



Whole Health System Approach to Long COVID: Specialty Care

Clinic Visit Guide

Nervous System

VA



U.S. Department
of Veterans Affairs

Qualifying statements

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

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. In the recommendation tables, evidence-informed statements 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.

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General guidance

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

General 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

- 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 the development of 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)
 - 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 (Herrera, Niehaus et al. 2021),(Melamed, Rydberg et al. 2023),(Navis 2023).

Laboratory

Consider the following laboratory studies on initial evaluation if not obtained in the prior 3 months (Melamed, Rydberg et al. 2023),(Greenhalgh, Sivan et al. 2022):

- 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 (consider high-sensitivity CRP if available)
- Erythrocyte sedimentation rate
- Vitamin B6 (pyridoxine), vitamin B9 (folate), vitamin B12 (cobalamin), vitamin D3 (cholecalciferol)
- Hemoglobin A1c

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

Personalized health plan: management and treatment

- Address life stressors and mental health conditions that may exacerbate Long COVID symptoms (Fine, Ambrose et al. 2022).
- 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 (Fine, Ambrose et al. 2022).
- 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 (Navis 2023).
- Address potential contributing factors such as nutritional status, physical activity, sleep, and stress (Navis 2023).

Orthostatic intolerance and autonomic dysfunction

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[Physical exam](#)

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Description of condition

Orthostatic intolerance (OI) is recognized as a frequent early and late complication of COVID. (Shouman, Vanichkachorn et al. 2021) 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.” (Cutsforth-Gregory 2020) 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. (Lamotte and Low 2023)

Prevalence and course

Infection with SARS-CoV-2 increases the risk of developing POTS. (Kwan, Ebinger et al. 2022) Among people with persistent symptoms after COVID, the prevalence of POTS ranged from 2% to 14%. (Anderson, Young et al. 2023) 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. (Anderson, Young et al. 2023),(van Campen, Rowe et al. 2022) 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, (Kwan, Ebinger et al. 2022) although this association is disputed. (Joffe 2023),(Kwan and Cheng 2023)

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. (Goldstein 2024)

Autoimmunity is currently the most popular hypothesis for the etiology of Long COVID-POTS. (El-Rhermoul, Fedorowski et al. 2023) 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. (Blitshteyn and Whitelaw 2021),(Blitshteyn 2015) Second, many antibodies have been associated with autonomic disorders in POTS patients with or without a history of COVID. (Davis, McCorkell et al. 2023),(Hall, Bourne et al. 2022) Third, POTS is often associated with constitutional features that may signify immune dysregulation, such as fatigue, malaise, or skin rashes.

Orthostatic intolerance and autonomic dysfunction

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Cause of symptoms

Reduced cardiac output and cerebral blood flow are believed to cause many of the symptoms of POTS and OH. (van Campen, Rowe et al. 2022) 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. (Blitshteyn and Fries 2016),(Lamotte and Low 2023) 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.” (van Campen, Rowe et al. 2022)

Clinical considerations and recommendations

Evidence-informed guidance and Good Practice Statements for Long COVID autonomic intolerance are summarized in [Table B](#). 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. (Raj, Guzman et al. 2020),(Raj, Fedorowski et al. 2022) Most treatments for POTS have not been studied in Long COVID-POTS patients. (Hira, Karalasingham et al. 2023)

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

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Evidence-informed recommendations

Blue boxes

For the evidence underlying these recommendations see: Anderson et al. 2023². Raj et al. 2020³; Raj et al. 2022⁴

Good practice statements

Tan boxes

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

History

Table B-1. Good practice statements

Topic	Details
Assessment of symptoms that may be related to OI	<p>Screen for orthostatic intolerance by:</p> <ul style="list-style-type: none"> 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. <p>Keep in mind that cognitive dysfunction and fatigue can be caused by autonomic dysfunction (Anderson, Young et al. 2023),(Isaac, Corrado et al. 2023).</p>
Assessment of symptoms that may be related to autoimmunity	<p>Ask specifically about:</p> <ul style="list-style-type: none"> Migraine Rashes History of autoimmune disorders such as Sjogren’s, Hashimoto’s thyroiditis, or celiac disease. <p>Keep in mind that a thorough review of systems may uncover symptoms of (undiagnosed) celiac disease, Sjogren’s, or another autoimmune condition.</p> <p>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 (Raj, Guzman et al. 2020).</p>

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.

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

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Topic	Details
Assessment of symptoms that may be related to autonomic dysfunction	<p>Ask about other autonomic symptoms such as:</p> <ul style="list-style-type: none"> • Gastrointestinal or genitourinary dysfunction • Abnormal sweating • Acrocyanosis • Dry mouth • Unexplained fever (Raj, Guzman et al. 2020)
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.

Physical exam

Table B-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 (Raj, Guzman et al. 2020),(Blitshteyn, Whiteson et al. 2022).
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 (Raj, Guzman et al. 2020),(Espinosa-Gonzalez, Master et al. 2023).

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

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Evaluation

Laboratory testing

Table B-3. Good practice statements

Topic	Details
Routine laboratory testing	<p>Consider the following laboratory studies on initial evaluation if not obtained in the prior 3 months (Melamed, Rydberg et al. 2023),(Greenhalgh, Sivan et al. 2022):</p> <ul style="list-style-type: none"> • 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 B-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) (Anderson, Young et al. 2023).
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 (Anderson, Young et al. 2023),(Fedorowski, Fanciulli et al. 2024).

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

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Diagnostic testing

Table B-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 B-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 (Raj, Guzman et al. 2020),(Espinosa-Gonzalez, Master et al. 2023).
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 B-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.

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

History	Physical exam	Evaluation	Personalized health plan
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Topic	Details
Nonpharmacologic interventions	<p>While evidence is sparse, routine management of POTS may include (Blitshteyn, Whiteson et al. 2022),(U.S. Department of Veterans Affairs 2022):</p> <ul style="list-style-type: none"> • A high salt and water diet when not contraindicated. Aim for 3 liters of water and 10 grams of salt(NaCl) 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 B-8. Evidence informed recommendations

Topic	Recommendation	Details
Counseling	Consider use	<p>When counseling about the natural history of POTS, inform the Veteran that:</p> <ul style="list-style-type: none"> • 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 (Anderson, Young et al. 2023),(Fedorowski and Sutton 2023).
Physical activity	Consider use	<p>If post-exertional malaise (PEM) is present, follow guidance for management of PEM (see Fatigue).</p> <p>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 (Anderson, Young et al. 2023).</p>

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

History	Physical exam	Evaluation	Personalized health plan
Topic	Recommendation	Details	
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) (Raj, Guzman et al. 2020).	
Treatment of orthostatic hypotension	No recommendation	<p>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).</p> <p>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.</p> <p>Within the VA, clinicians with expertise in Parkinson's disease, neuropathies, and traumatic brain injury may have the most experience using these medications (Raj, Guzman et al. 2020),(Blitshteyn, Whiteson et al. 2022).</p>	
Heart rate inhibitors	Consider use	<p>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).</p> <p>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 rate is weaker (including ivabradine 2.5–7.5 milligrams by mouth twice a day, pyridostigmine 30–60 milligrams by mouth three times a day, and clonidine 0.1–0.2 milligrams by mouth three times a day (Raj, Guzman et al. 2020).</p>	

Cognitive impairment

[History](#)

[Physical exam](#)

[Evaluation](#)

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Description of condition

Long COVID is associated with neurocognitive symptoms that may have a major impact on function and well-being. (Ceban, Ling et al. 2022), (Callan, Ladds et al. 2022) 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. (Anderson, Young et al. 2023) The term “brain fog” can refer to any of these complaints (and others). (McWhirter, Smyth et al. 2023)

Prevalence and course

In five systematic reviews, the proportion of adults reporting cognitive symptoms following COVID ranged from 0.6% to 22%. (Anderson, Young et al. 2023) 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 (Miskowiak, Fugledalen et al. 2022), 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 neurological diseases, hypoxic injury, microthrombosis, decreased cerebral perfusion, serotonin pathway dysregulation (Wong, Devason et al. 2023), persistent virus, or reactivation of latent herpesviruses. (Möller, Borg et al. 2023)

Cause of symptoms

Neuroimaging studies have not definitively linked different neurocognitive symptoms to specific regions of the brain. (Matias-Guiu, Herrera et al. 2023), (Cecchetti, Agosta et al. 2022) 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 C](#). For the evidence review underlying these statements, refer to the VA ESPCC’s Brief Evidence Assessment. (Anderson, Young et al. 2023) Good Practice Statements for Long COVID cognitive impairment are summarized in [Table C](#).

Table C. Guidance for cognitive impairment in Long COVID

[History](#)

[Physical exam](#)

[Evaluation](#)

[Personalized health plan](#)

Evidence-informed recommendations

Good practice statements

Blue boxes

For the evidence underlying these recommendations see: Anderson et al. 2023¹.

Tan boxes

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

History

C-1. Good practice statements

Topic	Details
Assessment of cognitive impairment symptoms	<p>Obtain a detailed history of cognitive symptoms including:</p> <ul style="list-style-type: none"> • 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) (Fine et al. 2022)

C-2. Evidence-informed recommendations

Topic	Recommendation	Details
Montreal Cognitive Assessment (MoCA) to identify cognitive impairment	Consider not using	<p>The MoCA should not be used alone to identify cognitive impairment.</p> <p>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.</p>

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.

Table C. Guidance for cognitive impairment in Long COVID

History	Physical exam	Evaluation	Personalized health plan
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Topic	Recommendation	Details
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

C-3. Good practice statements

Topic	Details
Components of the screening neurologic exam for face-to-face and virtual visits	<p>Face-to-face visit, assess:</p> <ul style="list-style-type: none"> • Vital signs • Gait: <ul style="list-style-type: none"> • 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 <p>Virtual visit, assess:</p> <p>As above except</p> <ul style="list-style-type: none"> • 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.

Table C. Guidance for cognitive impairment in Long COVID

[History](#)
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Evaluation

Laboratory testing

C-4. Good practice statements

Topic	Details
Routine laboratory testing	<p>Consider the following laboratory studies on initial evaluation or if not obtained in the prior 3 months:</p> <ul style="list-style-type: none"> • 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 (U.S. Department of Veterans Affairs Veteran Health Affairs Long COVID Care Strategies and Best Practices Workgroup 2023)
Additional laboratory testing	<p>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.</p>

Diagnostic testing

C-5. Good practice statements

Topic	Details
Computed tomography (CT) and magnetic resonance imaging (MRI)	<p>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 (U.S. Department of Veterans Affairs 2022).</p>

Table C. Guidance for cognitive impairment in Long COVID

[History](#)
[Physical exam](#)
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Personalized health plan: management and treatment

C-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.
Whole Health System 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. <i>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.</i>
Soft belly breathing	Consider use	Consider the use of soft belly breathing when high stress or affective symptoms are present. <i>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.</i>

Table C. Guidance for cognitive impairment in Long COVID

History	Physical exam	Evaluation	Personalized health plan
Topic	Recommendation	Details	
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.	
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 comorbid 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

History

Physical exam

Evaluation

Personalized health plan

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.” (Herrera, Niehaus et al. 2021) 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. [Strategies to Prevent Worsening of Symptoms | ME/CFS | CDC](#)

Severity of fatigue may vary in patients with Long COVID. Anecdotally, some individuals may be able to perform all of 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. (Sandler, Wyller et al. 2021) 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. (Nehme, Chappuis et al. 2023) 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 (Nehme, Chappuis et al. 2023) based on the DePaul brief questionnaire. (Nehme, Chappuis et al. 2023),(Cotler, Holtzman et al. 2018)

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. (Davis, McCorkell et al. 2023)

Fatigue and activity intolerance

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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 (Cotler, Holtzman et al. 2018), a core component of ME/CFS. Several studies examining patients with Long COVID and ME/CFS reported similar symptoms. (Cotler, Holtzman et al. 2018),(Anderson, Young et al. 2023) 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. (Herrera, Niehaus et al. 2021)

Clinical considerations and recommendations

Evidence-informed guidance for Long COVID fatigue and activity intolerance is summarized in [Table D](#). 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 D](#). (Anderson, Young et al. 2023)

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

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Evidence-informed recommendations

Good practice statements

Blue boxes

For the evidence underlying these recommendations see: Anderson et al. 2023¹.

Tan boxes

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

History

D-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 (Herrera, Niehaus et al. 2021).
Post-exertional malaise (PEM)	Assess how the patient responds to initiating and escalating activity and whether they have PEM (Herrera, Niehaus et al. 2021).
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) assessment	Assess whether the patient meets criteria for ME/CFS (Herrera, Niehaus et al. 2021).
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 (Herrera, Niehaus et al. 2021).
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 (Herrera, Niehaus et al. 2021). Its use supports consistent care across the VA system.

¹Anderson, 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.

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

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Physical exam

D-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) (Nurek, Rayner et al. 2021),(Greenhalgh, Sivan et al. 2022).
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 Batch Questionnaire because it can be used in a variety of settings including virtual visits and to follow trends over time (Herrera, Niehaus et al. 2021),(Greenhalgh, Sivan et al. 2022).

Evaluation

Laboratory testing

D-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 (Nurek, Rayner et al. 2021): <ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> • Creatine phosphokinase

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

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Diagnostic testing

D-4. Good practice statements

Topic	Details
Electrocardiogram (EKG)	<ul style="list-style-type: none"> 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). (Herrera, Niehaus et al. 2021)

Personalized health plan: management and treatment

D-5. Evidence-informed recommendations

Topic	Recommendation	Details
Paced activity and energy conservation	Consider use	<p>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.</p> <p>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 (Bateman, Bested et al. 2021).</p>

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

History	Physical exam	Evaluation	Personalized health plan
Topic	Recommendation	Details	
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.	
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. (Kuut et. al., 2023)	

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

History	Physical exam	Evaluation	Personalized health plan
Topic	Recommendation	Details	
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.	
Modafini	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

History

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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.” (Treede) Viral infections have historically been known to trigger new pain conditions of all types. (Tackey, Slepian et al.) 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. (Kerzhner, Berla et al.)

Pain, including post-COVID pain, can be classified as nociceptive, musculoskeletal, neuropathic, or nociplastic. (Di Stefano, Falco et al. 2023) 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. (Fitzcharles, Cohen et al. 2021)

Prevalence and course

An estimated 8-18% of individuals report persistent pain 1 year after COVID. (Alkodaymi, Omrani et al. 2022) 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. (Kerzhner, Berla et al.), (Anderson, Young et al. 2023) 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. (Anderson, Young et al. 2023)

Some Long COVID patients with chronic pain meet the diagnostic testing criteria for ME/CFS (Anderson, Young et al. 2023) (ICD-10 G93.32), POTS (ICD-10 G90.A), fibromyalgia (ICD-10-CM diagnostic code 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 (Anderson, Young et al. 2023) (up to 2.5 years of follow-up). (Komaroff and Lipkin 2023) The cardinal symptom of ME/CFS is post-exertional malaise, defined as worsening of symptoms after mental or physical exertion. (Davis, McCorkell et al. 2023) 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. (Anderson, Young et al. 2023)

Pain

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While ME/CFS symptoms can persist for years, it is not yet clear how long similar symptoms persist in people with Long COVID. (Oliveira, Jason et al. 2022),(Komaroff and Lipkin 2023) 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. (Oliveira, Jason et al. 2022) 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. (Bileviciute-Ljungar, Norrefalk et al. 2022)

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. (Davis, McCorkell et al. 2023)

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.

Pain

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Clinical considerations and recommendations

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. (Fernandez-de-Las-Penas, Palacios-Cena et al. 2021), (Fernández-de-Las-Peñas, Nijs et al. 2023)

While the reliability of this approach has not been established, (Fernandez-de-Las-Penas, Palacios-Cena et al. 2021) we considered it to be a potentially useful framework for incorporating evidence into recommendations for practice. (Fernández-de-Las-Peñas, Nijs et al.) For recommendations about evaluation and treatment of commonly encountered pain syndromes, we relied on evidence-informed, pre-COVID VA/DOD guidelines for headache (U.S. Department of Veterans Affairs 2023) and myofascial pain (Winslow, Vandal et al. 2023) (U.S. Department of Veterans Affairs, 2022), and on pre-COVID, informal clinical review articles about chest pain (Ayloo, Cvengros et al. 2013), neuropathy (Castelli, Desai et al. 2020), muscle weakness (Larson and Wilbur 2020), and fibromyalgia (Winslow, Vandal et al. 2023), some of which graded recommendations.

Table E. Guidance for pain in Long COVID

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Good practice statements

Tan boxes

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

History

E-1. Good practice statements

Topic	Details
Chest pain history elements	<p>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.</p> <p>Consider the following causes of musculoskeletal chest pain (Ayloo, Cvengros et al. 2013):</p> <ul style="list-style-type: none"> • 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 <p>If there is concern for a potential cardiac or pulmonary cause, perform an in-person evaluation.</p>
Headache history elements	<p>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 (2023). Additional reference material: Long COVID headache The Journal of Headache and Pain</p>

Table E. Guidance for pain in Long COVID

History	Physical exam	Evaluation	Personalized health plan
Topic	Details		
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 (Melamed, Rydberg et al. 2023). 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 (Melamed, Rydberg et al. 2023),(Nurek, Rayner et al. 2021),(Herrera, Niehaus et al. 2021).		
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 (Winslow, Vandal et al. 2023).		
Standardized pain assessments	Assess pain symptoms at initial and follow-up visits using tools such as (U.S. Department of Veterans Affairs Veteran Health Affairs Long COVID Care Strategies and Best Practices Workgroup, 2023): <ul style="list-style-type: none"> • VA Long COVID Questionnaire Batch • Pain, Enjoyment of Life, and General Activity Scale (PEG scale) • MIDAS (if headache) (MIDAS) 		

Physical exam

E-2. Good practice statements

Topic	Details
Routine physical exam elements	When pain is present, perform a musculoskeletal and neurologic examination (U.S. Department of Veterans Affairs Veteran Health Affairs Long COVID Care Strategies and Best Practices Workgroup, 2023).
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) (Ayloo, Cvengros et al. 2013). <ul style="list-style-type: none"> • For more information on evaluation of musculoskeletal chest pain see here: Evaluation and Treatment of Musculoskeletal Chest Pain.

Table E. Guidance for pain in Long COVID

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Evaluation

Laboratory testing

E-3. Good practice statements

Topic	Details
Routine laboratory testing	<p>Consider the following laboratory studies on initial evaluation if not obtained in the prior 3 months (Melamed, Rydberg et al. 2023),(Greenhalgh, Sivan et al. 2022):</p> <ul style="list-style-type: none"> • 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	<p>Additional laboratory testing should be offered based on the history and physical examination findings:</p> <ul style="list-style-type: none"> • 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.

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Diagnostic testing

E-4. Good practice statements

Topic	Details
Headache red flags or imaging	<p>Consider imaging if there are headache red flags, as recommended by VA-DoD Headache Pocket Card (U.S. Department of Veterans Affairs 2023):</p> <ul style="list-style-type: none"> • Systemic symptoms, illness, or condition <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • 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 • 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	<p>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) (Castelli, Desai et al. 2020):</p>

Table E. Guidance for pain in Long COVID

History	Physical exam	Evaluation	Personalized health plan
Topic	Details		
Peripheral neuropathy diagnostic testing (continued)	<ul style="list-style-type: none"> 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 <p>If initial evaluation is unrevealing, consider referral to neurology and/or physical medicine & rehabilitation</p>		
Myopathic pain diagnostic testing	<p>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) (Larson and Wilbur 2020):</p> <ul style="list-style-type: none"> Electrodiagnostic studies if the diagnosis is unclear after a history, physical examination, and targeted laboratory evaluation <p>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</p>		

Personalized health plan: management and treatment

E-5. Good practice statements

Topic	Details
General principles of pain management in Long COVID	<ul style="list-style-type: none"> Use a multidisciplinary approach to treatment that includes both pharmacologic and nonpharmacologic approaches (Melamed, Rydberg et al. 2023),(U.S. Department of Health and Human Services 2019). 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/arthritis.

Table E. Guidance for pain in Long COVID

History	Physical exam	Evaluation	Personalized health plan
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Topic	Details
General principles of pain management in Long COVID (continued)	<ul style="list-style-type: none"> 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 (U.S. Department of Veterans Affairs 2022).

Symptom specific recommendations

E-6. Good practice statements

Topic	Details
Treatment of neuropathic pain	<p>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 (Price, Smith et al. 2022):</p> <ul style="list-style-type: none"> 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, lidoderm patch, and topical capsaicin.
Treatment of musculoskeletal chest pain	<p>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 (Ayloo, Cvengros et al. 2013):</p> <ul style="list-style-type: none"> 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	<p>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</p>

Table E. Guidance for pain in Long COVID

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Topic	Details
<p>Treatment of fib omyalgia pain</p>	<p>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:</p> <p>Clinicians can consider the following interventions for pain consistent with fibromyalgia in Long COVID based on pre-COVID guidance:</p> <ul style="list-style-type: none"> • Cognitive Behavioral Therapy • Mindfulness-based therapies <ul style="list-style-type: none"> • Examples of mindful-based therapies include mindfulness-based stress reduction (MBSR) and meditation awareness training (MAT). • Emotion-focused therapy <ul style="list-style-type: none"> • 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 <p>VA/DoD CMI Guidelines found insufficient evidence to recommend for or against the use of:</p> <ul style="list-style-type: none"> • 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 <p>VA/DoD CMI Guidelines recommend against offering nonsteroidal anti-inflammatory drugs for chronic pain consistent with fibromyalgia.</p>

References

General guidance

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Appendix

Long COVID Clinic Questionnaire Batch

Please note: if you're accessing these questionnaires through the VA CPRS system, the name of the questionnaire batch is Long COVID-19 Questionnaire.

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.

Long COVID Whole Health Questions

All questions below were provided by the VA Clinical Services Product Line

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 Yorkshire Rehabilitation Scale¹

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)

a) Fatigue levels in your usual activities (not improved by rest)

NOW

PRE-COVID

¹Sivan, M., N. Preston, A. Parkin, S. Makower, J. Gee, 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.

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. Personal 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

Average score 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) Questionnaire²

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:

²Coleman 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 participant 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?