Inadequate evidence was found to inform a recommendation.
Low-dose naltrexone (LDN)	No recommendation	There is uncertainty about the effectiveness of LDN in Long COVID cognitive impairment, but clinical trials are underway. Thus, no recommendation is currently offered in cognitive impairment. Refer to the Fatigue and Pain tables for these symptom-specific recommendations. In patients with concomitant pain or fatigue, cognitive impairment may improve with improvement in these symptoms.

Topic	Recommendation	Details
Methylphenidate	No recommendation	Consider use in Veterans with deficits in processing speed and/or attention. Benefits may be similar to those seen in mild traumatic brain injury, but risks may be different (and potentially greater) due to sympathetic overdrive which may occur in Long COVID. Individualized decision-making is needed. Before prescribing consider the risks of tachycardia, hypertension, diversion, irritability, and sleep disturbances, especially in individuals with autonomic dysfunction or co-morbid cardiac disease. Collaborate closely with psychiatry if the Veteran has a diagnosis of bipolar disorder, anxiety disorder, or history of mania. Recommend not using to treat memory loss in the absence of deficits in processing speed or attention.

FATIGUE AND ACTIVITY INTOLERANCE

Description of condition

Fatigue can be defined as “a feeling of weariness, tiredness, or lack of energy. It can be physical, cognitive, or emotional, mild to severe, intermittent to persistent, and affect a person's energy, motivation, and concentration.” (6) Activity intolerance typically refers to the inability to perform activities of daily living or difficulty with instrumental activities of daily living. This can be due to weakness, dyspnea, inability to remain upright for prolonged periods (orthostatic intolerance), or exhaustion associated with exertion. A specific type of exhaustion is known as post-exertional malaise (PEM), which is "the worsening of [fatigue and other] symptoms following even minor physical or mental exertion, with symptoms typically worsening 12 to 48 hours after activity and lasting for days or even weeks. (57)

Severity of fatigue may vary in patients with Long COVID. Anecdotally, some individuals may be able to perform all their activities of daily living (ADLs) and even continue working but must avoid most non-essential or recreational activities. Instead of participating in these “extra” activities, they may need the time to recover. Others may have such profound fatigue that they are no longer able to perform their ADLs on their own or may avoid/delay them altogether. It can be very difficult for these patients to leave their home. Then there are those that fall in between the two extremes. They may have difficulty with doing housework, shopping, preparing meals and require frequent breaks or naps throughout the day. Often, they have had to stop work or attending school because of their fatigue. It is not uncommon for patients to report having “good” days, where they have the energy to do more chores or recreational activities than usual, with this being followed by an increase in their fatigue and usually their other post-COVID symptoms as well.

Prevalence and course

In a 2021 systematic review of patients with recent COVID, persistent fatigue was reported in a substantial minority of patients (13–33%) at 16 to 20 weeks after symptom onset. (58) In a cohort of 1,497 European adults with a positive test for SARS-CoV-2, 17% reported fatigue over an average of 32 weeks of follow-up. (59) In this cohort, cognitive impairment and pain were also more common among individuals who reported fatigue, with a higher prevalence among groups who reported severe fatigue or post-exertional malaise, or who met the criteria for chronic fatigue syndrome (59) based on the DePaul brief questionnaire. (59),(60)

Etiology of Long COVID fatigue

Mechanisms that have been hypothesized to contribute to Long COVID pathophysiology include immune dysregulation, autoimmunity, microbiota disruption, blood clotting and endothelial dysfunction, and dysfunctional signaling in the brainstem or vagus nerve. (23)

Cause of symptoms

Among patients who are hospitalized due to COVID, prolonged bedrest during hospitalization may lead to weakness and fatigue; however, Long COVID fatigue is also seen in individuals who were never hospitalized and are therefore unlikely to have profound deconditioning. Pandemic-related stressors such as social isolation, abandoned relationships, and lack of employment may also contribute.

Fatigue can be a component of multiple diagnoses including cardiac, pulmonary, endocrine/metabolic abnormalities, anemia, rheumatologic causes, psychological conditions, sleep disorders, and medication or substance side effects. As noted in the section on Orthostatic Intolerance and Autonomic Dysfunction above, Long COVID can also be complicated by PEM (60), a core component of ME/CFS. Several studies examining patients with Long COVID and ME/CFS reported similar symptoms. (60),(15) Thus, assessing for PEM is important as patients may appear asymptomatic during an activity, only to have worsening of their symptoms hours or even days afterward. (6)

Clinical considerations and recommendations

Evidence-informed guidance for Long COVID fatigue and activity intolerance is summarized in Table F. For the evidence review underlying these statements, refer to the VA Evidence Synthesis Program Coordinating Center's Brief Evidence Assessment. Good Practice Statements for Long COVID fatigue and activity intolerance are summarized in Table F. (15)

History

It is important to review the patient's acute COVID course because factors such as a prolonged hospitalization or time on a ventilator contribute to fatigue. Ask if the fatigue has been improving or getting worse with time and if they have ever been able to resume their normal activities after COVID. Assess how patients respond to initiating and escalating activity and whether they have PEM. Further, when PEM and significant fatigue are noted, clinicians should investigate whether criteria for ME/CFS are met. While there are multiple criteria reported for diagnosis of ME/CFS, the Centers for Disease Control and Prevention (CDC) lists the 2015 Institute of Medicine diagnostic testing criteria, which requires three symptoms and at least one of two additional manifestations.

The three required symptoms are:

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of activity that:
    - Lasts for more than 6 months
    - Is accompanied by fatigue that is:
        - often profound
        - of new onset (not life-long)
        - not the result of ongoing or unusual excessive exertion
        - not substantially alleviated by rest
2. Post-exertional malaise
3. Unrefreshing sleep

At least one of the following two additional manifestations must be present:

1. Cognitive impairment
2. Orthostatic intolerance (32)

Further, the level of fatigue should be at least moderate intensity and present at least 50% of the time over at least 6 months.

Fatigue in Long COVID may be multifactorial. Ask about orthostatic intolerance, exercise intolerance, and dyspnea on exertion, which often occur in Long COVID patients who have fatigue. Also ask about sleep and stress. To assess sleep, ask about sleep hygiene, insomnia, untreated or inadequately treated apnea, and whether sleep is refreshing. Ask about stressors and mental health problems and record medications, supplements, and environmental exposures. Finally, it is critical to understand the functional impact of fatigue including effect on basic activities of daily living, instrumental activities of daily living, work, and hobbies, especially in comparison with the time before their illness.

Use of assessment tools

Using a standardized and validated tool for fatigue can be helpful to assess severity and trend symptoms over time. Based on lack of adequate literature in Long COVID, no existing, validated fatigue-specific assessment tool can be recommended (including, Fatigue Severity Score, Pittsburg Fatiguability Scale, Brief Fatigue Impact Scale, Neurobehavioral Symptom Index, and National Institute of Health and Care Excellence). However, it is good practice to assess fatigue using a standardized test based on severity and functional limitations. In VA, the modified Yorkshire COVID-19 Rehabilitation Scale was chosen as a component of the recommended VA Long COVID Questionnaire Batch

to assess Long COVID symptoms. It has a fatigue and PEM subsection. VA clinicians should consider using this instrument to support consistent care across the system.

Physical exam

Physical examination should include collection of vital signs—such as resting heart rate, blood pressure, pulse, and respiratory rate—as well as focused cardiopulmonary and neurologic exams. All patients should be assessed for oxygen saturation at rest and with exertion, especially if their acute COVID course included a period of hypoxia. Assess vitals in the sitting and standing position if the history elicited symptoms consistent with autonomic dysfunction. Options include the NASA Lean Test and active stand test, along with assessing for heart rate variability (detailed in the Orthostatic Intolerance and Autonomic Dysfunction section above).

When possible, exercise capacity should be objectively measured at initial and follow-up visits. (6), (10) Options include the 30-second sit-to-stand or 1-minute sit-to-stand tests, a 2-minute step test, a 6-minute walk test, or a 10-minute walk test. While many of these tests have been studied in previous conditions, there are no rigorous studies evaluating their performance in Long COVID. To minimize burden on clinicians and patients, we encourage use of the 2-minute step test during VA Video Connect visits. This instrument is included as part of the VA Long COVID Questionnaire Batch.

Evaluation

Laboratory testing

For new patients or those without laboratory testing in the 3 months prior to their visit, a list of routine laboratory tests to consider for all Veterans presenting with a new nervous system-related symptom after COVID is offered in Good Practice Statements (Table B).

Diagnostic testing

When fatigue and dyspnea are present, obtain chest imaging per local practice, such as chest X-ray or chest CT. Advanced cardiac imaging (e.g., cardiac MRI) has demonstrated abnormalities, sometimes many months after the initial infection. However, given the uncertainty regarding the clinical significance, these modalities cannot be routinely recommended.

Obtain an EKG and consider ambulatory EKG monitoring for palpitations, lightheadedness, or dizziness.

Personalized health plan: management and treatment

Non-pharmacologic measures

A main factor in assessing and treating fatigue in Long COVID is the contribution of other conditions. Co-morbidities related to sleep; mood; or the cardiopulmonary, endocrine, or immune systems should be considered. Veterans with anxiety, depression, stress, or poor sleep may experience increased fatigue. Veterans with Long COVID may also have comorbidities such as anosmia and dysgeusia leading to decreased appetite, nutrient intake, and total caloric intake, which could contribute to fatigue. Thus, it is important to assess and optimize nutritional status. This may include counseling or education on dietary strategies to decrease swings in blood glucose levels.

Treatments have been developed for fatigue and activity intolerance in conditions such as Chronic Obstructive Pulmonary Disease (COPD), cancer, fibromyalgia, lupus, and chronic Lyme disease. Given the similarities seen in some of these conditions and Long COVID, clinicians have tried similar approaches to manage Long COVID fatigue and activity intolerance, including PEM. Some examples include:

Paced activity and energy conservation: This technique emphasizes activity limitation based on heart rate or symptoms. It can be considered in Long COVID fatigue, with a disclaimer that the recommendation is based on weak evidence, and adverse events have not been adequately studied. If paced activity is recommended, patients with

fatigue due to post-exertional malaise can be counseled to decrease the total amount of activity and restrict exposure to PEM triggers. Once a patient is effectively pacing without triggering PEM, it may be possible to engage in very short periods of activity to increase stamina. This must be individualized for the patient's level of severity and PEM triggers. (61)

Graded exercise therapy: In the context of ME/CFS, the term "Graded Exercise Therapy" (GET) means a fixed incremental increase in physical activity or exercise. Graded exercise protocols are not recommended for patients with Long COVID with fatigue and ME/CFS features. Other guideline groups—National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and National Institute for Health and Care Excellence (NICE)—have recommended against it based on internal findings that suggest graded protocols may be harmful. (15),(23) Consider recommending alternative exercise protocols that allow more flexibility and customizability based on specific symptomatology and response to exercise intervention.

Pulmonary rehabilitation: This is a specific multi-component approach to dyspnea and exercise capacity in lung diseases, mainly COPD. (15) Given the potential for intense exercise to trigger fatigue exacerbations in those with PEM, caution is recommended when considering pulmonary rehabilitation for a Veteran experiencing fatigue with PEM-features in the presence of underlying pulmonary conditions known to benefit from pulmonary rehabilitation. If a Veteran has fatigue due to an underlying pulmonary condition, particularly COPD or an interstitial lung disease, pulmonary rehabilitation may be helpful.

Cognitive Behavioral Therapy (CBT): CBT is a widely used approach to treat depression, anxiety, bulimia, personality disorders, sexual dysfunction, and substance use disorders. It may be considered for fatigue in Long COVID, with an important caveat. This recommendation applies only to the specific intervention studied in Long COVID. (62) It is a based on a single, well-done randomized controlled trial in Long COVID, but has applicability limitations given highly selected patients and performance outside the United States. CBT should be delivered by a healthcare professional with appropriate training and experience working with Long COVID or similar conditions (e.g., ME/CFS), and/or an understanding of evidence-based behavioral management of PEM. Finally, clinicians should note that CBT is a multi-visit process. As part of a Whole Health Systems approach to Long COVID care, it is important to minimize appointment fatigue, which may cause excessive stress and worsen fatigue.

Acupuncture: Although evidence for use in pain in Long COVID is limited to case reports (63), it is widely used and effective for people with fibromyalgia and migraine, and has been studied in people who have ME/CFS. (64),(65) As a therapy with relatively low risk of side effects, a trial of acupuncture can be offered to Veterans with Long COVID fatigue.

Pharmacologic measures

No medications have been proven to be effective in treating Long COVID fatigue, but medications with effectiveness in other fatigue syndromes have been used.

Low-dose Naltrexone (LDN): Naltrexone is an opioid antagonist that, at doses of 25-50 milligrams per day, is used in the treatment of alcohol use disorder and opioid use disorder. (66) At lower doses (1–4.5 milligrams), naltrexone appears to have anti-inflammatory and analgesic properties. (67) Low-dose naltrexone has been used in Crohn's disease, fibromyalgia, premenstrual syndrome, and other conditions. (66) Side effects, such as bad dreams, can be minimized by titrating the dosage slowly. An uncontrolled study reported subjective improvement in energy, limitations in activities of daily living, pain, concentration, and sleep disturbance, but important limitations were noted. Another uncontrolled study, conducted in a Long COVID clinic based in the VA, was recently published. (68) Although evidence from controlled trials of LDN in Long COVID patients is insufficient to inform a recommendation for the treatment of fatigue, use of LDN can be considered in Veterans who meet the diagnostic testing criteria for ME/CFS or fibromyalgia. For patients with Long COVID fatigue who do not have co-morbid ME/CFS or fibromyalgia, additional evidence is needed before a recommendation for LDN can be offered.

Amantadine: Amantadine is used to treat fatigue in multiple sclerosis. (69),(70) A clinical trial is currently underway to study the effect of amantadine on Long COVID fatigue; however, at the time of this writing, inadequate evidence was found to inform a recommendation.

Co-enzyme Q10: Co-enzyme Q10 is a component of the electron transport chain in the mitochondrial membrane and is essential to aerobic respiration. It is naturally present in the human body. The VA ESP review identified only a single, negative, Phase 2 randomized trial of co-enzyme Q10 in Long COVID. (71) While this evidence was inadequate to support a recommendation to use co-enzyme Q10, it was not a strong enough study to exclude the possibility of a benefit. Due to a plausible mechanism of action and some positive studies in ME/CFS, additional research in Long COVID fatigue is recommended.

If using co-enzyme Q10 for Long COVID fatigue, consider a trial of up to 200 milligrams daily in the evening (due to concern for untoward side effects at higher doses) for at least 12 weeks. Also note that at the time of writing, co-enzyme Q10 is unavailable for prescribing through the VHA. Thus, Veterans would need to obtain it elsewhere, and no specific brands can be recommended. Patients who take glucose-lowering medications and wish to try co-enzyme Q10 should be counseled that co-enzyme Q10 may lower fasting glucose levels.(72) Co-enzyme Q10 may interact with medications such as warfarin and cancer treatments, and patients should be counseled about these potential interactions. (72),(73)

Modafinil: The mechanism by which modafinil might treat fatigue is unknown. It may act by modulating histaminergic, glutaminergic, hypocretin, or adrenergic activity while at the same time reducing gamma-aminobutyric acid (GABA) activity in certain parts of the brain. (74) It is FDA approved to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. In obstructive sleep apnea, is also indicated as an adjunctive treatment for obstruction. (75) Off label, it has been used to treat fatigue in patients with multiple sclerosis and post-stroke fatigue. (66) The ESPCC found only a single small study in Long COVID, which had some methodological limitations. It is also unclear whether evidence from other populations with fatigue (e.g., traumatic brain injury) can be applied in patients with Long COVID fatigue. Thus, inadequate evidence was found to inform a recommendation in Long COVID fatigue who do not report daytime sleepiness.

Table F. Guidance for fatigue and activity intolerance in Long COVID

Evidence-informed recommendations	Good practice statements
Blue boxes For the evidence underlying these recommendations see: Anderson et al. 2023[6].	**Tan boxes** Good practice statements for history-taking, physical exam, and commonly used noninvasive diagnostic tests are based on consensus determinations of useful and safe care.

History

Table F-1. Good practice statements

Topic	Details
Distinguish symptoms	Distinguish between symptoms of fatigue, orthostatic intolerance, exercise intolerance, and post-exertional malaise (PEM) to determine etiology and appropriate evaluation (6).
Post-exertional malaise (PM)	Assess how the patient responds to initiating and escalating activity and whether they have PEM (6).
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) assessment	Assess whether the patient meets criteria for ME/CFS (6).
Fatigue functional impact assessment	Assess for functional impact of fatigue (general/overarching) including effect on basic activities of daily living, instrumental activities of daily living, work, and hobbies (6).
Standardized assessment instrument for fatigue in Long COVID	Consider using the modified Yorkshire COVID-19 Rehabilitation Scale to assess fatigue. Important Information: It is Good Practice to assess fatigue using a standardized test based on severity and functional limitations. Inadequate evidence was found to inform a recommendation for a specific standardized assessment instrument for fatigue in Long COVID. The modified Yorkshire COVID-19 Rehabilitation Scale was chosen for inclusion in the VA Long COVID Questionnaire Batch through a modified Delphi consensus process among VA Long COVID clinicians (6). Its use supports consistent care across the VA system.

[6] Anderson, J., S. Young, and K. Mackey, *Brief Evidence Assessment Guidance for Long COVID Clinics: Nervous System*. 2023, Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs: Washington, DC.

Physical exam

Table F-2. Good practice statements

Topic	Details
Hypoxia	Assess for hypoxia at rest and with exertion as a cause of fatigue (especially if acute COVID illness was complicated by hypoxia) (76),(10).
Assessment of exercise capacity	Assess fatigue and activity intolerance using an objective measure of exercise capacity. Options include 30-second sit-to-stand, 1-minute sit-to-stand, 2-minute step, 6-minute walk test, or 10-minute walk test. Comparative performance of these tests in Long COVID is unknown. While the 6-minute walk test is often viewed as the "gold standard," the shorter 2-minute step test was included in the VA Long COVID Questionnaire Batch because it can be used in a variety of settings including virtual visits and to follow trends over time (6),(10).

Evaluation

Laboratory testing

Table F-3. Good practice statements

Topic	Details
Routine laboratory testing	Consider the following laboratory studies on initial evaluation or if not obtained in the prior 3 months (76): • Complete blood count with differential • Complete metabolic panel including blood glucose, creatinine, magnesium, and liver studies (bilirubin, alanine aminotransferase, aspartate amino transferase, and alkaline phosphatase) • Thyroid stimulating hormone level and free T4 • C-reactive protein (CRP) (consider high-sensitivity CRP where available) • Hemoglobin A1c • Vitamin B9 (folate), vitamin B12 (cobalamin), vitamin D3 (cholecalciferol) • Erythrocyte sedimentation rate
Additional laboratory testing	Additional laboratory testing should be offered based on the history and physical examination findings. • Creatine phosphokinase

Diagnostic testing

Table F-4. Good practice statements

Topic	Details
Electrocardiogram (EKG)	• Obtain an EKG if there is a significant burden of palpitations, lightheadedness, or dizziness • Consider ambulatory monitoring
Chest imaging	If fatigue and dyspnea are present, obtain chest imaging per local practice (chest X-ray or chest CT). (6)

Personalized health plan: management and treatment

Table F-5. Evidence-informed recommendations

Topic	Recommendation	Details
Paced activity and energy conservation	Consider use	Consider paced activity and energy conservation, with a disclaimer that the recommendation is based on weak evidence, and adverse events have not been adequately studied. If paced activity is recommended, patients with fatigue due to post-exertional malaise (PEM) can be counseled to decrease the total amount of activity and restrict exposure to PEM triggers. Once a patient is effectively pacing without triggering PEM, it may be possible to engage in very short periods of activity to increase stamina. This must be individualized for the patient's level of severity and PEM triggers. Even for patients who can tolerate such activity, the expected level of improvement may be modest (61).
Graded Exercise Therapy	Consider not using	This recommendation specifically applies to graded exercise therapy. In the context of ME/CFS, the term "Graded Exercise Therapy" (GET) means a fixed incremental increase in physical activity or exercise. Graded exercise protocols are not recommended for patients with Long COVID with fatigue and ME/CFS features. Other guideline groups (NIH, CDC, and NICE) have recommended against it based on internal findings that suggest graded protocols may be harmful. Consider recommending alternative exercise protocols that allow more flexibility and customizability based on specific symptomatology and response to exercise intervention.
Pulmonary rehabilitation	Consider not using	Graded exercise intervention (which may be a component of pulmonary rehabilitation) has not been helpful in ME/CFS. Thus, use caution when considering pulmonary rehabilitation for fatigue due to PEM in the presence of underlying pulmonary conditions. However, in the absence of PEM, pulmonary rehabilitation may be helpful if fatigue is due to pulmonary disease, particularly chronic obstructive pulmonary disease or interstitial lung disease.

Topic	Recommendation	Details
Cognitive Behavioral Therapy (CBT)	Consider use	Consider CBT for fatigue in Long COVID, with an important caveat. This recommendation applies only to the specific intervention studied in Long COVID. CBT should be delivered by a healthcare professional with appropriate training and experience working with Long COVID or similar conditions (such as ME/CFS), and/or an understanding of evidence-based behavioral management of PEM. Finally, clinicians should note that CBT is a multi-visit process. As part of a Whole Health System approach to Long COVID care, it is important to minimize appointment fatigue.(62)
Low-dose naltrexone (LDN)	Consider use	Consider use for fatigue among Veterans meeting criteria for ME/CFS or fibromyalgia in the setting of Long COVID. Side effects are reported to be minimal. Inadequate evidence was found to inform a recommendation for the treatment of fatigue in a general Long COVID population.
Amantadine	No recommendation	Inadequate evidence was found to inform a recommendation.
Co-enzyme Q10	No recommendation	Inadequate evidence was found to inform a recommendation in Long COVID. Due to a plausible mechanism of action and some positive studies in ME/CFS, additional research in Long COVID fatigue is recommended. If prescribing co-enzyme Q10 for Long COVID fatigue, consider a trial of up to 200 milligrams daily (due to concern for untoward side effects at higher doses) for at least 12 weeks. Also note that at the time of writing, co-enzyme Q10 is unavailable for prescribing through the VHA. Thus, Veterans would need to obtain it elsewhere, and no specific brands can be recommended.
Modafinil	No recommendation	Inadequate evidence was found to inform a recommendation in Long COVID fatigue. This recommendation does not apply to individuals reporting daytime sleepiness.

PAIN

Description of condition

Pain is described as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”(77) Viral infections have historically been known to trigger new pain conditions of all types. (78) Chest pain, gastrointestinal pain, musculoskeletal pain including costochondritis and arthralgias, myositis or myalgia, neuropathic pain due to new or worsening neuropathy, headaches, and diffuse generalized pain have all been described with Long COVID. (79)

Pain, including post-COVID pain, can be classified as nociceptive, musculoskeletal, neuropathic, or nociplastic. (80) Nociceptive pain is caused by actual or threatened focal tissue injury that is detectable on examination or diagnostic tests. Musculoskeletal pain is nociceptive pain that refers to acute or chronic pain that affects bones, muscles, ligaments, or tendons, including in the chest. Neuropathic pain is caused by a lesion or disease of the nervous system. In recent years, pain experts have introduced the term "nociplastic" for fibromyalgia, tension headache, and other pain syndromes that cannot be classified as “nociceptive pain” or “neuropathic pain” using currently available diagnostic testing technologies. Nociplastic pain is often multifocal and occurs along with other CNS-derived symptoms, such as fatigue, sleep, memory, and mood problems. (81)

Prevalence and course

An estimated 8-18% of individuals report persistent pain 1 year after COVID. (82) Estimates for muscle pain, joint pain, general body pain, nervous system-related pain, chest pain, and gastrointestinal pain vary widely among studies, in part from differences in patient populations and definitions of Long COVID. (79), (15) Nervous system-related pain included headache and neuropathic pain. At the time of our evidence review, no reviews described pain severity or impact of pain in Long COVID on function. (15)

Some Long COVID patients with chronic pain meet the diagnostic testing criteria for ME/CFS (15) (ICD-10 G93.32), POTS (ICD-10 G90.A), fibromyalgia (ICD-10 M79.7), neuropathy, or chronic headache attributed to systemic viral infection (International Classification of Headache Disorders 3rd edition- code 9.2.2.2). As discussed below, these co-occurring diagnoses influence the course and management of pain symptoms. See Orthostatic Intolerance and Autonomic Dysfunction and Fatigue above.

Overlap with ME/CFS: From 40% to 59% of patients with Long COVID may meet the case definition for ME/CFS, and symptoms common in ME/CFS may predominate in patients with Long COVID over time (15) (up to 2.5 years of follow-up). (83) The cardinal symptom of ME/CFS *is post-exertional malaise*, defined as worsening of symptoms after mental or physical exertion. (23) In published studies, patients followed in Long COVID clinics who meet the diagnostic testing criteria for ME/CFS demonstrated similar functional performance compared with patients with longstanding ME/CFS outside of Long COVID, and worse function than Long COVID patients who did not meet the criteria for ME/CFS. (15)

While ME/CFS symptoms can persist for years, it is not yet clear how long similar symptoms persist in people with Long COVID. (84),(83) In a series of 34 patients with Long COVID, some symptoms—fatigue, PEM, brain fog, irritable bowel symptoms, and unsteadiness—improve in the first year of Long COVID. (84) In that same study, however, pain symptoms did not improve in that time.

Autonomic Nervous System Dysregulation: POTS, and other autonomic conditions, are associated with persistent pain, especially chest and "coat-hanger pain" (i.e., "a charley horse kind of sensation, in the back of the neck and shoulder areas in the distribution that's like a coat hanger"). Some patients with POTS also experience brain fog and PEM. See Orthostatic Intolerance and Autonomic Dysfunction.

Myalgia and Joint Pain: Fibromyalgia-like pain and joint pain are also common in Long COVID. In a convenience sample of 100 Swedish adults who participated in online Long COVID groups, generalized pain was self-reported by 75% of participants, with most painful sites being chest, lower extremities, head/face, and migrating sites. About 40% (39/100) met the 2016 diagnostic testing criteria for fibromyalgia. Among the participants fulfilling the criteria, 23 were completely healthy prior to COVID. (85)

Etiology of Long COVID pain

The etiology of Long COVID pain is not fully delineated and multiple hypotheses exist. Potential mechanisms include direct virus-mediated tissue injury due to focal inflammatory cascade, viral entry into cells within the musculoskeletal and nervous system mediated by angiotensin-converting enzyme 2 receptor, mitochondrial dysfunction/oxidative stress/reduced antioxidants, defective neurotransmitter modulation, thrombo-inflammatory-mechanisms contributing to focal tissue injury, autoimmune processes, or inactivity. (23)

Cause of symptoms

Determining the cause of Long COVID pain is complicated by the fact that there are multiple pain phenotypes noted within Long COVID. Further, while new-onset pain can develop after COVID, there may also be exacerbation of pre-existing pain symptoms in the setting of altered activity levels, sleep, nutritional intake, or medication usage in the setting of acute COVID illness. It is also often not possible to determine the specifics of the pain at the early stage.

Clinical considerations and recommendations

Direct evidence about managing pain in patients with Long COVID is sparse.

Our starting point was a position paper describing how clinicians could use the history, physical examination, and additional evaluation to distinguish nociceptive, musculoskeletal, neuropathic, nociplastic, or mixed pain syndromes, because this information will guide the physical examination, diagnostic testing, and treatment recommendations. (86), (87) While the reliability of this approach has not been established, (86) we considered it to be a potentially useful framework for incorporating evidence into recommendations for practice. (87) For recommendations about evaluation and treatment of commonly encountered pain syndromes, we relied on evidence-informed, pre-COVID VA/DOD guidelines for headache (88) and myofascial pain (89) (90), and on pre-COVID, informal clinical review articles about chest pain (91), neuropathy (92) , muscle weakness (93), and fibromyalgia (89), some of which graded recommendations.

History

For all patients with pain

Ascertain the anatomic location of pain, its character, and exacerbating and alleviating factors including food, medication, activity, and positional changes. Characterize the onset and course in relation to acute COVID infection and reinfection. Note the severity of acute COVID, hospitalizations, treatments, and vaccines pertaining to COVID to determine whether the Veteran was at risk for post-intensive care syndrome (PICS), and whether prone positioning was utilized as a treatment strategy. PICS, which occurs after critical illness, is characterized by prolonged cognitive, physical, and mental health impairments. Prone positioning, which may be used to treat hypoxemia in acute COVID pneumonia, is a marker of greater clinical severity for acute COVID and may place Veterans at higher risk for focal neuropathies.

As with any patient who has neurologic symptoms, assess for red flags including new/severe/progressive weakness, sensory changes, changes in bowel or bladder function, “worst headache of life,” or new syncopal/pre-syncopal episodes. Red flags for headache and for nerve pain originating from the spinal cord or spinal root are discussed below, in the context of imaging studies.

Ask about sleep and mood disturbance; both are known to be associated with myofascial and nociplastic pain, as well as with Long COVID. Stress may exacerbate pain and therefore evaluating for stress management and triggers may be helpful in understanding why Veterans may be experiencing less pain or more pain on certain days. (94) Asking about nutrition and food security is helpful, as pain may be exacerbated by a lack of certain vitamins and nutrients, particularly in light of dietary changes related to acute illness and/or abrupt financial/social changes in the setting of acute illness and being unable to work. Assess patterns of substance use, including caffeine and alcohol (e.g., a longstanding pattern of heavy alcohol use may suggest risk of polyneuropathy).

Asking about a Veteran's exercise habits and exercise tolerance can help determine whether they are experiencing PEM. This is important because current activity level and the presence or absence of PEM will affect treatment and activity recommendations. In ME/CFS patients, programs of exercise and/or increasing physical activity that are commonly recommended for pain syndromes may cause "crashes" and, overall, lead to longer periods of pain and inactivity. See Fatigue section.

Assessing for current performance and recent changes in independence in mobility, basic or instrumental activities of daily living, vocational and avocational activities, and method of transportation may help with diagnosis and treatment. Changes in function, including mobility, basic or instrumental activities of daily living may help to clarify the severity and impact of the pain complaints, as well as give the clinician some insight into altered biomechanics due to activity change. As with all Long COVID symptomatic evaluations, it is important to take health equity considerations into account, as well as social stressors associated with the COVID pandemic.

Ask about associated symptoms that may be neurologic in nature, including autonomic symptoms (e.g., dizziness, lightheadedness, presyncope, syncope, orthostatic intolerance), cognitive dysfunction (e.g., brain fog, slowed processing rate, and memory impairment), cognitive fatigue, and changes in gait/walking.

Chest pain

For patients with Long COVID who have chest pain, focus the history on differentiating between musculoskeletal, cardiac, and pulmonary etiologies. (10) We recommend requesting in-person evaluation if the presentation, urgency of the symptom, and pattern of presentation suggest a potential cardiac or pulmonary cause. Musculoskeletal chest pain may be associated with activity changes, coughing, and positioning changes. These symptoms should raise suspicion for costochondritis or Tietze syndrome, somatic rib dysfunction (e.g., "slipping rib syndrome"), painful xiphoid syndrome, myofascial pain, fibromyalgia, thoracic radiculopathy, or Herpes zoster. Evaluation and treatment of these conditions is outside the scope of this guide. See Evaluation and Treatment of Musculoskeletal Chest Pain for pre-pandemic guidance about the evaluation and treatment of musculoskeletal chest pain. (91)

Headache

Ask all Veterans seen in a Long COVID clinic whether they are experiencing headache symptoms. (95) There is limited information in the literature specifically pertaining to evaluation and treatment of headache within Long COVID. For this reason, until further information is available, we recommend the VA-DoD Clinical Practice Guidelines for the Management of Headache (88) to assist in differentiating types of headache. The International Headache Society's third edition of the International Classification of Headache Disorders (ICHD-3) website lists diagnostic testing criteria for different headache types. If a Veteran's primary complaint is headache, we recommend the Migraine Disability Assessment Scale (MIDAS).

Neuropathic pain

Neuropathic pain in Long COVID may be caused by a focal neuropathy in relation to positioning during acute illness; critical illness neuropathy in those who experienced critical illness; a newly developed or worsening peripheral polyneuropathy in the setting of inflammation, or worsening of a pre-COVID condition contributing to neuropathy, dietary changes, or other causes. If there is concern for possible neuropathic pain, assess for risk factors such as a personal history of diabetes, chemotherapy, alcohol use, autoimmune disorders, peripheral nerve injury or

compression, and history of toxic exposures. (8) For more information on evaluation and treatment of neuropathic pain related to peripheral neuropathy see: Peripheral Neuropathy: Evaluation and Differential Diagnosis | AAFP. (92)

Muscle pain, joint pain, or back pain

In obtaining history for possible myopathic pain (muscular pain *and* weakness), assess for exposure to paralytics or steroid use during acute COVID illness, as these interventions can be risk factors for the development of myopathy. Additionally, determine if there is a history of pain/injury predating COVID. (8) If a patient with Long COVID is experiencing new joint pain or back pain, consider whether an autoimmune process is the underlying etiology. As such, determine if a patient is also experiencing rash, prolonged morning stiffness of more than an hour, objective joint swelling, vasculitic rashes, recurrent fever, night sweats, mouth sores or ulcers, cold/pale/blue/red fingers/toes combined with numbness/tingling/burning, sharp chest pain, or blurry/decreased vision. Review the medical record to look for unexplained cytopenias. (6)

Generalized myofascial pain

Multisite pain without weakness should prompt consideration for the possibility of general myofascial pain or fibromyalgia. (89) Fatigue, cognitive issues, and unrefreshing sleep are often components of these syndromes. Recent (2019) diagnostic testing criteria require pain at 6 or more painful sites (out of 9), moderate to severe sleep problems or fatigue, and symptoms present for at least 3 months. Many conditions may overlap fibromyalgia, including irritable bowel, vulvodynia, ME/CFS, tension headaches, migraine, low back pain, and restless legs.

Physical examination

A complete physical exam should evaluate for underlying neuropathic processes (central and peripheral), myopathic processes, myofascial involvement, and/or focal joint involvement. The physical examination can often differentiate the underlying processes (nociceptive, musculoskeletal, neuropathic, or nociplastic). For example, note that nociplastic joint pain (rather than nociceptive pain) is more frequently experienced with palpation over the tendons and bursae rather than the joint lines themselves. In addition, assessing gait and functional tasks such as sit to stand can uncover altered biomechanics that might predispose Veterans to the development of new aches and pains.

Chest pain

To examine a patient for musculoskeletal causes of chest pain, evaluate the anterior and posterior chest wall for swelling, erythema, heat, or tenderness to palpation (including the sternum, costochondral junction, intercostals, and evaluation for trigger points), and perform a neurologic examination to rule out compression of nerve roots originating in the lower cervical or thoracic segments (sensation, strength, and reflexes). (91) Keep in mind that evaluation of the thoracic dermatomes requires sensory examination of the anterior and posterior chest. Somatic rib dysfunction may be a cause of chest pain and occurs when the movement or position of one or several ribs is altered or disrupted. Articular or myofascial restrictions of the ribs can directly impede respiratory motion and indirectly contribute to postural abnormalities, and may be caused by poor posture or cough, both of which may occur within Long COVID. Physical examination to evaluate for somatic rib dysfunction includes inspecting the position and symmetry of the ribs, evaluating for an elevated or depressed rib on one side compared to the other. This finding may be noted only during inhalation (noting that one side is freer to move than the other ribs, or more restricted than the others), or only during exhalation. Palpation of the painful area during inhalation and exhalation may also assist with noting a more prominent rib, and palpation of the intercostals in the region may also reproduce pain. For more information on evaluation of musculoskeletal chest pain see Evaluation and Treatment of Musculoskeletal Chest Pain.

Observe gait and functional tasks such as sit-to-stand as Long COVID symptoms can alter gait and movement patterns to create altered biomechanics, predisposing Veterans to the development of new aches and pains.

When possible, use standardized measures to track changes in symptoms and examination over time. We recommend utilizing the VA Long COVID Questionnaire Batch, which includes a 2-minute step test as well as

questions about pain. If a Veteran's primary complaint is pain, we additionally recommend the use of the Pain, Enjoyment of Life and General Activity Scale (PEG scale).

Evaluation

The choice of laboratory, imaging, or other studies for different types of pain should follow usual practice. In the absence of evidence specific to Long COVID, the best practice recommendation is to approach each pain complaint as one would in any other patient population, keeping in mind the most common underlying etiologies of pain within Long COVID, with particular consideration for the possibility of POTS, ME/CFS, and/or fibromyalgia.

Laboratory testing

For new patients or those without laboratory testing in the 3 months prior to their visit, a list of routine laboratory tests to consider for all Veterans presenting with a new nervous system-related symptom after COVID is offered in Good Practice Statements (Table B).

Additional laboratory testing orders should be based on the history, type of pain, and underlying comorbidities. If the patient has muscle, joint, and back pain and the history and examination raise concern for an autoimmune process, consider antinuclear antibodies (ANA), serum protein electrophoresis and immunofixation, and rheumatoid factor/anticitrullinated peptide antibodies. Typically, if these tests are abnormal *and* there are clinical signs and symptoms of a possible autoimmune process, further evaluation may be performed in conjunction with evaluation by a rheumatologist.

There are no routinely recommended laboratory studies if a patient is experiencing musculoskeletal chest pain. If the Veteran is presenting for a primary complaint of headache within Long COVID, laboratory testing is not routinely recommended.

For suspected neuropathic pain, which may include symptoms like weakness, numbness, tingling, allodynia, and hypersensitivity, serum protein electrophoresis with immunofixation may additionally be useful in evaluation for paraproteinemia as a potential contributor to neuropathy. Note that laboratory evaluation may be normal even if a Veteran is experiencing clinical neuropathic signs and symptoms. In this situation, if there is high suspicion, further evaluation may be warranted (see Table G below).

For suspected myopathy or myositis, consider creatine kinase (CK), aldolase, and/or lactate dehydrogenase.

If the history and physical examination suggest general myofascial pain or fibromyalgia (nociplastic pain), laboratory testing is not routinely recommended. (89) Key findings to support a clinical diagnosis include characteristic symptoms and associated symptoms or conditions, absence of muscle weakness, absence of synovitis on joint exam, and normal basic laboratory studies.

Diagnostic testing

We did not systematically review the literature regarding imaging or other diagnostic testing for pain in patients with Long COVID. The recommendations below are based on relevant pre-pandemic guidance statements for imaging of musculoskeletal chest pain (Evaluation and Treatment of Musculoskeletal Chest Pain; VA/DoD Clinical Practice Guideline for Management of Headache; Peripheral Neuropathy: Evaluation and Differential Diagnosis | AAFP). Further research is needed to the characterize the performance of imaging tests and other diagnostic testing studies in Long COVID-related pain.

Key points from these external guidance documents (Table G) are discussed below.

TABLE G. Key points in the evaluation of pain complaints from external resources.

Symptoms	Imaging	Additional testing
Musculoskeletal chest pain (91)	Not routine. Chest radiograph if there is chest wall tenderness and concern for fracture. MRI or Ultrasonography if patient doesn't respond to conservative treatment and there is concern for muscle injury, thoracic radiculopathy.	None
Headache (88)	Not routine. Get MRI if red flags for headache are present.	None
Neuropathic pain (92)	Not routine. In cases of potential polyradiculopathy, plexopathy, or radiculoplexus neuropathy, MRI may help in localizing an atypical neuropathy. In particular, get an MRI or CT if Red Flags for spinal cord or spinal root involvement are present.	Neuropathy: Electrodiagnostic studies in certain situations
Muscle weakness, joint pain, or back pain (93)	Depends on site, history, and exam findings.	Myopathy: Electrodiagnostic studies in certain situations
Generalized myofascial pain (89),(90)	When the history and physical exam strongly suggest fibromyalgia, and no muscle weakness or neuropathy is present, imaging is not routinely recommended.	None

1. Red flags for headache. Consider obtaining MRI if “red flags” are present:

- Systemic symptoms, illness, or condition (e.g., fever, chills, myalgias, night sweats, weight loss or gain, cancer, infection, giant cell arteritis, pregnancy or postpartum, or an immunocompromised state – including Human Immunodeficiency Virus)
- Neurologic symptoms/signs (e.g., confusion, impaired alertness or consciousness, changes in behavior or personality, diplopia, pulsatile tinnitus, focal symptoms or signs, meningismus, seizures, ptosis, proptosis, or pain with eye movements)
- Onset (e.g., abrupt or "thunderclap" where pain reaches maximal intensity immediately or within minutes after onset; first ever, severe, or "worst headache of life")
- Older onset (age older than 50 years)
- Progression or change in pattern (e.g., in headache frequency, severity, clinical features)
- Precipitated by Valsalva (e.g., coughing, bearing down)
- Postural aggravation or papilledema

2. Red flags for neuropathy. MRI or CT may be useful if there are red flag symptoms of spinal cord or spinal root involvement. (96) These include:

- Urinary retention, urinary or fecal incontinence
- Saddle anesthesia
- Changes in rectal tone
- Severe/progressive neurologic deficits
- Persistent fever
- Immunosuppression
- History of IV drug use
- History of osteoporosis
- Chronic use of corticosteroids
- Recent trauma
- History of cancer with new onset pain
- Unexplained weight loss

3. Indications for electrodiagnostic studies. In patients with neuropathic pain (92) or in patients with nociceptive pain accompanied by muscle weakness, (93) electrodiagnostic studies may be indicated. For neuropathy, electrodiagnostic studies are indicated if there is a rapidly progressive course, if complaints or examination findings are asymmetric, or if there are predominant motor or autonomic symptoms. Electrodiagnostic studies help with localizing a neuropathic lesion and with assessment of timeline of start of a neuropathic process. They can also help with determining prognosis as well as treatment. Additionally, if the initial laboratory work-up is normal, which is often the case, and symptoms are persistent and bothersome, electrodiagnostic studies may be useful for assisting with determination of an underlying diagnosis. If findings are classically consistent with a focal neuropathy or length-dependent sensorimotor peripheral polyneuropathy in a Veteran with known risk factors, and treatment planning is known, electrodiagnostic testing may not be necessary. For more details refer to AAFP's guidance on Peripheral Neuropathy: Evaluation and Differential Diagnosis.

4. If there is joint swelling, arthralgia, or another focal nociceptive complaint, we suggest referring to General Musculoskeletal Care Topics for guidance on imaging and diagnostic testing. See also AAFP's guidance on Muscle Weakness in Adults: Evaluation and Differential Diagnosis. (93)

Personalized health plan: management and treatment

Referrals

If the evaluation of neuropathic pain including specialized laboratory testing and electrodiagnostic evaluation is unrevealing, consider referral to neurology and/or PM&R physician. If the evaluation of nociceptive pain is unrevealing, consider referral to a neuromuscular specialist and/or rheumatology for further work-up, which may include MRI or ultrasonography of muscle tissue, and/or muscle biopsy. (97) For headache in Long COVID, consider a neurology referral if the diagnosis or etiology of the headache is unclear or if headaches are refractory to treatment or progressively worsening.

Non-pharmacologic measures

A multimodal approach is often needed to support patients in their Long COVID recovery and for the treatment of chronic pain. (9) This may entail participation in rehabilitation programs, pharmacological and supplement therapies for specific symptoms, and referrals to a multidisciplinary treatment team. Because patients with Long COVID may present with overlapping and related symptoms, a treatment team offering a multidisciplinary approach can be invaluable for care coordination. For patients with Long COVID-related pain that is affecting gait, mobility, or activities of daily living, input from specialists in PM&R, neurology, pain management, occupational therapy, physical

therapy, and CBT may be considered. These team members should preferably be familiar with treating sensorimotor deficits, autonomic dysfunction, and PEM. PM&R physicians diagnose and manage pain complaints (including medication management, interventional procedures such as injections, and coordinating therapy intervention), perform biomechanical evaluations, and lead multimodal care teams for medically complex patients with the overall focus on improving quality of life and function. If progressive neuropathy, weakness, or gait instability are present, neurologists are invaluable in adding to assessment and diagnosis of neuromuscular conditions, especially when the diagnosis is unclear. If pain is severe or does not respond to first-line medication therapy, pain management specialists can be helpful in managing chronic pain, including complex pharmacologic treatment plans and interventional procedures.

If there is functional impairment, physical therapy or occupational therapy may be useful. Case reports in patient with Long COVID have described improvements in function and quality of life after physical therapy. (98) Refer to physical therapy for strengthening, balance retraining, gait training, stretching (muscular and neural tension), and patient education on pain. Additionally, when appropriate, physical therapy can perform dry needling and utilize heat modalities and therapeutic ultrasound. Occupational therapy can offer desensitization, fine motor coordination, functional skills training (including safety and compensatory strategies for completion of activities of daily living), stretching (muscular and neural tension), and patient education on pain. In other chronic pain populations, CBT for pain is helpful. (96), (99), (90) Other referrals to consider include tai chi or formal exercise prescription and orthotics if braces or compression garments are needed for joint protection or stabilization.

Finally, Whole Health referral can also be useful when a Veteran may benefit from lifestyle coaching, assistance with forming healthcare goals, and to provide additional support. Because patients with Long COVID-related pain may have features consistent with ME/CFS or POTS, we advise caution in prescribing exercise and physical therapy, especially when the patient reports a history of "crashes" after physical, cognitive, or emotional exertion, described as symptom exacerbation that extends beyond 24 hours after the exertional activity (PEM). On the other hand, clinical experience in ME/CFS patients may not apply to Long COVID patients with pain without ME/CFS features. Thus, research is needed in this population. When prescribing exercise for pain in patients who are experiencing PEM or ME/CFS features, consider recommending paced activity and energy conservation as an option, with a disclaimer that the recommendation is based on weak evidence and that adverse events have not been adequately studied. Pacing is an individualized approach to energy conservation and management used to minimize the frequency, duration, and severity of PEM. (61) If paced activity is recommended, patients with pain due to PEM can be counseled to decrease the total amount of activity and restrict exposure to PEM triggers. Once a patient is effectively pacing without triggering PEM, it may be possible to engage in very short periods of activity to increase stamina. This must be individualized for the patient's level of severity and PEM triggers. Even for patients who can tolerate such activity, the expected level of improvement may be modest.

Musculoskeletal chest pain: We did not systematically review non-pharmacologic treatments for musculoskeletal chest pain in Long COVID. Consider the approach recommended in the review article: Evaluation and Treatment of Musculoskeletal Chest Pain, which describes non-pharmacologic treatment for musculoskeletal chest pain in the pre-pandemic era. Treatments suggested include focal heat and ice compresses; physical therapy referral for manual therapy with stretching exercises, and to address postural and ergonomic factors. If trigger points are present, referral to a qualified clinician for trigger point injections may be useful.

Headaches: Non-pharmacologic treatment options for headache include acupuncture, Cognitive Behavioral Therapy, biofeedback, mindfulness-based therapy, dietary trigger avoidance, and dry needling. Treatment options for tension-type and migraine-type headaches include physical therapy, aerobic exercise, and progressive strength training. We did not systematically review these treatments in Long COVID-related headache. Until there is better evidence in patients with Long COVID, we recommend clinicians approach the treatment of headache as they would outside of the Long COVID population, considering the type (migrainous, tension, or mixed-type) and comorbidities. We recommend using the VA/DoD Headache Guidelines for therapeutic treatment approaches: VA/DoD Clinical Practice

Guideline for Management of Headache. Consider a neurology referral if the clinician is unsure of the diagnosis/etiology of the headache, or if headaches are refractory to treatment or are progressively worsening.

Neuropathic pain: We did not systematically review non-pharmacologic treatments for neuropathic pain in Long COVID, and guidance from the pre-pandemic era is limited. Further research is recommended. In the absence of recommendations specific to Long COVID-related neuropathic pain, clinicians may consider the general recommendations for non-pharmacologic treatment of Long COVID pain (e.g., multimodal care).

Nociceptive pain including myopathic, joint, and back pain: We did not systematically review non-pharmacologic treatments for myopathy. If there is a focal nociceptive complaint, including joint swelling or arthralgia, treating clinicians may refer to Topic | AAFP for guidance. If trigger points are present on exam, injections or dry needling may be beneficial. These procedures may be performed by PM&R, pain medicine, rheumatology, and physical therapists, although this may vary by site. Clinicians may consider an interventional pain referral if they suspect a premorbid underlying disease process such as facet arthropathy or radiculitis may have been exacerbated by Long COVID.

Nociplastic pain including general myofascial pain and fibromyalgia: We did not systematically review non-pharmacologic treatments for nociplastic pain in Long COVID. Clinicians may refer to VA/DoD Clinical Practice Guideline for Management of Chronic Multisymptom Illness, which reviewed the treatment of fibromyalgia in the pre-pandemic era. Note that the recommendations regarding exercise were not evaluated in the context of Long COVID, and therefore exercise recommendations in these guidelines are not endorsed for patients with Long COVID. Pertinent non-pharmacologic recommendations from the guidelines include:

- Cognitive Behavioral Therapy for symptoms consistent with fibromyalgia
- Mindfulness-based therapies such as mindfulness-based stress reduction and meditation awareness training for symptoms consistent with fibromyalgia
- An emotion-focused therapy for symptoms consistent with fibromyalgia. Examples of emotion-focused therapy include emotional awareness and expression therapy and attachment-based compassion therapy. Patients must be able to cognitively participate in this specific treatment and process the material being taught.
- Yoga or tai chi for symptoms consistent with fibromyalgia
- Acupuncture as part of the management of symptoms consistent with fibromyalgia

The guidelines found insufficient evidence to recommend for or against the use of biofeedback modalities; manual musculoskeletal therapies (e.g., spinal manipulative therapy, spinal mobilization, and osteopathic manipulation); relaxation therapy (e.g., manual muscular relaxation therapy, breathwork, autogenic therapy relaxation approach, and functional relaxation); guided imagery or hypnosis; or deep tissue massage in patients with symptoms consistent with fibromyalgia.

Pharmacologic measures

Medications may be prescribed as part of a multifaceted treatment approach for Long COVID-related pain. However, it is important to consider the impact of polypharmacy and medication side effects that may exacerbate other Long COVID symptoms. There is limited evidence to guide the medical management of Long COVID-related pain. Until more evidence is available, clinicians may approach the medical management of Long COVID-related pain as they would similar chronic pain conditions outside of Long COVID. The VA/DoD Opioid Therapy for Chronic Pain Guidelines recommend against the long-term use of opioid medications for the management of chronic pain. (100)

Chest pain: Consider the approach recommended in the review article describing treatment of musculoskeletal chest pain in the pre-pandemic era: Evaluation and Treatment of Musculoskeletal Chest Pain. First-line medications include non-steroidal anti-inflammatory drugs, unless contraindicated.

Headache: We did not systematically review pharmacologic treatments for headache in Long COVID. In the absence of recommendations specific to Long COVID-related headache, clinicians may approach the treatment of headache as they would outside of the Long COVID population, considering the type (migrainous, tension, or mixed-type) and comorbidities. Additional research in this area is needed. Until more evidence is available, we recommend the VA/DoD Headache Guidelines for therapeutic treatment approaches: VA/DoD Clinical Practice Guideline for Management of Headache. Clinicians might also consider the presence of comorbid Long COVID symptoms (e.g., POTS, cognitive symptoms, or fatigue) in choosing treatments for headache. For example, a β blocker might do double duty for POTS and migraine. The VA/DoD guidelines do not offer recommendations regarding the use of co-enzyme Q10 for headache, which was of particular interest of the Long COVID Community of Practice.

Neuropathic pain: We did not systematically review the literature examining medications for the treatment of Long-COVID related neuropathic pain. Pre-pandemic guidelines emphasize that there is strong evidence for tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors (SNRIs), and GABA analogues, and weak evidence for lamotrigine, lacosamide, oxcarbazepine, lidocaine patches, and/or topical capsaicin. (101),(102) Until more evidence is available, we refer treating clinicians to: Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary.

Nociceptive pain including myopathic, joint, and back pain: We did not systematically review medications for the treatment of nociceptive pain. If there is concern for a myopathic process, consider referral to a neuromuscular specialist and/or rheumatology for management. If there is a focal nociceptive complaint, including joint swelling/arthralgia, treating clinicians may refer to General Musculoskeletal Care Topics for guidance.

Nociplastic pain including general myofascial pain and fibromyalgia: We did not systematically review medications for nociplastic pain in Long COVID, including low dose naltrexone. Clinicians may refer to VA/DoD Clinical Practice Guideline for Management of Chronic Multisymptom Illness, which reviewed the treatment of fibromyalgia in the pre-pandemic era. Pertinent pharmacologic recommendations from the guideline include a trial of serotonin-norepinephrine reuptake inhibitors or pregabalin. The guidelines found insufficient evidence to recommend for or against mirtazapine, selective serotonin reuptake inhibitors, or amitriptyline. The guidelines recommend against offering nonsteroidal anti-inflammatory drugs for the treatment of chronic pain that may be related to fibromyalgia.

Investigational treatments for Long COVID-related pain

To date, there is no strong evidence to support the use of supplements, gene therapy, laser intervention, electromagnetic stimulation, hyperbaric oxygen, or other investigational interventions in the treatment of Long-COVID related pain. (87) Some research in these areas is ongoing.

Table H. Guidance for pain in Long COVID

Good practice statements
Tan boxes Good practice statements for history-taking, physical exam, and commonly used noninvasive diagnostic tests that based on consensus determinations of useful and safe care.

History

Table H-1. Good practice statements

Topic	Details
Chest pain history elements	Focus the history on differentiating between musculoskeletal, cardiac, and pulmonary causes of chest pain. Recommended history for musculoskeletal chest pain can be found here: Evaluation and Treatment of Musculoskeletal Chest Pain. Consider the following causes of musculoskeletal chest pain (91): • Costochondritis or Tietze syndrome • Somatic rib dysfunction (such as "slipping rib syndrome") • Painful xiphoid syndrome • Muscle strain of intercostal muscles, pectoralis muscles, internal and external oblique muscles, and serratus anterior muscles • Myofascial pain • Fibromyalgia • Precordial catch syndrome • Thoracic radiculopathy • Herpes zoster If there is concern for a potential cardiac or pulmonary cause, perform an in-person evaluation.
Headache history elements	Obtain a headache history as recommended in the VA/DoD Clinical Practice Guidelines for Management of Headache: VA-DoD Clinical Practice Guidelines for the Management of Headache (35). Additional reference material: Long COVID headache | The Journal of Headache and Pain
Neuropathic pain history elements	If there is concern for neuropathic pain, assess for a personal history of diabetes, chemotherapy, alcohol use, autoimmune disorders, peripheral nerve injury or compression, and history of toxic exposures. Additionally, assess for prolonged hospital stay, hospital stay including intensive care unit stay and/or prone positioning (8). For more detailed recommendations, see Peripheral Neuropathy: Evaluation and Differential Diagnosis | AAFP.
Myopathic, myofascial, or musculoskeletal pain history elements	Assess for prolonged hospital stay, intensive care unit stay, and duration of hospitalization or bed rest, and for exposure to paralytics or steroids during acute COVID illness. Determine if there is a history of pain or injury predating COVID (8),(76),(6).
Nociplastic pain history elements	If nociplastic pain is present, ask about symptoms of fibromyalgia, dysautonomia, POTS, or ME/CFS, keeping in mind that pain may be a symptom of dysautonomia. Refer to Autonomic Dysfunction and Fatigue for further details (89).

Topic	Details
Standardized pain assessments	Assess pain symptoms at initial and follow-up visits using tools such as (35): • VA Long COVID Questionnaire Batch • Pain, Enjoyment of Life, and General Activity Scale (PEG scale) • MIDAS (if headache) (MIDAS)

Physical exam

Table H-2. Good practice statements

Topic	Details
Routine physical exam elements	When pain is present, perform a musculoskeletal and neurologic examination (35).
Musculoskeletal chest pain exam elements	If there is concern for a musculoskeletal contribution of chest pain, evaluate the anterior and posterior chest wall for swelling, erythema, warmth, or tenderness to palpation (sternum, costochondral junction, intercostals, evaluation for trigger points). Perform a neurologic examination to rule out compression of nerve roots originating in the lower cervical or thoracic segments (sensation, strength, reflexes) (91). • For more information on evaluation of musculoskeletal chest pain see here: Evaluation and Treatment of Musculoskeletal Chest Pain.

Evaluation

Laboratory testing

Table H-3. Good practice statements

Topic	Details
Routine laboratory testing	Consider the following laboratory studies on initial evaluation if not obtained in the prior 3 months (8),(10): • Complete blood count with differential • Complete metabolic panel including blood glucose, creatinine, magnesium, and liver studies (bilirubin, alanine aminotransferase, aspartate amino transferase, and alkaline phosphatase) • Thyroid stimulating hormone • C-reactive protein (CRP) (consider high-sensitivity CRP if available) • Erythrocyte sedimentation rate • Vitamin B6 (pyridoxine), vitamin B9 (folate), vitamin B12 (cobalamin), vitamin D3 (cholecalciferol), Hemoglobin A1c
Additional laboratory testing	Additional laboratory testing should be offered based on the history and physical examination findings:

Topic	Details
Additional laboratory testing (Continued)	• If concern for neuropathic pain: serum protein electrophoresis with immunofixation • If concern for myopathy/myositis: creatine kinase (CK), aldolase, lactate dehydrogenase • If concern for possible autoimmune disease: anti-nuclear antibodies, serum protein electrophoresis and immunofixation, rheumatoid factor/anticitrullinated peptide antibodies • If concern for myofascial pain or fibromyalgia, laboratory testing is not routinely recommended.

Diagnostic testing

Table H-4. Good practice statements

Topic	Details

Headache red flags for imaging	Consider imaging if there are headache red flags, as recommended by VA-DoD Headache Pocket Card (88):
	• Systemic symptoms, illness, or condition
	  ○ Fever
	  ○ Chills
	  ○ Myalgias
	  ○ Night sweats
	  ○ Weight loss or gain
	  ○ Cancer
	  ○ Infection
	  ○ Giant cell arteritis
	  ○ Pregnancy or postpartum
	  ○ An immunocompromised state (including HIV)
	• Neurologic symptoms/signs
	  ○ Confusion
	  ○ Impaired alertness or consciousness
	  ○ Changes in behavior or personality
	  ○ Focal neurologic symptoms or signs
	  ○ Meningismus
	  ○ Seizures
	  ○ Ptosis
	  ○ Proptosis
	  ○ Pain with eye movements
	• Abrupt or "thunderclap" onset where pain reaches maximal intensity immediately or within minutes after onset; first ever, severe, or "worst headache of life"
	• Age ≥50 years

Topic	Details
Headache red flags for imaging (Continued)	• Progression or change in pattern (including headache frequency, severity, clinical features) • Precipitated by Valsalva (coughing, bearing down) • Postural aggravation and/or papilledema
Peripheral neuropathy	If there is concern for a focal or peripheral neuropathy contributing to pain in Long COVID, consider the following as recommended by the American Academy of Family Physicians (Peripheral Neuropathy: Evaluation and Differential Diagnosis | AAFP) (92): ▪ Electrodiagnostic studies only if symptoms are worrisome (acute onset, asymmetric, predominant motor or autonomic symptoms, rapidly progressive course) or if initial laboratory evaluation is normal but symptoms persist ▪ Imaging should not be routinely ordered to aid in the diagnosis of peripheral neuropathy. In suspected polyradiculopathy, plexopathy, or radiculoplexus neuropathy, magnetic resonance imaging may help in localizing an atypical neuropathy If initial evaluation is unrevealing, consider referral to neurology and/or physical medicine & rehabilitation.
Myopathic pain diagnostic testing	If myopathic pain is suspected (muscle pain and weakness), consider the following recommended by the American Academy of Family Physicians (Muscle Weakness in Adults: Evaluation and Differential Diagnosis) (93): ▪ Electrodiagnostic studies if the diagnosis is unclear after a history, physical examination, and targeted laboratory evaluation If initial evaluation is unrevealing, consider referral to a neuromuscular specialist and/or rheumatology for further work-up, which may include MRI or ultrasonography of muscle tissue, and/or muscle biopsy.

Personalized health plan: management and treatment

Table H-5. Good practice statements

Topic	Details
General principles of pain management in Long COVID	• Use a multidisciplinary approach to treatment that includes both pharmacologic and nonpharmacologic approaches (8),(103). • Because of the high prevalence of PEM among patients with Long COVID, exercise protocols should allow more flexibility and customizability based on specific patient symptomatology and response to exercise intervention. Avoid Graded Exercise Therapy (i.e., a fixed incremental increase in physical activity or exercise) because of harms. (see Fatigue Section) • Refer to AAFP for diagnosis-specific treatment guidance for diagnosis-specific treatment guidance if there is a focal nociceptive complaint, including joint swelling/arthralgia. • The guidelines do not offer recommendations regarding the use of co-enzyme Q10 for Long COVID pain. • VA/DoD Opioid Chronic Pain Guidelines recommend against the long-term use of opioid medications for the management of chronic pain (100).

Symptom-specific recommendations

Table H-6. Good practice statements

Topic	Details
Treatment of neuropathic pain	Pharmacologic treatments recommended in conditions such as diabetic polyneuropathy may be useful as part of a multifaceted approach to neuropathic pain in Long COVID, as recommended by Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary (101): • First-line options include gabapentin, pregabalin, duloxetine, nortriptyline, amitriptyline, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors • Second-line options include lamotrigine, lacosamide, oxcarbazepine, lidocaine patch, and topical capsaicin.
Treatment of musculoskeletal chest pain	In the treatment of musculoskeletal chest pain in Long COVID, consider the approach recommended in the review article: Evaluation and Treatment of Musculoskeletal Chest Pain (91): • Reassurance • Pain control via non-steroidal anti-inflammatories if not contraindicated, application of local heat and ice compresses • Physical therapy for manual therapy with stretching exercises, and to address postural and ergonomic factors • Referral to a qualified clinician for trigger point injections if trigger points are present
Treatment of headache	Consider a neurology referral for post-COVID headache if the diagnosis or etiology is unclear or if headaches are refractory to treatment or progressively worsening. VA/DoD Headache Pocket Card

Treatment of fibromyalgia pain	A VA/DOD Practice Guideline for Management of Chronic Multisymptom Illness (CMI) provided guidance for the treatment of fibromyalgia in the pre-COVID era. A summary of recommendations that may be relevant to fibromyalgia in Long COVID are presented here. Guidance regarding exercise is not endorsed in the context of Long COVID:
	Clinicians can consider the following interventions for pain consistent with fibromyalgia in Long COVID based on pre-COVID guidance:
	• Cognitive Behavioral Therapy
	• Mindfulness-based therapies
	  ○ Examples of mindful-based therapies include mindfulness-based stress reduction (MBSR) and meditation awareness training (MAT)
	• Emotion-focused therapy
	  ○ Examples of emotion-focused therapy include: emotional awareness and expression therapy (EAET), attachment-based compassion therapy (ABCT). Patients must be able to cognitively participate in this specific treatment and process the material being taught.
	• Yoga or tai chi
	• Acupuncture
	• A trial of serotonin-norepinephrine reuptake inhibitors
	• Pregabalin

Topic	Details
Treatment of fibromyalgia pain (Continued)	VA/DoD CMI Guidelines found insufficient evidence to recommend for or against the use of: • Biofeedback • Manual musculoskeletal therapies (including spinal manipulative therapy, spinal mobilization, and osteopathic manipulation) • Relaxation therapy (including manual muscular relaxation therapy (MMRT), breathwork, autogenic therapy relaxation approach (AT), and functional relaxation (FR) • Guided imagery and hypnosis • Deep tissue massage • A trial of mirtazapine, selective serotonin reuptake inhibitors, or amitriptyline VA/DoD CMI Guidelines recommend against offering nonsteroidal anti-inflammatory drugs for chronic pain consistent with fibromyalgia.

APPENDIX

1. VA Long COVID Questionnaire Batch

The Long COVID Community of Practice and the Field Advisory Board developed a recommended list of instruments for assessing and monitoring Long COVID symptoms. Called the VA Long COVID Questionnaire Batch, these include the Modified Yorkshire COVID-19 Rehabilitation Survey, the VA Whole Health Well-Being Signs (WBS), the Exercise Vital Signs (EVS) Questionnaire, the 2-Minute Step Test, and Whole Health questions such as 1) what do you want your health for; 2) and what is most important for you to discuss in the Long COVID Clinic during your medical appointment? The VA Long COVID Questionnaire Batch has been incorporated into a note template available to all VA clinicians. Providers can pick and choose which options to include in their note – The Modified Yorkshire will be completed in MHAWEB. The person completing this note should be able to open MHAWEB from the toolbar and administer it while in this note if they choose.

Utilize and adapt this script to administer the VA Long COVID Questionnaire Batch

"This visit includes questions that will:

- Give us insight into your experience with Long COVID
- Provide us with a 'running start' to create a personalized Long COVID health plan with you
- May be repeated upon follow-up with the Long COVID Clinic
- Allow us to monitor how symptoms are changing over time

These questions will take about 45 minutes to complete. If you would like to take a break or stop for any reason, please let me know. We appreciate any information you can provide to us.

Do you have any questions before we begin?"

The following is the rest of the VA Long COVID Questionnaire Batch, formatted so that a personal template could be created if access to CPRS is not available.

The questionnaire batch below was provided by the VA Clinical Services Product Line.

Long COVID Whole Health Questions

In 2-3 sentences, please respond to the following questions:

1. When was the last time you felt well?

2. What do you want your health for?

3. What are your strengths?

The Modified COVID-19 Yorkshire Rehabilitation Scale[7]

Symptom severity
Please answer the questions below to the best of your knowledge.

'Now' refers to how you feel now/this week (last 7 days).

"Pre-COVID refers to how you were feeling prior to contracting the illness.

If you are unable to recall this, just state 'don't know'

Rate the severity of each problem on a scale of 0-3:

0= None; no problem
1= Mild problem; does not affect daily life
2= Moderate problem; affects daily life to a certain extent
3= Severe problem; affects all aspects of daily life; life-disturbing

1. **Breathlessness**

a) At Rest
NOW
PRE-COVID

b) Changing position e.g. from lying to sitting or sitting to lying
NOW
PRE- COVID

c) On dressing yourself
NOW
PRE-COVID

d) On walking up a flight of stairs
NOW
PRE-COVID

2. **Cough/throat sensitivity/ voice change**

a) Cough/throat sensitivity
NOW
PRE-COVID

b) Change of voice
NOW
PRE-COVID

3. **Fatigue (tiredness)**

[7] Sivan M, Preston N, Parkin A, Makower S, Gee J, et. al (2022). The modified COVID-19 Yorkshire Rehabilitation Scale (C19-YRSm) patient-reported outcome measure for Long Covid or Post-COVID-19 syndrome. Journal of Medical Virology.

a) Fatigue levels in your usual activities (not improved by rest)
NOW
PRE-COVID

4. Smell/taste

a) Altered smell
NOW
PRE-COVID

b) Altered taste
NOW
PRE-COVID

5. Pain/discomfort

a) Chest pain
NOW
PRE-COVID

b) Joint pain
NOW
PRE-COVID

c) Muscle pain
NOW
PRE-COVID

d) Headache
NOW
PRE-COVID

e) Abdominal pain
NOW
PRE-COVID

6. Cognition

a) Problems with concentration
NOW
PRE-COVID

b) Problems with memory
NOW
PRE-COVID

c) Problems with planning
NOW
PRE-COVID

7. Palpitations/dizziness

a) Palpitations in certain positions, activity or at rest
NOW
PRE-COVID

b) Dizziness in certain positions, activity or at rest
NOW
PRE-COVID

8. Post-exertional malaise (worsening of symptoms)

a) Crashing or relapse hours or days after physical, cognitive or emotional exertion
NOW
PRE-COVID

9. Anxiety/ mood

a) Feeling anxious
NOW
PRE-COVID

b) Feeling depressed
NOW
PRE-COVID

c) Having unwanted memories of your illness or time in hospital
NOW
PRE- COVID

d) Having unpleasant dreams about your illness or time in hospital
NOW
PRE- COVID

e) Trying to avoid thoughts or feelings about your illness or time in hospital
NOW
PRE- COVID

10. Sleep

a) Sleep problems, such as difficulty falling asleep, staying asleep or oversleeping
NOW
PRE- COVID

11. Communication

a) Difficulty with communication/word finding difficulty/understanding others
NOW
PRE- COVID

12. Walking or moving around

a) Difficulties with walking or moving around
NOW
PRE- COVID

13. Care

a) Difficulties with personal tasks such as using the toilet or getting washed and dressed
NOW
PRE- COVID

14. Other activities of Daily

a) Living Difficulty doing wider activities, such as household work, leisure/sporting, activities, paid/unpaid work, study or shopping
NOW
PRE- COVID

15. Social role

a) Problems with socializing/interacting with friends *or caring for dependents* related to your illness and not due to social distancing/lockdown measures
NOW
PRE- COVID

Other symptoms

Please select any of the following symptoms you have experienced since your illness in the last 7 days. Please also select any previous problems that have worsened for you following your illness.

- Fever
- Skin rash/ discoloration of skin
- New allergy such as medication, food etc.
- Hair loss
- Skin sensation (numbness/tingling/itching/nerve pain)
- Dry eyes/ redness of eyes
- Swelling of feet/ swelling of hands
- Easy bruising/ bleeding
- Visual changes
- Difficulty swallowing solids
- Difficulty swallowing liquids
- Balance problems or falls
- Weakness or movement problems or coordination problems in limbs
- Tinnitus
- Nausea
- Dry mouth/mouth ulcers
- Acid Reflux/heartburn
- Change in appetite
- Unintentional weight loss
- Unintentional weight gain
- Bladder frequency, urgency or incontinence
- Constipation, diarrhea or bowel incontinence
- Change in menstrual cycles or flow
- Waking up at night gasping for air (also called sleep apnea)
- Thoughts about harming yourself

- Other symptoms

Overall health

How good or bad is your health overall in the last 7 days?

For this question, a score of 10 means the BEST health you can imagine. 0 means the WORST health you can imagine.

a) Now:

b) Pre-Covid:

Employment

Occupation:

Has your COVID-19 illness affected your work??

- No change
- On reduced working hours
- On sickness leave
- Changes made to role/ working arrangements (such as working from home or lighter duties)
- Had to retire/ change job
- Lost job

Any other comments/concerns:

Partner/family/carer perspective

This is space for your partner, family or carer to add anything from their perspective:

Well-Being Signs

*If the average score is less than 20%, please notify patient's provider.

Introductory script:
"I'd like to ask you some questions about how you are doing in your overall life. These questions may seem different than the typical questions you are asked at the VA. It is important for us to ask these questions because they will help your healthcare team have a better understanding on how you are doing in general. This will help us provide better care to you. The three questions I am about to ask are very broad questions so it is okay to estimate or give your best answer."

For these questions, please consider the most important things that you do, or wish to do, in your daily life. This might include having a job, spending time with family and friends, participating in leisure-time activities, or managing your health or finances.

Over the past 3 months, what percentage of the time have you been:

1. Fully satisfied with how things are going in these aspects of life? (0-100% or declined to answer)

2. Regularly involved in all aspects of life that are important to you? (0-100% or declined to answer)

3. Functioning your best in aspects of life that you do participate in? (0-100% or declined to answer)

Exercise Vital Sign (EVS) Questionnaire[8]

1. On average, how many days per week do you engage in moderate intensity or greater (like a brisk walk)?

2. On average, how many minutes do you engage in exercise at this level:

[8] Coleman KJ, Ngor E, Reynolds K, Quinn VP, Koebnick C, Young DR, Sternfeld B, Sallis RE. Initial validation of an exercise "vital sign" in electronic medical records. Med Sci Sports Exerc. 2012 Nov;44(11):2071-6.

2 Minute Step Test

Number of steps taken in 2 minutes:
Resting heart rate and SpO2 (optional):
Post-exertion heart rate and SpO2 (optional):

2 Minute Step Test Testing Information:

- The 2-minute step test indicates the level or aerobic endurance of the participant whereby higher scores indicate greater levels of aerobic capacity.
- It is associated with the ability to perform lifestyle tasks such as walking and climbing stairs. This is an alternative test if there is not sufficient time and space to conduct the 6-minute walk test.
- This test is intended to be repeated to record changes over time within an individual. There are currently no normative values for Long COVID patients.
- Administer this test by counting how many times the patient's right knee reaches a pre-determined height while marching in place for 2 minutes. A person with reduced balance may use a table, wall, or chair as a touch-hold for stability. If preferred, the examiner may also utilize pulse oximetry both at rest and at the conclusion of the 2-minute step test.
- If examiner or Veteran have concern for safety with marching, it is best to abstain from performing this test via telehealth.

Equipment required:

- A stopwatch
- If in-person visit: A tape measure or meter ruler
- If virtual visit: sticky note or marker (arrow) on computer or device if applicable (to mark height participate must lift knee on computer screen)
- Optional: pulse ox, tally counter

Establishing the knee lift height

1. If performing the test virtually, have the participant stand in front of the camera in order to mark a point on the participant's thigh, halfway between the participant's patella (knee) and iliac crest (top of the hip) on their computer monitor. (Participant may have to step away from the camera for optimal viewing.)
2. Place a sticky note (or arrow) on your computer screen at the participant's mid-thigh position. Use the top of the sticky note (or arrow) as your reference point. (Practicing the height of knee lift may take a few tries due to the participate not having the sticky note on his/her/their screen as guidance.)
3. Have the participant step in place and instruct them how high the knee must come up in order to reach the reference level of the sticky note (or arrow).
4. If performing the test in-person, measure from the point to the ground with the tape measure or ruler and place a sticky note on the wall.

Long COVID Whole Health Wrap-up:

Considering your personal experiences and what we have covered today, what is most important for you to discuss in the Long COVID Clinic during your next medical appointment?

Table I. Symptomatology recommendation and good practice tables

Table I-1. Good practice statements for the care of all Veterans with Long COVID presenting with neurologic symptoms

Good practice statements
Tan boxes Recommendations for history-taking, physical exam, and commonly used noninvasive diagnostic tests are based on consensus determinations of useful and safe care.

History
Consider social drivers/determinants of health, marginalized groups, and intersectional identities in evaluation and management (6),(7).

Obtain a full patient history, including:
 	
• Current symptoms
  ○ Timing in onset compared to acute COVID illness (if known)
  ○ Trajectory over time (new, improving, worsening, or unchanged)
  ○ How symptoms may correlate/cluster with each other
  ○ Triggers (including food, medications, activity, and positional changes)
  ○ Concerning symptoms or exam findings that warrant evaluation for an alternative process
• Symptoms that may be neurologic in nature, including:
  ○ Autonomic symptoms (including dizziness, lightheadedness, presyncope, syncope, orthostatic intolerance)
  ○ Headaches including migraine
  ○ Exercise intolerance
  ○ Cognitive dysfunction (including brain fog, slowed processing rate, and memory impairment)
  ○ Cognitive fatigue
  ○ Changes in gait/walking
  ○ Pain
• Relevant hospitalizations, time course and severity of acute COVID illness(es), treatments, vaccines/boosters
• Possible manifestations of post-intensive care syndrome (PICS) among Veterans who experienced critical illness, including prolonged new or worsening cognitive, physical, and mental health problems
• Review of pertinent prior medical comorbidities, and any changes since contracting COVID, including:
  ○ Pain or psychiatric conditions
  ○ Renal/endocrine condition
  ○ Cardiovascular conditions
  ○ Neurologic conditions
  ○ Respiratory conditions
• Social history and functional history, including:
  ○ Previous and/or current alcohol and substance use
  ○ Diet and exercise
  ○ Physical and cognitive activity

History

- Social drivers/determinants of health (including, housing, employment, family, insurance, access to

Changes in basic activities of daily living (including grooming, eating, dressing) and instrumental activities of daily living (participation in work, school, community avocational activities, such as hobbies (6),(8),(9).

Laboratory

Consider the following laboratory studies on initial evaluation if not obtained in the prior 3 months (8),(10):

- Complete blood count with differential
- Complete metabolic panel including blood glucose, creatinine, magnesium, and liver studies (bilirubin, alanine aminotransferase, aspartate amino transferase, and alkaline phosphatase)
- Thyroid stimulating hormone
- C-reactive protein (CRP) (consider high-sensitivity CRP if available)
- Erythrocyte sedimentation rate
- Vitamin B6 (pyridoxine), vitamin B9 (folate), vitamin B12 (cobalamin), vitamin D3 (cholecalciferol)
- Hemoglobin A1c

Personalized health plan: management and treatment

- Address life stressors and mental health conditions that may exacerbate Long COVID symptoms (7).
- Acknowledge Veterans for their psychological resilience. Encourage Veterans with Long COVID to maintain social engagement and lean on support systems, which may include Veteran peer support specialists (7).
- Consider a multimodal approach to support Veterans with Long COVID in their recovery. This often entails rehabilitation programs, pharmacological therapies for specific symptoms, and referrals to appropriate multidisciplinary clinicians (9).
- Address potential contributing factors such as nutritional status, physical activity, sleep, and stress (9).

Table I-2. Guidance for orthostatic intolerance (OI) and autonomic dysfunction in Long COVID

Evidence-informed recommendations	Good practice statements
Blue boxes For the evidence underlying these recommendations see: Anderson et al. 2023[9]. Raj et al. 2020[10]; Raj et al. 2022[11]	**Tan boxes** Good practice statements for history-taking, physical exam, and commonly used noninvasive diagnostic tests are based on consensus determinations of useful and safe care.

History

Good practice statements

Topic	Details
Assessment of symptoms that may be related to OI	Screen for orthostatic intolerance by: • Reviewing VA Long COVID Questionnaire Batch responses • Asking about palpitations, dizziness, "electric shock" sensation on standing, breathlessness, postural or exertional tachycardia, chest tightness, and other relevant symptoms. Keep in mind that cognitive dysfunction and fatigue can be caused by autonomic dysfunction (15),(39).
Assessment of symptoms that may be related to autoimmunity	Ask specifically about: • Migraine • Rashes • History of autoimmune disorders such as Sjogren's, Hashimoto's thyroiditis, or celiac disease. Keep in mind that a thorough review of systems may uncover symptoms of (undiagnosed) celiac disease, Sjogren's, or another autoimmune condition. In the pre-COVID era, mast cell disorders and Ehlers-Danlos syndrome were also associated with POTS, although their relevance to Long COVID-POTS is not well-established (26).
Assessment of symptoms that may be related to autonomic dysfunction	Ask about other autonomic symptoms such as: • Gastrointestinal or genitourinary dysfunction • Abnormal sweating • Acrocyanosis • Dry mouth • Unexplained fever (26)
Use of structured assessment tools	Use a structured assessment tool such as the COMPASS-31 or the Malmö POTS symptom score to assess the likelihood of POTS.

[9] Anderson, J., S. Young, and K. Mackey, *Brief Evidence Assessment Guidance for Long COVID Clinics: Nervous System*. 2023, Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs: Washington, DC.

[10] Raj SR, Guzman JC, Harvey P, Richer L, Schondorf R, Seifer C, et al. Canadian Cardiovascular Society Position Statement on Postural Orthostatic Tachycardia Syndrome (POTS) and Related Disorders of Chronic Orthostatic Intolerance. Can J Cardiol. 2020;36(3):357-72.

[11] Raj SR, Fedorowski A, Sheldon RS. Diagnosis and management of postural orthostatic tachycardia syndrome. Cmaj. 2022;194(10):E378-E85.

Physical exam

Evidence-informed recommendations

Topic	Recommendation	Details
Physical exam elements	Recommend use	When the history suggests flexible joints, use the Beighton scale to look for findings of Ehlers-Danlos syndrome (26),(40).
Physical exam elements	Recommend use	When the history suggests orthostatic intolerance or other symptoms of autonomic dysfunction, perform a NASA LEAN test or an active stand test. Observe the patient for symptoms and signs including brain fog, dizziness, and discoloration or discomfort in the feet (26),(41).

Evaluation

Laboratory testing

Good practice statements

Topic	Details
Routine laboratory testing	Consider the following laboratory studies on initial evaluation if not obtained in the prior 3 months (8),(10): • Complete blood count with differential • Complete metabolic panel including blood glucose, creatinine, magnesium, and liver studies (bilirubin, alanine aminotransferase, aspartate amino transferase, and alkaline phosphatase) • Thyroid stimulating hormone • C-reactive protein (CRP) (consider high-sensitivity CRP if available) • Erythrocyte sedimentation rate • Vitamin B6 (pyridoxine), vitamin B9 (folate), vitamin B12 (cobalamin), vitamin D3 (cholecalciferol) • Hemoglobin A1c
Additional laboratory testing	Additional laboratory testing should be offered based on the history and physical examination findings.

Evidence-informed recommendations

Topic	Recommendation	Details
Specialized laboratory testing	Consider use	Use the initial evaluation to guide further laboratory testing for autoimmunity, mast cell disorders, or infection (for example, testing for Sjögren syndrome if the patient complains of dry eyes) (15).
Specialized laboratory testing	Consider not using	Thyroid antibodies, GAchR ab, FGFR3 Ab, TS-HDS, G protein coupled receptors, and reactivation of EBV have all been seen in Long COVID patients, but their role in clinical evaluation is still unclear (15),(42).

Diagnostic testing

Good practice statements

Topic	Details
Chest imaging	Obtain chest imaging. This might include plain radiographs or computed tomography of the chest.
Additional testing	Additional cardiac testing or referral to an autonomic medicine expert may be used per local practice but are not routine.

Evidence-informed recommendations

Topic	Recommendation	Details
Routine use of echocardiography	Consider not using	Echocardiography is not routinely indicated to evaluate suspected orthostatic intolerance or tachycardia (26),(41).
Routine use of head-up tilt table testing or autonomic function testing	Consider not using	Head-up tilt table testing and autonomic testing are not routinely required to diagnose POTS. Indications for heads-up tilt table testing in patients with Long COVID are not well established.

Personalized health plan: management and treatment

Good practice statements

Topic	Details
Multidisciplinary care	Patients benefit from working with a multidisciplinary team that includes specialists with expertise in autonomic dysfunction. This may include expertise in physical medicine and rehabilitation, physical therapy, and occupational therapy where available.
Nonpharmacologic interventions	While evidence is sparse, routine management of POTS may include (40),(43): • A high salt and water diet when not contraindicated. Aim for 3 liters of water and 10 grams of salt (NaCl) taken by mouth daily. • Stopping medications that exacerbate tachycardia or hypotension when possible • Limiting or avoiding symptom triggers such as exertion in hot weather, alcohol consumption • Lifestyle modification, including slowly getting out of bed before standing and use of compression stockings • Frequent small, balanced meals with whole foods, protein, vegetables, and fruits, and high in fiber

Evidence-informed recommendations

Topic	Recommendation	Details
Counseling	Consider use	When counseling about the natural history of POTS, inform the Veteran that:

Topic	Recommendation	Details
Counseling (Continued)		• Before COVID, 70% to 80% of young adults and adolescents with POTS recovered in 1–4 years • Most patients with Long COVID-POTS improve within a year • For those who do not improve within a year, the longer term prognosis is unclear (15),(44).
Physical activity	Consider use	If post-exertional malaise (PEM) is present, follow guidance for management of PEM (see Fatigue). If PEM is not present, and the patient has had a prolonged hospitalization or period of inactivity, consider an exercise program under the supervision of a therapist experienced in Long COVID. For most patients, exercise in POTS patients begins with recumbent exercise and advances as tolerated (15).
Pharmacologic treatment for POTS	Consider use	If nonpharmacological measures are insufficient, consider medications. The Canadian Cardiovascular Society (CCS) rated the evidence for various interventions. The choice of medication depends on the symptoms (see figure 4 in the CCS paper) (26).
Treatment of orthostatic hypotension	No recommendation	For patients with low blood pressure, treatments are midodrine (2.5–15 milligrams by mouth every 4 hours 2–3 times per day; moderate evidence) and fludrocortisone (0.1–0.3 milligrams by mouth daily; low evidence). In the VA, however, use of these medications is limited because a high proportion of patients have conditions such as heart failure or renal disease. Within the VA, clinicians with expertise in Parkinson's disease, neuropathies, and traumatic brain injury may have the most experience using these medications (26),(40).
Heart rate inhibitors	Consider use	For persistent postural orthostatic tachycardia syndrome (POTS) symptoms in the absence of hypotension, use a heart rate inhibitor. The evidence is strongest for a β blocker (propranolol 10–20 milligrams up to 4 times a day). Start with a low dose, especially in patients who developed hypotension on an active standing or LEAN test. Evidence for other drugs used to reduce heart rate in POTS is weaker (including ivabradine 2.5–7.5 milligrams by mouth twice a day, pyridostigmine 30–60 milligrams by mouth 3 times a day, and clonidine 0.1–0.2 milligrams by mouth 3 times a day (26).

Table I-3. Guidance for cognitive impairment in Long COVID

Evidence-informed recommendations	Good practice statements
Blue boxes For the evidence underlying these recommendations see: Anderson et al. 2023[12].	**Tan boxes** Good practice statements for history-taking, physical exam, and commonly used noninvasive diagnostic tests are based on consensus determinations of useful and safe care.

History

Good practice statements

Topic	Details
Assessment of cognitive impairment symptoms	Obtain a detailed history of cognitive symptoms including: • Attention (brain fog, lost train of thought, concentration problems) • Processing speed (slowed thoughts) • Motor function (slowed movements) • Language (word finding problems, reduced fluency) • Memory (poor recall, forgetting tasks) • Mental fatigue (exhaustion, brain fog) • Executive function (poor multitasking or planning) Visuospatial domains (neglect) (104)

[12] Anderson, J., S. Young, and K. Mackey, *Brief Evidence Assessment Guidance for Long COVID Clinics: Nervous System*. 2023, Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs: Washington, DC.

Evidence-informed recommendations

Topic	Recommendation	Details
Montreal Cognitive Assessment (MoCA) to identify cognitive impairment	Consider not using	The MoCA should not be used alone to identify cognitive impairment. In the presence of conditions such as sleep apnea, depression, and others, a low MoCA score may not reflect true cognitive impairment. A low MoCA score should prompt consideration of these other potential etiologies. Conversely, a patient with a normal score may still have cognitive impairment. In Veterans with known dementia and Long COVID symptoms, the MoCA may be used longitudinally to follow clinical trajectory.
Mini-Mental State Examination (MMSE)	No recommendation	Inadequate evidence was found to inform a recommendation.
Saint Louis University Mental Status (SLUMS)	No recommendation	Inadequate evidence was found to inform a recommendation.

Physical exam

Good practice statements

Topic	Details

Components of the screening neurologic exam for face-to-face and virtual visits	*Face-to-face visit, assess:*
	• Vital signs
	• Gait:
	  ○ Test ability to walk independently
	  ○ Test tandem walking
	• Romberg
	• Muscle stretch reflexes (MSR): Knees
	• Motor: Check drift by holding arms up for 10 seconds
	• Any abnormal movements
	• Cranial nerves: Ask patient to smile, assess symmetry
	
	Virtual visit, assess:
	As above except
	• MSR (knees): Ask the patient to cross one leg over the other and tap their knee with the edge of their hand.
	• Before testing gait, consider the safety of the environment and assess for symptoms that point to unsafe gait.

Evaluation

Laboratory testing

Good practice statements

Topic	Details
Routine laboratory testing	Consider the following laboratory studies on initial evaluation or if not obtained in the prior • Complete blood count with differential • Complete metabolic panel including blood glucose, creatinine, magnesium, and liver studies (bilirubin, alanine aminotransferase, aspartate amino transferase, and alkaline phosphatase) • Thyroid stimulating hormone • C-reactive protein (CRP) (consider high-sensitivity CRP where available) • Erythrocyte sedimentation rate • Vitamin B1 (thiamine), vitamin B6 (pyridoxine), vitamin B9 (folate), vitamin B12 (cobalamin), vitamin D3 (cholecalciferol) • Hemoglobin A1c (35)
Additional laboratory testing	Additional laboratory testing should be offered based on the history and physical examination findings. For example, antinuclear antibody testing can be done if there is a history consistent with autoimmune symptoms.

Diagnostic testing

Good practice statements

Topic	Details
Computed tomography (CT) and magnetic resonance imaging (MRI)	The decision to order CT or brain MRI is based on usual practice. We did not review evidence about the diagnostic testing or therapeutic impact of neuroimaging in cognitive impairment in Long COVID (43).

Personalized health plan: management and treatment

Evidence-informed recommendations

Topic	Recommendation	Details
Cognitive rehabilitation	Consider use	Consider referral for rehabilitation interventions (commonly, speech therapy, neuropsychology, and/or occupational therapy) to address cognitive and/or functional problems. Attention to Long COVID-specific issues like pacing, post exertional malaise and posture may be needed, which may require rehabilitation clinicians to have additional training. No recommendation about specific cognitive rehabilitation interventions is offered due to inadequate evidence.

Topic	Recommendation	Details
Whole Health Systems interventions for sleep optimization, stress management, and nutrition optimization	Consider use	Sleep problems, high stress, mood symptom, and nutritional issues are common among patients with Long COVID. *Evidence was inadequate to inform specific recommendations. This recommendation was offered based on low risk of harm and because these interventions are commonly offered as part of the VA's Whole Health System program.*
Soft belly breathing	Consider use	Consider the use of soft belly breathing when high stress or affective symptoms are present. *Evidence was inadequate to inform a recommendation. This recommendation was offered based on low risk of harm and because this intervention is commonly offered as part of the VA's Whole Health System program.*
Amantadine	Consider not using	Evidence of effectiveness in traumatic brain injury was inadequate and applicability to Long COVID was unclear. Side effects such as orthostatic hypotension and syncope, dizziness, falls, impulse control and related disorders, livedo reticularis, neuropsychiatric symptoms (including confusion and disorientation), and withdrawal syndromes have been reported. Thus, we suggest not using amantadine for cognitive impairment in Long COVID until more evidence is available.
Donepezil	Consider not using	No evidence regarding the use of donepezil in Long COVID was identified. No evidence for benefit has been demonstrated in relevant populations such as mild traumatic brain injury. Harms of treatment in Long COVID are unknown. Thus, we suggest not using donepezil for cognitive impairment in Long COVID until more evidence is available.
Coenzyme Q10	No recommendation	Inadequate evidence was found to inform a recommendation.
Low-dose naltrexone (LDN)	No recommendation	There is uncertainty about the effectiveness of LDN in Long COVID cognitive impairment, but clinical trials are underway. Thus, no recommendation is currently offered in cognitive impairment. Refer to the Fatigue and Pain tables for these symptom-specific recommendations. In patients with concomitant pain or fatigue, cognitive impairment may improve with improvement in these symptoms.

Topic	Recommendation	Details
Methylphenidate	No recommendation	Consider use in Veterans with deficits in processing speed and/or attention. Benefits may be similar to those seen in mild traumatic brain injury, but risks may be different (and potentially greater) due to sympathetic overdrive which may occur in Long COVID. Individualized decision-making is needed. Before prescribing consider the risks of tachycardia, hypertension, diversion, irritability, and sleep disturbances, especially in individuals with autonomic dysfunction or co-morbid cardiac disease. Collaborate closely with psychiatry if the Veteran has a diagnosis of bipolar disorder, anxiety disorder, or history of mania. Recommend not using to treat memory loss in the absence of deficits in processing speed or attention.

Table I-4. Guidance for fatigue and activity intolerance in Long COVID

Evidence-informed recommendations	Good practice statements
Blue boxes For the evidence underlying these recommendations see: Anderson et al. 2023[13].	**Tan boxes** Good practice statements for history-taking, physical exam, and commonly used noninvasive diagnostic tests are based on consensus determinations of useful and safe care.

History

Good practice statements

Topic	Details
Distinguish symptoms	Distinguish between symptoms of fatigue, orthostatic intolerance, exercise intolerance, and post-exertional malaise (PEM) to determine etiology and appropriate evaluation (6).
PEM	Assess how the patient responds to initiating and escalating activity and whether they have PEM (6).
Myalgic encephalomyelitis/chronic fatigue syndrome assessment	Assess whether the patient meets criteria for ME/CFS (6).
Fatigue functional impact assessment	Assess for functional impact of fatigue (general/overarching) including effect on basic activities of daily living, instrumental activities of daily living, work, and hobbies (6).
Standardized assessment instrument for fatigue in Long COVID	Consider using the modified Yorkshire COVID-19 Rehabilitation Scale to assess fatigue. Important Information: It is Good Practice to assess fatigue using a standardized test based on severity and functional limitations. Inadequate evidence was found to inform a recommendation for a specific standardized assessment instrument for fatigue in Long COVID. The modified Yorkshire COVID-19 Rehabilitation Scale was chosen for inclusion in the VA Long COVID Questionnaire Batch through a modified Delphi consensus process among VA Long COVID clinicians (6). Its use supports consistent care across the VA system.

[13] Anderson, J., S. Young, and K. Mackey, *Brief Evidence Assessment Guidance for Long COVID Clinics: Nervous System*. 2023, Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs: Washington, DC.

Physical exam

Good practice statements

Topic	Details
Hypoxia	Assess for hypoxia at rest and with exertion as a cause of fatigue (especially if acute COVID illness was complicated by hypoxia) (76),(10).
Assessment of exercise capacity	Assess fatigue and activity intolerance using an objective measure of exercise capacity. Options include 30-second sit-to-stand, 1-minute sit-to-stand, 2-minute step, 6-minute walk test, or 10-minute walk test. Comparative performance of these tests in Long COVID is unknown. While the 6-minute walk test is often viewed as the "gold standard," the shorter 2-minute step test was included in the VA Long COVID Questionnaire Batch because it can be used in a variety of settings including virtual visits and to follow trends over time (6),(10).

Evaluation

Laboratory testing

Good practice statements

Topic	Details
Routine laboratory testing	Consider the following laboratory studies on initial evaluation or if not obtained in the prior 3 months (76): • Complete blood count with differential • Complete metabolic panel including blood glucose, creatinine, magnesium, and liver studies (bilirubin, alanine aminotransferase, aspartate amino transferase, and alkaline phosphatase) • Thyroid stimulating hormone level and free T4 • C-reactive protein (CRP) (consider high-sensitivity CRP where available) • Hemoglobin A1c • Vitamin B9 (folate), vitamin B12 (cobalamin), vitamin D3 (cholecalciferol) • Erythrocyte sedimentation rate
Additional laboratory testing	Additional laboratory testing should be offered based on the history and physical examination findings. • Creatine phosphokinase

Diagnostic testing

Good practice statements

Topic	Details
Electrocardiogram (EKG)	• Obtain an EKG if there is a significant burden of palpitations, lightheadedness, or dizziness • Consider ambulatory monitoring

Topic	Details
Chest imaging	If fatigue and dyspnea are present, obtain chest imaging per local practice (chest X-ray or chest CT). (6)

Personalized health plan: management and treatment

Evidence-informed recommendations

Topic	Recommendation	Details
Paced activity and energy conservation	Consider use	Consider paced activity and energy conservation, with a disclaimer that the recommendation is based on weak evidence, and adverse events have not been adequately studied. If paced activity is recommended, patients with fatigue due to post-exertional malaise (PEM) can be counseled to decrease the total amount of activity and restrict exposure to PEM triggers. Once a patient is effectively pacing without triggering PEM, it may be possible to engage in very short periods of activity to increase stamina. This must be individualized for the patient's level of severity and PEM triggers. Even for patients who can tolerate such activity, the expected level of improvement may be modest (61).
Graded Exercise Therapy	Consider not using	This recommendation specifically applies to graded exercise therapy. In the context of ME/CFS, the term "Graded Exercise Therapy" (GET) means a fixed incremental increase in physical activity or exercise. Graded exercise protocols are not recommended for patients with Long COVID with fatigue and ME/CFS features. Other guideline groups (NIH, CDC, and NICE) have recommended against it based on internal findings that suggest graded protocols may be harmful. Consider recommending alternative exercise protocols that allow more flexibility and customizability based on specific symptomatology and response to exercise intervention.
Pulmonary rehabilitation	Consider not using	Graded exercise intervention (which may be a component of pulmonary rehabilitation) has not been helpful in ME/CFS. Thus, use caution when considering pulmonary rehabilitation for fatigue due to PEM in the presence of underlying pulmonary conditions. However, in the absence of PEM, pulmonary rehabilitation may be helpful if fatigue is due to pulmonary disease, particularly chronic obstructive pulmonary disease or interstitial lung disease, as studies in these conditions have demonstrated that pulmonary rehabilitation improves quality of life.
Cognitive Behavioral Therapy (CBT)	Consider use	Consider CBT for fatigue in Long COVID, with an important caveat. This recommendation applies only to the specific intervention studied in Long COVID. CBT should be delivered by a healthcare professional with appropriate training and experience working with Long COVID or similar conditions (such as ME/CFS), and/or an understanding of evidence-based behavioral management of PEM. Finally, clinicians should note that CBT is a multi-visit process. As

Topic	Recommendation	Details
CBT (Continued)		part of a Whole Health System approach to Long COVID care, it is important to minimize appointment fatigue (61).
Low-dose naltrexone (LDN)	Consider use	Consider use for fatigue among Veterans meeting criteria for ME/CFS or fibromyalgia in the setting of Long COVID. Side effects are reported to be minimal. Inadequate evidence was found to inform a recommendation for the treatment of fatigue in a general Long COVID population.
Amantadine	No recommendation	Inadequate evidence was found to inform a recommendation.
Co-enzyme Q10	No recommendation	Inadequate evidence was found to inform a recommendation in Long COVID. Due to a plausible mechanism of action and some positive studies in ME/CFS, additional research in Long COVID fatigue is recommended. If prescribing co-enzyme Q10 for Long COVID fatigue, consider a trial of up to 200 milligrams daily (due to concern for untoward side effects at higher doses) for at least 12 weeks. Also note that at the time of writing, co-enzyme Q10 is unavailable for prescribing through the VHA. Thus, Veterans would need to obtain it elsewhere, and no specific brands can be recommended.
Modafinil	No recommendation	Inadequate evidence was found to inform a recommendation in Long COVID fatigue. This recommendation does not apply to individuals reporting daytime sleepiness.

Table I-5. Guidance for pain in Long COVID

Good practice statements
Tan boxes Good practice statements for history-taking, physical exam, and commonly used noninvasive diagnostic tests are based on consensus determinations of useful and safe care.

History

Good practice statements

Topic	Details
Chest pain history elements	Focus the history on differentiating between musculoskeletal, cardiac, and pulmonary causes of chest pain. Recommended history for musculoskeletal chest pain can be found here: Evaluation and Treatment of Musculoskeletal Chest Pain. Consider the following causes of musculoskeletal chest pain (91): • Costochondritis or Tietze syndrome • Somatic rib dysfunction (such as "slipping rib syndrome") • Painful xiphoid syndrome • Muscle strain of intercostal muscles, pectoralis muscles, internal and external oblique muscles, and serratus anterior muscles • Myofascial pain • Fibromyalgia • Precordial catch syndrome • Thoracic radiculopathy • Herpes zoster If there is concern for a potential cardiac or pulmonary cause, perform an in-person evaluation.
Headache history elements	Obtain a headache history as recommended in the VA/DoD Clinical Practice Guidelines for Management of Headache: VA-DoD Clinical Practice Guidelines for the Management of Headache (35). Additional reference material: Long COVID headache | The Journal of Headache and Pain
Neuropathic pain history elements	If there is concern for neuropathic pain, assess for a personal history of diabetes, chemotherapy, alcohol use, autoimmune disorders, peripheral nerve injury or compression, and history of toxic exposures. Additionally, assess for prolonged hospital stay, hospital stay including intensive care unit stay and/or prone positioning (8). For more detailed recommendations, see Peripheral Neuropathy: Evaluation and Differential Diagnosis | AAFP
Myopathic, myofascial, or musculoskeletal pain history elements	Assess for prolonged hospital stay, intensive care unit stay, and duration of hospitalization or bed rest, and for exposure to paralytics or steroids during acute COVID illness. Determine if there is a history of pain or injury predating COVID (8),(76),(6).
Nociplastic pain history elements	If nociplastic pain is present, ask about symptoms of fibromyalgia, dysautonomia, POTS, or ME/CFS, keeping in mind that pain may be a symptom of dysautonomia. Refer to Autonomic Dysfunction and Fatigue for further details (89).

Topic	Details
Standardized pain assessments	Assess pain symptoms at initial and follow-up visits using tools such as (35): • VA Long COVID Questionnaire Batch • Pain, Enjoyment of Life, and General Activity Scale (PEG scale) • MIDAS (if headache) (MIDAS)

Physical exam

Good practice statements

Topic	Details
Routine physical exam elements	When pain is present, perform a musculoskeletal and neurologic examination (35).
Musculoskeletal chest pain exam elements	If there is concern for a musculoskeletal contribution of chest pain, evaluate the anterior and posterior chest wall for swelling, erythema, warmth, or tenderness to palpation (sternum, costochondral junction, intercostals, evaluation for trigger points). Perform a neurologic examination to rule out compression of nerve roots originating in the lower cervical or thoracic segments (sensation, strength, reflexes) (91). • For more information on evaluation of musculoskeletal chest pain see here: Evaluation and Treatment of Musculoskeletal Chest Pain.

Evaluation

Laboratory testing

Good practice statements

Topic	Details
Routine laboratory testing	Consider the following laboratory studies on initial evaluation if not obtained in the prior 3 months (8),(10): • Complete blood count with differential • Complete metabolic panel including blood glucose, creatinine, magnesium, and liver studies (bilirubin, alanine aminotransferase, aspartate amino transferase, and alkaline phosphatase) • Thyroid stimulating hormone • C-reactive protein (CRP) (consider high-sensitivity CRP if available) • Erythrocyte sedimentation rate • Vitamin B6 (pyridoxine), vitamin B9 (folate), vitamin B12 (cobalamin), vitamin D3 (cholecalciferol) • Hemoglobin A1c
Additional laboratory testing	Additional laboratory testing should be offered based on the history and physical examination findings:

Topic	Details
Additional laboratory testing (Continued)	• If concern for neuropathic pain: serum protein electrophoresis with immunofixation • If concern for myopathy/myositis: creatine kinase (CK), aldolase, lactate dehydrogenase • If concern for possible autoimmune disease: anti-nuclear antibodies, serum protein electrophoresis and immunofixation, rheumatoid factor/anticitrullinated peptide antibodies • If concern for myofascial pain or fibromyalgia, laboratory testing is not routinely recommended.

Diagnostic testing

Good practice statements

Topic	Details

Headache red flags for imaging	Consider imaging if there are headache red flags, as recommended by VA-DoD Headache Pocket Card (88):
	• Systemic symptoms, illness, or condition
	  ○ Fever
	  ○ Chills
	  ○ Myalgias
	  ○ Night sweats
	  ○ Weight loss or gain
	  ○ Cancer
	  ○ Infection
	  ○ Giant cell arteritis
	  ○ Pregnancy or postpartum
	  ○ An immunocompromised state (including HIV)
	• Neurologic symptoms/signs
	  ○ Confusion
	  ○ Impaired alertness or consciousness
	  ○ Changes in behavior or personality
	  ○ Focal neurologic symptoms or signs
	  ○ Meningismus
	  ○ Seizures
	  ○ Ptosis
	  ○ Proptosis
	  ○ Pain with eye movements
	• Abrupt or "thunderclap" onset where pain reaches maximal intensity immediately or within minutes after onset; first ever, severe, or "worst headache of life"
	• Age ≥50 years

Topic	Details
Headache red flags for imaging (Continued)	• Progression or change in pattern (including headache frequency, severity, clinical features) • Precipitated by Valsalva (coughing, bearing down) • Postural aggravation and/or papilledema
Peripheral neuropathy diagnostic testing	If there is concern for a focal or peripheral neuropathy contributing to pain in Long COVID, consider the following as recommended by the American Academy of Family Physicians (Peripheral Neuropathy: Evaluation and Differential Diagnosis | AAFP) (92): ▪ Electrodiagnostic studies only if symptoms are worrisome (acute onset, asymmetric, predominant motor or autonomic symptoms, rapidly progressive course) or if initial laboratory evaluation is normal but symptoms persist ▪ Imaging should not be routinely ordered to aid in the diagnosis of peripheral neuropathy. In suspected polyradiculopathy, plexopathy, or radiculoplexus neuropathy, magnetic resonance imaging may help in localizing an atypical neuropathy If initial evaluation is unrevealing, consider referral to neurology and/or physical medicine & rehabilitation.
Myopathic pain diagnostic testing	If myopathic pain is suspected (muscle pain and weakness), consider the following recommended by the American Academy of Family Physicians (Muscle Weakness in Adults: Evaluation and Differential Diagnosis) (93): ▪ Electrodiagnostic studies if the diagnosis is unclear after a history, physical examination, and targeted laboratory evaluation If initial evaluation is unrevealing, consider referral to a neuromuscular specialist and/or rheumatology for further work-up, which may include MRI or ultrasonography of muscle tissue, and/or muscle biopsy.

Personalized health plan: management and treatment

Good practice statements

Topic	Details
General principles of pain management in Long COVID	• Use a multidisciplinary approach to treatment that includes both pharmacologic and nonpharmacologic approaches (8),(103). • Because of the high prevalence of PEM among patients with Long COVID exercise protocols should allow more flexibility and customizability based on specific patient symptomatology and response to exercise intervention. Avoid Graded Exercise Therapy (i.e., a fixed incremental increase in physical activity or exercise) because of harms. (see Fatigue Section) • Refer to AAFP for diagnosis-specific treatment guidance for diagnosis-specific treatment guidance if there is a focal nociceptive complaint, including joint swelling/arthralgia. • The guidelines do not offer recommendations regarding the use of co-enzyme Q10 for Long COVID pain. • VA/DoD Opioid Chronic Pain Guidelines recommend against the long-term use of opioid medications for the management of chronic pain (100).

Symptom-specific recommendations

Good practice statements

Topic	Details
Treatment of neuropathic pain	Pharmacologic treatments recommended in conditions such as diabetic polyneuropathy may be useful as part of a multifaceted approach to neuropathic pain in Long COVID, as recommended by Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary (101): • First-line options include gabapentin, pregabalin, duloxetine, nortriptyline, amitriptyline, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors. Second-line options include lamotrigine, lacosamide, oxcarbazepine, lidocaine patch, and topical capsaicin.
Treatment of musculoskeletal chest pain	In the treatment of musculoskeletal chest pain in Long COVID, consider the approach recommended in the review article: Evaluation and Treatment of Musculoskeletal Chest Pain (91): • Reassurance • Pain control via non-steroidal anti-inflammatories if not contraindicated, application of local heat and ice compresses • Physical therapy for manual therapy with stretching exercises, and to address postural and ergonomic factors • Referral to a qualified clinician for trigger point injections if trigger points are present
Treatment of headache	Consider a neurology referral for post-COVID headache if the diagnosis or etiology is unclear or if headaches are refractory to treatment or progressively worsening. VA/DoD Headache Pocket Card

Treatment of fibromyalgia pain	A VA/DOD Practice Guideline for Management of Chronic Multisymptom Illness (CMI) provided guidance for the treatment of fibromyalgia in the pre-COVID era. A summary of recommendations that may be relevant to fibromyalgia in Long COVID are presented here. Guidance regarding exercise is not endorsed in the context of Long COVID:
	Clinicians can consider the following interventions for pain consistent with fibromyalgia in Long COVID based on pre-COVID guidance:
	• Cognitive Behavioral Therapy
	• Mindfulness-based therapies
	  ○ Examples of mindful-based therapies include mindfulness-based stress reduction (MBSR) and meditation awareness training (MAT).
	• Emotion-focused therapy
	  ○ Examples of emotion-focused therapy include: emotional awareness and expression therapy (EAET), attachment-based compassion therapy (ABCT). Patients must be able to cognitively participate in this specific treatment and process the material being taught.
	• Yoga or tai chi
	• Acupuncture

Topic	Details
Treatment of fibromyalgia pain (Continued)	• A trial of serotonin-norepinephrine reuptake inhibitors • Pregabalin VA/DoD CMI Guidelines found insufficient evidence to recommend for or against the use of: • Biofeedback • Manual musculoskeletal therapies (including spinal manipulative therapy, spinal mobilization, and osteopathic manipulation) • Relaxation therapy (including manual muscular relaxation therapy (MMRT), breathwork, autogenic therapy relaxation approach (AT), and functional relaxation (FR) • Guided imagery and hypnosis • Deep tissue massage • A trial of mirtazapine, selective serotonin reuptake inhibitors, or amitriptyline VA/DoD CMI Guidelines recommend against offering nonsteroidal anti-inflammatory drugs for chronic pain consistent with fibromyalgia.

Acronyms Used

ADHD	Attention-deficit/hyperactivity disorder
ANA	Antinuclear Antibodies
BP	Blood Pressure
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CFS	Chronic Fatigue Syndrome
COMPASS-31	Composite Autonomic Symptom Score
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
EKG	Electrocardiogram
ESP	Evidence Synthesis Program
ESPCC	Evidence Synthesis Program Coordinating Committee
EVS	Exercise Vital Signs
GABA	Gamma-aminobutyric acid
HR	Heart Rate
HUTT	Head-up tilt table testing
ILD	Interstitial Lung Disease
LDN	Low-dose Naltrexone
MRI	Magnetic Resonance Imaging
MCV	Mean corpuscular volume
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MSR	Muscle Stretch Reflexes
NASA	National Aeronautics and Space Administration
NESS	Nutrition Exercise Sleep Stress
NICE	National Institute for Health and Care Excellence (UK)
NIH	National Institutes of Health
OH	Orthostatic Hypotension
OI	Orthostatic Intolerance
PASC	Post-Acute Sequelae of SARS-CoV-2
PCC	Post-COVID Condition
PEM	Post Exertional Malaise
PM&R	Physical Medicine and Rehabilitation
PICS	Post-Intensive Care Syndrome
POTS	Postural Orthostatic Tachycardia Syndrome
PT/OT	Physical Therapy/ Occupational Therapy
SLUMS	Saint Louis University Mental Status Examinations
SMART	Specific, Measurable, Attainable, Realistic, and Time-bound
SNRI	Serotonin and Norepinephrine Reuptake Inhibitors
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
WBS	Well-Being Signs
WHS	Whole Health System

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