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Review Article

Evaluation and treatment approaches for neurological post-acute sequelae of COVID-19: A consensus statement and scoping review from the global COVID-19 neuro research coalition

Jennifer A. Frontera [a,*], Alla Guekht [h,i], Ricardo F. Allegri [b], Mariam Ashraf [c], Betül Baykan [d], Lucía Crivelli [b], Ava Easton [e,f], David Garcia-Azorin [g], Raimund Helbok [j,k], Jatin Joshi [c], Julia Koehn [l], Igor Koralnik [ab], M. Netravathi [m], Benedict Michael [f,n,o], Annacarmen Nilo [p], Aynur Özge [q], Karanbir Padda [a], Gaia Pellitteri [p], Kameshwar Prasad [r], Marina Romozzi [s,t], Deanna Saylor [u,v], Adam Seed [o], Kiran Thakur [w], Derya Uluduz [d], Alberto Vogrig [p,x], Tamara M. Welte [l,y], Erica Westenberg [y], Dmitry Zhuravlev [h], Mikhail Zinchuk [h], Andrea S. Winkler [y,z,aa]

[a] Department of Neurology, New York University Grossman School of Medicine, New York, NY, USA
[b] Department of Cognitive Neurology, Fleni, Buenos Aires, Argentina
[c] Department of Anesthesiology, Weill Cornell Medical Center, New York Presbyterian Hospital, New York, NY, USA
[d] Department of Neurology, Istanbul University, Istanbul Faculty of Medicine, and EMAR Medical Center, Istanbul, Turkey
[e] The Encephalitis Society, Malton, UK
[f] Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, UK
[g] Department of Neurology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain
[h] Moscow Research and Clinical Center for Neuropsychiatry, Moscow, Russia
[i] Pirogov Russian National Research Medical University, Moscow, Russia
[j] Department of Neurology, Neuro-Intensive Care Unit, Medical University of Innsbruck, Innsbruck, Austria
[k] Department of Neurology, Johannes Kepler University, Linz, Austria
[l] Department of Neurology, Universitätsklinikum Erlangen, Erlangen, Germany
[m] Department of Neurology, National Institute of Mental Health & Neurosciences, Bangalore, India
[n] National Institute for Health Research Health Protection Research Unit in Emerging and Zoonotic Infections, University of Liverpool, UK
[o] The Walton Centre NHS Foundation Trust, Liverpool, UK
[p] Clinical Neurology, Santa Maria della Misericordia University Hospital, Azienda Sanitaria Universitaria Friuli Centrale (ASU FC), Udine, Italy
[q] Department of Neurology, Faculty of Medicine, Mersin University, Mersin, Turkey
[r] Chief Executive Office, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India
[s] Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[t] Dipartimento Universitario Di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy
[u] Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[v] Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia
[w] Department of Neurology, Columbia University Irving Medical Center/New York Presbyterian Hospital, New York, NY, USA
[x] Department of Medicine, University of Udine Medical School, Udine, Italy
[y] Department of Neurology, Center for Global Health, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany
[z] Department of Community Medicine and Global Health, Institute of Health and Society, University of Oslo, Oslo, Norway
[aa] Blavatnik Institute of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA
[ab] Departmentof Neurology, Northwestern Feinberg School of Medicine, Chicago, IL, USA

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ABSTRACT

Post-acute neurological sequelae of COVID-19 affect millions of people worldwide, yet little data is available to guide treatment strategies for the most common symptoms. We conducted a scoping review of PubMed/Medline from 1/1/2020–4/1/2023 to identify studies addressing diagnosis and treatment of the most common post-acute neurological sequelae of COVID-19 including: cognitive impairment, sleep disorders, headache, dizziness/

* Corresponding author at: NYU Department of Neurology, 150 55th St., Brooklyn, NY 11231, USA.
E-mail address: jennifer.frontera@nyulangone.org (J.A. Frontera).

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lightheadedness, fatigue, weakness, numbness/pain, anxiety, depression and post-traumatic stress disorder. Utilizing the available literature and international disease-specific society guidelines, we constructed symptom-based differential diagnoses, evaluation and management paradigms. This pragmatic, evidence-based consensus document may serve as a guide for a holistic approach to post-COVID neurological care and will complement future clinical trials by outlining best practices in the evaluation and treatment of post-acute neurological signs/symptoms.

1. Introduction

Post-acute sequelae of COVID-19 (PASC), sometimes known as "long COVID", "long-haul COVID", has been identified as a major international public health concern with profound socio-economic ramifications [1]. A study by the Brookings Institute conducted in August 2022 reported that an estimated 16 million Americans aged 18–65 years have PASC, and 2–4 million people may be unable to work due to long-COVID symptoms, resulting in $170–230 billion in lost wages annually [2]. In a prospective study of PASC, 12-months after hospitalization, 45% of patients reported that neurological symptoms limited their ability to work at their pre-COVID level, 50% were unable to perform routine household responsibilities, and 54% were limited in their ability to engage in leisure activities [3,4]. Ongoing cases of COVID-19 mean the population of people affected by these long-term consequences will continue to grow. Additionally, there may be associated impacts on health and social care systems.

Despite the far-reaching impacts of PASC, there is a dearth of data available on the evaluation and management of the most common PASC neurological signs/symptoms, in part because the underlying pathophysiology of PASC is poorly understood. Since the biological signatures of PASC are still under investigation, the diagnosis remains a clinical one, and criteria for diagnosis vary across world organizations. While the World Health Organization (WHO) developed consensus criteria based on a Delphi process that calls for new or continued symptoms ≥3 months after index SARS-CoV-2 [5], the U.S. Centers for Disease Control and Prevention (CDC) define "long COVID" as signs, symptoms and conditions that continue or develop ≥4 weeks after the initial infection [6]. Based on either criteria, signs and symptoms should not be attributable to another disorder. Additionally, more than 70% of patients report several different PASC symptoms [3], necessitating a multidisciplinary, holistic approach to patient management [7]. While some studies have demonstrated that COVID-19 vaccination may prevent the development of PASC [8,9], much less is known about treatment options in those who have already developed signs/symptoms. Strategies for management of acute neurological events in COVID-19 have been addressed by the WHO and others [10,11], however, less guidance is available for therapeutic interventions in the post-acute time frame. In response to the urgent need for global consensus-based evaluation and treatment strategies for neurological PASC, the Global COVID-19 Neuro Research Coalition, together with members of the WHO Brain Health COVID-19 Task Force, formed a working group to review the current COVID-19 literature and provide evidence-based management algorithms for the most common PASC neurological sequelae including: cognitive impairment, headache, dizziness/lightheadedness, numbness/tingling, muscle weakness, sleep disorders, fatigue, anxiety, depression and PTSD. While other neurological sequelae of COVID-19 have been reported including movement disorders [12,13], neuro-ophthalmological disorders [14], and functional disorders [15], among others, we attempted to narrow the scope of this document to the most commonly reported sequelae [3,4,16]. This pragmatic document is meant to guide clinical care, as well as complement future clinical trials by outlining best practices in the evaluation and treatment of PASC neurological symptoms.

2. Methods

2.1. Panel composition

The writing group included members of the Global COVID-19 Neuro Research Coalition [17,18], which is an international group of neurologists, neuroscientists and allied professionals that works closely with the WHO Brain Health COVID-19 task force and its COVID-19 long-term follow-up group. The group is composed of 120 neurologists and researchers from 38 high, middle and low income countries. Members with subspecialty training in cognition, headache, dysautonomia, neuromuscular disorders, neuroinfectious disease, pain management, sleep and neuropsychiatric disorders representing 11 countries (including low and middle-income countries) were recruited to develop this consensus statement. All panel members were required to comply with standard conflict of interest and commercial relationship disclosures including review of any financial, intellectual, or other relationships that may be construed as a possible conflict of interest. All members of the consensus panel were determined to be free of conflicts of interest.

2.2. Study population

This consensus statement applies to post-acute neurological signs/symptoms in hospitalized and non-hospitalized adults (aged ≥18 years) with laboratory evidence of SARS-CoV-2 infection. We specifically focused on the most commonly reported signs/symptoms of cognitive impairment, headache, dizziness/lightheadedness, numbness/tingling, muscle weakness, sleep disorders, fatigue, anxiety, depression and PTSD.

2.3. Inclusion and exclusion criteria

Study inclusion criteria were: 1) adult patients (aged ≥18 years) with neurological symptoms present ≥4 weeks after COVID-19 diagnosis (based on Centers for Disease Control and Prevention [CDC] diagnostic criteria) [6,19]; and 2) evaluation, diagnosis and/or treatment of PASC neurological symptoms or disorders in the domains of cognition, sleep disorders, headache, dizziness/lightheadedness, fatigue, numbness/tingling, muscle weakness, anxiety, depression or PTSD. Included study designs were observational, prospective, retrospective, case series with >10 subjects, or clinical trials. We excluded preclinical and non-human studies, case reports, gray literature and non-English literature. Review articles and meta-analyses were utilized to identify original articles that met inclusion criteria. Additionally, international society guidelines that pertained to each sign/symptom area were reviewed and incorporated into management algorithms, as applicable.

2.4. Search strategy

We conducted a scoping review of PubMed/Medline using the following search terms: "COVID", OR "COVID-19", OR "SARS-CoV-2", OR "coronavirus", AND "long COVID", OR "post-acute", OR "sequelae", OR "outcomes", OR "long hauler", AND "therapy", OR "therapeutics", OR "management", OR "treatment", OR "diagnosis", OR "evaluation" in conjunction with sign/symptom specific key words for each domain of cognition, headache dizziness/lightheadedness, numbness/tingling,

Table 1
Differential Diagnosis of PASC Cognitive Dysfunction.

Category	Etiology/Subtype	Features
Dementia	• Alzheimer's disease • Vascular dementia • Lewy body dementia • Parkinson's dementia • Frontotemporal dementia • Normal pressure hydrocephalus • Prion disease • Alcohol related dementia • Progressive supranuclear palsy • Multiple system atrophy • Corticobasal degeneration	Gradual short-term memory loss with functional impairment in basic activities of daily living (feeding, bathing, grooming, dressing, toileting) and instrumental activities of daily living (cooking, cleaning, shopping, paying bills, driving). Vascular dementia classically presents with a step-wise decline. Parkinsonian symptoms (tremor, stiffness, bradykinesia) occur in Parkinson's dementia, dementia with Lewy bodies, Multiple System Atrophy, Corticobasal degeneration, and Progressive Supranuclear Palsy. Mixed neuropathology occurs in 20–45% of patients with probable Alzheimer's or mild cognitive impairment [232,233].
Cerebrovascular disease	• Ischemic stroke • Subarachnoid hemorrhage • Intraparenchymal hemorrhage	Sudden onset, focal findings, abrupt decrease in level of consciousness. Long-lasting static focal deficits.
Medical illness	• Hypo/hyperthyroidism • Hypo/hyperparathyroidism • Adrenal insufficiency • Uremia • Hepatic encephalopathy • Hearing loss • Hypoxic/ischemic brain injury • Hypertensive encephalopathy	May present as delirium with abrupt decline in cognitive function with fluctuating levels of attention, or with subacute decline. Typical history, physical and laboratory findings present. Improved cognitive state with treatment of underlying disorder.
Psychiatric illness	• Depression • Bipolar disorder • Thought disorder (e.g. schizophrenia)	Memory loss accompanied by depressed mood, decreased concentration, impaired judgement, feelings of hopelessness, worthlessness, suicidal ideations, bizarre thinking, auditory hallucinations, disorganization
Infection/ Inflammation	• Septic encephalopathy • HIV • Lyme disease • Syphilis • Meningitis/encephalitis • Lupus, sarcoid, autoimmune disease • Autoimmune encephalitis • Paraneoplastic disorders • Multiple sclerosis	May present as delirium with abrupt decline in cognitive function with fluctuating levels of attention, or with subacute decline. Typical history, physical and laboratory findings present. Improved cognitive state with treatment of underlying disorder.
Vitamin deficiency	• B12 deficiency • Thiamine deficiency • Niacin deficiency • Folate deficiency	May present as delirium with abrupt decline in cognitive function with fluctuating levels of attention, or with subacute decline. Typical history, physical and laboratory findings present. Improved cognitive state with treatment of underlying disorder.
Metabolic derangement	• Hypo/hyperglycemia • Hypo/hypernatremia • Hypo/hypercalcemia • Hyper/hypophosphatemia • Hyper/hypomagnesemia • Acidosis • Hypoxemia • Hypercapnia • Inborn errors of metabolism	Delirium with abrupt decline in cognitive function with fluctuating levels of attention, improved cognitive state with treatment of underlying disorder
Sleep disorder	• Insomnia • Sleep-related breathing disorders (e.g. sleep apnea) • Central disorders of hypersomnolence (e.g. narcolepsy)	Excessive daytime sleepiness, fragmented or poor sleep, snoring, short sleep latency
Seizure disorder	• Focal seizures with impaired awareness (complex partial seizure) [234] • Non-convulsive/subtle seizures • Nonmotor generalized seizure (Absence seizures) [234]	Accompanied by history of behavior arrest, staring spells, episodes of losing time or getting lost interspersed with periods of normal cognition. Preceding risk factors such as meningitis/encephalitis, febrile seizures, head trauma, mass lesion etc.
Medication side effects	• Opiates • Anti-psychotics • Antihistamines • Anticholinergics • Beta-blockers • Digoxin • Benzodiazepines • Barbiturates • Antiemetics • Dopamine agonists • Muscle relaxants • SSRIs, SNRIs, tricyclics, lithium	Medication history, eliminate polypharmacy or drugs with sedating effects
Substance abuse	• Alcohol • Opiates • Marijuana • Barbiturates • Amphetamines • Hallucinogens	Accompanying exposure history
Toxins/Exposure	• Lead • Arsenic • Other heavy metals • Carbon monoxide • Ethylene glycol • Methanol • Hypo/hyperthermia	Accompanying exposure history, other physical stigmata typically present
Structural brain lesion	• Brain tumor • Demyelinating disease • Abscess • Head trauma/concussion	Typically accompanied by focal deficits, with appropriate history, imaging findings

muscle weakness, sleep disorders, fatigue, anxiety and depression. Domain specific search terms can be found in **Supplemental Table 1.** For each neurological symptom domain we discuss the epidemiology, differential diagnosis, treatment options and present a consensus-based algorithm for overall evaluation and treatment.

3. Results

3.1. Brain fog and cognitive disorders

Epidemiology: Cognitive dysfunction in previously healthy, cognitively normal individuals has been widely described following COVID-19, and particularly affects domains of memory and attention, with a high co-occurrence with depression [20–36]. The prevalence of cognitive impairment in the acute period after SARS-CoV-2 infection (i.e. first month) ranges from 15% in mixed cohorts of hospitalized and non-

Table 2
Evaluation of PASC Cognitive Dysfunction.

PASC Cognitive Evaluation		
NEUROPSYCHOLOGICAL TESTING		
Study	Examples	Interpretation/ Consideration
Global Cognition Screening tools	Montreal Cognitive Assessment (MoCA)	>26/30 normal with a 1-point adjustment for years of education (≤12 years) 18–25 mild cognitive impairment (MCI) 10–17 moderate cognitive impairment ≤10 severe cognitive impairment.
	Mini-mental State Examination (MMSE)	MMSE: Normal Score ≥ 25; scores <24 abnormal, indicating cognitive impairment. The use of normal scores from equivalent language, age, and education populations is recommended.
LABORATORY TESTING		
Study	**Examples**	**Interpretation/ Consideration**
Lumbar puncture	In specific patients: To rule out other diseases that can mimic dementia (e.g. meningitis, encephalitis, leptomeningeal cancer, paraneoplastic disorder)	To evaluate other dementia types (e.g. Alzheimer's disease (beta-amyloid, tau, Phosphorylated tau, ratio of amyloid/Tau), Creutzfeldt-Jakob Disease (14–3-3, RT QuIC), paraneoplastic panel, flow-cytometry/cytology
Serology tests	Screening for B12 deficiency and hypothyroidism is recommended by the AAN [235].	In select cases: Chemistry panel, liver function tests, complete blood count, HIV, serology for syphilis, APOE genotyping Note- there are no guideline recommended biomarkers for mild cognitive impairment or dementia
NEUROIMAGING		
Study	**Examples**	**Interpretation/ Consideration**
MRI or CT with contrast (most clinicians prefer MRI when imaging is indicated)	In specific patients: Brain structural lesions, normal pressure hydrocephalus, etc.	Can be considered based on history and physical exam. Used to exclude other causes of cognitive impairment
Advanced imaging (in select cases, often part of a research protocol)	In specific patients: FDG-PET Amyloid PET DaTscan SPECT	FDG-PET may show hypometabolism in hippocampus, mesial parietal, lateral parietal and posterior temporal cortex in Alzheimer's dementia Amyloid PET for Alzheimer's dementia DaTscan visualizes striatal dopamine transporters for Parkinsonian syndromes and suspected dementia with Lewy bodies

hospitalized patients [37] to 62–80% in moderate to severely ill hospitalized COVID-19 patients [38]. In the post-acute timeframe, persistent cognitive impairment lasting up to 12- months, has been reported in 50–65% of COVID-19 who required hospitalization during index SARS-CoV-2 infection [39,40]. The prevalence of cognitive impairment in patients not requiring hospitalization is suspected to be much lower, though population-based data is lacking. It is important to note that subjective cognitive dysfunction and objective findings of cognitive impairment post-COVID-19 may be incongruous. In a prospective study of 100 hospitalized and 500 non-hospitalized COVID-19 patients referred to a COVID-19 neurological follow-up clinic and evaluated a

Table 3
Treatment Options for PASC Cognitive Dysfunction based on WHO [60] and AAN [61] guidelines.

Type of intervention	Description	Quality of Evidence [60] Strength of Recommendation
Non-pharmacologic		
Cognitive Training [60]	• Cognitive rehabilitation therapy, cognitive remediation [236,237]: selection of specific cognitive activities to acquire compensatory and environmental strategies that sustain and improve functionality. • Cognitive Stimulation Therapy [238]: psychosocial group intervention, focusing on implicit information processing to improve cognition and quality of life. • Attention processing training [239]: Aims to improve the ability to focus on relevant material and ignore irrelevant distractions. It aims to improve the speed of information processing. • Virtual Reality [240,241]: simulation of virtual places and environments that allow the user to experience the sensation of being present. • Neurofeedback [242]: Aims to improve cognitive function through the regulation of brain activity, using different technologies (EEG, fMRI, fNIRS). • Technical assistive support [243]: Use of assistive technologies, such as touch screen devices for stimulation, entertainment and quality of life enhancement. Also used for reminiscence through pictures, music, and apps. It has also been used as a memory aid or even for medication managers. • Meditation [244]: Yogic breathing and guided meditation; cognitive behavioral therapy with mindfulness, meditation, and applied stretching; Acceptance and Commitment Therapy (ACT) components; psychoeducation.	Very low to low/ Conditional
Cardiovascular exercise and physical activity [60,245]	• Diverse modality therapy including dance, walking, cycling, handball, and aerobic exercise. It has been found to improve attention, processing speed, executive functioning, and memory. • Cardiopulmonary rehabilitation [246,247]:	Moderate/Strong for adults with normal cognition Low/Conditional for MCI

(continued on next page)

Table 3 (*continued*)

Type of intervention	Description	Quality of Evidence [60] Strength of Recommendation
	Nutritional counseling, risk factor modification, psychosocial treatment, patient education, and physical training.	
Weight management [60]	For mid-life overweight or obese patients	Low to Moderate/ Conditional
Tobacco cessation [60]	Both cognitive benefits and other health benefits. May be particularly useful for reducing vascular dementia risks	Low/Strong
Alcohol use [60]	Interventions to reduce or cease hazardous or harmful alcohol use in both normal cognition and mild cognitive impairment	Moderate/ Conditional
Nutritional interventions [60,248,249]	Mediterranean diet, balanced health diet recommended. Vitamins B, E, PUFA and multi-complex supplementation not recommended	Moderate/ Conditional for diet Moderate/Strong against supplements
Pharmacologic		
Cholinesterase inhibitors	• Donepezil • Galantamine • Rivastigmine	Approved for use in Alzheimer's disease, suggested for use in dementia with Lewy Bodies. May be useful for vascular dementia, Parkinson dementia or mixed dementias. Data suggests they are possibly ineffective in mild cognitive impairment
NMDA Receptor antagonist	• Memantine	Approved for moderate-severe Alzheimer's
Monoclonal antibodies against amyloid beta	• Aducanumab • Lecanemab	Benefit for adjucanumab in Alzheimer's is uncertain. Evidence supporting lecanemab use in early Alzheimer's is stronger [250]. Both are expensive with serious side effect profiles.
Antioxidants	• Vitamin E • Selegiline (monoamine oxidase inhibitor)	Vitamin E may slow functional decline in Alzheimer's dementia, but limited benefits in MCI [251]. There is little data to support the use of selegiline
Management of Vascular Risk factors [60]	• Hypertension • Diabetes • Dyslipidemia	Very low to low/ Conditional

Abbreviations: EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; fNIRS, functional near-infrared spectroscopy; MCI, mild cognitive impairment; FDA, Food and Drug Administration.

mean of 6.8 months after index infection, 86% of post-hospitalization and 80% of non-hospitalized patients reported brain fog ($P = 0.21$) [41]. However, post-hospitalization patients performed significantly worse on cognitive tests, particularly in domains of processing speed, attention and working memory [41]. Conversely, in a longitudinal cohort study of 174 patients evaluated 12-months after hospitalization for COVID-19, 20% of patients reported symptoms of cognitive impairment, while 44% tested in the abnormal range on the telephone Montreal Cognitive Assessment test [4,16]. These data imply that a degree of anosognosia may be present in some patients.

Risk factors for PASC cognitive symptoms include older age, life stressors, history of depression/mood disorders, unemployment pre-COVID, poor baseline functional status, fewer years of education, APOE-e4 status, index COVID-19 severity and pre-COVID cognitive impairment [4,41–46]. Recent epidemiological and neurological studies also suggest that persons with COVID-19, and especially severely affected COVID-19 patients with protracted hypoxia, may be predisposed to the development of neurodegenerative disorders that include Alzheimer's dementia due to latent viral effects on brain structure, function, and homeostasis [47–54].

Differential Diagnosis: The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for major neurocognitive disorders (previously "dementia") are listed in **Supplemental Table 2** [55]. Evaluation of factors that can impact cognition, other than dementia, are critical for the initial patient assessment. Medical and psychiatric comorbidities, social factors and substance abuse history should be explored prior to more extensive neuropsychological testing. The differential diagnosis for symptoms of cognitive dysfunction can be found in Table 1.

Diagnostic Evaluation: A thorough history, physical and neurological exam should be conducted addressing possible dementia mimics listed in Table 1**.** A study partner/informant should also be interviewed for collateral information on memory loss and impact on functional activities. All patients presenting with PASC cognitive impairment should undergo screening tests for cognition as well as depression, anxiety, fatigue and sleep disorders. In resource-available settings we recommend performing an in-depth neuropsychological assessment using a comprehensive cognitive battery. In addition, we recommend collecting data on disease characteristics of acute COVID-19 (disease severity: mild, moderate, and severe), co-existing medical conditions (including premorbid cognitive impairment), substance abuse screening, assessment of life stressors and evaluation of premorbid functional status. Diagnostic strategies for evaluating PASC cognitive function are outlined in Table 2**and Supplemental Table 3.**

Therapeutic options

COVID-19 Specific Treatments: A scoping review identified four clinical trials that addressed PASC cognitive symptoms. One study randomized patients with PASC cognitive disturbances to 40 sessions of hyperbaric oxygen therapy over two months ($N = 37$) compared to sham sessions ($N = 36$) [56]. The authors hypothesized that hyperbaric oxygen therapy would improve cerebral blood flow and induce neuroplasticity. Overall, there was a modest, but significant improvement in neuropsychological scores measured before and 1–3 weeks after therapy. However, the control group also improved spontaneously over time and the durability of this effect, as well as the cost-benefit ratio, remains unknown. Another small study of patients with PASC olfactory dysfunction (38% of whom also had "mental clouding") randomized subjects to the nutritional supplements palmitoylethanolamide and luteolin with or without olfactory training [57]. While there was significant improvement in subjective measures of "brain fog" in each group after 3-months, both groups received the nutritional supplement and there was no control group. Hence, spontaneous improvement could account for the observed cognitive changes. A third study evaluated the α2A-adrenoceptor agonist, guanfacine plus *N*-acetylcysteine in 12 patients with PASC cognitive symptoms [58]. Guanfacine was chosen because it may hypothetically strengthen prefrontal cortex connectivity and *n*-acetylcysteine may reduce kynurenic acid blockade of NMDA receptors and act as a mitochondrial protectant. Subjective cognitive improvement was reported in 8 of 12 patients, though there was no formal neuropsychometric testing and there was no control group. Last, a randomized study of a four-week neuro-meditation program, including sound and light therapy and coach-guided meditation, found improvements in both subjective cognitive symptoms and performance on computerized cognitive tasks in $N = 17$ study subjects compared to N =

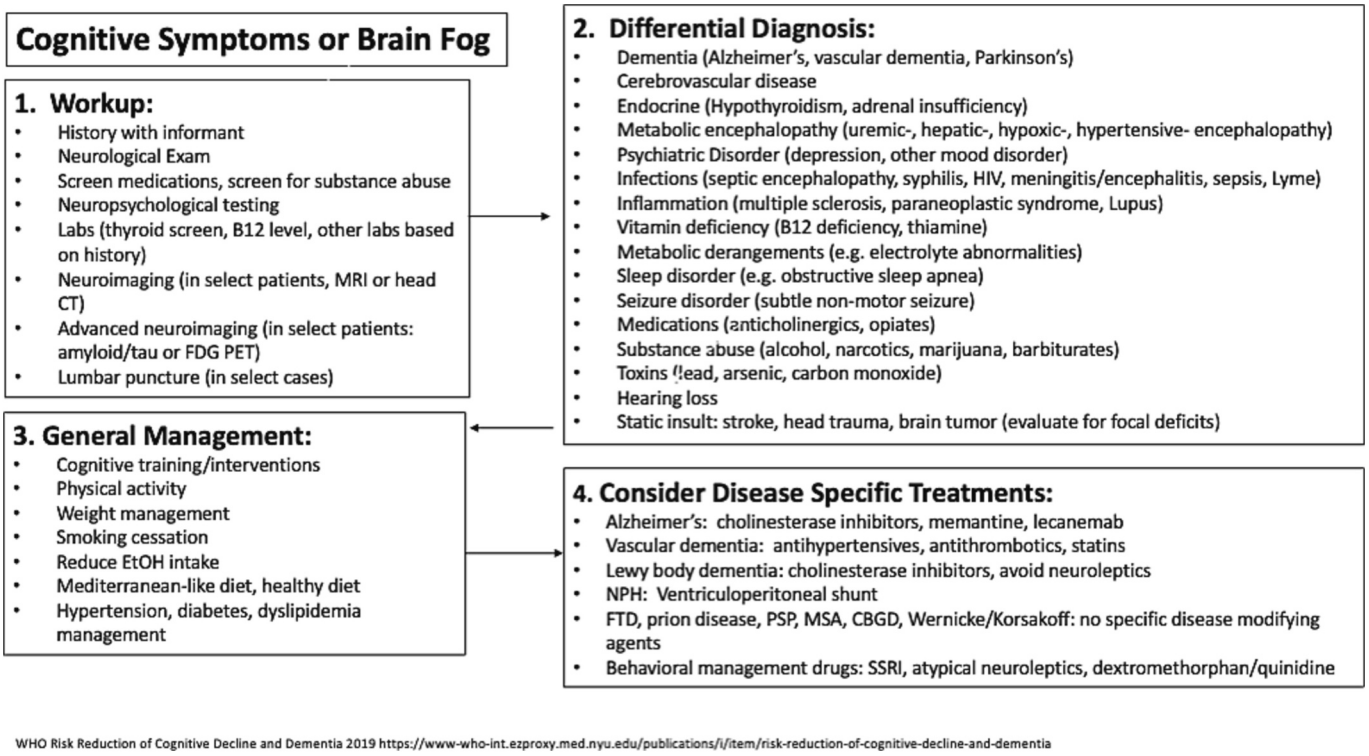

Fig. 1. Evaluation and Management of PASC cognitive symptoms.
ETOH, alcohol; PTSD, post-traumatic stress disorder; NPH, normal pressure hydrocephalus; FTD, frontal-temporal dementia; PSP, progressive supranuclear palsy; MSA, multi-system atrophy; CBGD, cortical basal ganglionic degeneration.

Table 4
Differential Diagnosis of Excessive Daytime Sleepiness.

Category	Examples
Primary Sleep Disorder	See Table 5.
Insufficient Sleep	• Environmental intrusions • Sleep deprivation, volitional sleep loss
Medication use	• Benzodiazepines • Opiates • Antihistamines • Antiseizure medications • Neuroleptics • Antidepressants • Barbiturates • Beta-blockers
Substance abuse	• Alcohol • Narcotics • Amphetamine withdrawal • Marijuana
Medical comorbidities	• Neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, dementia with Lewy Bodies, multiple system atrophy, amyotrophic lateral sclerosis • Prion disease including Creutzfeldt-Jacob disease, Fatal Familial Insomnia • Multiple Sclerosis • Structural lesions of the hypothalamus, thalamus or brainstem reticular activating system • Encephalitis lethargica • Hypothyroidism • End-stage renal disease/uremia • Advanced liver cirrhosis/hepatic encephalopathy • Adrenal insufficiency • Prader-Willi syndrome • Kleine-Levin syndrome • Niemann-Pick type C
Psychiatric disorders	• Depression • Anxiety • Post-traumatic stress disorder • Psychogenic sleepiness

17 controls with PASC cognitive symptoms. Symptoms of anxiety, depression, and sleep disruption were also improved with meditation [59]. Despite the encouraging findings, each of these trials is small and exploratory. Larger, controlled trials are needed prior to recommending any of the above therapies.

Current WHO Post-COVID guidelines provide a conditional recommendation for combining education, skills training on self-management strategies and cognitive exercises [11]. In the absence of robust clinical trial data specific to PASC cognitive impairment, adhering to society guidelines for the general management of cognitive disorders, including those from the WHO [60] and AAN [61], may be reasonable (Table 3). Pharmacological interventions are suggested only for patients with specific, appropriate dementia diagnoses. Addressing dementia mimics discussed in Table 2. should represent a first step in management. A summary of the evaluation and management of PASC cognitive symptoms can be found in Fig. 1.

3.2. Sleep disorders

Epidemiology: COVID-19 has severely affected sleep quality, sleep patterns, diagnosis, and management of sleep disorders [62]. The term "coronasomnia" was coined to include all sleep disorder symptoms commonly observed during the pandemic, including insomnia, impaired sleep quality, and circadian rhythm sleep-wake alterations [62,63]. Indeed, the pandemic-related lockdown restrictions contributed to a tendency to delay sleep and wake-times, with a reduction of night sleep duration and an increase of daytime napping, promoting not only insomnia, but also changes to usual circadian rhythms [64,65]. In addition, poor sleep quality itself has been recognized as a risk factor for the development of PASC [66]. Meta-analyses including 10,000 to 257,000 COVID-19 survivors, with a follow-up period ranging from one month to more than 12 months have identified insomnia and "sleep disturbance" in about 24–44% of COVID-19 patients [67–72]. However, several authors observed a decreasing prevalence of sleep disorders as

Table 5
Classification of Sleep Disorders.

Disease	Subtypes	Key Features	Subcategories and Notes
Insomnia	Chronic Insomnia Disorder (ICSD-3)	Difficulty initiating sleep, maintaining sleep, waking up earlier than desired with an inability to return to sleep, occurring at least 3 nights per week for at least 3 months; not better explained by other environmental factors, medical conditions, psychiatric disorders, medications or substances; associated with diurnal symptoms (e.g., EDS, fatigue, cognitive and behavioral impairment, reduced daily functioning)	• Insomnia with medical comorbidity: Most commonly with arthritis, cancer, hypertension, chronic pain, coronary heart disease, and diabetes • Insomnia with mental comorbidity: Most commonly with anxiety, depression, panic disorder, adjustment disorder, somatoform disorders, and personality disorders. • Insomnia with drug or substance intake: Herbal remedies, licit substances (e.g., caffeine, nicotine, alcohol), licit drugs that may be abused (e.g., methylphenidate, modafinil, sodium oxybate), illicit stimulants (e.g., cocaine, ecstasy) and depressants (e.g., cannabis, opioids) can precipitate and perpetuate insomnia • Insomnia with other sleep disorders: Most commonly with sleep-related breathing disorders, circadian rhythm sleep-wake disorders, parasomnias and sleep-related movement disorders
	Short-term Insomnia Disorder (ICSD-3)	Insomnia symptoms lasting less than 3 months but otherwise meeting all criteria with regard to frequency, intensity, distress, and/or impairment	
Sleep-related Breathing Disorders	Obstructive sleep apnea	Repetitive episodes of partial (hypopnea) or complete (apnea) obstruction of the upper airway during sleep; associated nocturnal symptoms include snoring, gasping, choking, awakenings, restless sleep, dry mouth; daytime symptoms include EDS, fatigue, cognitive impairment, mood disorders, morning headache	Mimics include: • Sleep-related laryngospasm or choking • Mucous plugging • Snoring without apnea • Nocturnal asthma • Gastroesophageal reflux disease • Nocturnal seizures Associated conditions: • Obesity • Micrognathia, retrognathia • Tonsillar, uvular hypertrophy • Macroglossia • High-arched palate • Nasal obstruction • Hypertension • Atrial fibrillation • Stroke • Pulmonary hypertension • Diabetes • End-stage renal disease • Pregnancy • Acromegaly • Hypothyroidism • Polycystic ovary disease • Congestive heart failure • Chronic obstructive lung disease or restrictive lung disease • Neuromuscular disease with bulbar and/or respiratory muscle involvement
	Central sleep apnea	Repetitive episodes of partial (hypopnea) or complete apnea during sleep	• With or without Cheyne-Stokes breathing • Due to high altitude periodic breathing (at least 2500 m) • Central sleep apnea of infancy • Central sleep apnea of prematurity • Treatment-emergent central sleep apnea • Associated with heart failure, stroke, opiate use • Ondine's curse- impaired autonomic control of ventilation caused by brainstem tumors, medullary strokes
	Sleep-related hypoventilation	Defined by elevations in PaCO2 levels	• Obesity hypoventilation syndrome • Congenital central alveolar hypoventilation syndrome • Late-onset central hypoventilation with hypothalamic dysfunction • Idiopathic central alveolar hypoventilation
Central Disorders of Hypersomnolence	Narcolepsy	EDS with irresistible sleep attacks, mean sleep latency $\leq$8 min, two sleep onset rapid eye movement periods within 15 min of sleep onset, cataplexy (only in NT1), sleep paralysis, hypnagogic and hypnopompic hallucinations, fragmented nocturnal sleep and sleep maintenance insomnia; weight gain, endocrine dysfunction psychiatric disorders are commonly associated symptoms	• Narcolepsy Type 1: cataplexy and/or CSF hypocretin-1 deficiency $<$110 pg/mL. Influenza A (H1N1) infection and vaccination have been previously recognized as potential triggering factors of NT1 (no similar data for COVID-19 infection or vaccination) • Narcolepsy Type 2: neither cataplexy, nor hypocretin-1 deficiency are present
	Kleine-Levin syndrome	Recurrent episodes of severe hypersomnia that last a few days to several weeks separated by weeks to months of normal sleep	• More common in males, and Ashkenazi Jews • Hypersomnia accompanied by confusion, compulsive eating, hypersexuality, apathy or derealization. • Infection triggered Kleine-Levin has been reported following EBV, varicella zoster, herpes zoster, influenza A and B, H1N1, adenovirus, enterovirus, *Salmonella typhi* and *Streptococcus* infections [252,253]

(*continued on next page*)

Table 5 (*continued*)

Disease	Subtypes	Key Features	Subcategories and Notes
Circadian Rhythm Sleep-Wake Disorders	Delayed sleep-wake phase disorder	Chronic or recurrent sleep-wake cycle disruption caused by alterations in endogenous circadian timing system accompanied by insomnia and/or excessive sleepiness and associated with distress or impairment	Natural sleep phase later than required by common society norms; difficulty in anticipating bedtime, falling asleep at night, and waking up in the morning; no sleep difficulties in the absence of social pressures (e.g., on vacation, weekends); sleep initiating insomnia
	Advanced sleep-wake phase disorder	Chronic or recurrent sleep-wake cycle disruption caused by alterations in endogenous circadian timing system accompanied by insomnia and/or excessive sleepiness and associated with distress or impairment	Natural sleep phase earlier than required by common society standards; sleepiness occurring in the early evening or late afternoon hours, difficulty in postponing bedtime, advanced wake-up time in the morning; no sleep difficulties in the absence of social pressures (e.g., on vacation, weekends)
	Shift Work Disorder or Jet Lag	Symptoms of insomnia or EDS occurring as a result of work hours that overlap the normal sleep period	
Sleep-related Movement Disorders	Restless legs syndrome	Urge to move the legs; worsening of symptoms with rest, in the evening or at night; improvement of symptoms with movement; the disorder is not better explained by other conditions	Risk Factors: • Iron deficiency • Uremia • Diabetes • Family history • Pregnancy
	Periodic limb movement disorder	Periodically recurring series of a minimum of 4 sequential limb movements lasting 0.5–10.0 s, interspersed with 5–90 s periods of rest between each movement; associated with symptoms of either insomnia or EDS which are not better explained by other conditions or sleep disorders	Other sleep movement disorders: • Sleep-related cramps • Sleep-related bruxism • Propriospinal myoclonus at sleep onset • Sleep-related rhythmic movement disorder • Benign sleep myoclonus of infancy • Hypnic jerks
Parasomnias	NREM parasomnias	Disorders of arousal with recurrent episode of incomplete awakening with abnormal behaviors, absent or inappropriate responsiveness, limited cognition or recall of the event	• Usually occurring in the first half of the night out of slow-wave sleep. • Sleepwalking • Sleep terrors • Sleep-related eating disorders • Confusional arousals
	REM parasomnias	Repeated episodes of intrusion of features of REM sleep into wakefulness, including behaviors or vocalization accompanied by evidence of REM sleep without atonia during polysomnography.	• Dream enactment • Sleep paralysis • Nightmare disorder • REM behavior disorder, which can antedate the onset of a synucleinopathy (e.g. Parkinson's disease) by decades. • Some drugs (e.g. serotonin reuptake blockers) can result in REM behavior-like disorders

Abbreviations: CRSD, circadian rhythm sleep-wake disorders; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EBV, Epstein-Barre Virus; EDS, excessive daytime sleepiness; H1N1, subtype of influenza A virus; ICSD-3, International Classification of Sleep Disorders, Third Edition; RBD, REM behavior disorder; REM, rapid eye movement; NREM non-rapid eye movement.

time elapses from index COVID-19 diagnosis [73–77]. In a meta-analysis of 22 studies and 23,000 patients, with a median follow-up of 125 days, the pooled risk difference of insomnia, hypersomnia, and poor sleep quality was not significantly higher in that sample compared to unaffected controls [78]. Conversely, one meta-analysis including 18 studies with 10,530 subjects, found increasing rates of sleep disorders between mid- and long-term follow-up [72].

Risk factors for post-COVID-19 insomnia and poor sleep quality include female sex [79–81], older age [82], migraine [83], hypertension [84], and the severity of the index SARS-CoV-2 infection [85–88]. In addition, poor sleep quality has been associated with neuropsychiatric disorders in COVID-19 survivors, namely anxiety, depression and PTSD [73,81,89,90]. A retrospective cohort study, including 278 patients with and without a history of COVID-19, showed that the presence of a previous COVID-19 infection correlated with an increased risk of developing delayed sleep-wake phase disorder by 1.5 times, which the authors attributed to increased anxiety [91]. The consequences of post-COVID-19 sleep disorders are multifold and include higher levels of fatigue [92] and worse quality of life [81,85].

Differential Diagnosis: The *International Classification of Sleep Disorders(ICSD-3)* [93] and the *DSM* [94] promote the concept of "insomnia disorder" in which insomnia and coexisting comorbidities should be treated separately [95]. A complete medical history including sleep habits, medical and psychiatric comorbidities, medications and substance abuse history may help in recognizing incident sleep disorders or previously undiagnosed sleep disorders exacerbated in the context of SARS-COV-2 infection or pandemic-related stressors. Common symptoms that lead to a sleep evaluation include excessive daytime sleepiness (EDS), difficulty initiating or maintaining sleep, early morning awakening, sleep related movement disorders, and parasomnias including sleep terrors, sleepwalking, nightmare disorder, sleep paralysis or sleep-related eating disorders. Table 4 outlines the differential diagnosis for EDS and Table 5 lists common sleep disorders diagnoses.

Diagnostic Evaluation: The diagnostic evaluation of sleep disorders in long-COVID patients is similar to that used outside the context of COVID-19 (Table 6). It should begin with the identification of the most relevant symptoms, including insomnia, EDS, episodic nocturnal movements or behaviors, sleep-disordered breathing or a combination of these concerns. A comprehensive sleep history should include 24-h sleep-wake routine, daytime and nocturnal symptoms, psychiatric and medical comorbidities, family history, social background, and work/school schedule. The use of drugs or substances that could cause insomnia or hypersomnolence (e.g. CNS stimulants, bronchodilators, beta-blockers, corticosteroids, sedative-hypnotics, caffeine, nicotine) should also be investigated; many of these drugs are used in the context of COVID-19 as well [96]. Based on the clinical suspicion, a wide range

Table 6
Diagnostic Evaluation of PASC Sleep Disorders.

CLINICAL DATA		
Study	Results	Interpretation/ Consideration
Sleep history with a focus on: Sleep initiation	• Advanced • Delayed	• Advanced Sleep-Wake Phase Disorder; Central Disorders of Hypersomnolence; Obstructive Sleep Apnea • Insomnia; Delayed Sleep-Wake Phase Disorder; Sleep-related Movement Disorders (mostly RLS)
Sleep history with a focus on: Sleep maintenance	Fragmentation	Insomnia; Sleep-related Breathing Disorders (mostly OSA); Irregular Sleep-Wake Rhythm Disorder; Narcolepsy; Sleep-related movement disorders
Sleep history with a focus on: Sleep termination	• Advanced • Delayed	• Insomnia; Advanced Sleep-Wake Phase Disorder • Delayed Sleep-Wake Phase Disorder; Central Disorders of Hypersomnolence
Sleep history with a focus on: Sleep differences between work days, weekends, and vacations	Variations	Circadian Rhythm Sleep-Wake Disorder; Insufficient Sleep Syndrome; Shift-Work Disorder; Insomnia with comorbid depression/ anxiety
Sleep history with a focus on: Nocturnal symptoms	• Snoring/apnea • Movements	• Sleep-related Breathing Disorders (mostly OSA) • Sleep-related Movement Disorders; Parasomnias
Sleep history with a focus on: Daytime symptoms	• Excessive daytime sleepiness • Morning headache, morning xerostomia • Cataplexy, sleep hallucinations, sleep paralysis	• Insomnia; Sleep-related Breathing Disorders (mostly OSA); Central Disorders of Hypersomnolence; Circadian Rhythm Sleep-Wake Disorder; Parasomnias; • Sleep-related Movement Disorders (mostly RLS); Sleep-related Breathing Disorders (mostly OSA) • Central Disorders of Hypersomnolence (mostly Narcolepsy Type I and Insufficient Sleep Syndrome)
Medical conditions, Psychiatric disorders, Medications and substances	Present	Insomnia; Sleep-related Breathing Disorders (OSA and central sleep apnea); Central Disorders of Hypersomnolence; Sleep-related Movement Disorders (mostly RLS); Parasomnias
Familial and social context; School and work schedule	Variable	Poor sleep hygiene; Insomnia; Insufficient Sleep Syndrome; Shift-Work Disorder; Parasomnias
Sleep log/diary	Variable sleep-wake patterns	Useful in recognizing poor sleep hygiene, insomnia, Central Disorders of Hypersomnolence, Circadian Rhythm Sleep-Wake Disorder Includes information on bedtime, arising time, subjective sleep latency, number of awakenings, subjective total sleep time, feelings on arousal, daytime naps
LABORATORY		
Study	**Results**	**Interpretation/ Consideration**
Blood exams, CSF examination in highly selected cases	Typically normal, abnormal in sleep disorders secondary to other medical conditions	CSF studies can reveal inflammatory alterations in autoimmune encephalitis presenting with sleep disturbances (e.g. anti-Ma2 or anti-IgLON5 syndromes); CSF hypocretin-1 deficiency in Narcolepsy Type 1
NEUROPHYSIOLOGY		
Study	**Results**	**Interpretation/ Consideration**
Wrist actigraphy	Variable sleep-wake patterns	Useful in recognizing poor sleep hygiene, insomnia, Central Disorders of Hypersomnolence, Circadian Rhythm Sleep-Wake Disorder (higher accuracy compared to the patient's sleep log).
Home sleep apnea testing (HSAT) *(recording channels: airflow, nasal pressure, respiratory effort, ECG, oxygen saturation)*	AHI 5–14 AHI 15–29 AHI $\geq$ 30 Effort yes/no	Mild OSA Moderate OSA Severe OSA OSA/central sleep apnea
Home polysomnography (PSG) *(recording channels: EEG, EOG, mentalis and anterior tibialis EMG, airflow, nasal pressure, respiratory effort, ECG, oxygen saturation)*	Hypnogram alterations, abnormal EMG activity	Refractory insomnia, RLS, Periodic Leg Movement Disorder, REM Without Atonia (compatible with both REM sleep Behavior Disorder and narcolepsy).
Video-polysomnography (vPSG) *(simultaneous PSG and video-EEG)*	Hypnogram alterations, abnormal EMG and EEG activity, video-recorded motor episodes during sleep	NREM and REM parasomnias, differential diagnosis with sleep-related hypermotor epilepsy.
Multiple Sleep Latency Test (MSLT) *(recording channels: EEG, EOG, mentalis EMG; a PSG should be performed on the night before).*	mSL $\leq$ 8 min $\geq$ 2 SOREMPs $\leq$ 1 SOREMP	Narcolepsy type 1 and 2; Idiopathic Hypersomnia Narcolepsy type 1 and 2 Idiopathic Hypersomnia
NEURORADIOLOGY		
Brain MRI	Typically normal, abnormal in some conditions with secondary sleep disturbances	Hypothalamic involvement in neoplastic (e.g. craniopharyngioma) or inflammatory (e.g. anti-Ma2 encephalitis) brain disorders

Abbreviations: AHI, Apnea/Hypopnea Index; CSF, Cerebrospinal Fluid; ECG; Electrocardiogram; EEG, Electroencephalogram; EMG, Electromyography; EOG, Electrooculogram; MRI, Magnetic Resonance Imaging; mSL, median sleep latency; NREM, Non-rapid eye movement; OSA, Obstructive Sleep Apnea; REM, rapid-eye movement; RLS, Restless Legs Syndrome; SOREMP, Sleep Onset REM Period.

of clinical questionnaires (**Supplemental Table 4**) can be adopted to increase the specificity of the diagnosis, or to quantify the severity of sleep disorders [96].

Physical exam is particularly important. Patients with suspected obstructive sleep apnea (OSA) should be checked for altered anatomic conformation of the head, neck and thorax. Hepatomegaly may suggest alcohol abuse. Neurologic examination and mental status testing may

Table 7
Treatment options for PASC sleep disorders based on the American Academy of Sleep Medicine Clinical Practice Guidelines [254–267].

INSOMNIA		
Pharmacologic [254]	Recommendation: strength	Level of Evidence
Melatonin 2 mg Melatonin agonists: Ramelteon 8 mg	• Not recommended • Recommended for sleep onset insomnia: weak	Very low Very low
Other preparations L-tryptophan 250 mg Valerian	• Not recommended • Not recommended	High Low
Benzodiazepines: Triazolam 0.25 mg Temazepam 15 mg	• Recommended for sleep onset insomnia: weak • Recommended for sleep onset and maintenance insomnia: weak	High Moderate
Benzodiazepine receptor agonists: Eszopiclone 2–3 mg Zaleplon 10 mg Zolpidem 10 mg	• Recommended for sleep onset and maintenance insomnia: weak • Recommended for sleep onset insomnia: weak • Recommended for sleep onset and maintenance insomnia: weak	Very low Low Very Low
Orexin receptor agonists Suvorexant 10–20 mg	• Recommended for sleep maintenance insomnia: weak	Low
Heterocyclics Doxepin 3–6 mg Trazodone 50 mg	• Recommended for sleep maintenance insomnia: weak • Recommended for sleep onset and maintenance insomnia: weak	Low Moderate
Not-Pharmacological [257]	**Recommendation: strength**	**Level of Evidence**
Cognitive behavioral therapy for insomnia (CBT-I): multicomponent	• Recommended for chronic sleep onset and maintenance insomnia: strong • Recommended for chronic sleep onset and maintenance insomnia: conditional	High
Sleep hygiene		Low
CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS		
Pharmacological [255,256]	**Recommendation: strength**	**Level of Evidence**
Sleep-promoting medications (benzodiazepines or benzodiazepine receptor agonist)	• Not recommended for Advanced Sleep-Wake Phase Disorder, Delayed Sleep-Wake Phase Disorder and Irregular Sleep-Wake Rhythm Disorder: strong • Recommended for Shift-Work Disorder and Jet-Lag Disorder: weak • Recommended for Delayed Sleep-Wake Phase Disorder and Irregular Sleep-Wake Rhythm Disorder and Non-24-Hour Sleep-Wake Rhythm Disorder: weak • Recommended for Shift-Work Disorder and Jet-Lag Disorder: strong • Not recommended for Advanced Sleep-Wake Phase Disorder, Delayed Sleep-Wake Phase Disorder and Irregular Sleep-Wake Rhythm Disorder: strong • Recommended for Shift-Work Disorder: weak	High for elderly Low
Timed oral administration of melatonin or melatonin agonists		Low for adults; Moderate for children/ adolescents Moderate
Wakefulness-promoting medications Modafinil 100–200 mg Caffeine		High Low Very Low
• Recommended for Shift-Work Disorder and Jet-Lag Disorder: weak		
Not-Pharmacological [255,256]	**Recommendation: strength**	**Level of Evidence**
Prescribed sleep-wake scheduling and sleep hygiene	• Not recommended for any type of Circadian Rhythm Sleep-Wake Disorder • Recommended for Advanced Sleep-Wake Phase Disorder and Irregular Sleep-Wake Rhythm Disorder: weak • Recommended for Shift-Work Disorder: moderate	High
Light therapy		Very Low Moderate
SLEEP-RELATED BREATHING DISORDERS		
Pharmacological [258]	**Recommendation: strength**	**Level of Evidence**
Sleep-promoting agents	• Not recommended	Low
Short-acting nasal decongestants	• Not recommended	Low
Topic nasal corticosteroids	• Recommended for patients with OSA and concurrent rhinitis: weak	Moderate
Modafinil 200–400 mg	• Recommended for OSA patients with residual excessive daytime sleepiness despite positive airway pressure treatment: moderate	High
Pitolisant 4.5–18 mg	• Recommended for OSA patients with residual excessive daytime sleepiness despite positive airway pressure treatment: strong	High
Solriamfetol 37.5–150 mg	• Recommended for OSA patients with excessive daytime sleepiness despite positive airway pressure treatment: strong	High
Not-Pharmacological [259–262]	**Recommendation: strength**	**Level of Evidence**
Nocturnal supplemental oxygen	• Not recommended for OSA • Recommended for Central Sleep Apnea Syndrome related to congestive heart failure: strong	Very Low High
Oral Appliances (mandibular advancement device; mandibular repositioning device; mandibular advancement splint; mandibular advancement appliance)	• Recommended for primary snoring without OSA: weak • Recommended for OSA with oral and upper airway abnormality: conditional	High Low
Positional therapy	• Recommended for positional OSA as adjunctive treatment: weak	Moderate
Continuous Positive Airway Pressure (CPAP) therapy	• Recommended for OSA in adults with excessive daytime sleepiness: strong • Recommended for Central Sleep Apnea Syndrome related to congestive heart failure: strong	High High
Bilevel Positive Airway Pressure (BiPAP) therapy	• Not recommended for OSA • Recommended for Central Sleep Apnea Syndrome related to congestive heart failure resistant to CPAP and oxygen therapies: weak • Recommended for patients with Chronic Alveolar Hypoventilation: strong	Low Low High

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Table 7 (*continued*)

INSOMNIA		
Pharmacologic [254]	Recommendation: strength	Level of Evidence
Dietary weight loss	• Recommended for patients with OSA and obesity with BMI > 35: strong	Moderate
Bariatric surgery	• Recommended for patients with OSA and obesity with BMI ≥ 35, intolerant to positive airway pressure: strong	Moderate
CENTRAL DISORDERS OF HYPERSOMNOLENCE		
Pharmacological [263]	**Recommendation: strength**	**Level of Evidence**
Modafinil 200–400 mg	• Recommended for excessive daytime sleepiness in patients with narcolepsy types 1 and 2 and Idiopathic Hypersomnia: strong	High
Armodafinil 150–250 mg	• Recommended for excessive daytime sleepiness in patients with narcolepsy types 1 and 2 or other neurological disorders: conditional	Low
Pitolisant 4,5–36 mg	• Recommended for excessive daytime sleepiness and cataplexy in patients with narcolepsy types 1 and 2: strong • Recommended for excessive daytime sleepiness in patients with Idiopathic Hypersomnia: conditional	High Very Low
Solriamfetol 75–150 mg	• Recommended for excessive daytime sleepiness in patients with narcolepsy type 1: strong • Recommended for excessive daytime sleepiness and cataplexy in patients with narcolepsy type 1: strong	High
Sodium oxybate 4.5–9 g	• Recommended for excessive daytime sleepiness in patients with Idiopathic Hypersomnia or other neurological disorders: conditional	High Very low
Methylphenidate 5–20 mg	• Recommended for excessive daytime sleepiness in patients with narcolepsy type 1 and Idiopathic Hypersomnia: conditional	Very Low
Lithium 300–1200 mg	• Recommended for Kleine-Levine Syndrome: conditional	Low
Caffeine 200 mg	• Not recommended for excessive daytime sleepiness in patients with narcolepsy types 1 and 2	Very Low
Bupropion 150–300 mg Venlafaxine 37.5–75 mg	• Recommended for excessive daytime sleepiness in patient with mood disorders: option	Very Low
Not-Pharmacological [263]	**Recommendation: strength**	**Level of Evidence**
Behavioral and lifestyle techniques (Scheduled 15-min naps, sleep hygiene, dietary manipulations, physical activity)	• Recommended for patients with narcolepsy types 1 and 2: weak	Low
SLEEP-RELATED MOVEMENT DISORDERS		
Pharmacological [264]	**Recommendation: strength**	**Level of Evidence**
Dopaminergics Pramipexole 0.18–0.75 mg Ropinirole 0.78–4 mg Rotigotine 2–3 mg		High High Moderate High High
Pergolide Levodopa with dopa decarboxylase inhibitor 100–200 mg	• Recommended for RLS: strong • Recommended for RLS: strong • Not recommended for RLS • Not recommended for RLS • Recommended for RLS: moderate	
α2δ Ligands Gabapentin enacarbil 600–1200 mg Gabapentin 200–800 mg Pregabalin 150–450 mg	• Recommended for RLS: moderate • Recommended for RLS: weak • Recommended for RLS: weak	High Low Low
Opioids Oxycodone/naloxone 5/2.5–40/20 mg	• Recommended for resistant forms of RLS: moderate	Low
Carbamazepine	• Recommended for RLS: option	Low
Clonidine	• Recommended for RLS: option	Low
Supplemental iron Ferrous sulfate 325 mg	• Recommended for RLS patient with low ferritin levels (≤75 μg/L): option	Very low [268]
Benzodiazepines Clonazepam 1–2 mg	• Not recommended for RLS and/or Periodic Leg Movement Disorder alone	Very low
Antidepressants	• Not recommended in RLS patients with mood disorder	Very low
Not-Pharmacological [264]	**Recommendation: strength**	**Level of Evidence**
Accommodative strategies, sleep hygiene, behavioral and stimulation therapies, compression devices, exercise, nutritional considerations	• Not recommended for RLS and/or Periodic Leg Movement Disorder	Very low
PARASOMNIAS		
Pharmacologic [265–267]	**Recommendation: strength**	**Level of Evidence**
Clonazepam 1–2 mg Clonazepam 0.25–4 mg	• Not recommended for PTSD-associated nightmares • Recommended for other NREM-parasomnias (such as sleep-walking and night-mares): weak • Recommended for REM-Behavior Disorder: moderate	Moderate Low High
Atypical antipsychotics (olanzapine, risperidone and aripiprazole)	• Recommended for PTSD-associated nightmares: option	Very low
Tricyclic antidepressants and trazodone	• Recommended for PTSD-associated nightmares: option	Very Low
Prazosin	• Recommended for PTSD-associated nightmares: option	Very Low
Melatonin Melatonin 3–12 mg	• Not recommended for NREM-parasomnias • Recommended for REM-Behavior Disorder: moderate	Very Low Moderate
Sodium oxybate	• Recommended for REM-Behavior Disorder: weak	Very Low
Dopaminergics Pramipexole 0.5–1.5 mg L-DOPA	• Recommended for REM-Behavior Disorder: weak • Suggested for REM-Behavior Disorder: very weak	Very low Very low
Zoplicone 3.75–7.5 mg	• Recommended for REM-Behavior Disorder: very weak	Very low
Acetylcholinesterase inhibitors Donepezil 10–15 mg Rivastigmine 9–12 mg	• Recommended for REM-Behavior Disorder: very weak	Very low

(*continued on next page*)

Table 7 (*continued*)

INSOMNIA		
Pharmacologic [254]	Recommendation: strength	Level of Evidence
Not-Pharmacological [265–267]	**Recommendation: strength**	**Level of Evidence**
Image rehearsal therapy	• Recommended for PTSD-associated nightmares and nightmare disorder: strong • Recommended for PTSD-associated nightmare disorder: option	High
Cognitive Behavioral Therapy	• Recommended for nightmare disorder: moderate • Recommended for sleep-walking: moderate	Moderate Moderate Low
Parent/caregiver education/ prevention	• Recommended for sleep-walking and nightmare disorder in children: strong	High
Exposure, relaxation and rescripting therapy	• Recommended for nightmare disorder: weak	Low
Hypnosis	• Recommended for sleep-walking and nightmares: weak	Low
Sleep hygiene	• Recommended for NREM-parasomnias (such as sleep-walking and nightmares): weak	Low
Modifying sleep environment	• Recommended for REM-Behavior Disorder: strong	High

suggest psychiatric or neurologic disorders that may cause or contribute to disturbed sleep [96].

A sleep log kept by the patient for a 2-week period is a valuable indicator of sleep hygiene, representing a useful tool in the evaluation of insomnia, hypersomnia and circadian-rhythm sleep disorders [97]. Wrist actigraphy can augment the sleep diary, providing more accurate estimates of sleep and wakefulness over multiple sleep-wake cycles [98]. Depending on the clinical hypothesis, different neurophysiological tests can be performed at home or in a sleep laboratory. In patients with suspected OSA, a home sleep apnea test is often sufficient to confirm the diagnosis [99]. The evaluation of sleep-related movement disorders, parasomnias, central disorders of hypersomnolence, and intractable cases of insomnia, may require a complete video-polysomnography (vPSG) and/or a multiple sleep latency test (MSLT) in a sleep laboratory setting [100].

Brain magnetic resonance imaging should be considered to rule out secondary causes of EDS, frequently due to structural brain lesions involving the hypothalamus, including neoplastic (e.g. craniopharyngioma) or inflammatory disorders (e.g. neurosarcoidosis, neuromyelitis optica spectrum disorders, or anti-Ma2 encephalitis) [101]. In the latter scenario, lumbar puncture can reveal inflammatory cerebrospinal fluid (CSF) and/or the presence of neuronal antibodies. Measurement of CSF hypocretin-orexin is helpful in the diagnosis of narcolepsy (low in narcolepsy type 1, NT1), where cataplexy is generally present. CSF analysis is helpful in the diagnosis of anti-IgLON5 encephalitis, which is characterized by REM behavior disorder, NREM

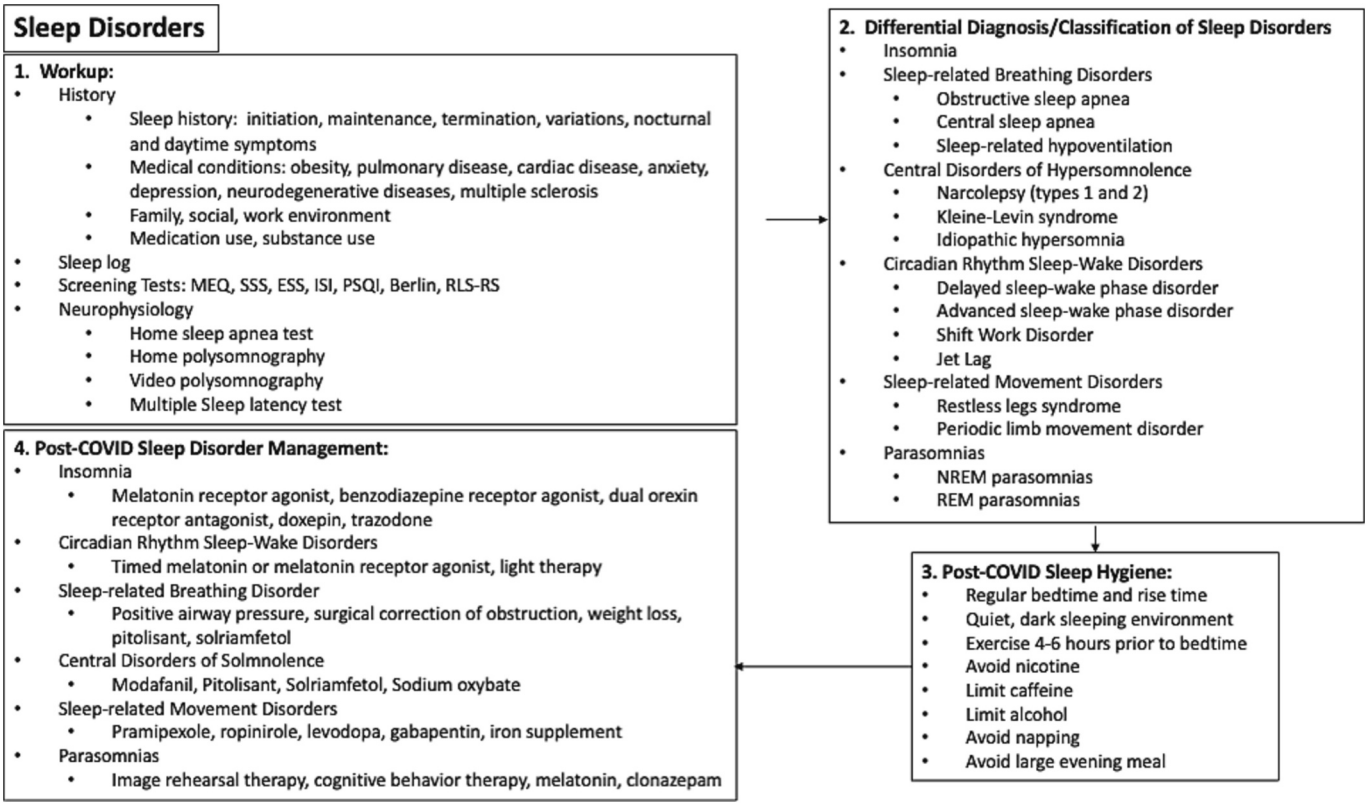

Fig. 2. Evaluation and Management of PASC Sleep Disorders.
MEQ, morningness-eveningness questionnaire; SSS, Stanford sleepiness scale; ESS, Epworth Sleepiness Scale; ISI, Insomnia severity index; PSQI, Pittsburgh Sleep Quality Index; RLS-RS, Restless Legs Syndrome Rating Scale.

parasomnias, sleep-related breathing disorders, along with gait, bulbar, and cognitive symptoms [102].

Therapeutic options

COVID-19 Specific Treatments: We identified one randomized trial that evaluated progressive muscle relaxation in addition to pulmonary telerehabilitation compared to pulmonary telerehabilitation alone in 52 patients after COVID-19 hospitalization. After six weeks, those in the intervention group reported significantly higher sleep quality (Pittsburg Sleep Quality Index), as well as lower fatigue (Fatigue Severity Scale) and anxiety (Hospital Anxiety and Depression Scale) compared to the control group [103].

In general, for all sleep disorders, promotion of good sleep hygiene is suggested, including regular sleep and wake times, maintaining a quiet, dark sleep environment, exercise 4–6 h prior to bedtime, avoidance of nicotine, limiting caffeine and alcohol intake, avoiding long daytime naps and avoidance of large evening meals. Additionally, clinical practice guidelines from the American Academy of Sleep Medicine can be applied to PASC patients with sleep disorder symptoms (Table 7). A summary of the evaluation and management of PASC sleep disorders is found in Fig. 2.

3.3. Headache

Epidemiology: Headache is a common COVID-19 symptom and occurs in over 60% of patients during the acute phase of infection [37]. In the post-acute timeframe, a meta-analysis that included 28 studies and 28,438 COVID-19 survivors, found the prevalence of headache was 10.2%, 16.5%, 10.6% and 8.4% one, two, three and six months after COVID-19, respectively [104]. Some data suggests that headache may be a more prominent symptom with certain SARS-CoV-2 strains. In a study done in the United Kingdom including 27,692 COVID-19 patients,

Table 8
International Classification of Headache Disorders (ICHD-3) Diagnostic Criteria for Primary Headache Disorders Commonly Reported after COVID-19 [108]. For each diagnostic category, the symptoms must not be better accounted for by another ICHD-3 diagnosis.

Headache Type	Diagnostic Criteria
Migraine	Without Aura- At least 5 attacks fulfilling the below criteria: 1. Headache lasting 4–72 h 2. At least two of the following: unilateral location, pulsating, moderate-severe intensity, impedes or aggravated by routine activity 3. Accompanied by one of the following: nausea/vomiting, photophobia/phonophobia With Aura- all of the above plus at least 2 attacks fulfilling the below criteria: 1. One or more reversible aura symptom including: visual, sensory, motor, brainstem, speech/language, retinal 2. At least 3 of the following: one aura that spreads over ≥5 min, ≥2 symptoms in succession, each aura symptom lasting 5–60 min, at least one aura symptom is unilateral, at least one symptom is positive (such as tingling, scintillations etc.), the aura is accompanied or followed by headache within 60 min
Tension-type	At least 10 episodes fulfilling the following criteria: 1. Headache lasting 30 min to 7 days 2. At least 2 of the following: bilateral location, pressing or tightening quality, mild-moderate intensity, not aggravated by routine physical activity 3. Both of the following: no nausea or vomiting, may have photophobia or phonophobia but not both
Daily persistent headache	The pain may be migraine-like or tension-like, or have features of both. Must meet both of the following criteria: 1. Distinct and memorable onset date with pain becoming unremitting and continuous within 24 h 2. Present for more than 3 months

Table 9
Differential Diagnosis for PASC Secondary Headache Disorders.

Category	Diagnoses	Key Features
Vascular	• Subarachnoid hemorrhage • Cerebral venous sinus thrombosis (CVST) • Arterial dissection • Dural arterio-venous fistula • Arteriovenous malformation • Reversible cerebral vasoconstriction syndrome (RCVS) • Pituitary apoplexy	Sudden onset, severe pain, may be accompanied by decreased level of consciousness (in the context of intracranial hemorrhage). Specific physical or medication triggers (dissection, RCVS) may be present. May be accompanied by focal neurological deficits. Neck pain and/or Horner's syndrome may be present with dissection. Thunderclap headache should raise concern for subarachnoid hemorrhage or RCVS. Risk factors including pregnancy or hypercoagulable state may be present with CVST. CVST has been associated with acute COVID-19 infection and adenovirus vector-based COVID-19 vaccines [269].
Infection/ Inflammatory	• Meningitis/encephalitis • Giant cell arteritis • Trigeminal neuralgia • Sinusitis	Fever, meningeal signs (meningitis/encephalitis). Shooting brief facial pain in trigeminal neuralgia with specific triggers. Jaw claudication, transient monocular vision loss, h/o polymyalgia rheumatica may indicate giant cell arteritis. Note that sinusitis is an uncommon cause of headache, though it is frequently diagnosed.
Intracranial Pressure (ICP) related	• Elevated ICP due to space occupying lesion (e.g. tumor, abscess), obstructive hydrocephalus or idiopathic intracranial hypertension • Spontaneous intracranial hypotension, CSF leak	Headache varies with posture (recumbency), may be worse with sneezing, coughing or Valsalva. Focal neurological deficits may be present including papilledema or vision loss. Seizures may occur with mass lesions. Evidence of rhinorrhea or otorrhea may occur with CSF leak.
Trauma related	• Post-concussive headache • Chronic subdural hematoma	Post-traumatic onset, focal deficits may be present, unilateral pain that does not switch sides
Toxin	• Carbon monoxide poisoning	May be accompanied by nausea, vomiting, confusion, blurred vision. Environmental exposure history present.
Medication-related	• Medication overuse headache • Vaccine-related headache	Medication overuse headache is typically preceded by an episodic headache disorder. Can occur in the context of caffeine, NSAIDs, opiates, barbiturates, triptans and other analgesics. Vaccine-related headaches have been reported following COVID-19 vaccines [269]. They are usually shorter and less severe than post-COVID headache, bilateral, without accompanying phenomena typical of migraine. Post-COVID vaccine headache often occurs with fever and other vaccine-related side effects such as fatigue. If the headache begins >5 days post-

(continued on next page)

Table 9 (*continued*)

Category	Diagnoses	Key Features
		vaccination, is accompanied by other atypical features and red flags or becomes persistent, a secondary cause, specifically CVST, must be ruled out [270].
Ophthalmologic	• Acute-closure glaucoma • Optic neuritis	Sudden, severe, unilateral vision loss with pain (optic neuritis), halos around lights (acute-closure glaucoma), nausea/vomiting (acute-closure glaucoma), conjunctival redness, corneal edema/cloudiness, mid-dilated, poorly reactive pupil (acute-closure glaucoma), afferent pupillary defect (optic neuritis), papillitis (optic neuritis)
Hypertension-related	• Acute hypertensive emergency	Acute severely elevated blood pressure, consider medication withdrawal, illicit drug use (cocaine, amphetamines), preeclampsia, pheochromocytoma in the appropriate setting
Sleep related	• Obstructive sleep apnea	Early morning headache, snoring, obese habitus
Genetic	• Familial hemiplegic migraine	Autosomal dominant channelopathies typically caused by variants in CACNA1A, ATP1A2, SCN1A genes

headache was the most frequent symptom reported by patients infected with the Alpha or Delta COVID-19 variants [105]. In another cohort study of 614 patients, headache was most common in those infected with the Delta variant [106]. The median duration of post-COVID-19 headache was 14 days in one prospective cohort study that evaluated 905 COVID-19 survivors. In this study, headache persisted after 3 months in 19% of cases, and was still present 9 months later in 16% of cases [107]. Similarly, a prospective cohort study 242 hospitalized COVID-19 patients found that persistent headache was present in 22% of patients 12-months after index SARS-CoV-2 infection [3].

Differential Diagnosis: The most commonly reported post-COVID-19 headache subtypes are: daily persistent headache, migraine and tension-type headaches [108,109]. While worsening of underlying headache disorders are reported in the context of SARS-CoV-2 infection, new headache disorders can develop [108,109]. Indeed, the 3rd edition of the International Classification of Headache Disorders (ICHD-3) endorsed by the International Headache Society recognizes viral infections as a possible cause of secondary headache. "Chronic headache attributed to systemic viral infection" can be diagnosed when headaches persist for 3-months following infection. International Headache Society Criteria for the diagnosis of primary headache disorders are listed in Table 8**.** The differential diagnosis of secondary headache disorders can be found in Table 9**.**

Diagnostic Evaluation: A thorough history, physical and neurological exam is critical for the diagnosis of primary headache disorders and essential for ruling out dangerous causes of secondary headache. Key findings that may prompt additional evaluation are outlined in Table 10.

Therapeutic options

COVID-19 Specific Treatments: A few retrospective studies have explored specific treatments for PASC headache. A case series of 100 patients with post-COVID-19 headache were evaluated in a median of 7 months from index SARS-CoV-2 infection. For acute headache abortion, the proportion of patients achieving a $\geq$ 50% reduction in headache

Table 10
Diagnostic evaluation of PASC headache.

CLINICAL DATA		
Study	Examples	Interpretation/ Consideration
History	• Frequency, intensity, duration • Quality, location of pain • Associated symptoms (e.g. aura, autonomic symptoms, nausea/vomiting, photo/ phonophobia) • Precipitating, relieving factors (e.g. physical activity, recumbency) • Other neurological symptoms (weakness, numbness vision changes, pulsatile tinnitus) • Medication and illicit substance history • Medical comorbidities • Sleep history (snoring, sleep apnea) • Pregnancy, menstruation history • Family history • Toxin exposure (e.g. carbon monoxide)	Red flags: • Sudden, severe onset • New onset headache in older individual (onset after age 50) • Strictly unilateral pain that does not change sides • Progressive worsening in severity or duration • Pattern change compared to prior headaches • Positional quality (better or worse with recumbency) • Vision loss or pain with eye movement • Neck pain preceding headache • Jaw claudication • Pregnancy or puerperium • History of cancer • Post-traumatic onset • Immunosuppressed state (e.g. HIV) • Focal neurological symptoms • Seizures
Physical exam	• Blood pressure, temperature • Neurological exam including fundoscopy • Head and scalp exam	Red flags: • Severe hypertension • Fever • Focal neurological deficits • Altered mental status • Meningeal signs/nuchal rigidity • Papilledema, papillitis • Horner's syndrome • Clouded cornea, conjunctival erythema, dilated, poorly reactive pupil • Bruits • Temporal artery tenderness • Occipital nerve tenderness
NEURORADIOLOGY		
Imaging Modality	**Headache Type**	**Level of Appropriateness**
Head Computed Tomography (CT) without contrast	• Sudden onset severe headache that reaches maximal intensity in 1-h, initial imaging • Headache with features of intracranial hypertension, initial imaging • Headache with new onset or pattern during pregnancy or puerperium, initial imaging • Headache with one or more red flag: increasing severity or frequency, fever, neurological deficit, history of cancer or immunocompromised state, age > 50 years at time of onset, post-traumatic onset, initial imaging	Usually appropriate per American College of Radiology Appropriateness Criteria for Headache [271]
	• Primary migraine or tension-type headache, normal neurologic exam, initial imaging	Usually *not* appropriate per American College of Radiology Appropriateness Criteria for Headache [271]

(*continued on next page*)

Table 10 (*continued*)

CLINICAL DATA		
Study	Examples	Interpretation/ Consideration
	• Primary trigeminal autonomic cephalgias, initial imaging • Headache with features of intracranial hypotension • Headache *without* any of the following red flags: sudden onset, thunderclap, features of intracranial hypertension or hypotension, new onset or pattern during pregnancy or puerperium, increasing severity or frequency, fever, focal neurological deficit, history of cancer or immunocompromised state, age > 50 years at time of onset, post-traumatic onset, initial imaging	
MRI with or without contrast	• Primary trigeminal autonomic cephalgias, initial imaging • Headache with features of intracranial hypertension, initial imaging • Headache with features of intracranial hypotension • Headache with new onset or pattern during pregnancy or puerperium, initial imaging • Headache with one or more red flag: increasing severity or frequency, fever, neurological deficit, history of cancer or immunocompromised state, age > 50 years at time of onset, post-traumatic onset, initial imaging	Usually appropriate per American College of Radiology Appropriateness Criteria for Headache [271]
	• Primary migraine or tension-type headache, normal neurologic exam, initial imaging • Headache *without* any of the following red flags: sudden onset, thunderclap, features of intracranial hypertension or hypotension, new onset or pattern during pregnancy or puerperium, increasing severity or frequency, fever, focal neurological deficit, history of cancer or immunocompromised state, age > 50 years at time of onset, post-traumatic onset, initial imaging	Usually *not* appropriate per American College of Radiology Appropriateness Criteria for Headache [271]
Advanced imaging	• CT angiogram • MR angiogram • MR venogram • Digital subtraction angiography • Spine MRI	May be appropriate in certain circumstances depending on history and physical exam per American College of Radiology Appropriateness Criteria for Headache [271]. Imaging of cerebral venous sinuses should be obtained if there is any suspicion of CVST
LABORATORY STUDIES		
Type	**Specific Tests**	**Notes**
Lumbar puncture	• Opening pressure • Cells and differential, culture, protein, glucose • PCR infection panels	Indicated in patients with suspected meningitis/ encephalitis, carcinomatous leptomeningitis, suspected subarachnoid hemorrhage with negative head CT, and suspected intracranial hypertension
Serum studies	• ESR/CRP	Elevated in giant cell arteritis
	• CBC, PT/aPTT, fibrinogen, D-Dimer, PF4 antibody testing	Low platelets, elevated D-Dimer and positive anti-PF4 occur with Vaccine Induced Immune Thrombotic Thrombocytopenia which has been associated with adenovirus vector COVID-19 vaccines.
	• Thrombophilia tests (e.g. Antithrombin III, activated protein C resistance/factor V Leiden, Protein C and S levels, prothrombin gene mutation, anticardiolipin, beta-2 glycoprotein, lupus anticoagulant, JAK2 mutation, homocysteine	Can be considered in cases of suspected CVST

Abbreviations: HIV: Human immunodeficiency virus. CT: Computerized Tomography. MRI: Magnetic Resonance Imaging. ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein. CVST: Cerebral venous sinus thrombosis.

symptoms was 58% for triptan medications, 54% for ibuprofen, and 43% for paracetamol [110]. Indomethacin was studied as an acute abortive medication in a retrospective study of 37 patients with post-COVID headache (93% of whom had pre-COVID migraines). In this study, 36/37 patients had greater than 50% headache relief after treatment with indomethacin (50 mg twice daily) [111]. Regarding preventative medications, a study of 100 subjects with PASC headache found that 75% required preventative treatment, most commonly amitriptyline (in 66%), followed by anesthetic blockade in 18% and onabotulinumtoxin in 11% [110]. A reduction in the number of headache days per month by ≥50% occurred in 45% of those who received amitriptyline, 39% who received anesthetic blockade and 27% who received onabotulinumtoxin [110]. Another retrospective study of 48 patients with post-COVID-19 headaches treated with amitriptyline (10–75 mg daily), found a median reduction in headache frequency of 10 days per month, and 44% of subjects had at least a 50% reduction in the number of headache days per month [112]. A study of greater occipital nerve block in 27 PASC headache patients identified a statistically significant reduction in pain scores and analgesic use [113]. Treatment options based on the American Headache Society [114] and European Federation of Neurological Societies Recommendations [115] for the most common headache syndromes reported post-COVID-19 are listed in Table 11. An algorithm for the evaluation and management of PASC headache is shown in Fig. 3.

3.4. Dizziness/lightheadedness

Epidemiology: In the acute phase following SARS-CoV-2 infection, dizziness has been reported in 7% (95% CI 5–8%) of patients based on meta-analysis data [116]. Similarly, in the post-acute timeframe, dizziness/lightheadedness have been reported in roughly 7% of patients up to 12-months after index infection [3]. Dysautonomia, specifically orthostatic intolerance syndromes, including orthostatic hypotension (OH) and postural tachycardia syndrome (POTS), occur in an estimated 2.5% of COVID-19 patients [117–125].

Table 11
Treatment options for the most common subtypes of PASC Headache based on American Headache Society [114] and European Federation of Neurological Societies Recommendations [115].

Headache Type	Treatment	Recommendation
PHARMACOLOGIC ACUTE TREATMENTS		
Migraine	• Triptans • NSAIDS (aspirin, diclofenac, ibuprofen, naproxen) • Ergotamine derivatives	Established efficacy per American Headache Society [114]. ≥50% response rate for PASC headache reported in 97% of patients who received indomethacin [111], 58% who received triptans, 54% who received ibuprofen and 43% who received paracetamol [110]. The frequency of acute medication resistance is as high as 19% [272]
	• Ergotamine or dihydroergotamine • Other NSAIDS (ketoprofen, ketorolac, flurbiprofen) • IV magnesium • Isomethetene-containing compounds • Antiemetics (prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)	Probably effective per American Headache Society [114]
Tension-type	• NSAIDS: ibuprofen, ketoprofen, aspirin, naproxen, diclofenac • Paracetamol/Acetaminophen • Ketorolac, metoclopramide, chlorpromazine may be options for patients with severe symptoms who cannot tolerate oral medications	EFNS level A recommendations [115] for NSAIDs and Paracetamol/ Acetaminophen
Daily Persistent headache	• Screen for medication overuse headache and switch from overused medication to alternative symptomatic therapy or add temporary bridging therapy to wean off overused therapy	Topiramate, corticosteroids and amitriptyline are suggested for medication overuse headache management per EFNS guidelines [273].
NON-PHARMACOLOGIC ACUTE TREATMENTS		
Migraine	• Transcutaneous supraorbital nerve stimulation/electrical trigeminal nerve stimulation • Transcranial magnetic stimulation • Non-invasive vagal nerve stimulation • Remote electrical neuromodulation	Established efficacy per American Headache Society [114]; suggested for patients who prefer nondrug treatments or in patients with drug intolerance, contraindication or inadequate drug response.
PHARMACOLOGIC PREVENTATIVE TREATMENTS		
Migraine	• Antiseizure medications: valproic acid, topiramate • Beta-blockers: metoprolol, propranolol, timolol • Triptans: frovatriptan • OnabotulinumtoxinA	Established efficacy per American Headache Society [114]; ≥50% response rate for PASC headache reported in 0% with topiramate, 14% with beta-blockers, 27% with onabotulinumtoxinA [110]
	• Antidepressants: Amitriptyline, Venlafaxine • Beta-blockers: Atenolol, nadolol	Probably effective per American Headache Society [114]. ≥50% response rate for PASC headache reported in 44–46% with amitriptyline [110,112], 0% with venlafaxine, 25% with duloxetine, 40% with mirtazapine [110]
	• ACE inhibitors: lisinopril • Angiotensin receptor blockers: candesartan	Possibly effective per American Headache Society [114]
	• Alpha-agonists: clonidine, guanfacine • Antiseizure medications: carbamazepine • Beta-blockers: nebivolol, pindolol • Antihistamines: cyproheptadine	
	• Antiseizure medications: gabapentin • Antidepressants: fluoxetine, fluvoxamine, protriptyline • Antithrombotics: coumadin, acenocoumarin, picotamide • Beta-blockers: bisoprolol • Calcium channel blockers: verapamil, nicardipine, nifedipine, nimodipine • Acetazolamide • Cyclandelate	Inadequate evidence to support or refute use per American Academy of Neurology (AAN) guidelines [274]
	• Lamotrigine • Clomipramine • Acebutolol • Clonazepam • Nabumetone • Oxcarbazepine • Telmisartan	AAN guidelines [274] suggest these treatments may be ineffective
	• Monoclonal antibodies targeting the calcitonin gene-related peptide: Erenumab, galcanezumab, fremanezumab, eptinezumab. • Calcitonin gene-related peptide antagonists (Rimegepant, atogepant)	Emerging preventative options per American Headache Society [114]. Suggested for patients with an inadequate response, or inability to tolerate a 6-week trial of standard preventative medications.
Tension-type	• First line: amitriptyline (30–75 mg daily) • Second line: mirtazapine (30 mg daily), venlafaxine (150 mg daily) • Third line: clomipramine (75–150 mg daily), maprotiline (75 mg daily), mianserin (30–60 mg daily), topiramate, gabapentin	EFNS level A recommendation for amitriptyline and level B for all others [115]. ≥50% response rate for PASC headache reported in 44–46% received amitriptyline [110,112], 0% venlafaxine, 25% with duloxetine, 40% with mirtazapine [110]
Daily Persistent headache	• Muscle relaxants (baclofen, tizanidine) • Antidepressants: amitriptyline, nortriptyline, fluvoxamine, paroxetine • Antiseizure medications: valproic acid, topiramate, gabapentin • Beta-blockers: propranolol • Peripheral nerve blocks	Data limited to case reports and anecdotes. Can follow treatment paradigms for tension-type or migraine headache depending on the phenotype. ≥50% response rate for PASC headache reported in 39% who received peripheral nerve block [110,113]
Vaccination	• COVID-19 vaccination	Patients who got infected by SARS-CoV-2 after adequate vaccination were less likely to develop persistent COVID-19-related headache: (OR 0.317, 95% CI 0.163–0.616) (n = 923, 18.2% vaccinated) [9]

Differential Diagnosis: Identifying the underlying cause of dizziness begins with drilling down on the specific symptom experienced. Disentangling symptoms of vertigo (classically room spinning, though symptom quality alone is unreliable), from cardiac presyncope/syncope, orthostatic intolerance, vasovagal reflex, or other forms of dysautonomia can be accomplished with a thorough history from the patient and/or informant. Triggering factors, such as position, activity at the time of onset, duration and severity of symptoms, and accompanying symptoms

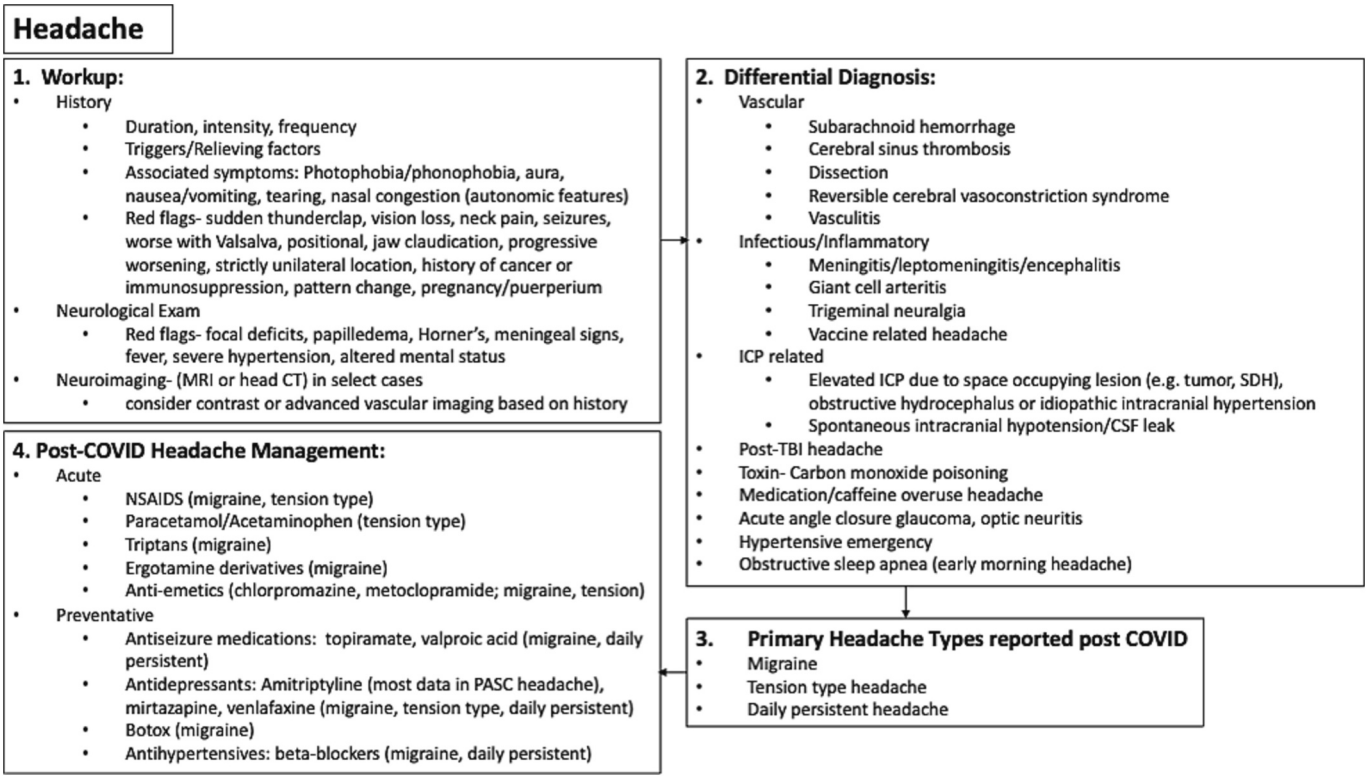

Fig. 3. Evaluation and Management of PASC Headache.
ICP, intracranial pressure; CSF, cerebrospinal fluid; SDH, subdural hematoma; TBI, traumatic brain injury.

(e.g. nausea, vomiting, chest pain, palpitations, headache, aura, focal neurological findings or brainstem signs such as diplopia, dysphagia, ataxia) can help narrow a differential diagnosis. Key features of different causes of dizziness can be found in Table 12**.**

Diagnostic Evaluation: Every patient with symptoms of dizziness/lightheadedness after a COVID-19 infection should undergo a detailed history, a basic physical examination, an active standing test, as well as a 12-channel ECG and basic laboratory studies to identify major underlying non-COVID and COVID-related conditions that may cause dizziness, lightheadedness, vertigo and/or ataxia. Additional diagnostics and referral to autonomic or other specialty departments may be considered for advanced evaluation in patients with persistent or severe symptoms. A diagnostic algorithm can be found in Table 13 [117,126,127].

Therapeutic options

COVID-19 Specific Treatments: We did not identify any clinical trials specifically addressing PASC lightheadedness, dizziness or orthostatic intolerance. However, the WHO has issued a conditional recommendation for the clinical rehabilitation of PASC orthostatic intolerance suggesting the combination of education and skills training on self-management strategies, and physical exercise training (in the absence of post-exertional symptom exacerbation) [11]. In patients with post-exertional symptom worsening, the WHO suggests education and training in energy conservation techniques, such as pacing approaches [11]. Initial therapeutic approaches should primarily focus on non-pharmacological interventions [128]. If symptoms persist for >2 months despite consistent conservative interventions, and/or an underlying autonomic dysfunction has been diagnosed, a pharmacological treatment may be considered, although clear benefits on functional outcome in post-COVID have not been described thus far [129–132]. In general, supportive psychosomatic co-intervention should be offered, especially if associated anxiety- or mood-disorders are present [133,134]. Treatments for PASC orthostatic intolerance syndromes are outlined in Table 14**.** An algorithm for the evaluation and management of PASC dizziness/lightheadedness is shown in Fig. 4.

3.5. Fatigue

Epidemiology: Fatigue is one of the most common post-COVID-19 symptoms and refers to an exhaustion that is disproportionate to the preceding exertion and cannot be relieved by sleep [135–137]. It is more commonly found to be prolonged in COVID-19 patients requiring ICU admissions [136,138], although any patient can be affected irrespective of the severity of initial SARS-CoV-2 infection [136,139,140]. During the acute phase of illness, fatigue has been reported in over 70% of COVID-19 patients [37]. In the post-acute setting, 3–6 months after index SARS-CoV-2 infection, 5–53% of patients reported persistent fatigue [140–143]. At nine months post-COVID-19 almost 20% of patients note clinically relevant fatigue, compared to only 8% of matched non-COVID-19 controls [144]. At 12 months, 10% of patients hospitalized for index COVID-19 infection reported persistent fatigue [3,16], though 48% had improved NeuroQoL fatigue scores between 6 and 12-months post hospitalization [16].

The pathophysiology of post COVID-19 fatigue is not clearly understood. It is thought to represent, among other explanations, an autoimmune process [145], or an ongoing inflammation of the central nervous system, as in some cases cytokines levels fail to return to normal levels [139].

Risk factors for post-COVID fatigue include: younger age, female sex, the severity of index COVID-19 illness, pre-existing psychiatric, lung or autoimmune disease, fewer years of education, pre-COVID disability,

Table 12
Differential Diagnosis of PASC Dizziness/Lightheadedness.

Category	Diagnoses	Key Features
SYNCOPE/PRESYNCOPE		
Reflex mechanisms	• Vasovagal syncope • Situational syncope (Micturition, Defecation, Deglutition, Cough) • Carotid sinus syndrome	Most common cause of syncope. Lightheadedness or near syncope, syncope, pallor, sweating following typical activity, accompanied by bradycardia and/or peripheral vasodilation. Carotid sinus disorders (tumor, shaving, tight collar, carotid stenting) can lead to carotid sinus hypersensitivity
Orthostatic intolerance syndromes	Orthostatic hypotension (OH) • Volume depletion (nausea, vomiting, diarrhea, poor oral intake, hemorrhage) • Medication related (blood pressure medications, diuretics, antidepressants, SGLT-2 inhibitors) • Neurogenic orthostatic hypotension: A. Primary autonomic failure: synucleinopathies such as Parkinson's Disease, Dementia with Lewy bodies, Multiple System Atrophy, pure autonomic failure, traumatic brain injury, spinal cord injury B. Secondary autonomic failure due to neuropathy: small fiber peripheral neuropathy from diabetes, amyloidosis, Sjogren's, renal failure, B12 deficiency, syphilis, Lyme, HIV, Chagas, sarcoid, porphyria, Guillain-Barre, autoimmune autonomic impairment with ganglionic nicotinic acetylcholine receptor antibodies, anti-Hu/ANNA paraneoplastic neuropathy, familial dysautonomia (Riley-Day), familial autonomic ganglionopathy	Lightheadedness/ dizziness after prolonged standing, change in position from sitting to standing, following meals, or exertion. Relieved in recumbent position; Associated symptoms: near syncope, syncope, darkening of visual fields, headache, fatigue
	Postural tachycardia syndrome (POTS)	Fatigue, lightheadedness, exercise intolerance, cognitive deficits when in upright position accompanied by tachycardia but no drop in blood pressure. Relieved by sitting or reclining. Symptoms often worse in morning hours, hot weather, illness, stress. Inability to stand in warm shower is a classic feature. Anxiety, sleep disturbance, gastrointestinal symptoms, headache, fatigue and cognitive dysfunction can be accompanying symptoms
Cardiovascular	• Structural heart disease [275] (ischemic cardiomyopathy, nonischemic/dilated cardiomyopathy, hypertrophic obstructive cardiomyopathy, valvular abnormalities, aortic dissection, cardiac tamponade, obstructive cardiac tumors, pericardial disease, pulmonary hypertension, pulmonary emboli, arrhythmogenic right ventricular cardiomyopathy) • Electrical [275] (tachyarrhythmia, bradyarrhythmia, inherited channelopathies, drug-induced)	Not position-related, sometimes activity-related. Associated symptoms: chest pain, dyspnea, palpitations, limb edema, syncope, abnormal ECG, abnormal echocardiography
Psychiatric/ Psychosomatic	• Panic Disorder/Anxiety Attack • Psychogenic pseudosyncope	Palpitations, hyperventilation, trembling, tingling in fingers; triggers are not position-related; typically accompanied by fear, impending sense of doom etc. Apparent syncope, but not actual loss of consciousness in absence of identifiable cardiac, reflex, neurological or metabolic causes
Cerebrovascular	• Vertebrobasilar insufficiency • Perfusion failure syndromes • Subarachnoid hemorrhage	Focal neurological deficits or even syncope related to drops in blood pressure in patients with high grade stenosis or occlusion of extra or intracranial cerebral vessels. Symptoms are stereotyped and blood pressure dependent. Syncope may occur at the time of aneurysm rupture with subarachnoid hemorrhage, typically following severe headache onset
Seizure	• Focal aware or unaware seizures [234] • Generalized seizure • Subtle/non-convulsive seizure	Stereotyped semiology, witnessed seizure activity, staring spells, automatisms, behavior arrest, seizure risk factors (structural brain lesion, meningitis, febrile seizures, substance abuse, alcohol), EEG findings
Metabolic disorders	• Hypo/hyperglycemia • Hypoxia • Anemia • Electrolyte- or hormone abnormalities	Corresponding laboratory abnormalities
VERTIGO		
Peripheral	• Benign paroxysmal positional vertigo (BPPV) • Meniere disease • Vestibular neuritis • Herpes zoster otitis • Medication toxicity • Otitis media • Perilymphatic fistula • Semicircular canal dehiscence • Vestibular schwannoma	Specific Peripheral Vertigo findings: Spinning sensation, tilt illusion, spatial disorientation, oscillopsia, impaired balance, inability to walk, nausea/vomiting, hearing loss, worsened with head movement, may be related to head position (BPPV), can be brief and recurrent

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Table 12 (*continued*)

Category	Diagnoses	Key Features
	• Labyrinthine concussion • Cogan syndrome	(BPPV, Meniere) or last days (vestibular neuritis), may be accompanied by viral syndrome, may fall toward side of lesion, typically more severe than central vertigo, with nausea/vomiting, BPPV often post head trauma, unilateral hearing loss or tinnitus with Meniere. Nystagmus is horizontal, torsional, suppresses with visual fixation and does not change with gaze direction
Central	• Brainstem stroke/TIA/ischemia (including Wallenberg syndrome, cerebellar stroke, labyrinth artery occlusion, vertebrobasilar insufficiency) • Rotational vertebral artery syndrome • Seizure • Chiari I malformation • Multiple sclerosis • Disembarkment syndrome • Vestibular migraine • Episodic ataxia type 2	Specific Central Vertigo findings: Spinning sensation, tilt illusion, spatial disorientation, oscillopsia, impaired balance, inability to walk, nausea/vomiting, hearing loss, worsened with head movement, may be accompanied by focal neurological deficits, usually vascular risk factors, sudden onset with persistent symptoms, less severe symptoms than peripheral vertigo. Nystagmus can be vertical, horizontal, torsional, can change with gaze direction, does not suppress with visual fixation.
ATAXIA		
Peripheral neuropathy with impaired proprioception	• Diabetes • Alcohol-related • Vitamin B12 deficiency • Uremic neuropathy • Hypothyroidism • Lyme disease • HIV • Toxins • Paraneoplastic • Sjogren's/autoimmune • Hereditary (e.g. Charcot-Marie Tooth)	Deterioration with eyes closed, associated limb weakness, numbness and/or pain or other focal deficits
Cerebellar/brainstem lesion	• Stroke (ischemic or hemorrhagic) • Multiple sclerosis • Tumor • Alcohol-related atrophy • Paraneoplastic • Spinocerebellar ataxia • Infections cerebellitis (e.g. VZV) • Denatorubral-pallidoluysian atrophy • Episodic ataxia syndrome	Deterioration with eyes closed, associated limb weakness, numbness and/or pain or other focal deficits
Spinal cord lesion	• Cervical spondylosis • Vitamin B12 deficiency • Vitamin E deficiency • Zinc/Copper deficiency • Spinal cord trauma • Infection (HTLV 1,2, HIV, Lyme, Syphilis, strongyloides etc.)	Long track signs, numbness, weakness, hyperreflexia

Table 13
Diagnostic Evaluation of PASC Dizziness/Lightheadedness based on American College of Cardiology/American Heart Association practice guidelines [127].

Study	Results	Interpretation/Consideration
Screening Questionnaire	COMPASS-31 [276]	Six domains of autonomic function: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor. Score range 0–100 with higher scores indicating more severe autonomic dysfunction
PHYSICAL EXAMINATION		
Active standing test (5 min in lying position→ measurement in standing position for at least 3 min)	• Decrease of SBP >20 mmHg or DBP >10 mmHg • Typical symptoms and HR increase of ≥30 bpm (≥ 40 bpm in patients 12–19 years), or absolute HR >120 bpm, within the first 10 min of standing, in the absence of blood pressure drop	• Orthostatic hypotension • POTS
Neurological Exam	• Brainstem or cerebellar findings: ataxia, dysphagia, diplopia, dysarthria, hemiparesis, hemisensory loss, crossed signs • Rigidity, tremor, positive pull sign, turning en bloc • Reduced reflexes, stocking glove sensory loss, diminished proprioception and/or vibration	• Central lesion (e.g. stroke, hemorrhage, tumor, multiple sclerosis) • Consider synucleinopathy with dysautonomia (e.g. Parkinsonism, multi-system atrophy, dementia with Lewy bodies) • Peripheral neuropathy, autonomic neuropathy (e.g. diabetes, amyloidosis, Sjogren syndrome, renal failure, vitamin B12 deficiency, syphilis, Lyme, HIV, Chagas, sarcoid, porphyria)
Nystagmus	• Horizontal, torsional, suppresses with visual fixation and does not change with gaze direction • Can be vertical, horizontal, torsional, can change with gaze direction, does not suppress with visual fixation.	• Peripheral vertigo • Central vertigo
Dix-Hallpike	• 2–20 s latent period before onset of nystagmus, duration of nystagmus <1 min, fatigues with repetition, severe vertigo • No latency period, nystagmus lasts >1 min, non-fatiguing, less severe symptoms	• Peripheral vertigo • Central vertigo
Head Impulse/Head Thrust test	• Eyes move off fixation target with saccades back to target	• Peripheral vertigo • Central vertigo

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Table 13 (*continued*)

Study	Results	Interpretation/ Consideration
	• Eyes remain on target	
Skew deviation	• No movement of eyes on cover/ uncover test • Vertical or diagonal movement of eye on cover/uncover test	• Peripheral vertigo • Central vertigo
Hearing loss	Weber and/or Rinne tests lateralizes or abnormal	Unilateral sensorineural hearing loss suggests peripheral lesion
Romberg test	• Unable to put feet together and maintain balance even with eyes open • Loss of balance when feet together and eyes closed	• Cerebellar lesion • Proprioceptive abnormality
LABORATORY STUDIES		
12-channel ECG	Arrhythmia, cardiac disease, atrio-ventricular block, long QT syndrome, Brugada syndrome, Wolf-Parkinson-White syndrome, pacemaker malfunction	• In evaluation of patients with syncope, a resting 12-lead ECG is useful (ACC/AHA/ HRS I) [127]
Basic laboratory studies	Metabolic dysfunction, hypovolemia, anemia, hyper/hypoglycemia, elevated hemoglobin A1C fasting glucose	• Targeted blood tests are reasonable in the evaluation of select patients with syncope based on history, physical exam and ECG. (ACC/AHA/HRS IIa) [127]
ADVANCED STUDIES		
Tilt-table test (continuous measurement of BP and HR)	• Vasovagal syncope: decrease of SBP ≥ 40 mmHg or decrease of ≥60 bpm for heart rate (without loss of consciousness) and/ or reproduction of typical symptoms [277] • Orthostatic hypotension: immediate decline in SBP >20 mmHg or DBP >10 mmHg with or without an increase in heart rate or delayed response in 3–5 min after posture change • Severe primary or secondary autonomic failure: abrupt drop in SBP with upright posture that does not recover and may necessitate test termination. • POTS: Typical symptoms and HR increase of ≥30 bpm (≥ 40 bpm in patients 12–19 years), or absolute HR >120 bpm, within the first 10 min of standing [277]	• Tilt-table can be useful for suspected vasovagal syncope if the diagnosis is unclear after initial evaluation (ACC/AHA/HRS IIa) [127] • Tilt-table can be useful for syncope with suspected delayed orthostatic hypotension when initial evaluation is not diagnostic (ACC/AHA/ HRS IIa) [127] • Tilt-table testing is reasonable to distinguish convulsive syncope from epilepsy (ACC/AHA/HRS IIa) [127] • Tilt-table can be used to establish a diagnosis of pseudosyncope (ACC/AHA/HRS IIa) [127] • Tilt-table testing is not recommended to predict response to medical treatments for vasovagal syncope (ACC/AHA/HRS III) [127] • Autonomic evaluation can be useful for patients with suspected neurodegenerative disease and syncope

Table 13 (*continued*)

Study	Results	Interpretation/ Consideration
	• Symptoms of syncope, near-syncope	(ACC/AHA/HRS IIa) [127] • Typically not helpful for situational vagal syncope (micturition, defecation, etc.) and not necessary in most patients presenting with lightheadedness.
Electronystagmography, video nystagmography	Abnormal spontaneous and induced nystagmus	Central and peripheral vertigo
Vestibular evoked myogenic potentials (VEMP)	Cervical and ocular VEMPs abnormal	Useful for otolith function, semicircular canal dehiscence
Heart rate variability	Reduced	Autonomic dysfunction
Electromyography, Nerve Conduction Study (EMG/ NCS)	Autonomic neuropathy	Consider in select patients based on history and exam. Autonomic neuropathy is typically associated with normal EMG/NCS unless there are additional superimposed neuropathies (i.e. as in diabetic neuropathy, amyloid neuropathy)
Biopsy	Skin biopsy for abnormal small, unmyelinated nerve fibers consistent with autonomic neuropathy	Skin biopsy may useful for diagnosis of small-fiber neuropathy [278]. Nerve biopsy typically not performed, but may be useful for suspected amyloid neuropathy, or vasculitic neuropathy [278]
Neurovascular studies	CT angiogram, MR angiogram, digital subtraction angiography with basilar stenosis/ occlusion or bilateral carotid stenosis/ occlusion	• Carotid artery imaging is not recommended in the routine evaluation of patients with syncope in the absence of focal neurological findings that support further evaluation (ACC/AHA/HRS III) [127] • Vessel imaging should be performed in patients with suspected vertebrobasilar insufficiency or hypoperfusion syndromes based on history, physical exam and the presence of blood pressure dependent focal neurological symptoms
Electroencephalogram (EEG)	Seizure, epileptiform discharges	• Routine EEG is not recommended in the evaluation of patients with syncope in the absence of specific neurological features suggestive of seizure (ACC/AHA/HRS III) [127]
Brain MRI or head CT	Structural defects, neurodegenerative disease	• Consider in context of focal neurological symptoms and/or exam findings • MRI and CT are not recommended in the routine evaluation of patients with syncope in the absence of focal

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Table 13 (*continued*)

Study	Results	Interpretation/ Consideration
		neurological findings or head injury that support further evaluation (ACC/AHA/HRS III) [127]
Echocardiography	• Hypertrophic obstructive cardiomyopathy • Aortic stenosis • Prior myocardial infarction • Other structural abnormalities	• Transthoracic echocardiography can be useful in selected patients with syncope if structural heart disease is suspected (ACC/AHA/HRS IIa) [127]
Exercise stress test	Tachy/brady arrhythmias with exertion	• Exercise stress testing can be useful in select patients with syncope/presyncope during exertion (ACC/AHA/HRS IIa) [127]
Long-term ECG (24 h)	Tachy/brady arrhythmias	• Ambulatory ECG monitoring can be useful in patients with syncope of suspected arrhythmic etiology (ACC/AHA/HRS IIa) [127]
Advanced laboratory (e.g. catecholamines) and/or CSF (antineuronal antibodies)	Metabolic/ endocrinological/ paraneoplastic/ autoimmune abnormalities	In select patients based on history, exam and preliminary test results

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate, POTS, postural orthostatic tachycardia syndrome, ECG, electrocardiogram; ACC/AHA/HRS, American College of Cardiology/American Heart Association; MI, myocardial infarction; NCS/EMG, nerve conduction study, electromyography; CSF, cerebrospinal fluid.

and neurological complications during index hospitalization [4,144,146–149]. It is important to note that life stressors and socioeconomic factors can contribute substantially to fatigue, particularly in the context of the COVID-19 pandemic. In a study of 999 subjects with (N = 76) and without (N = 923) a history of COVID-19, significant predictors of worse NeuroQoL fatigue scores in multivariable analysis included social isolation, relationship problems with household members, fear of illness and political conflict with friends/family or colleagues [146]. Of note, a history of COVID-19 was *not* a significant independent predictor of fatigue after controlling for other factors [146]. Among patients hospitalized for acute COVID-19, poor NeuroQoL fatigue scores at 12 months were significantly associated with the presence of at least one life stressor, and fatigue scores correlated with the number of stressors a patient faced (e.g. financial insecurity, social isolation, unemployment, death of a close contact) [4].

Differential Diagnosis: Underlying medical or psychiatric causes of fatigue can be identified in over two-thirds of COVID-19 patients presenting with fatigue [150,151]. Broad categories of disorders that can lead to fatigue are listed in Table 15. Because PASC pulmonary and cardiac symptoms are relatively common, screening for these causative factors should be undertaken as part of the initial evaluation.

In cases where an immediate medical or psychiatric cause of fatigue cannot be identified, patients may be evaluated for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which is a diagnosis of exclusion. Recent evidence suggests that as many as 20% of individuals with post COVID-19 fatigue meet ME/CFS criteria [181] and, in up to 80% of patients that meet ME/CFS criteria, the onset of illness was associated with an infection [196]. Diagnostic criteria for ME/CFS are listed in Table 16 [152,153]. ME/CFS should be distinguished from

Table 14
Treatment options for PASC orthostatic intolerance syndromes according to the European Society of Cardiology Syncope Guidelines [279].

Disease	Treatment	Recommendation
	NON-PHARMACOLOGICAL	
Orthostatic hypotension	Education and avoidance of exacerbating factors	• Explanation of the diagnosis, risk of recurrence and counseling on avoidance of triggers and situations (e.g. avoiding rapid changes of body positioning, prolonged standing, hot environment, dehydration, alcohol and caffeine, recommend small and frequent meals) (European Society of Cardiology Syncope Guidelines Class I, Level C [279])
	Diet modifications	• Adequate hydration and salt intake are indicated (European Society of Cardiology Syncope Guidelines Class I, Level C [279])
	Medication management	• Modification or discontinuation of hypotensive drug regimens should be considered (European Society of Cardiology Syncope Guidelines Class IIa, Level B [279])
	Exercise	• Isometric physical counter-pressure maneuvers should be considered (European Society of Cardiology Syncope Guidelines Class IIa, Level C [279]) • Examples include: sustained muscle tensioning, crossing arms/legs, folding arms and leaning forward, squatting or lifting legs
	Support devices	• Abdominal binders and/or support stockings to reduce venous pooling should be considered (European Society of Cardiology Syncope Guidelines Class IIa, Level B [279])
	Sleep position	• Head-up tilt sleeping (>10 degrees) to increase fluid volume should be considered (European Society of Cardiology Syncope Guidelines Class IIa, Level C [279])
POTS	Exercise	• A regular, structured and progressive exercise program can be effective (Heart Rhythm Society Consensus Statement, Class IIa, Level B-R [280])
	Diet	• The consumption of up to 2–3 L of water and 10–12 g of salt per day may be considered (Heart Rhythm Society Consensus Statement, Class IIb, Level E [280])
	PHARMACOLOGICAL	
Orthostatic hypotension	Midodrine (2.5–10 mg TID)	• Midodrine should be considered if symptoms persist following non-pharmacological interventions (European Society of Cardiology Syncope Guidelines Class IIa, Level B [279]) • Can cause supine hypertension
	Fludrocortisone (0.1–0.3 mg daily)	• Fludrocortisone should be considered if symptoms persist following non-pharmacological interventions (European Society of Cardiology Syncope Guidelines Class IIa, Level C [279]) • Stimulates volume expansion.
POTS	Intravenous fluid	• It is reasonable to treat patients with short-term clinical decompensations with an acute intravenous infusion of up to 2 L of saline (Heart Rhythm Society Consensus Statement, Class IIa, Level C [280])

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Table 14 (*continued*)

Disease	Treatment	Recommendation
	Fludrocortisone	• It seems reasonable to treat POTS patients with fludrocortisone (Heart Rhythm Society Consensus Statement, Class IIb, Level C [280])
	Midodrine	• Treatment with midodrine may be considered (Heart Rhythm Society Consensus Statement, Class IIb, Level B-R [280])
	Pyridostigmine	• It seems reasonable to treat POTS patients with pyridostigmine (Heart Rhythm Society Consensus Statement, Class IIb, Level C [280]) [281]
	Propranolol	• Treatment with low-dose propranolol may be considered (Heart Rhythm Society Consensus Statement, Class IIb, Level B-R [280])
	Clonidine	• It seems reasonable to treat POTS patients who have prominent hyperadrenergic features with clonidine (Heart Rhythm Society Consensus Statement, Class IIb, Level E [280])
	Alpha-methyldopa	• It seems reasonable to treat POTS patients who have prominent hyperadrenergic features with alpha-methyldopa (Heart Rhythm Society Consensus Statement, Class IIb, Level E [280])
	Norepinephrine reuptake inhibitors	• Drugs that block norepinephrine reuptake (e.g. SNRI, duloxetine, nortriptyline, tapentadol) can worsen symptoms in patients with POTS and should not be administered (Heart Rhythm Society Consensus Statement, Class III, Level B-R [280]).
	Invasive procedures	• Chiari I malformation correction, radiofrequency sinus node modification, balloon dilation or stenting of the jugular vein are not recommended for POTS treatment and are potentially harmful (Heart Rhythm Society Consensus Statement, Class III, Level B-NR [280]).

POTS = postural tachycardia syndrome. Class of Recommendation and Level of Evidence are based on the American Guidelines and complemented by the European Guidelines (see below), Legend: Class I: is recommended/indicated, Class IIa: is reasonable/should be considered, Class IIb: may be reasonable/may be considered, Class III: is not recommended/potentially harmful; Level A: highest evidence from multiple randomized clinical trials or meta-analyses; Level B: moderate evidence, from randomized trials (B–R) or well-executed non-randomized trials (B-NR); Level C: evidence from studies with significant limitations (small, retrospective, registries) (C-LD), or consensus/expert opinion (E).

postinfectious fatigue syndrome (PIFS), which can be severe, but usually has a self-limiting course and has been described in infections like with Epstein-Barr-Virus [154]. Some groups have defined post-COVID-19 PIFS as fatigue lasting for at least 6 months with scores of 2 or above on the Chalder fatigue scale [138,155].

Similarly, there are numerous overlapping symptoms between fibromyalgia and post-COVID-19 fatigue. Indeed, up to 30% of patients with post-COVID syndrome meet fibromyalgia criteria [156]. The core diagnostic criteria for fibromyalgia include both of the following present for ≥3 months: multisite pain in at least 6 of 9 locations, and moderate to severe sleep problems or fatigue [157]. Fibromyalgia should be distinguished from polymyalgia rheumatica (PMR) which occurs in patients ≥50 years old, is characterized by bilateral shoulder pain, proximal muscle pain in the upper and/or lower extremities, and abnormal C-reactive protein and/or erythrocyte sedimentation rate [158]. PMR patients may have hip pain or restricted hip range of motion, but typically do not have other joint involvement. Ultrasound may show subdeltoid bursitis, biceps tenosynovitis, glenohumeral synovitis, hip synovitis, or trochanteric bursitis in PMR [158]. PMR symptoms are classically improved with steroid treatment, and the absence of steroid responsiveness should suggest an alternate diagnosis.

Diagnostic Evaluation: Patients should be assessed for activity levels and fatigue patterns, in particular post-exertional malaise, to guide recommendations on physical activity [135]. A detailed history regarding basic and instrumental activities of daily living should be taken along with details on endurance and activity tolerance, followed by a thorough clinical examination. Standard questionnaires may help the classification of fatigue, post-exertional malaise, functional impairment and impact on quality of life [137,159]. Routine evaluation and laboratory screening tests are shown in Table 17. Further endocrine, autoimmune/rheumatological, cardiopulmonary, and autonomic function tests can be tailored to individual patients based on history and comorbidities. A medication review should always be undertaken to identify those that can contribute to, or worsen fatigue. Assessment of mood is needed as both depression and anxiety are associated with post-viral fatigue.

Therapeutic options

COVID-19 Specific Treatments: A limited number of clinical studies have been conducted among patients with post-COVID-19 fatigue. A randomized trial of 114 patients with severe fatigue (3–12 months post-COVID) assigned patients to either cognitive behavioral therapy or routine care. Those who received cognitive behavioral therapy had significantly lower fatigue severity scores on the Checklist Individual Strength scale at 6-months [160]. In a double-blind, parallel-group, sham-controlled study, 50 patients with post-COVID-19 chronic fatigue were randomized to transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex versus sham procedure [161]. Significant improvements at one month were noted in Modified Fatigue Impact Scale scores in the intervention group compared to controls. Depression scores as measured by the Beck Depression Inventory were also significantly improved, however, no changes in cognitive scores (Stroop test) were identified. Similarly, a randomized trial of high-definition tDCS found significantly improved Modified Fatigue Impact Scale scores, particularly in cognitive and psychosocial domains, compared to a sham procedure in 70 patients with PASC fatigue [162].

Nutritional supplements have also been evaluated in several studies. One non-randomized trial assessed 43 patients with PASC and found a 47% reduction in fatigue symptoms on the Chalder fatigue questionnaire with the use of oxaloacetate [163]. A single-blinded, randomized controlled trial of 50 PASC fatigue patients compared L-arginine plus vitamin C to placebo and found significantly longer 6-min walk distances and improved handgrip strength in the intervention group [164]. Another unblinded survey compared 869 patients who received L-arginine plus vitamin C to 521 who received a multivitamin, and found reduced self-reported asthenia, dyspnea, chest tightness, dizziness, GI problems, headache, anosmia, concentration difficulty and sleeplessness in the L-arginine group compared to the multivitamin group [165]. In another randomized study of 388 PASC patients, fatigue measures improved in patients who consumed qingjin yiqi granules along with standard rehabilitation treatments compared to those who received rehabilitation alone [166]. Other alternative medical regimens have been evaluated. For example, a randomized trial of aromatherapy for 2

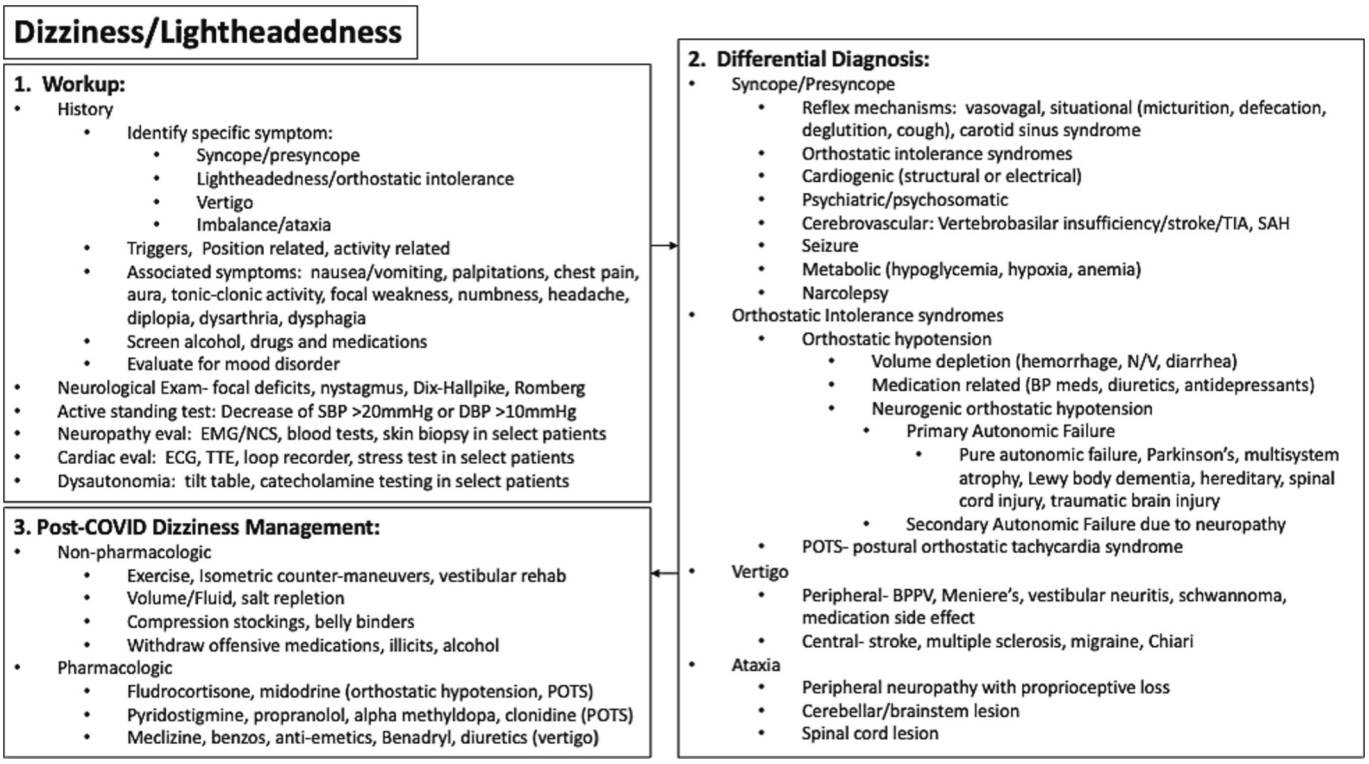

Fig. 4. Evaluation and Management of PASC Dizziness/Lightheadedness.
SAH, subarachnoid hemorrhage; ECG, electrocardiogram; EMG/NCS, electromyography, nerve conduction study; TTE, transthoracic echocardiography.

weeks (thyme, orange, clove bud, frankincense) in 40 women with PASC fatigue identified lower multidimensional Fatigue Symptom Inventory scores with aromatherapy compared to placebo [167]. Another single arm study found improved Fatigue Severity Scale scores in 100 PASC fatigue patients treated with oxygen-ozone autohemotherapy [168]. Similarly, hyperbaric oxygen therapy improved subjective symptoms in two case-series [169,170]. Among PASC patients with fatigue and orthostatic symptoms, enhanced external counterpulsation using lower extremity pressure cuffs has shown some benefit [171,172].

For all patients, underlying medical and psychiatric disorders that can cause fatigue should be directly addressed as first line treatment. Additionally, offensive medications should be eliminated, if possible, and substance abuse issues should be managed. The WHO has issued guidelines on management of post-COVID-19 fatigue [11]. Specifically, a combination of education, skills-training on energy conservation techniques, and a cautious return to symptom-titrated physical exercise training (in the absence of post-exertional symptom exacerbation) is suggested. For those with post-exertional symptom exacerbation, education and skills training on energy conservation and pacing approaches is suggested [11]. Additional treatment strategies based on NICE ME/CFS guidelines are outlined in Table 18 [173]. An algorithm for the evaluation and management of PASC fatigue is shown in Fig. 5**.** Of note, several ME/CFS trials have found no benefit for certain interventions including: acyclovir [174], antibiotics [175], Anakinra (cytokine inhibitor) [176], galantamine [177], modafinil [178] and rituximab [179]. Studies have shown mixed results and unclear benefit for steroids [180,181], immunoglobulin [182,183], methylphenidate [184], rintatolimod [185], and graded exercise therapy [173].

3.6. *Weakness, numbness and pain*

Epidemiology: In the acute phase of SARS-CoV-2 infection, sensory impairment has been reported in 2% of patients [116], and newly diagnosed neuropathy, including critical illness neuropathy or compression neuropathy (i.e. secondary to proning or immobility) has been reported in 0.8–1% of hospitalized COVID-19 patients [116,186–188]. Acutely, cranial neuropathies, including Bell's Palsy have been reported in approximately 0.1–2% of patients with COVID-19 who present to an emergency department [116,189]. Guillain-Barre syndrome has also been reported in 0.1–0.3% of hospitalized COVID-19 patients, typically within 6 weeks of index infection [116,186,190]. While acute demyelinating and axonal variants of Guillain-Barre have most commonly been described in relationship to SARS-CoV-2 infection, other variants including Miller Fisher syndrome, pharyngeal-cervical-brachial and polyneuritis cranialis variants, have also been reported [190].

There are limited data available to estimate the prevalence of neuropathy syndromes in the post-acute time frame. Though some studies report prevalence rates as high as 25–50% [71,191–193], these are gross overestimates skewed by referral biases and inappropriate denominators. Nonetheless, there is electrophysiological and skin biopsy data to suggest that post-COVID-19 neuropathic pain syndromes related to small-fiber peripheral neuropathy do occur, and may be associated with neuropathic pain [193–195]. The underlying pathophysiology is suspected to involve systemic inflammation from immune dysregulation, demyelination or ischemic neuropathy from microthrombosis of the vasa nervorum [196,197]; these processes may be acting in combination.

Table 15
Differential Diagnosis of PASC Fatigue [137,159].

Disease/disorders/syndromes	Key Features (in addition to fatigue)
Pulmonary	Shortness of breath – at rest/on exertion, cough, wheeze, poor activity tolerance
• Lung fibrosis • Chronic obstructive pulmonary disease (COPD) • Pulmonary embolism	
Cardiovascular	Chest pains, palpitations, sweating, leg swelling and pain, dyspnea on exertion or at rest, orthopnoea, poor activity tolerance
• Heart failure, preserved or reduced ejection fraction (left or right ventricular failure) • Coronary artery disease, angina • Post viral, post-vaccination myocarditis [282] • Myocardial fibrosis/scarring • Arrhythmias	
Gastrointestinal	Bloating, nausea, vomiting, constipation, diarrhea, pruritus, malabsorption syndrome
• Inflammatory bowel disease • Celiac disease • Chronic intestinal infections (e.g. amebiasis, salmonellosis) • Primary biliary cirrhosis/primary sclerosing cholangitis • Liver failure/cirrhosis	
Renal	Electrolyte imbalance, elevated BUN, creatinine, proteinuria, hypoalbuminemia, edema
• Primary kidney disease (e.g. glomerulonephritis) • Secondary kidney disease (e.g. autoimmune and vascular disorders, hypovolemia, diabetes, hypertension)	
Infections (acute and chronic)	Fever, weight loss, joint pain/swelling, myalgia, cognitive impairment
• Viral infections (e.g. herpes viruses) • Fungal infections • Parasitic infections (e.g. Chagas disease, malaria) • Tuberculosis/mycobacterial infections • Lyme disease • Hepatitis • HIV/AIDS • Syphilis • Endocarditis	
Endocrine/Electrolyte	Palpitations, dizziness, weight gain/loss, loss of hair, chills/fever/hypothermia, irregular menstrual cycle, excessive thirst/urination, hypotension, electrolyte abnormalities
• Hypothyroidism (e.g. Hashimoto thyroiditis) • Hyperthyroidism • Adrenal insufficiency (e.g. Addison's disease) • Hypogonadism • Diabetes mellitus • Hyponatremia • Hypercalcemia • Hypermagnesemia	
Autoimmune and Rheumatologic	Joint and muscle pains, stiffness, fever, mouth ulcers, rashes, dry eyes or mouth, Raynaud's phenomenon, numbness/ tingling/burning in fingers/toes, blurry/ decreased vision, impairment of different organs according to prevailing disorder/syndrome
• Fibromyalgia • Polymyalgia rheumatica • Rheumatoid arthritis • Adult-onset Still's disease • Vasculitis (e.g. Wegener's, eosinophilic, polyarteritis nodosa) • Lupus/mixed connective tissue disorders • Sarcoidosis • Behcet's • Sjögren syndrome	
Hematologic and oncologic	Blood dyscrasias, abnormalities of biochemical and immunologic parameters, weight loss
• Anemia • Malignancy • Immunodeficiency syndromes (e.g. common variable immunodeficiency) • Paraneoplastic syndrome	
Neuropsychiatric	Depression, anxiety, irritability, chest tightness, low frustration tolerance, mood swings, cognitive impairment, poor non restorative sleep, muscle weakness and other neurological signs/symptoms
• Anxiety • Depression • Post-Traumatic Stress Disorder (PTSD) • Chronic stress/grief • Traumatic brain injury • Multiple sclerosis • Myasthenia gravis/neuromuscular junction disorders • Chronic inflammatory demyelinating polyneuropathy	

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Table 15 (*continued*)

Disease/disorders/syndromes	Key Features (in addition to fatigue)
• Motor neuron disease • Myopathy (see weakness section below) • Neurodegenerative disorders (Parkinson's, Alzheimer's etc.)	
Sleep Disorders (See sleep section above) • Obstructive sleep apnea • Insomnia • Narcolepsy	Snoring, poor sleep initiation, maintenance or termination, short sleep latency
Drugs • Antiseizure medication • Antidepressants • Anticholinergics • Antihistamines • Antiemetics • Beta-blockers • Benzodiazepines • Muscle relaxants • Opioids • Cancer therapies including radiotherapy • Alcohol • Marijuana	Other drug-specific side effects, history of exposure

Table 16
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) 2015 Institute of Medicine Diagnostic Criteria [152,153].

Requirements	Symptoms
A. All 3 symptoms must be present, and should occur at least 50% of the time with moderate, substantial or severe intensity	1. A substantial reduction in the ability to engage in pre-illness levels of personal, social, educational or occupational activities for ≥6 months, which is accompanied by new onset fatigue (often profound) that is not due to excessive or ongoing exertion, and is not substantially alleviated by rest. 2. Post-exertional malaise with worsening of symptoms after physical or cognitive activity that would have been tolerated pre-diagnosis 3. Unrefreshing sleep
B. At least one of these symptoms is also required and should occur at least 50% of the time with moderate, substantial or severe intensity	1. Cognitive impairment that is exacerbated by effort, exertion, or stress 2. Orthostatic intolerance-worsening symptoms in upright position, relieved by recumbency or elevation of the feet.

Table 17
Diagnostic Evaluation of PASC Fatigue [135,137,159].

Study	Results	Interpretation/Consideration
CLINICAL ASSESSMENT		
History	• Evaluate onset, course, duration and relationship to illness or life events • Alleviating or exacerbating factors • Relationship of symptoms with exertion • Impact of symptoms on daily function • Screen for depression and anxiety • Sleep history • Screen medications, alcohol and illicits	Screening Questionnaires: • Fatigue Severity Scale (degree of fatigue severity) • Fatigue Assessment Scale • PROMIS/NeuroQoL Fatigue • DePaul symptom questionnaire (degree of post-exertional malaise (PEM)) • Bell score (functional impairment in the context of ME/CFS) • PHQ-2/PHQ-9 Depression screen • GAD-7 Anxiety screen
Physical Exam	• Exam for stigmata of cardiopulmonary disease, malignancy, thyroid disease, neurological disease • Evaluate for point tenderness associated with fibromyalgia or polymyalgia rheumatica	Assess for underlying medical causes of fatigue
LABORATORY ASSESSMENT		
Blood tests	• Complete blood count, chemistry panel, thyroid function tests, liver function tests, creatinine kinase, erythrocyte sedimentation rate, C-reactive protein, as indicated • Age-appropriate cancer screening	Choice of testing may be guided by history and physical
Advanced testing	• Cardiac testing: Electrocardiogram, echocardiogram, exercise stress test, Holter monitoring • Pulmonary testing: pulmonary function tests (PFT), chest imaging • Sleep study • Additional lab tests: HIV, hepatitis panel, PPD, quantiferon, drug levels, ANA, anti-dsDNA, cortisol, viral antibody titers, Lyme antibodies, SPEP/UPEP • Dysautonomia testing (see lightheadedness/dizziness section)	In select patients based on the differential diagnosis and exposure

Table 18
Treatment Options for PASC Fatigue based on NICE guidelines [173].

Treatment	Recommendation
Energy management and adaptive pacing therapy [159,173,283–285]	• Development of an individual plan for energy management including physical, cognitive, emotional, and social activity • Avoidance of continuous overexertion and focusing on rest • Pacing of physical activity • Pacing of cognitive activity (e.g., limit reading time) • Use of assistive devices (e.g., shower chairs) • Limit sensory stimulation (e.g., ear plugs, eye masks, perfume-free environment) • School or work accommodations (e.g., flexible hours, work from home) • Home health aides in severe cases
Exercise program [173,283,284]	• Post-exertional malaise typically occurs 12–48 h and can last for days to weeks. Hence, exercise programs should be gradual and incremental • Personalized exercise program for patients who feel ready to progress their physical activity or would like to incorporate it into their management strategy. • Interval or time-based activity • Start with physical activity below a patient's baseline level that do not worsen symptoms with gradual and flexible adjustments to physical activity • Recognition of a flare-up or relapse, with reduction of physical activity if needed
Cognitive behavioral therapy [173]	• May be offered to help manage symptoms, improve function and reduce distress, but should not be considered a curative therapy

Muscle pain and body aches have been reported in 20–50% of patients during acute SARS-CoV-2 infection [37,116,198]. During hospitalization for COVID-19, critical illness myopathy has been reported in approximately 0.5–2% of patients [116,186] and rhabdomyolysis has been reported in 0.4% [116]. In these patients, immobility, cytokine storm, illness severity, patient factors (such as underlying sarcopenia and malnutrition) and iatrogenic factors such as proning and dexamethasone use contribute to myopathy risk [198,199]. Additionally, autopsy studies in patients who died acutely after COVID-19 demonstrate evidence of post-infectious immune-mediated myositis, with features that differ from typical critical illness myopathy [200]. It is unclear whether patients experiencing muscular symptoms after mild or moderate COVID-19 manifest the same processes. Despite this, quantitative electromyography (EMG) myopathic changes have been demonstrated in patients who were not hospitalized for COVID-19 [201], suggesting myopathy occurs following less severe illness and is not purely driven by proning, dexamethasone or other treatments delivered in hospital setting.

As with post-COVID neuropathy, the prevalence of myopathy in the post-acute period is difficult to estimate and the literature is mainly limited to case reports of polymyositis [202,203], IgG-related autoimmune inflammatory necrotizing myositis [204] and type I interferonopathy [205]. In two cohort studies, including a total of 36 long COVID patients referred to a neuromuscular clinic, 55–75% had myopathic

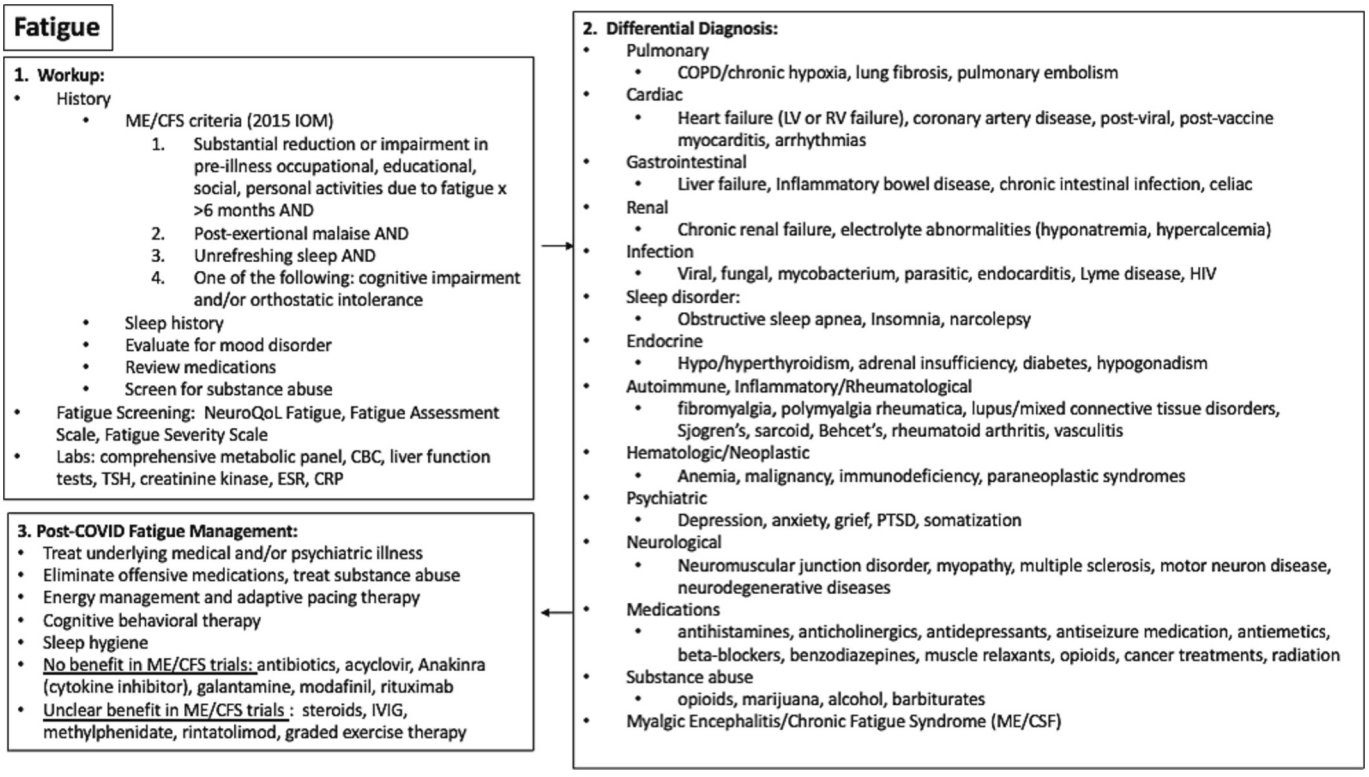

Fig. 5. Evaluation and Management of PASC Fatigue.
ME/CFS, myalgic encephalitis/chronic fatigue syndrome.

Table 19
Differential Diagnosis of PASC Numbness and Neuropathic Pain.

Diagnosis	Key Features
PAINFUL SENSORY NEUROPATHIES	
Diabetic neuropathy	Poor glucose control, elevated hemoglobin A1C, primarily axonal, length-dependent "glove-and-stocking" distribution, can be isolated painful, small-fiber sensory neuropathy, or diabetic amyotrophy. Most common cause of autonomic neuropathy
Paraproteinemic neuropathy	Features of multiple myeloma (back pain, anemia, hypercalcemia, renal impairment), monoclonal gammopathy (often IgM), can present as mononeuritis multiplex, distal polyneuropathy, radiculopathy, plexopathy
Vasculitic neuropathy	Usually in context of systemic vasculitis, e.g. Sjogren's, polyarteritis nodosa, ANCA-associated vasculitis, Lupus, rheumatoid arthritis, hepatitis B or C, cryoglobulinemia, sarcoid
Paraneoplastic sensory neuropathy	Anti-Hu (ANNA-1), CV2/CRMP5, PCA-2 (MAP1B), anti-amphiphysin, solid tumor cancers (most commonly lung cancer), asbestos exposure, tobacco use, weight loss, focal symptoms indicating primary tumor, lymphadenopathy, anemia, painful neuronopathy
Amyloid polyneuropathy	Can be familial or acquired, history of plasma cell dyscrasia, autonomic dysfunction, monoclonal gammopathy, transthyretin antibodies
Hereditary neuropathies	Pes cavus or hammer toe, family history, porphyria, Fabry disease
Idiopathic small fiber neuropathy	Risk increases with older age, diminished sudomotor function
Post-herpetic neuralgia	Dermatomal distribution, vesicular lesions
Radiculopathy	Back or neck pain, dermatomal distribution of symptoms, spinal degenerative joint disease
Alcohol neuropathy	Sensory, motor and autonomic involvement that is primarily axonal, but can be demyelinating with coexisting nutritional deficiencies. Stocking-glove pattern.
Uremic neuropathy	Present in over 60% of patients on dialysis, can also be present in non-dialysis patients with chronic kidney disease. Sensorimotor, primarily axonal, stocking glove distribution, small fiber neuropathy, becomes painful, burning with more advanced neuropathy.
HIV neuropathy	Distal, axonal, symmetric polyneuropathy, small fiber neuropathy, can be complicated by antiretroviral-induced neuropathy
Complex Regional Pain Syndromes	The pathogenesis involves classic inflammation, neurogenic inflammation and maladaptive changes/central sensitization in pain perception. Typically occurs in distal part of limb, does not involve head/face, and may not correspond to the territory of a nerve or nerve root. Involvement of the sympathetic nervous system with autonomic features is common. Clinical criteria include: continuing pain disproportionate to the inciting event, AND at least one symptom in three of the four categories (sensory, vasomotor, sudomotor/edema, motor/trophic) AND at least one sign in two of four categories (sensory, vasomotor, sudomotor/edema, motor/trophic) [286].
Toxin-related neuropathies	• Medication-related (chemotherapy, colchicine, amiodarone, nitrofurantoin, antiretroviral drugs) • Heavy metals, n-hexane, ethylene glycol, carbon disulfide etc.
ICU-RELATED NEUROPATHIES	
Compression neuropathy	History of prone positioning, prolonged immobility, ICU stay. Commonly involves ulnar nerve injury [187], lateral femoral cutaneous nerve injury [287], brachial plexopathy, lumbo-sacral plexopathy. Injury is typically due to demyelination
Critical illness neuropathy	Severe COVID-19 requiring hospitalization +/− intensive care; axonal sensorimotor peripheral neuropathy on nerve conduction studies.
AUTONOMIC NEUROPATHIES	
Secondary autonomic failure due to small, unmyelinated fiber neuropathy	• Diabetes (most common etiology) • Amyloidosis, including hereditary transthyretin mutations • Inflammatory/Autoimmune: Sjogren's, sarcoid, Guillain-Barre, autoimmune autonomic impairment with ganglionic nicotinic acetylcholine receptor antibodies • Renal failure • Vitamin B12 deficiency • Infections: syphilis, Lyme, HIV, Chagas • Alcohol • Paraneoplastic: anti-Hu/ANNA paraneoplastic neuropathy, anti-PCA-2, anti-CRMP-5, anti-nAChR • Hereditary: porphyria, familial dysautonomia (Riley-Day), familial autonomic ganglionopathy
OTHER	
Central pain syndromes	Post-stroke, Dejerene Roussy, multiple sclerosis, lesions involving the thalamus, spinothalamic tracts, or trigeminal nerve

changes on quantitative electromyography and all patients reported concomitant fatigue [201,206]. Thus, it is conceivable that some PASC fatigue patients may have undiagnosed underlying myopathy.

Differential Diagnosis: Though a history of SARS-CoV-2 infection preceding neurological symptoms may hint at a post-COVID syndrome, as more of the population is exposed to and recovers from COVID-19, an antecedent infection may not signal causality. Clinicians must be mindful to exclude other common, reversible and/or serious causes for neuropathic pain or myopathic weakness. Since neuropathic pain is a common feature of PASC neuropathy, a tailored differential diagnosis can be found in Table 19.

When evaluating PASC weakness, it is important to determine initially if there is objective muscle weakness, or if the patient is referring to generalized fatigue or deconditioning, in which case an evaluation of cardiopulmonary disease, anemia, hypothyroidism, depression, joint disease or malignancy might be appropriate. In particular, fibromyalgia is associated with generalized subjective weakness, musculoskeletal pain, fatigue, cognitive disturbances, psychiatric symptoms, and paresthesias, but objective weakness is atypical. Diagnostic criteria for fibromyalgia include: multisite pain in $\geq$6 of 9 possible body regions, moderate to severe sleep problems or fatigue, and presence of symptoms for $\geq$3 months [157]. If objective weakness is present on neurological exam, the localization and distribution of weakness may aid in diagnosis (e.g. central/upper motor neuron, anterior horn cell, peripheral nerve, neuromuscular junction or muscle). Asymmetric weakness may hint at a central etiology or isolated nerve/nerve root injury, whereas symmetric weakness may signal an anterior horn cell disorder, polyneuropathy, neuromuscular junction disorder or myopathy. Proximal, symmetric weakness with wasting/atrophy, or muscle tenderness is suggestive of a myopathy. Table 20. provides differential diagnoses of myopathy.

Diagnostic Evaluation: Evaluation of neuromuscular disorders begins with the history and neurological exam. In many cases the next step would be nerve conduction studies (NCS) and electromyography (EMG).

Table 20
Differential Diagnosis of PASC Myopathic Weakness.

Category	Diseases and Key Features
ICU myopathy	• Severe COVID-19 requiring hospitalization +/− intensive care, immobilization, steroid use, sepsis, paralytic agents, hyperglycemia, flaccid quadriparesis, difficulty with ventilator weaning, muscle atrophy
Rhabdomyolysis	• Crush injury, Immobility • Seizures • Heat stroke/malignant hyperthermia
Drug and toxin-induced myopathy	• Medications: statins, corticosteroids, amiodarone, colchicine, antimalarial drugs, zidovudine, penicillamine, immune checkpoint inhibitors (e.g. ipilimumab), interferon-alpha • Alcohol
Inflammatory myopathy	• Polymyositis: proximal muscle weakness, no rash • Immune-mediated necrotizing myopathy: more extensive necrosis on biopsy than polymyositis • Dermatomyositis: heliotropic rash, associated with cancer, interstitial lung disease • Inclusion body myositis: older, more often men; early involvement of deep finger flexors, quadriceps, foot extensors and and/or selective biceps, triceps or iliopsoas weakness • Vasculitis • Juvenile dermatomyositis • Rheumatoid arthritis • Sjogren's syndrome • Lupus
Endocrine disorders	• Hypothyroidism: may have myoedema, or muscle pseudohypertrophy • Cushing's disease
Electrolyte disorders	• Hypokalemia • Hypophosphatemia • Hypocalcemia • Hypermagnesemia
Infections	• Viruses (influenza, parainfluenza, HIV, cytomegalovirus, Coxsackie, adenovirus, echovirus, EBV) • Bacterial (Lyme, pyomyositis) • Parasitic (trichinosis, toxoplasmosis)
Genetic	• Muscular dystrophies: muscle weakness is progressive, associated with atrophy, contractures may be present, e.g. Duchenne, Becker, myotonic dystrophy, Limb-girdle, oculopharyngeal, distal, congenital dystrophies, Emery-Dreifuss, fascioscapulohumeral
Metabolic	• Disorders of glycogen/glucose metabolism: exercise intolerance, recurrent myoglobinuria, muscle stiffness induced by exercise, “second wind” phenomenon, cramps, contractures, may have jaundice or hepatomegaly; e.g. glucose-6-phosphatase deficiency, acid maltase deficiency/ Pompe disease, glycogen debrancher deficiency, McArdle disease, phosphofructokinase deficiency, etc.) • Disorders of lipid metabolism: symptoms induced by fever, exercise, prolonged fasting, involvement of tissues dependent on fatty acid oxidation such as heart, muscle, liver, hypoketotic hypoglycemia, alterations in plasm/tissue carnitine; e.g. carnitine deficiency syndromes, fatty acid transport defects, neutral lipid storage disease abnormalities, lipin-1 deficiency, defects in beta-oxidation enzymes • Mitochondrial disorders: exercise intolerance, resting lactic acidosis, may have short-stature, deafness, maternal inheritance, cardiomyopathy; e.g. MERRF, MELAS, MNGIE, Leigh syndrome

Table 21
Diagnostic Evaluation of PASC Neuropathy and Myopathy incorporating AAN practice parameters for the evaluation of distal symmetric polyneuropathy [288].

Study	Neuropathy	Myopathy
CLINICAL ASSESSMENT		
History	• Numbness, tingling, burning, stocking-glove or specific nerve distribution. Radicular pain typically radiates from neck/back down a nerve distribution. Can have motor weakness as well in some cases. Often worse symptoms at night, allodynia, temperature sensitivity/insensitivity, orthostatic intolerance (autonomic neuropathy) • Screen medications, alcohol use, • Screen medical history (diabetes, hypothyroidism, alcohol use, chronic kidney disease, malignancy, HIV, rheumatologic disease)	• Proximal muscle weakness, difficulty rising from seated position, difficulty brushing hair/lifting arms overhead, myalgia, exercise intolerance, no sensory symptoms • Screen medications, medical history (hypothyroidism, alcohol use)
Physical exam	• Large fiber: light touch, vibration, proprioception loss, fasciculation (motor neuron disease), atrophy, reduced deep tendon reflexes • Small fiber: pain, temperature loss, dysautonomia • RED FLAG atypical features that may warrant more extensive evaluation: asymmetry, non-length dependent, motor predominance, acute, progressive or severe course, prominent autonomic involvement, sensory ataxia	• Atrophy, reduced muscle bulk, muscle tenderness to palpation in some cases, myotonia (myotonic dystrophy), myoedema (hypothyroidism), pseudohypertrophy (hypothyroidism, Duchenne muscular dystrophy), normal deep tendon reflexes unless advanced atrophy is present
LABORATORY TESTING		
Serum	Initial tests (highest yield per AAN practice parameter [288]): • Hemoglobin A1C, fasting glucose • TSH, free T4 • Vitamin B12 • SPEP, UPEP with immunofixation • BUN, Creatinine Additional testing (based on history, exam): • Rheumatologic studies (ANA, anti-Ro, anti-La, rheumatoid factor, ANCA) • Lyme titers (in proper context) • HIV • Hepatitis screen • Thiamine levels • Paraneoplastic panels: Anti-Hu (ANNA-1), CV2/CRMP5, PCA-2 (MAP1B), anti-amphiphysin • Heavy metal, porphyria screening • Anti-MAG, Anti-GM1 (if suspect demyelinating)	Initial tests: • Creatine kinase (most sensitive), elevated in inflammatory myopathies, extremely elevated in rhabdomyolysis • TSH, free T4 Additional testing (based on history, exam): • Lactate dehydrogenase, aldolase, AST, ALT • Myositis antibodies: Antisynthetase antibodies (anti-Jo-1, anti-PL-12, OJ, EJ, PL-7, KS, Zo, Ha; present in 1–5% of inflammatory myopathies), Anti-SRP, Anti-Mi-2, anti-MDA5, anti-NXP-2, anti-TIF-1gamma, anti-SAE, anti-HMGCR (statin use) • Rheumatologic antibodies: anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-ribonucleoprotein, anti-PM-Scl, anti-Ku, ANA, ANCA
EMG/ NCS	• NCS Axonal neuropathy: reduced amplitude of compound motor action potentials (CMAPs) and sensory nerve action potential	• NCS: normal SNAPs, CMAPs usually normal but may have reduced amplitude with normal conduction velocities and distal latencies in advanced myopathy

(*continued on next page*)

Table 21 (*continued*)

Study	Neuropathy	Myopathy
	(SNAPs), relatively preserved conduction velocities • NCS Demyelinating neuropathy: reduced conduction velocity, conduction block • EMG: neuropathic motor units have increased amplitude, are polyphasic, with prolonged duration, delayed recruitment, and reduced interference pattern • EMG/NCS typically normal in small, unmyelinated fiber neuropathy	• EMG: myopathic motor units are small, low amplitude, short duration, polyphasic, with early recruitment, increased interference pattern, and increased insertional activity. Spontaneous activity including sharp waves and fibrillations may occur, particularly with inflammatory myopathies.
Biopsy	• Skin biopsy may useful for diagnosis of small-fiber neuropathy [278] • Nerve biopsy typically not performed, but may be useful for suspected amyloid neuropathy, or vasculitic neuropathy [278]	• Muscle biopsy useful for dermatomyositis, polymyositis, inclusion body myositis, vasculitic myopathy, muscular dystrophy diagnoses and certain drug-induced myopathies
Other	• Autonomic testing may be useful in patients with small fiber sensory neuropathy [278], however, it is typically reserved for patients who fail initial treatment or those who have severe autonomic symptoms (syncope) • Quantitative sudomotor axon reflex testing (QSART) can be used for identifying peripheral sympathetic denervation in patients with autonomic symptoms.	• Genetic testing for muscular dystrophies and metabolic myopathies

Abbreviations: EMG/NCS, electromyography, nerve conduction study.

The EMG/NCS will identify if a neuropathy is present, whether it is axonal, demyelinating or mixed, and the distribution of nerves affected, which will inform the differential diagnosis. The EMG can differentiate neuropathic muscle changes from primary myopathy. Select serum studies, biopsy or advanced autonomic testing may be indicated based on EMG/NCS results.

Post-COVID electrophysiological studies, along with skin biopsy data are suggestive of a predominantly small-fiber peripheral neuropathy [201,207–209]. Additionally, there is evidence suggesting a link between post-COVID muscle symptoms and long-term use of hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) [210]. Rapidly worsening muscular symptoms in a COVID-19 patient taking statins may represent an autoimmune myopathy, especially with elevated CK and should prompt measurement of anti-HMG-CoA reductase antibodies [211]. However, post-COVID myopathic quantitative EMG changes have been found with normal-range CK [201], so normal CK does not exclude a post-COVID myopathy. Diagnostic evaluation strategies for PASC numbness and weakness are outlined in Table 21.

Therapeutic options

COVID-19 Specific Treatments: Intravenous immunoglobulins (IVIG) and steroids have been used in subjects with post-COVID small fiber neuropathy, though data is limited to small case series [209,212,213]. In a small randomized trial of patients with painful idiopathic small fiber neuropathy, IVIG was not found to have any significant effect on pain [214]. Given that IVIG is a blood product and is associated with rare, but serious side effects, it cannot be recommended at this time for PASC small-fiber neuropathy.

The mainstay of treatment of neuropathy or myopathy is addressing the underlying cause of the neuromuscular disorder (e.g. glucose control in diabetes, Vitamin B12 repletion in those with deficiency, treatment of

Table 22
Treatment options for PASC Neuropathy and Myopathy based on AAN guidelines for the treatment of painful polyneuropathy [289], Peripheral Nerve Society Guidelines [290], and International Conference on Sarcopenia and Frailty Research (ICSFR) recommendations for the treatment of myopathy [291].

NEUROPATHY PHARMACOLOGICAL THERAPIES		
Disease	Treatment	Recommendation
Neuropathic pain	• Gabapentinoids (gabapentin, pregabalin, mirogabalin	AAN Level B [289]
	• SNRI (duloxetine, desvenlafaxine, venlafaxine)	
	• Tricyclic antidepressants (amitriptyline)	
	• Sodium channel blockers (lamotrigine, lacosamide, oxcarbazepine)	
	• Medications should be titrated to a demonstrated efficacious dose for approximately 12 weeks, and only considered a failure when there is not clinically significant pain reduction or when side effects outweigh benefit after this time frame.	AAN Level B [289]
	• Valproic acid should not be prescribed unless multiple other agents have failed, given its side effect profile	AAN Level B [289]
	• Opioids should not be used for neuropathic pain	AAN Level B [289]
	• Tramadol and tapentadol (opioid/SNRI) should not be used for neuropathic pain	AAN Level C [289]
Demyelinating neuropathy: Guillain-Barre and chronic inflammatory demyelinating polyneuropathy (CIDP)	• IVIG • Plasma-exchange • Corticosteroids (CIDP only)	AAN Level A, Class II [292] IVIG and plasma-exchange are equally effective
Vasculitic neuropathy	• Corticosteroids • Immunosuppressants: methotrexate, azathioprine, cyclophosphamide, rituximab	Peripheral Nerve Society Guideline, Level U [290]
Dysautonomia	• See treatment options in "Dizziness/lightheadedness" section	See treatment options in "Dizziness/lightheadedness" section
NEUROPATHY NON-PHARMACOLOGICAL THERAPIES		
Neuropathic pain	• Topicals (Capsaicin, Glyceryl trinitrate spray, *Citrullus colocynthis*, lidocaine patch)	AAN Level C [289]
	• *Ginkgo biloba*	
	• Cognitive behavioral therapy, exercise, physical therapy	
	• Acupuncture	
Compressive neuropathy	• Surgical decompression • Peripheral nerve block	Under guidance of pain specialist
MYOPATHY PHARMACOLOGICAL THERAPIES		
Polymyositis, dermatomyositis, idiopathic inflammatory myositis	• Corticosteroids • Steroid sparing agents: azathioprine, methotrexate, rituximab, mycophenolate	Note that inclusion body myositis does not respond to steroids
MYOPATHY NON-PHARMACOLOGICAL THERAPIES		
Sarcopenia, non-inflammatory myopathy	• Resistance-based training may be effective to improve lean muscle mass, strength and physical function	International Conference on Sarcopenia and Frailty Research (ICSFR) [291] Strong recommendation, moderate certainty of evidence
	• Protein supplementation, and/or a protein-rich diet	International Conference on Sarcopenia and

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Table 22 (*continued*)

NEUROPATHY PHARMACOLOGICAL THERAPIES		
Disease	Treatment	Recommendation
	should be considered for older adults with sarcopenia • Nutritional (protein) intervention should be combined with a physical activity intervention	Frailty Research (ICSFR) [291] Conditional recommendation, low certainty of evidence

thyroid disease), and withdrawal of any offensive medications or toxins (e.g. statins in patients with anti-HMGCo-A reductase antibodies, reducing alcohol use). Symptom-based therapy may be the only option for patients with certain small-fiber or axonal polyneuropathies, while demyelinating polyneuropathies and inflammatory myositis' may require immune-modulating therapies (see Table 22). An algorithm for the evaluation and management of PASC numbness, pain and weakness is shown in Fig. 6.

3.7. Anxiety, depression, and post-traumatic stress disorder

Epidemiology: Depression, anxiety, and post-traumatic stress disorder (PTSD) are common post-COVID neuropsychiatric sequelae. Studies have found 30–40% of patients experience clinically significant depression and/or anxiety symptoms during the acute phase of illness [215], persisting 12 months or more following infection [4,76,88,190,216,217]. A systematic review found nearly 30% of patients experience generalized anxiety disorder (GAD) [218], while up to 30% of COVID patients exhibit PTSD 3 months after infection [76,88,216,217]. Risk factors associated with COVID-19 psychiatric symptoms include female sex, history of psychiatric disorder, COVID-19 illness severity, perceived discrimination, life stressors and social isolation [4,219]. A pre-COVID-19 history of psychiatric disorder is not necessarily observed, with one study showing that 74% of patients reporting post-COVID depression and anxiety did not have a pre-COVID history of a mental health disorder [220].

Differential Diagnosis: Similar to other systemic medical illnesses, accurate diagnosis of post-COVID psychiatric morbidity is challenging [221]. Symptoms of fatigue, insomnia, decreased appetite/weight loss, difficulty concentrating, gastrointestinal upset, palpitations, muscle tension, headache, dizziness, and pain are seen in major depressive disorders (MDD) and anxiety disorders, but can also occur as part of other post-COVID syndromes in the absence of psychiatric illness [156]. MDD is more highly suspected in the presence of persistent guilt, feelings of worthlessness, suicidal ideation or recurrent thoughts of death, tearfulness, hopelessness, social withdrawal, decreased talkativeness, and pessimism [222,223]. Generalized anxiety disorder (GAD) is suspected when worries are pervasive, pronounced, and distressing. Both MDD and GAD should be distinguished from a normal reaction to impaired physical functioning and decreased quality of life as a result of post-COVID symptoms [222]. The constellation of symptoms in PTSD is more easily distinguished by the presence of a traumatic event followed by intrusion symptoms, avoidance symptoms, negative alterations in

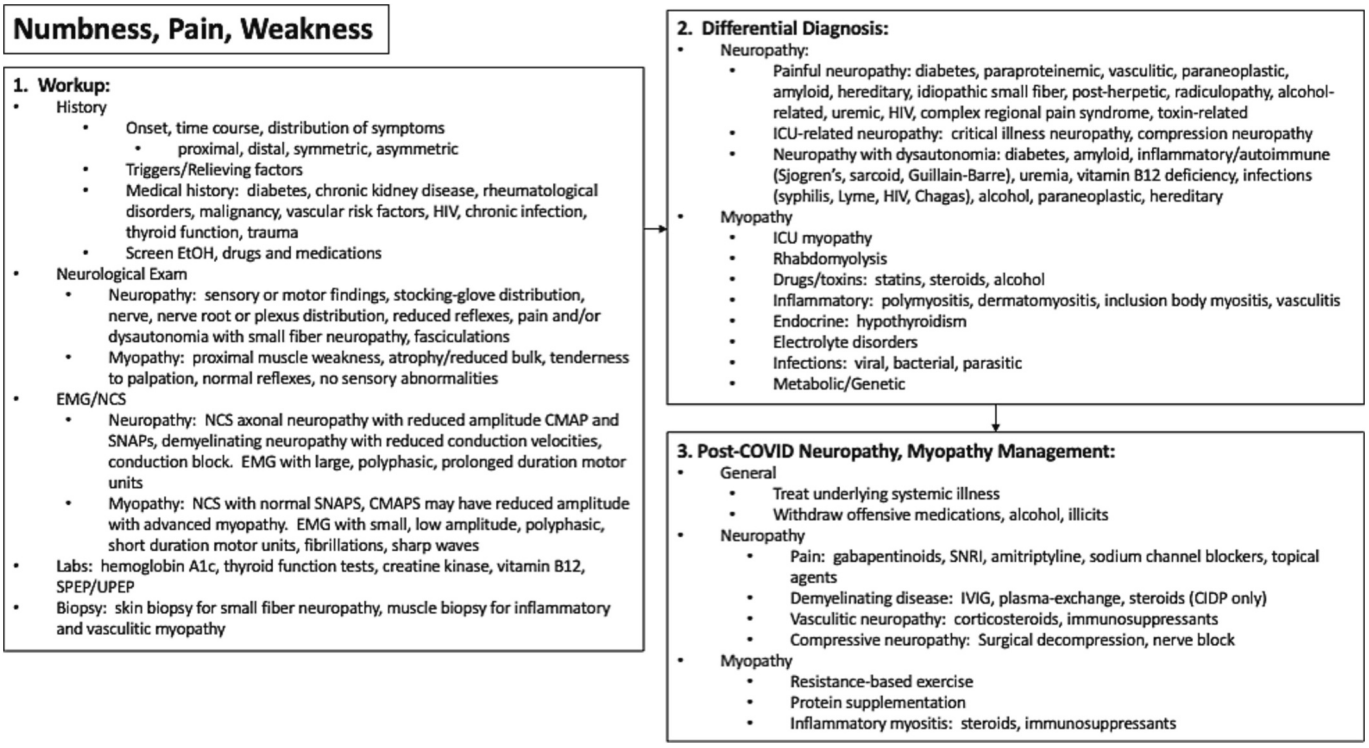

Fig. 6. Evaluation and Management of PASC Numbness, Pain, Weakness.
EMG/NCS, electromyography/nerve conduction study; CMAP, compound muscle action potential; SNAP, sensory nerve action potential; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; CIDP, chronic inflammatory demyelinating polyneuropathy; SNRI, serotonin-norepinephrine reuptake inhibitor; IVIG, intravenous gamma globulin.

Table 23
Differential Diagnosis of PASC Depression, Anxiety and PTSD [293].

Category	Depression Differential	Anxiety Differential	PTSD Differential
Psychiatric	• Major depressive disorder, unipolar depression • Bipolar disorder, Type I or II, current episode depressed • Persistent depressive disorder (dysthymia) • Premenstrual dysphoric disorder • Acute stress disorder • Normal Grief • Persistent Complex Bereavement Disorder • Adjustment Disorder with depressed mood • Burnout	• Generalized Anxiety disorder • Panic disorder • Obsessive-compulsive disorder • Somatic symptom disorder • Illness Anxiety Disorder • Acute stress disorder • Phobias • Social anxiety	• Post-traumatic stress disorder • Acute stress disorder • Depersonalization/ Derealization disorder • Adjustment disorder • Somatic symptom disorder • Borderline personality disorder
Metabolic/Endocrine	• Hypothyroidism • Adrenal insufficiency • Anemia • Hyperparathyroidism • Uremia • Hypopituitarism • Porphyria • Electrolyte abnormalities: hyponatremia, hypokalemia, hypomagnesemia • Vitamin D, B1, B3, B6, B12, deficiency	• Hyperthyroidism • Hyperparathyroidism • Pheochromocytoma • Cushing syndrome • Hypoglycemia • Porphyria • Vitamin B1, B3, B6, B12 deficiency	–
Infectious	• HIV • Tuberculosis • Epstein Barr infection • Tertiary syphilis • Encephalitis and post-encephalitis • Lyme disease	• Tertiary syphilis • Lyme disease	–
Inflammatory/ Rheumatologic	• Multiple sclerosis • Lupus • Rheumatoid arthritis • Fibromyalgia	• Multiple sclerosis • Fibromyalgia • Lupus • Rheumatoid arthritis	–
Vascular/Cardiac	• Stroke • Heart failure, cardiomyopathy	• Stroke • Arrhythmia • Pulmonary embolism	–
Gastrointestinal	• Inflammatory bowel disease • Irritable bowel syndrome • Wilson's disease • Cirrhosis	• Inflammatory bowel disease • Irritable bowel syndrome	• Irritable bowel syndrome
Sleep disorder	• Obstructive sleep apnea • Insomnia	• Insomnia	• Insomnia • REM parasomnias
Neurodegenerative/ other neurologic	• Alzheimer's disease • Huntington's disease • Parkinson's disease • Lewy Body dementia • Frontotemporal dementia • Traumatic brain injury, concussion	• Alzheimer's disease • Huntington's disease • Parkinson's disease • Lewy Body Dementia • Traumatic brain injury, concussion • Epilepsy • Vestibular dysfunction	• Traumatic brain injury, concussion
Neoplastic	• Primary or secondary brain cancer • Carcinomatosis • Paraneoplastic syndromes	• Primary or secondary brain cancer • Paraneoplastic syndromes	–
Medications	• Cardiovascular agents: clonidine, guanethidine, methyldopa, reserpine, beta-blockers • Cholinesterase inhibitors • Chemotherapy agents • Reserpine • Antihistamines (e.g. cimetidine) • Interferon • Isotretinoin • Antivirals (eg. efavirenz) • Benzodiazepines • Varenicline • Hormonal agents: oral contraceptives, gonadotropin releasing hormone, tamoxifen • Corticosteroids • Opiates	• Sympathomimetics or other bronchodilators • Stimulants: methylphenidate, amphetamine salts, modafinil • Ketamine, esketamine • Insulin • Thyroid preparations • Oral contraceptives • Anticholinergics • Corticosteroids • Anticonvulsants • Lithium carbonate • Antipsychotic medications • Antidepressant medications	• Ketamine
Drugs/Toxins	• Alcohol • Barbiturates • Phencyclidine intoxication • Other hallucinogens intoxication (e.g. psilocybin, LSD) • Inhalant intoxication • Opioid intoxication/withdrawal (e.g. heroin, fentanyl) • Sedative, hypnotics, or anxiolytics intoxication/withdrawal (e.g. benzodiazepines, *Z*-drugs, barbiturates) • Amphetamine or cocaine withdrawal • Heavy metal poisoning (e.g. mercury, arsenic)	• Alcohol intoxication • Caffeine intoxication • Cannabis intoxication • Phencyclidine intoxication • Other hallucinogens intoxication • Opioid withdrawal • Sedative, hypnotics, or anxiolytics withdrawal • Stimulants intoxication/withdrawal • Organophosphate • Carbon monoxide • Carbon dioxide • Carbon disulfide • Mercury • Arsenic • Volatile substances (e.g. gasoline, paint)	• Phencyclidine intoxication • Other hallucinogens intoxication (e.g. psilocybin, LSD) • Cocaine • Amphetamines

Table 24
Diagnostic evaluation of Depression, Anxiety and PTSD.

	Depression Evaluation	Anxiety Evaluation	PTSD Evaluation
History	• Evaluate mood, severity, duration, context, atypical features, impact on social and occupational function, screen for mania/ hypomania • Evaluate suicide risk • Family psychiatric history • Screen psychosocial stressors, lifestyle assessment, social support • Screen medications, alcohol and illicits • Assess comorbid medical or neurological conditions	• Evaluate mood, severity, duration, context, impact on social and occupational function • Evaluate for obsessions compulsions, panic attacks, and avoidance behaviors • Family psychiatric history • Screen psychosocial stressors, lifestyle assessment, social support • Screen medications, alcohol and illicits • Assess comorbid medical or neurological conditions	• Assess cardinal criteria of: traumatic event, intrusion symptoms, avoidance symptoms, negative conditions or mood, arousal and reactivity changes • Evaluate for dissociative features (depersonalization, derealization, psychosis) • Evaluate suicide risk • Family psychiatric history • Screen psychosocial stressors, lifestyle assessment, social support • Screen medications, alcohol and illicits • Assess comorbid medical or neurological conditions
Laboratory Studies	• Complete blood count • Comprehensive metabolic panel including liver function tests • Thyroid function tests • In certain cases based on history: HIV, RPR, ANA, rheumatoid factor, vitamin D, B1, B3, B6, B12 levels, urine drug screen, pregnancy test, iron studies	• Complete blood count • Comprehensive metabolic panel including liver function tests • Thyroid function tests • ECG to screen for arrhythmias (if palpitations or cardiac symptoms) • In certain cases based on history: HIV, RPR, ANA, rheumatoid factor, vitamin B1, B3, B6, B12 levels, urine drug screen, pregnancy test, iron studies, heavy metal testing	–
Imaging	• Consider brain imaging if focal neurological exam findings or evidence of other neurological diagnosis	• Consider brain imaging if focal neurological exam findings or evidence of other neurological diagnosis	• Consider brain imaging if focal neurological exam findings or evidence of other neurological diagnosis

Table 25
Treatment options for PASC Generalized Anxiety Disorder, Depression (moderate-severe) and PTSD according to NICE [294,295] and VA/DOD [296] guidelines.

Treatment Class	Specific Therapy	Notes
MAJOR DEPRESSION 1st line treatment [294] Combination of Cognitive Behavioral Therapy (CBT) and an Antidepressant	First line pharmacotherapy: • Selective seratonin reuptake inhibitor (SSRI): sertraline, escitalopram, citalopram, fluoxetine, paroxetine, fluvoxamine • Serotonin-norepinephrine inhibitor (SNRI): duloxetine, venlafaxine, desvenlafaxine • Atypical antidepressants: mirtazapine, bupropion • SSRI/5-HT1A partial agonist: vilazodone, vortioxetine Second line pharmacotherapy: • Tricyclic antidepressant (TCA): amitriptyline, amoxapine, desipramine, imipramine, clomipramine, nortriptyline, doxepin, protriptyline, trimipramine, maprotriptyline Third line pharmacotherapy: • Monoamine oxidase inhibitors (MAOs): phenelzine, tranylcypromine, isocarboxaxid, selegiline (MAO-B selective), moclobemide (MAO-A selective)	• The combination of CBT and an antidepressant allows for the provision of support while the antidepressant may take 4 weeks or more to show an effect • Retrospective studies showed efficacy for SSRIs and vortioxetine for treatment of post-COVID major depression [228,229] • Risk of QT prolongation with citalopram, escitalopram and TCAs; drug-drug interactions with fluoxetine, paroxetine, and fluvoxamine; and overall sexual side effects in the SSRI drug class • SNRIs and TCAs can treat comorbid neuropathic pain, migraines, fibromyalgia, complex regional pain syndromes • SNRIs can increase blood pressure • Bupropion associated with less weight gain and sexual side effects but is contraindicated in comorbid eating disorders and seizure disorders • Bupropion can treat comorbid tobacco use disorder • Mirtazapine can target insomnia and poor appetite but can cause significant weight gain • Avoid TCAs in actively suicidal patients as TCAs are fatal in overdose • Avoid TCAs in patients with cardiac instability or ischemia • Risk of anticholinergic effects (especially in elderly) with TCAs • MAOIs: Ingestion of tyramine-rich foods can cause hypertensive crisis. Requires dietary restrictions: must avoid aged cheeses or meats, fermented products, yeast extracts, broad beans, red wine, draft beers, overripe foods • MAOIs have high risk of serotonin syndrome if combined with other serotonergic agents • MAOIs have risk of orthostatic hypotension, weight gain, and sexual side effects

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Table 25 (*continued*)

Treatment Class	Specific Therapy	Notes
2nd Line Treatment [294] Individual CBT	Typically ≥16 sessions delivered by a practitioner with therapy-specific training and competence	• Focuses on how beliefs, attitudes, thoughts, feelings and behavior interact and teaches coping skills • Requires insight and motivation • Goal-oriented and structured
2nd Line Treatment [294] Individual behavioral activation	Typically 12–16 sessions delivered by a practitioner with therapy-specific training and competence	• Focuses on identifying links between activities and mood. • Goal-oriented and structured • Does not directly target thoughts and feelings
2nd Line Treatment [294] Antidepressant medication alone	As above	• Treatment effects should be apparent in 4 weeks
2nd Line Treatment [294] Individual problem-solving	Typically 6–12 sessions delivered by a practitioner with therapy-specific training and competence	• Focuses on identifying problems, generating alternate solutions and evaluating if solutions were efficacious • Goal-oriented and structured • Requires insight and motivation
2nd Line Treatment [294] Counseling	Typically 12–16 sessions delivered by a practitioner with therapy-specific training and competence	• Focuses on emotional processing to help patients find their own solutions and coping strategies • Provides empathic listening, facilitates emotional exploration and provides encouragement • Uses emotion focused activities to increase self-awareness of themselves, and their relationships with others • Useful for individuals with psychosocial, relationship or employment problems contributing to their depression
2nd Line Treatment [294] Short-term psychodynamic psychotherapy	Typically ≥16 sessions delivered by a practitioner with therapy-specific training and competence	• Focuses on identifying patterns of feelings in relationships and stressful situations • Both insight-oriented and affect focused • Focuses on painful experiences in close relationships that could be distressing
2nd Line Treatment [294] Interpersonal psychotherapy	Typically ≥16 sessions delivered by a practitioner with therapy-specific training and competence	• Focuses on how relationships are related to feelings of depression, and explores changing interpersonal responses. The goal is to change the relationship patterns • May be useful for those with depression associated with interpersonal difficulties, adjustments to transitions in relationships, loss or changing interpersonal roles.
3rd Line [294] Guided self-help	Typically 6–8 sessions delivered by a practitioner with therapy-specific training and competence who facilitates completion of self-help training and evaluates outcomes	• More therapist contact preferred for more severe depression • Patient provided with materials for self-instruction including structured CBT, behavioral activation, problem-solving and psychoeducation. • Requires self-motivation and willingness to work alone • Need access to computer for materials
3rd Line [294] Group exercise	Group physical activity lead by a trained practitioner with ≥1 session per week for 10 weeks. Usually 8 participants per group	• More therapist contact preferred for more severe depression • Allows for peer support • May need to be adapted based on person's physical abilities
GENERALIZED ANXIETY DISORDER		
Initial Intervention [295]	Low-intensity psychological interventions	• Individual non-facilitated self-help • Guided self-help (see above) • Psychoeducational groups (usually ratio of 1 therapist to 12 participants over 6 weekly sessions)
Secondary intervention for those with persistent symptoms after initial intervention [295]	Individual high-intensity psychological intervention	• Cognitive behavioral therapy • Applied relaxation
Secondary intervention for those with persistent symptoms after initial intervention [295]	Pharmacotherapy	First Line: • SSRI (sertraline, escitalopram, citalopram, fluoxetine, paroxetine, fluvoxamine) • SNRI (duloxetine, venlafaxine) • SSRI/5-HT1A partial agonist (vilazodone, vortioxetine) may be as effective as SSRIs but limited data Second Line if first line treatments fail: • TCAs (imipramine, nortriptyline) • MAO inhibitor (phenelzine) Adjunctive treatments: • Mirtazapine (may be used as monotherapy in those with comorbid insomnia) • 5HT1a partial agonist (buspirone) • GABAergic agents (pregabalin has greater risk of addiction and dependence than gabapentin) Avoid: • Do not use benzodiazepine for primary or secondary treatment except as a

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Table 25 (*continued*)

Treatment Class	Specific Therapy	Notes
		short-term measure during crises • Do not offer an antipsychotic for the treatment of GAD in primary care
PANIC DISORDER		
Mild to moderate symptoms [295]	Low-intensity psychological interventions	• Individual non-facilitated self-help • Guided self-help
Moderate to severe symptoms [295]	Cognitive behavioral therapy OR Pharmacotherapy	• CBT for 7–14 h • SSRI (sertraline, escitalopram, citalopram, paroxetine) • SNRI (venlafaxine) • TCAs (imipramine, clomipramine) can be used as second line • Benzodiazepines should not be prescribed • Sedating antihistamines or antipsychotics should not be prescribed
PTSD		
1st line treatment [296]	Individual trauma-focused psychotherapy	• Primary component of exposure and/or cognitive restructuring • Therapies include: prolonged exposure, cognitive processing therapy, eye movement desensitization and reprocessing, brief eclectic psychotherapy, narrative exposure therapy, cognitive behavior therapies for PTSD, and written narrative exposure
2nd line treatment [296]	Pharmacotherapy	• Recommend: Sertraline, paroxetine, fluoxetine or venlafaxine • Suggest for: Nefazodone, Imipramine, Phenelzine • Suggest against: prazosin (excluding the treatment of PTSD related nightmares), quetiapine, olanzapine, citalopram, amitriptyline, lamotrigine, topiramate • Recommend against: valproic acid, tiagabine, guanfacine, risperidone, benzodiazepines, D-cycloserine, hydrocortisone, ketamine
2nd line treatment [296]	Individual non-trauma-focused psychotherapy	• Stress inoculation training, present-centered therapy, interpersonal psychotherapy

cognition or mood, arousal/reactivity states and/or dissociative reactions [222]. The differential diagnosis for post-COVID depression, anxiety, and posttraumatic stress symptoms are listed in Table 23.

Diagnostic Evaluation: An initial assessment should include a general medical and psychiatric history, family history of mental health disorders, social history with review of life stressors (financial insecurity, food insecurity, interpersonal conflict, divorce, personal loss etc.), screening for alcohol and substance abuse, and evaluation of suicide/violence risk. Triggers, relieving factors, temporal patterns, the presence of psychosis and/or mania should be evaluated. Bipolar disorder may initially present as major depression prior to the first manic/hypomanic episode. Care should be taken in the assessment of younger patients, those with a family history of bipolar disorder, or psychotic disorders, and those with manic or psychotic features. As multiorgan system effects are well documented in SARS-CoV-2 infection, physical examination and laboratory testing is important in ruling out medical etiologies of psychiatric symptoms **(**Table 24**)** [224].

Psychiatric assessment tools may be utilized to assist in screening for MDD, GAD, and PTSD (**Supplemental Table 5**), although caution should be exercised with tools that heavily rely on somatic symptoms that may overlap with post-COVID symptoms [224]. Though screening may be useful in identifying patients that require further psychiatric evaluation or pharmacological intervention, more complicated or nuanced cases may require a structured interview following DSM-5 guidelines. The DSM-5 [55] diagnostic criteria for depression, anxiety, PTSD and related disorders are listed in **Supplemental Tables 6, 7 and 8**.

Therapeutic options

COVID-19 Specific Treatments: We identified several randomized trials that specifically evaluated therapeutic interventions for post-COVID mental health disorders. One study randomized 158 subjects with PASC symptoms lasting >4 weeks from index infection to an online breathing and wellbeing program (English National Opera Breathe program) versus usual care and found improved mental health scores (HRQoL mental health composite) after 6 weeks [225]. Another study randomized 360 patients to a 17-week psychosocial education and behavior activation program versus usual care ($N = 355$) and found significantly lower PHQ-9 scores in the intervention group compared to the control group at 8-months (PHQ-9 < 10 in 63% intervention group vs. 44% control group [$P < 0.001$]) [226]. A third study randomized 65 patients with persistent complex bereavement disorder, PTSD and/or depression post-COVID to a self-guided online grief-specific cognitive behavioral therapy intervention versus a waitlist for routine evaluation [227]. Those who received 8 weeks of online cognitive behavioral therapy had lower symptom levels of bereavement, PTSD and depression than those who did not receive the intervention.

In regards to pharmacological interventions, several small retrospective studies were identified. One study evaluated the treatment effect of selective serotonin receptor inhibitors (SSRIs) in 60 patients with a major depressive episode within 6 months of COVID-19. Though there was no control group, this study found that 92% of patients demonstrated a clinical response characterized by a $\geq$ 50% reduction in Hamilton Depression Rating Scale scores after 4 weeks of SSRI treatment, and patients continued to show improvement in scores at 6-months [228]. Vortioxetine, a SSRI and serotonin receptor modulator, which is known to have anti-inflammatory and anti-oxidant qualities, was studied retrospectively in 80 patients with post-COVID major depression. Significant improvements were observed at 1- and 3-months post-treatment in Hamilton Depression Rating Scale scores, as well as in cognitive scores evaluated with the Digital Symbol Substitution Test [229].

The choice of pharmacologic versus non-pharmacologic intervention for PASC psychiatric symptoms depends on the severity of the symptom and the patient's preferences for management. The WHO guidelines for the treatment of post-COVID anxiety and depression suggest using psychological support, mindfulness training, peer support groups and physical exercise training (in the absence of post-exertional symptom exacerbation) [11]. Table 25**.** outlines both pharmacological and non-pharmacological strategies supported by international guidelines. An

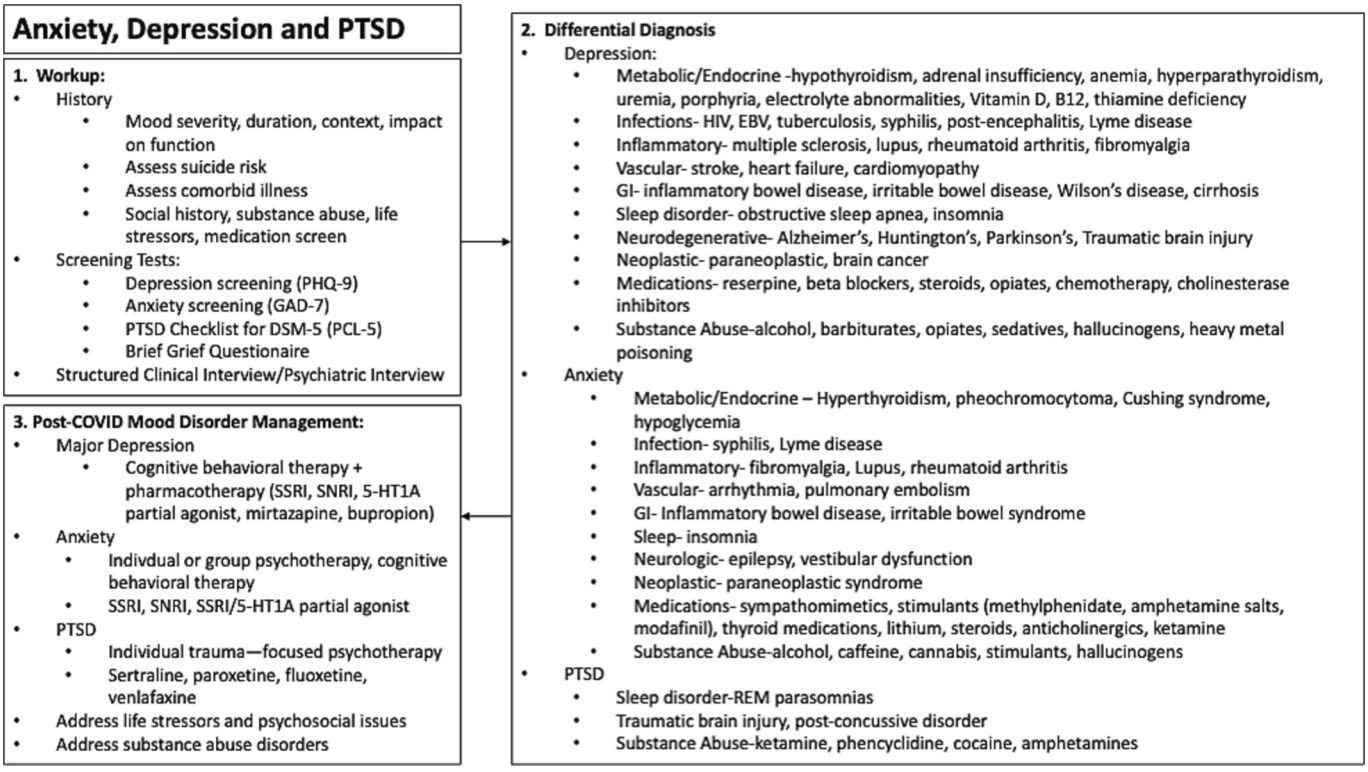

Fig. 7. Evaluation and Management of PASC Anxiety, Depression and PTSD.
SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; EBV, Epstein-Barr virus; GI, gastrointestinal; REM, rapid eye movement.

algorithm for the evaluation and management of PASC depression, anxiety and PTSD is shown in Fig. 7.

4. Conclusions

Though some studies specific to the treatment of PASC neurological symptoms have been published, there remains a dearth of direct data on both the underlying pathophysiological mechanisms of PASC, and proven therapeutic strategies. We present one of the first comprehensive guides to the evaluation and management of PASC neurological events. Using the best available data and international guidelines for the management of commonly encountered neurological symptoms, the evaluation and treatment of PASC patients can be approached in a standardized, evidence-based fashion. The ongoing NIH funded RECOVER clinical trials (RECOVER-VITAL, SLEEP, NEURO, AUTONOMIC and ENERGIZE) [230,231] may provide future insights into therapeutic options for specific PASC symptoms.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2023.120827.

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