

Beyond the basics: exploring non-conventional treatment for fatigue in post-acute COVID-19 syndrome

Exploration du traitement non conventionnel de la fatigue dans le syndrome post-COVID-19

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ABSTRACT

Introduction: Post-acute 2019 coronavirus disease syndrome (PACS) is a multifaceted, multisystem disorder affecting an estimated 75 million individuals globally (in May 2024). Defined by symptoms persisting beyond four weeks post-infection, PACS manifests in subacute (4-12 weeks) and chronic (>12 weeks) phases, with fatigue being a prominent and debilitating feature. Comprehensive management of PACS-associated fatigue needs diverse therapeutic strategies extending beyond conventional rehabilitation.

Aim: This narrative review explored non-conventional interventions for PACS-related fatigue, focusing on treatments involving nutritional rehabilitation, physical modalities, and other innovative therapies.

Methods: Narrative review.

Results: Treatments reported in the literature include melatonin, QingjinYiqi, nutritional supplements, aromatherapy, antioxidants, Tai Chi, acupuncture, yoga, singing, hyperbaric oxygen therapy (HBOT), pulsed electromagnetic field therapy, and whole-body vibration. Melatonin and QingjinYiqi have shown notable improvements in fatigue and overall health. Nutritional supplements such as vitamin-minerals combinations have demonstrated enhancements in muscle strength, physical performance, and quality of life. Tai Chi, acupuncture, and yoga have shown positive effects on fatigue, muscle strength, and overall well-being. Aromatherapy, singing, HBOT, pulsed electromagnetic field therapy, and whole-body vibration effectively reduce fatigue while enhancing physical and cognitive functions.

Conclusion: These non-conventional treatments offer promising supplementary benefits to conventional rehabilitation.

Keywords: Acupuncture Therapy; Aromatherapy; Complementary Therapy; COVID-19; Fatigue; Long COVID-19; Rehabilitation

RÉSUMÉ

Introduction: Le syndrome post-maladie à coronavirus 2019 (COVID-19) est une affection multi-systémique complexe qui touche environ 75 millions de personnes dans le monde (Mai 2024). Le syndrome est défini par des symptômes persistant au-delà de quatre semaines après l'infection et se manifeste en phases subaiguë (4-12 semaines) et chronique (>12 semaines). La fatigue est l'un des symptômes les plus fréquents et invalidants, altérant considérablement la qualité de vie des patients atteints de ce syndrome. Sa prise en charge nécessite des stratégies thérapeutiques diversifiées allant au-delà des approches conventionnelles de rééducation.

Objectif: Cette revue narrative examine les interventions non conventionnelles utilisées dans le traitement de la fatigue liée au syndrome post-COVID-19, en mettant en avant les approches nutritionnelles, les modalités physiques et d'autres thérapies innovantes.

Méthodes: Revue narrative.

Résultats: Parmi les traitements rapportés dans la littérature figurent la mélatonine, le QingjinYiqi, les compléments nutritionnels, l'aromathérapie, les antioxydants, le Tai Chi, l'acupuncture, le yoga, le chant, l'oxygénothérapie hyperbare (OTHB), la thérapie par champ électromagnétique pulsé et la vibration corporelle globale. La mélatonine et le QingjinYiqi ont montré des effets bénéfiques sur la fatigue et la santé globale. Des compléments nutritionnels comme des combinaisons de vitamines et de minéraux améliorent la force musculaire, la performance physique et la qualité de vie. Le Tai Chi, l'acupuncture et le yoga réduisent la fatigue et renforcent le bien-être général. L'aromathérapie, le chant, l'OTHB et les thérapies électromagnétiques favorisent la récupération physique et cognitive.

Conclusion: Ces traitements non conventionnels constituent des approches complémentaires prometteuses aux stratégies de rééducation classiques.

Mots clés: Aromathérapie; COVID-19; COVID long; Fatigue; Rééducation; Thérapie complémentaire; Thérapie par acupuncture

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INTRODUCTION

In recent years (ie, after 2020), global public health has confronted an unprecedented challenge posed by the Coronavirus Disease 2019 (COVID-19) pandemic (1, 2). The rapid spread of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, resulted in a worldwide pandemic in 2020 (1). While the majority of individuals infected with SARS-CoV-2 survive, with a case fatality rate of 1% among the general population and 13% among hospitalized patients (3), a significant proportion experience long-term complications, known as long COVID or Post-Acute COVID-19 Syndrome (PACS) (3). PACS is defined as a complex multisystem condition that can persist even after a relatively mild acute illness (4). With an estimated incidence of approximately 10% among infected individuals and over 775 million confirmed cases as of May 2024, it is estimated that about 75 million people worldwide are living with PACS (5).

Multiple definitions for PACS have been proposed by various authors in the last two years (ie; 2023 and 2024) to standardize the symptomatology described by patients in the post-acute phase of the infection (6-8). PACS is characterized as COVID-19 infection symptoms persisting more than four weeks after the initial onset, along with any delayed or long-term complications (7). It can be categorized into two types: (i) subacute or ongoing symptomatic COVID-19, encompassing symptoms and abnormalities occurring between 4 to 12 weeks following the initial onset of acute COVID-19, and (ii) chronic or PACS, involving symptoms and abnormalities persisting for more than 12 weeks after the initial onset of acute COVID-19, without being attributed to other underlying conditions (9). The most commonly reported symptoms in patients with PACS include dyspnea and fatigue (10). Nearly half of PACS patients also meet the criteria for myalgic encephalomyelitis/chronic fatigue syndrome (11), which entail a "substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than six months" and is associated with fatigue (12). Treatment approaches for this debilitating symptom are diverse and encompass both pharmacological and non-pharmacological therapies (13), with rehabilitation serving as the cornerstone of management (14). Cardiopulmonary rehabilitation (14-16) and therapeutic exercise (17) have been extensively studied and demonstrated efficacy in ameliorating fatigue in this population.

The objective of this review was to underscore other non-conventional treatments utilized in addressing PACS-related fatigue.

INTERVENTIONS BASED ON NUTRITIONAL REHABILITATION

Melatonin

Melatonin emerges as a safe, effective, and cost-efficient

natural supplement that has been recommended as a treatment option since the onset of the COVID-19 pandemic (18, 19). Possessing antioxidant, anti-inflammatory, and immuno-modulatory properties (20), melatonin offers several clinically significant benefits, including enhancement of sleep quality, cognitive function, physical performance, mood status, and reduction of cardiovascular risk, notably myocarditis in the context of COVID-19 infection (21). Moreover, melatonin stands out as potentially the sole treatment addressing the diverse underlying pathophysiological mechanisms of fatigue in long COVID, encompassing oxidative stress, mitochondrial dysfunction, a pro-inflammatory state, and autoimmune disturbances (18, 19). A 2025 review explored the therapeutic potential of melatonin in the treatment of long COVID, focusing on its effects on widespread pain syndrome and inflammation (22).

QingjinYiqi (QJYQ)

QJYQ, a traditional Chinese medicine, comprises 16 herbs (ie; Renshen (Ginseng Radix Et Rhizoma), Maidong (Ophiopogonis Radix), Wuweizi (Schisandrae Chinensis Fructus), Fuling (Poria), Banxia (Pinelliae Rhizoma), Xuanshen (Scrophulariae Radix), Cangzhu (Atractylodis Rhizoma), Chenpi (Citri Reticulatae Pericarpium), Gancao (Glycyrrhizae Radix Et Rhizoma), Chaihu (Bupleuri Radix), Shengma (Cimicifugae Rhizoma), Yiyiren (Coicis Semen), Huangqin (Scutellariae Radix), Mabiancao (Verbenae Herba), Lugen (Phragmitis Rhizoma), and Danzhuye (Lophatheri Herba) (21). The herbs are initially extracted with water, concentrated, and subsequently spray-dried into powder form (23). Following this process, excipients are incorporated, and the resulting mixture is pelletized using the dry granulation method. Each package contains 10 grams, equivalent to 52 grams of the raw medication (23).

In a study involving 388 participants, where fatigue was the predominant symptom (29.6%), the efficacy and safety of QJYQ granules in treating PACS-related fatigue were evaluated (23). Participants were divided into two groups: the intervention group receiving standard rehabilitation and QJYQ, and the control group undergoing standard rehabilitation without QJYQ. Over a period of 14 days, the intervention group orally consumed 10 grams of QJYQ twice daily. Fatigue was assessed using the Borg scale. Results indicated a significant improvement in the Borg scale for the intervention group compared to the control group.

Nutritional supplements

During the onset of the COVID-19 pandemic, various nutritional supplements were proposed to mitigate the severity of the infection (24). These recommendations were rooted in the anti-inflammatory and antioxidant properties of certain supplements, suggesting their potential to lessen the severity of the infection (25, 26). Galluzo et al. (27) investigated the impact of daily supplementation with a vitamin-minerals combination

on fatigue in 30 COVID-19 survivors exhibiting decreased exercise tolerance. The vitamin-minerals combination used in this study was a nutritional supplement comprising 19 nutrients, including group B vitamins, amino acids, plant extracts such as *Eleutherococcus senticosus* and *Panax ginseng*, and minerals in Sucrosomial® forms, such as iron, magnesium, zinc, and selenium (27). Over the course of 28 days of supplementation, participants experienced a significant increase in muscle strength and physical performance, accompanied by an improvement in self-rated health status between the initial and control visits.

In another investigation, Rossato et al. (28) administered one sachet of the same vitamin-minerals combination per day to 201 subjects consecutively for 28 days. PACS-related fatigue was evaluated in its two manifestations: chronic fatigue, utilizing the Functional Assessment of Chronic Illness Therapy Fatigue Scale (29), and mental fatigue, assessed using the modified Chalder questionnaire (30). Additionally, the EuroQol-5 Dimensions questionnaire (31) was employed to evaluate the quality of life (QoL) and health status. A notable improvement across all parameters was observed after 14 days of follow-up, with these improvements sustained at the 28-day mark. Specifically, chronic fatigue scores displayed enhancements in 77% and 90% of subjects after 14 days and 28 days, respectively. Landi et al. (32) conducted a case-control study involving 66 COVID-19 survivors, divided into two groups. The intervention group, comprising 33 subjects, received an 8-week treatment consisting of a multi-component dietary supplement containing 10 amino acids along with malic, succinic, and citric acids. Conversely, the control group, also comprising 33 subjects, did not receive any treatment (32). Significant improvements were observed in the intervention group in various parameters, including muscle strength (as assessed by handgrip strength), skeletal muscle mass (measured by the skeletal muscle index), fatigue (evaluated through the 1-minute chair-stand test and 6-minute walk test), and QoL (measured using the EuroQol scale) (32).

Aromatherapy

Aromatherapy involves the utilization of concentrated essential oils derived from herbs, flowers, and other plant components to address various disorders (33). Hawkins et al. (34) investigated the effectiveness of aromatherapy in alleviating fatigue associated with PACS in 44 otherwise healthy females. Each participant was provided with a 15 ml-bottle containing a blend of essential oils extracted from specific plants, including thyme (*Thymus vulgaris*), orange peel (*Citrus sinensis*), clove bud (*Eugenia caryophyllus*), and frankincense (*Boswellia carterii*) (34). Over a span of 14 days, participants were instructed to inhale the aroma for 15 minutes each morning and evening. Fatigue was assessed using the Multidimensional Fatigue Symptom Inventory (35). The study revealed significantly reduced fatigue scores with no reported adverse effects.

Antioxidant agents

Antioxidant therapy is recognized for its ability to elevate glutathione levels, a pivotal natural antioxidant crucial for maintaining redox balance and bolstering the immune system (36, 37). Oxidative stress and mitochondrial dysfunction are significant contributors to fatigue in patients with PACS (38, 39), suggesting the potential utility of antioxidant agents in this population (26).

N-acetylcysteine emerges as an effective therapeutic agent capable of enhancing redox status during oxidative stress (36, 40). Moreover, it appears that N-acetylcysteine supplementation improves dyspnea in gynecologic patients with PACS (40). In addition, N-acetylcysteine is recommended in treating COVID-19-related neuropsychiatric symptoms (41).

INTERVENTIONS BASED ON PHYSICAL METHODS

Tai Chi

Tai Chi, a meditative martial art with deep roots in Chinese tradition, is increasingly practiced worldwide (42). It involves a sequence of gentle movements that promote both physical and mental well-being (43). While there are various styles of Tai Chi, they all emphasize core principles such as flexibility, proper alignment, and mindfulness (44). The incorporation of Tai Chi in the management of chronic obstructive pulmonary disease and other complex conditions has demonstrated improvements in QoL and clinical parameters, including muscle strength, mobility, balance, and relaxation capacity (45). Studies have shown that high-intensity Tai Chi can significantly reduce serum levels of inflammatory markers such as tumor necrosis factor-alpha, interleukin-6, and C-reactive protein (46). This suggests a potential positive impact of Tai Chi on fatigue in patients with PACS. Indeed Castro et al. (47) recommended Tai Chi as a means to alleviate fatigue associated with PACS. Their recommendation is supported by evidence suggesting that Tai Chi may enhance lung function by mitigating fibrotic scar formation and increasing muscular strength, mobility, and vitality (47).

Acupuncture

Acupuncture, one of the world's oldest recognized medical practices, has been utilized for millennia to address illness, manage pain, and enhance overall well-being (48). Acupuncture needles are remarkably thin, sturdy, and filiform, allowing them to be inserted smoothly without causing skin damage, with minimal to no bleeding upon removal (49, 50). Additionally, acupuncture has been shown to effectively mitigate symptoms of anxiety (51) and possesses various immunomodulatory properties (52), suggesting its potential utility in managing PACS-related fatigue due to its multifaceted action. A meta-analysis revealed that acupuncture can alleviate PACS symptoms by reducing inflammation, modulating the

adaptive immune response, and influencing nitric oxide production (53). In a case study, acupuncture followed by rehabilitation, termed as symptom-titrated physical activity (STPA), resulted in full recovery for a 50-year-old woman experiencing PACS-related symptoms (54). The treatment protocol comprised seven sessions of scalp, auricular, and body acupuncture, followed by six sessions of STPA lasting 30 minutes each (54).

Yoga

Yoga, an ancient practice with roots dating back thousands of years, adopts a holistic mind-body approach aimed at alleviating both spiritual and physical distress (55, 56). It encompasses three fundamental pillars: asana (body postures), pranayama (breathing exercises), and meditation (56, 57). Over the years, yoga has been associated with numerous health benefits, including enhanced production and activity of melatonin, anti-viral and anti-inflammatory effects, and cardioprotective properties (58). Additionally, yoga has demonstrated efficacy in improving fatigue symptoms among cancer survivors (59) and patients with chronic obstructive pulmonary disease (60). Emerging evidence also suggests that tele-yoga may be a beneficial intervention for individuals with long COVID, helping to alleviate stress, anxiety, and insomnia, particularly in those experiencing moderate psychological distress (61). Collectively, these findings suggest that yoga may hold promise in treating PACS-related fatigue, although further research is warranted.

Singing and vocal exercises

Singing entails an active exercise that produces musical sounds involving rapid, forceful inspirations followed by controlled, prolonged expirations (62). Thus, precise respiratory control is essential for singing. Moreover, regular singing involves a specific type of breathing exercise that necessitates diaphragmatic contractions for full inspirations and sustained contractions of expiratory muscles against partially closed vocal cords during expirations (63). Singing has been demonstrated to be a feasible and safe practice for enhancing QoL and pulmonary function in patients with conditions such as chronic obstructive pulmonary disease (64). In a pilot study called SingStrong, 27 patients with PACS underwent a 10-week, bi-weekly online program comprising a 45-minute session of mindfulness, breathing retraining, vocal exercises, and singing (65). This study revealed significant improvements in fatigue, dyspnea symptoms, level of daily activities, pain/disability, voice quality, and communication/cognition (65).

OTHER METHODS

Hyperbaric oxygen therapy (HBOT)

HBOT aims to elevate levels of oxygen in the blood (ie; hyperoxemia) and tissues (ie; hyperoxia) by

administering pure oxygen at high pressure, typically 2–3 atmospheres (66). Beyond enhancing oxygen supply, HBOT contributes to the release of vascular endothelial growth factor, modulation of inflammation, reduction of edema, immune regulation, and stimulation of various stem cell populations (67). For these reasons Pawlik et al. (67) suggested that HBOT could improve long COVID symptoms. In addition, in a case study involving a 55-year-old man with PACS, HBOT was employed (68). Over a span of 12 weeks, the patient underwent sixty sessions of HBOT, each lasting 90 minutes and administered at 100% oxygen at 2 atmosphere absolute pressure, with 5-minute air breaks every 20 minutes. Significant improvements were observed in brain perfusion and microstructure, cognitive function, and physical capacity. Notably, the enhancement in cognitive functions correlated with increased cerebral blood flow, as assessed by perfusion magnetic resonance imaging.

Pulsed electromagnetic field (PEMF) therapy

PEMF therapy is a noninvasive method renowned for its utilization of electromagnetic fields to generate microcurrents throughout the entire body or selectively in specific body tissues (69, 70). PEMF therapy was employed in the management of a 55-year-old female with PACS' symptoms persisting for 6.5 months (71). The treatment regimen consisted of 10 sessions of PEMF lasting 30 minutes each, administered twice a week over a span of 5 weeks. Improvement in fatigue was noted, as evidenced by a decline in the brief fatigue inventory score from 6.33 at baseline to 0.11 at 6 weeks post-treatment (71).

Whole body vibration (WBV)

WBV is a non-invasive technique recommended for integration into lung rehabilitation programs and utilized within intensive care settings (72). WBV seems to have interesting virtues that may be helpful in the management of patients with PACS, especially in improving related fatigue (73). From a specific perspective, WBV induces vibrations that increase pulsatile shear stress either locally or throughout the body, enhancing the availability of nitric oxide and other mediators (73-75). Furthermore, the increased shear stress may enhance nitric oxide's antiviral effects and inhibit the endothelial impacts of COVID-19 (74). A 2020 narrative review from the world association of vibration exercise experts' panel have expected that WBV exercise could help infected individuals to attenuate the decline in physical function, improve post COVID-19 recovery and allowing more individuals to be treated (73). The experts' panel provided recommendations regarding the reduction of fatigue and the risk of dyspnea, the improvement of the inflammatory and redox status favoring cellular homeostasis and the overall improvement in the QoL (73). More broadly, but notably, WBV has demonstrated a beneficial effect on muscle power, balance, pain, and fatigue in the general population (72, 73, 75), suggesting this technique as a treatment option in PACS. WBV seems

to be a safe and protective treatment option in PACS in general, improving PACS-related fatigue (76). These non-conventional treatments offer promising complementary benefits to conventional rehabilitation by targeting various mechanisms involved in PACS-related persistent fatigue, including oxidative stress, inflammation, and neurophysiological imbalances (Figure 1). By enhancing muscle strength, physical performance, cognitive function, and overall well-being, they contribute to a more comprehensive and personalized approach to patient care. Their integration into existing therapeutic protocols could optimize clinical outcomes and significantly improve the QoL for individuals suffering from PACS.

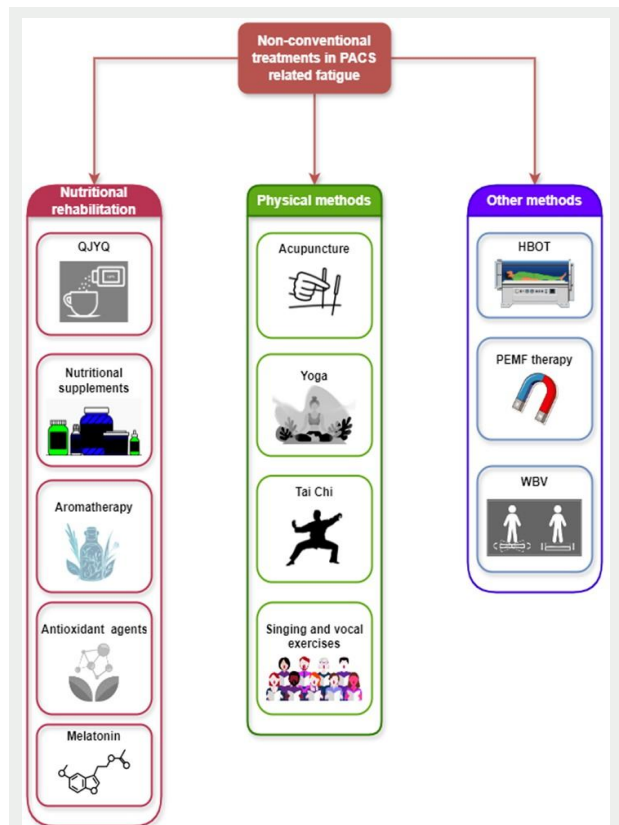


Figure 1. Non-conventional treatments in post-acute COVID-19 syndrome (PACS) related fatigue

QJYQ: QingjinYiqi. COVID-19: Coronavirus Disease 2019. HBOT: Hyperbaric Oxygen Therapy. PEMF: Pulsed Electromagnetic Field. WBV: Whole-Body Vibration.

CONCLUSION

Managing symptoms of long COVID is challenging and may sometimes lead to insufficient and unsatisfactory results. Fatigue, in particular, is one of the hardest symptoms to treat due to its complex and multi-factorial pathophysiological mechanisms. While rehabilitation remains the cornerstone of management, multiple other therapeutic options that have been proven safe and efficient should be considered to enhance and maintain results.

DECLARATION. The authors wish to disclose that an artificial intelligence tool (ie; ChatGPT ephemeral) was utilized to enhance the clarity and coherence of the manuscript' writing. The tool was utilized for language refinement purposes only, ensuring the text was clear and coherent without altering the scientific content or generating any new text (77).

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ABBREVIATIONS' LIST

COVID-19: Coronavirus Disease 2019

HBOT: Hyperbaric Oxygen Therapy

PACS: Post-Acute COVID-19 Syndrome

PEMF: Pulsed Electromagnetic Field

QJYQ: QingjinYiqi

QoL: Quality of Life

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

STPA: Symptom-Titrated Physical Activity

WBV: Whole-Body Vibration

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