REVIEW

Pain Management in the Post-COVID Era—An Update: A Narrative Review

Salah N. El-Tallawy [ID] · Joseph V. Perglozzi · Rania S. Ahmed ·

Abdullah M. Kaki [ID] · Mohamed S. Nagiub · JoAnn K. LeQuang ·

Mamdouh M. Hadarah

ABSTRACT

An extensive computer search (from January 2020 to January 2023) was conducted including literature from the PubMed, Scopus, MEDLINE, Web of Science, and EMBASE databases. According to preset criteria, a total of 58 articles were included in this review article. Generally, any patient who becomes infected with COVID-19 can develop post-COVID-19 conditions. The course of COVID-19 is divided into three main stages: acute COVID-19 (up to 4 weeks), post-acute COVID-19 (from 4 to 12 weeks), and post-COVID (from 12 weeks to 6 months). If a more protracted course of COVID (over 6 months) is demonstrated, the term "long-COVID" is used. Although the acute stage of COVID-19 infection most commonly manifests with acute respiratory symptoms, one very common symptom of the disease is pain, while the most common symptoms of post-COVID syndrome are shortness of breath, dry cough, fatigue, loss of olfactory and gustatory function, tightness and chest pain, sleep and mood disturbances, body aches, muscle and joint pain, sore throat, fever,

S. N. El-Tallawy (✉)
Anesthesia and Pain Department, College of Medicine, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia
e-mail: salaheltallawy@yahoo.com

S. N. El-Tallawy
Anesthesia Department, Faculty of Medicine, Minia University and NCI, Cairo University, Giza, Egypt

J. V. Perglozzi · J. K. LeQuang
NEMA Research, Inc, Naples, FL, USA

J. V. Perglozzi
e-mail: jpergolizzi@adminnemaresearchcom.on microsoft.com

J. K. LeQuang
e-mail: joannlequang@gmail.com

R. S. Ahmed · M. S. Nagiub
College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

R. S. Ahmed
e-mail: raniasalah246890@gmail.com

M. S. Nagiub
e-mail: hamadasalah13579@gmail.com

A. M. Kaki
Anesthesiology and Pain Medicine, International Medical Center, Jeddah, Saudi Arabia
e-mail: amkaki@yahoo.com

M. M. Hadarah
Anesthesia and Pain Management, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
e-mail: hadmaa@icloud.com

△ Adis

and persistent headaches. All observations demonstrated a high incidence of chronic pain syndromes of various localization in the post- and long-COVID period. Post-COVID chronic pain might include a newly developed chronic pain as a part of post-viral syndrome; worsening of preexisting chronic pain due to the associated changes in the medical services, or a de novo chronic pain in healthy individuals who are not infected with COVID. Chronic pain during and post-COVID-19 pandemic is an important health issue due to the significant impacts of pain on the patients, health care systems, and society as well. Therefore, it is important that patients with chronic pain receive effective treatment according to their specific needs. Accordingly, the main goal of this review article is to provide a broad description about the post-COVID pain and to explore the impact of long COVID-19 on chronic pain patients, and also to give brief reports about the prevalence, risk factors, possible mechanisms, different presentations, and the management tools through a systematic approach.

Keywords: COVID-19; Long COVID; Post-COVID pain; Post-COVID pain syndromes; Post-COVID chronic pain; Post-COVID neuropathic pain; Post-COVID musculoskeletal pain; Post-COVID headache; Telemedicine

Key Summary Points

Why carry out this study?

Post-COVID-19 pain is prevalent and can develop into more challenging and persistent pain. Accordingly, the main objectives of this review are:

To give a brief report about the challenges facing the chronic pain management during post-COVID-19.

To describe the prevalence, risk factors, and possible mechanisms of chronic pain conditions associated with long COVID-19.

To focus on the strategies to overcome the limitations in healthcare delivery and providing the appropriate management for chronic pain patients.

To explore the practical tips for the management of post-COVID chronic pain.

What was learned from the study?

The post-COVID era represents a great challenge to the health care services and has changed our approaches to medicine.

All observations demonstrated a high incidence of chronic pain syndromes of various localization in the post- and long-COVID period.

COVID-19 is having a profound effect on patients with pain. Delaying, or stopping, treatment will have negative consequences on chronic pain patients.

Evidence is promising that new tools such as telemedicine and mobile opioid treatment programs can help to provide ongoing services to chronic pain patients.

INTRODUCTION

Health care systems worldwide are facing extraordinary challenges since the COVID-19 pandemic. Globally, with the end of 2022 and the beginning of a new year, the COVID-19 epidemiological update showed that there have been 657,977,736 confirmed cases of COVID-19, including 6,681,433 deaths globally. This number should be taken with caution, as many countries have changed the practice of routine COVID-19 testing, resulting in underestimations of the actual numbers [1].

The COVID-19 pandemic has changed our approaches to medicine and created a whole new generation of people who have chronic pain. Many pending answers on COVID-19 and its sequelae remain unclear and will remain a challenge for the foreseeable future [2, 3]. The COVID-19 pandemic has drawn attention to the

weaknesses of health systems around the world [4].

A significant proportion of patients with COVID-19 experienced long-term and persistent symptoms. Published reports indicate that approximately 10–20% of COVID-19 patients experience persistent long COVID symptoms from a few weeks to a few months following acute infection [5]. This syndrome is characterized by a wide range of health problems including "brain fog" with cognitive disturbances, fatigue, dyspnea, myalgia and muscle weakness, depression, and persistent headaches [6]. Furthermore, a recent comprehensive systematic review and meta-analysis estimated the prevalence of long COVID, and showed that 45% of COVID-19 survivors were experiencing a wide range of unresolved symptoms for at least 4 months after a confirmed COVID-19 infection [7].

Chronic pain is an important health issue and is the most common reason to seek medical care. It ranks among the ten most prevalent diseases worldwide and years lost to disability. For this reason, chronic pain should be properly managed to avoid further complications [8]. COVID-19 is having a profound effect on patients with chronic pain. Delaying or stopping treatment for chronic pain patients will have negative consequences, including increases in pain, disability, and depression. The management of chronic pain during the COVID-19 pandemic is a challenging process, especially with growing evidence that COVID-19 infection is associated with persistent myalgias, referred pain, and widespread hyperalgesia [9].

METHODS

An extensive computer search was conducted including literature from the PubMed, Scopus, MEDLINE, Web of Science, and EMBASE databases. Manual screening of references was also conducted, and additional references were added from sites for pain organizations, e.g., International Association for the Study of Pain (IASP) and the World Health Organization (WHO). Relevant guidelines from the American

Society of Anesthesiologists (ASA), American Society of Regional Anesthesia (ASRA), American Society of Interventional Pain Physicians, and American Academy of Physical Medicine and Rehabilitation, European Pain Federations, and The WHO database on COVID-19 were screened for relevant publications. The search strategy was restricted to articles that were published between January 2020 and January 2023. The following related keywords were used for the search ("COVID-19", "coronavirus and SARS-CoV-2", "post-COVID pain", "post-COVID pain syndromes", "post-COVID headache", "post-COVID chronic pain" "post-COVID neuropathic pain" and "post-COVID musculoskeletal pain"). Articles that met the inclusion criteria, such as articles relevant to the condition and presented information on the post-COVID pain conditions, articles published in English language and involving adult humans were included. The search included observational study, cross-sectional study, cohort study, case–control study, longitudinal study, systematic reviews, and meta-analysis. The exclusion criteria included non-English-language articles, failure to get the full articles, post-COVID pain in children, case report, editorials, or expert opinions. The selected articles for inclusion were screened by two independent reviewers using the same method of evaluation. The final reviewing strategy of the literature search results in a total of 58 articles in this review (Fig. 1) [10]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DEFINITIONS

Various definitions have been developed to define different stages of COVID-19 based on the durations and clinical presentations. Standardized definitions are important for the proper diagnosis and management of those patients. The following definitions can be used to differentiate different stages of both ongoing or post-COVID-19 signs and symptoms [1, 11, 12].

- *Acute COVID-19 infection:* Signs and symptoms of COVID-19 for up to 4 weeks [1].
- *Ongoing symptomatic COVID-19:* Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks [1].
- *Post-COVID-19 syndrome:* Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks to 6 months and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed [1, 11].
- *Long COVID:* there are different definitions with more or less similar meanings.

Fig. 1 Flow chart of inclusion of studies (PRISMA, 2009) [10]

o *According to the National Institute for Health and Care Excellence (NICE)* guidelines, long COVID is commonly used to describe signs and symptoms that continue or develop after acute infection consistent with COVID-19 and persist longer than 4 weeks. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). If a more protracted course of COVID (over 6 months) is discussed, the term "long-COVID" is used [11, 12].
o *Centers for Disease Control and Prevention (CDC, 2021):* "Wide range of new, returning, or ongoing health problems people can experience 4 or more weeks after first being infected with the virus that causes COVID-19" [13].
o *World Health Organization (WHO, 2021):* "Illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection, usually within 3 months from the onset of COVID-19, with symptoms and effect that last for at least 2 months, that cannot be explained by an alternative diagnosis" [1].
o *National Health Service (NHS, 2021):* "Symptoms lasting weeks or months after the infection has gone [11, 14].

- *Post-COVID-19 condition* is defined as the illness that occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction, but also others, and generally have an impact on everyday functioning. Symptoms may be new-onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time [13].
- *Post-COVID headache: The International Classification of Headache* disorders uses a headache duration of more than 3 months
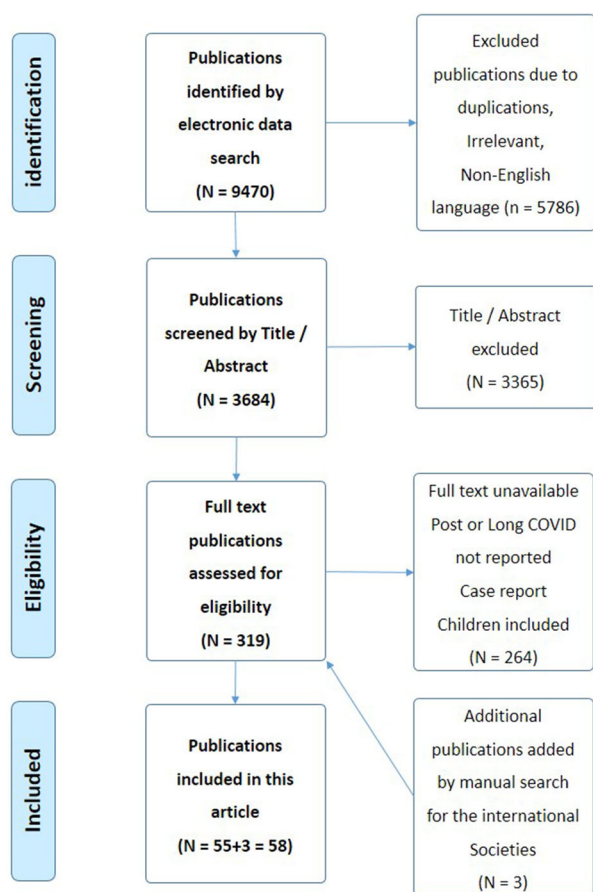
after the acute infection for the diagnosis of "Chronic headache attributed to systemic viral infection" [15].

- **Chronic pain:** chronic pain is defined from the International Association for the Study of Pain (IASP) as persistent or recurrent pain lasting more than 3 months or beyond the normal tissue healing [16].
- **Nociplastic pain:** the IASP defines nociplastic pain that 'arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain' [17].
- **Musculoskeletal pain**: The Pain Task Force of the (IASP), defines Chronic Primary Musculoskeletal Pain (CPMP) as "chronic pain in the muscles, bones, joints, or tendons that is characterized by significant emotional distress (i.e., anxiety, anger, frustration, and depressed mood) or functional disability" [9, 18].

Challenges Facing Post-COVID-19 Chronic Pain Management

Chronic pain patients may experience additional potential risk of functional and emotional deterioration during a pandemic, which can increase the long-term health burden [19, 20].

The ongoing and long COVID-19 pandemic are associated with new problems affecting chronic pain management. Difficult access to health care facilities, a lack of resources, burdened health care services, mental health problems, and a patient's associated comorbidities may add more burden to the chronic pain patients [9, 21]. All of these factors contribute to making the delivery of effective pain management more challenging.

- **Problems related to the pandemic:** [19, 20, 22].
  - o Lockdown, travel restrictions, social and physical distances, and isolation.
  - o Fear of infection or the health care facilities get infected.

- o Decrease the risk of exposure of the health care workers to severe infection overtly burdened health care system.
- o All elective consultations and interventions are cancelled or postponed.
- o Interrupted care due to isolations and closing many services such as physiotherapy & supportive services.

- **Problems related to the overstretched health care systems:** [9, 23]
  - o Increased demand on the health care systems, health care workers, and facilities.
  - o The overuse of imaging as a result of the pandemic and its sequel. Around 69% of general practitioners would refer patients for radiography at first presentation, despite routine use discouraged due to a poor relationship of imaging findings with symptoms.
  - o The rate of some surgical procedures, e.g., orthopedic and spine surgeries, has increased markedly in recent years.

- **Problems related to the rehabilitation programs:** [9, 20].
  - o Lack of physical activities, impacting patients who relied on physical therapy or exercise programs as part of their pain management regiment.
  - o Closure or overloaded rehabilitation services due to the pandemic.

- **Patient-related factors:** [18, 24, 25]
  - o Failure to provide education or advice.
  - o Limited access to the health care facilities.
  - o Difficulty to get refill of pain medications, especially for controlled medications and opioids.
  - o Significant number of patients are elderly with many comorbidities and multiple medications.
  - o They are more susceptible to morbidity and mortality from COVID-19.
  - o Possible immune suppression, fatigue, weakness, and associated comorbidities.

- **Mental health problems:** [24, 25].

o Onset of new or exacerbation of mental health concerns, including anxiety, stress, depression, and post-traumatic stress disorder, have become significant concerns.

o Less access to treatment facilities due to isolation, social distancing, and fear of infection, lifting opioid tolerant patients struggling with addiction.

o This interruption has had serious consequences, as it has led to an increase in chronic pain, psychological worsening, and decrease in the quality of life.

– *Interaction between treatment of chronic pain and COVID-19 pandemic:* [16, 26]

o Painkillers such as NSAIDs and paracetamol may mask the symptoms of COVID-19 infection, e.g., fever and myalgias.

o Pain medications may interact with the immune system or mask the signs or symptoms of COVID-19 infection.

o Chronic opioid therapy with high doses may induce immunosuppression.

o Oral or injectable steroids (e.g., used for interventional pain procedures) are immunosuppressive.

o Steroid injections for pain managements may affect the efficacy of COVID-19 vaccines.

PREVALENCE OF POST-COVID-19 PAIN

Approximately 10–20% of acute infection with COVID-19 patients go on to develop prolonged symptoms that may be post-COVID-19 condition [1]. In the United States, there are more than 80 million patients and survivors of COVID-19, which is the highest number in the world [27]. A recent comprehensive systematic review and meta-analysis estimated the prevalence of long COVID, regardless of hospitalization status. A total of 194 studies including 735,006 participants worldwide were included in the analysis. Results showed that 45% of COVID-19 survivors experienced a wide range

of unresolved symptoms for at least 4 months after COVID-19 infection [7].

Pain can be an early symptom of acute COVID-19 infection, including sore throat, myalgias, back pain, and headache [28]. It seems that no relationship exists between the initial severity of COVID-19 infection and the likelihood of developing post-COVID-19 conditions(5). Chronic pain might affect up to 50% of the general population, while the prevalence of post-COVID-19 chronic pain was estimated to be 63.3% [29].

Patients with chronic pain infected with COVID-19 are at higher risk for exacerbation of their symptoms, and this is attributed to many factors including social threats, discontinuation of therapy, reduced access to treatments, or associated mental health problems and concerns about health outcomes [25, 30, 31]. COVID-19 may exacerbate preexisting pain or be associated with the appearance of new pain. Another study compared two groups of patients, one group admitted to the hospital due to COVID-19 infection and the other group admitted due to other causes. Results showed that COVID-19 infection was associated with a significantly higher prevalence of de novo chronic pain, chronic daily headache, and new-onset pain in general, which was associated with persistent anosmia [32].

Chronic pain has a positive relationship to viral infection, psychological stress, and consequences of admission to the hospital or intensive care unit (ICU). Post-COVID-19 chronic pain may include either regional or widespread pain [33, 34]. It often causes peripheral or central neurological complications, either through direct invasion of the nervous system or through immune reactions (35, 36).

– *Prevalence of chronic pain according to the demographics:* A cross-sectional study showed that more than three out of five COVID-19 survivors experience chronic pain. Increasing age and female sex correlated with the presence of chronic pain in this population [37].

– *Prevalence of chronic pain according to the site of pain:* COVID-19 pain was more frequently located in the head/neck and

lower limbs ($p < 0.05$), followed by joint pain. New-onset fatigue was more common in COVID-19 survivors necessitating inpatient hospital care. The presence of insomnia in COVID-19 patients correlates with the presence of more new-onset pain (83.3%) compared to those who did not (48.0%, $p = 0.024$) [32, 38].

– *Prevalence of chronic pain according to the pathophysiological type of pain:* Post-COVID chronic pain exhibits both musculoskeletal and neuropathic pain features. The discrimination between nociceptive, neuropathic, and nociplastic pain represents a current challenge for clinicians [9]. The prevalence of neuropathic pain was estimated to be 24.4% [29]. Preliminary evidence suggests the presence of neuropathic pain in individuals exhibiting post-COVID pain. The neuropathic pain symptoms was positively associated with the duration of post-COVID pain, anxiety levels, and kinesiophobia level. It was found that almost 25% of previously hospitalized COVID-19 survivors with "de novo" post-COVID pain reported a neuropathic pain component [30, 31].

– *Prevalence in non-hospitalized patients:* Few reports that included long-term follow-up in non-admitted patients suggest that (31–53%) still have one or several persistent painful symptoms 1 year after COVID-19 infection, which would translate to a significant number of people worldwide [21, 39, 40]. A recent meta-analysis has revealed that more than 60% of patients exhibited at least one post-COVID-19 symptom. The most prevalent post-COVID-19 symptoms experienced by both hospitalized and non-hospitalized patients were fatigue and dyspnea were. The other symptoms including headache, anosmia, chest pain, or joint pain was lower and more variable [41]. In non-hospitalized patients, the most frequent symptoms were fatigue (34.8), breathlessness (20.4%), muscle pain/myalgia (17.0%), impaired sleep (15.3%), and loss of sense of smell (12.7%) [7].

– *Prevalence in hospitalized patients:* The reported prevalence of musculoskeletal pain post-COVID-19 in previously hospitalized patients ranged from (11–45%) at 6 months or more after discharge [42]. Patients with post-COVID musculoskeletal pain showed a greater number of COVID-19 symptoms at hospital admission, with a greater prevalence of myalgia and headache, longer stay of hospitalization, and higher incidence of ICU admission than those not reporting long-term musculoskeletal post-COVID pain [43]. In hospitalized patients, the five most prevalent symptoms reported were fatigue (28.4%), pain/discomfort (27.9%), impaired sleep (23.5%), breathlessness (22.6%), and impaired usual activity (22.3%) [7].

Risk Factors for Post-COVID-19 Chronic Pain

– *General risk factors:* it is clear that patients with chronic pain infected with COVID-19 sometimes experience exacerbation of their symptoms, which may be due to multiple factors including social threats, discontinuation of therapy, reduced access to treatments, or associated mental health problems and concerns about health outcomes [30, 31].

– *Risk factors in (non-hospitalized) COVID-19 patients:* COVID-19 itself is associated with painful symptoms, including myalgia, arthralgia, abdominal pain, headache, and chest pain, and even those not admitted to critical care environments may have pain requiring opioids for symptom management [21, 44]. Post-COVID headache was relatively higher in patients managed in an outpatient setting [45]. These persistent symptoms, which can change over time, confirm that post-COVID-19 chronic pain has a multi-systemic involvement even after mild infection in healthy younger individuals. It has been reported that the risk factors for persistent symptoms 12 months after COVID-19 infection include lower physical fitness, low physical activity, obesity (body mass index > 25 kg/m^2), associated co-morbidities (particularly hypertension and chronic pain), and having more than seven

of the general COVID-19 symptoms at the onset [44, 45].

It is commonly understood that long-term symptoms can occur regardless of acute infection severity. However, acute phase severity, hospitalization, greater age, female sex, high body mass index (BMI), and any chronic diseases are factors associated with post-COVID-19 [37, 46]. Several features such as social distancing and isolation at home in addition to the mental health specific problems such as depression, anxiety, post-traumatic stress disorder (PTSD), and cognitive impairment, have well-recognized with chronic pain [25].

– **Risk factors in (hospitalized) COVID-19 patients:** risk factors for the development of persistent and chronic pain post-COVID-19 in hospitalized patients and their mechanisms have been identified. In addition to the general risk factors such as being elderly, having a high body mass index (BMI), and associated comorbidities, potential risk factors for chronic pain include pre-existing painful conditions, acute pain, length of hospital stay, immobility, illness severity such as length of stays in ICU, and number of days on mechanical ventilation, neuromuscular blockade, repeating proning, and neurological insult [35, 47, 48]. Patient weakness may contribute to rapid deconditioning and joint-related pain. Other risk factors include social isolation during hospital admission and post discharge. Pandemic-specific psychological and mental health burden [49–52].

– **Risk factors due to ICU sitting:** unfortunately, pain has received low priority, poor assessment, and management for patients admitted to the ICU during the pandemic. This is attributed to the associated heavy workload by the exhausted health workers [21, 41]. COVID-19 patients are likely to have sustained a prolonged period of ICU admission with immobilization, sedation, and mechanical ventilation. The ICU management protocols add additional risk factors such as the use of neuromuscular block, corticosteroids and the risks of procedural pain such as intubation, tracheostomy, suction, cannulations, sampling, and catheterization. The presence of sepsis, neuro-immune response to infection, painful neurological sequelae, e.g., stroke and multi-organ dysfunction, may worsen the situation. This sitting in the ICU puts patients at high risk of muscle weakness, joint stiffness, myopathy, polyneuropathy, and muscle atrophy. Complications associated with proning sedated patients include brachial plexopathy, joint subluxation, and soft tissue damage. These have the potential to result in persistent neuropathic and musculoskeletal pain after ICU discharge. Patient weakness may contribute to rapid deconditioning and joint-related pain, which may help to explain why chronic shoulder pain has been particularly prevalent in patients who were seen in the ICU for coronavirus treatment [53, 54].

Possible Pathophysiology and Mechanisms

Possible Etiology of Post-COVID Chronic Pain

Post-COVID chronic pain can be associated with any type of pain; it can be nociplastic, neuropathic, or nociceptive. Possible causes may include genetic factors, previous pain experience, and traumatic events that could be physical or emotional [55]. Post-COVID chronic pain might include: a newly developed chronic pain which is a part of post-viral syndrome due to organ damage; exacerbation of preexisting chronic pain due to the abrupt changes, limited access to medical services and the associated mental health problems; or newly developed chronic pain in healthy individuals who are not infected with COVID due to associated risk factors (e.g., poor sleep, inactivity, fear of infection, anxiety, and depression) [30]. Chronic pain conditions can be triggered by psychosocial stressors or organ-specific biological factors. Post-COVID-19 pandemic has many characteristics that could potentially increase the prevalence of chronic pain, especially with stressors extending over many months [25, 30, 55].

Possible Mechanisms/Pathophysiology of Long COVID Pain

The exact mechanisms causing post-COVID pain remain unclear. Recent findings indicated that there were four pathophysiological categories involved: virus-specific pathophysiological variations, oxidative stress, immunologic abnormalities, and inflammatory damage [56–60]. However, the following proposed mechanisms may be responsible for post-COVID pain:

- The virus may directly attack multiple tissue types including nerves, the spinal cord, and brain with the associated encephalopathy and structural changes [33, 34].
- Another proposed mechanism was the direct viral entry of cells of the musculoskeletal and nervous systems mediated by angiotensin-converting enzyme 2 (ACE2) receptor [42, 61, 62].
- The association of persistent symptoms such as fatigue, diffuse myalgia, and joint and musculoskeletal pain are all linked to mitochondrial dysfunction, oxidative stress, and reduced antioxidants [56].
- A phenomenon of protracted immunosuppression, known as PICS (persistent inflammation, immunosuppression, and catabolism syndrome), has been presented as a potential major contributing factor for the presentation of post-COVID symptoms [63].
- The inflammatory cascades may over-activate and attack the body's tissues and organs.
- The neurotrophism of COVID-19 infection could cause neurodegenerative problems with an inflammatory base [56, 57, 61].
- Bradykinins contribute to pro-inflammatory state and also sensitize the sensitive fibers, leading to hyperalgesia [56, 57, 61, 64].
- The excessive blood clotting triggered by the virus may lead to symptoms such as phantom limb pain [56, 57].
- The potential contribution of psychosocial factors and mental health problems [25, 65].

Characteristic Symptoms of Post-COVID-19 Syndrome

The initial symptoms of acute COVID-19 infection are mainly fever, dry cough or dyspnea, although pain has also been an early symptom such as sore throat, myalgia, low back pain, and headache [24, 28]. Post-COVID chronic pain is the result of the interaction of biological, psychological, and social factors. Clinical studies showed that at least 50% of patients who have been infected with and survived COVID-19 will continue to suffer from symptoms for 6 months or longer [66]. A recent comprehensive systematic review and meta-analysis estimated the prevalence of long COVID, regardless of hospitalization status, and showed that the ten most frequent symptoms are fatigue/weakness, breathlessness, impaired usual activities, taste, smell, depression, muscle pain/myalgia, joint pain, affected sleep, and gastrointestinal symptoms [7]. It appears from the previous publications that post-COVID pain symptoms are fixed and presented ($\geq 50\%$) among the top ten post-COVID-19 symptoms.

Post-COVID-19 Painful Conditions

Acute pain associated with viral infection is common in the early stages of acute COVID-19. The situation is worsened due to additional procedural pain, lack of resources, and overstretched health care services making low priority for symptomatic management of pain [21], while long COVID-19 is associated with an increased number of chronic pain patients either due to worsening of preexisting chronic pain or appearance of new painful conditions. The most common symptoms of people suffering from long COVID-19 painful conditions include generalized body pain, headache, muscle and joint tenderness, and pain due to increased levels of physical or mental stress with painful levels of anxiety or depression [21, 67].

Headache
Headache is one of the most common symptoms during infection, and post-COVID. It has been shown to be a potential long-term

problem as a part of the long COVID syndrome [9]. According to The International Classification of Headache Disorders, a headache duration longer than 3 months following the acute infection is used for the diagnosis of "Chronic headache attributed to systemic viral infection" [27, 68, 69].

In a meta-analysis that evaluated 35 studies, accounting for 28,348 COVID-19 survivors, the prevalence of post-COVID headache was higher in patients that were managed in an outpatient setting during the acute phase [45]. It affects between 14 and 60% of patients during the acute COVID-19 phase [70, 71]. Persistent headache in patients with long COVID has a prevalence of 18%, is more prevalent in middle-aged women, and began 2 weeks after the subsiding of respiratory symptoms [27, 69].

Headache is one of the most disabling symptoms of long COVID and may manifest alone or in combination with other symptoms such as muscle weakness, dizziness, and vertigo as well as insomnia or other sleep impairments that may occur with long COVID-19 [67].

Post-COVID headache can present in the form of worsening of a preexisting primary headache or de novo daily headache. Headache may be manifested with a migraine or more frequently, with a tension-type-like phenotype. The intensity of headache ranged between moderate and severe headache and involves the upper part of the head [27].

The pathogenesis of persistent headache may be attributed to cytokine storm with persistent activation of the immune system as demonstrated by the evidence of altered blood levels of cytokines and interleukins. Persistent glial activation and trigeminal-vascular activation are thought to play a role [72, 73].

Effective treatment of post-COVID headache should take into consideration the type of headache (migrainous vs. tension-type-like), comorbidities, and if present, additional post-COVID-19 symptoms such as insomnia, mood disorders, and cognitive difficulties [15, 74]. There are many proposed modalities for the treatment of long-term headaches associated with COVID-19 [24, 35, 60, 75].

Non-pharmacological treatment for post-COVID-19 headache includes patient education with recommendations for lifestyle changes, physical therapy, psychological therapy, and the management of pre-existing comorbidities [62, 76].

Pharmacological treatment in the form of prophylactic treatment for tension-type headache and this includes the tricyclic antidepressant amitriptyline is considered the drug of choice, followed by venlafaxine or mirtazapine [72].

Treatment guidelines recommend simple analgesics (e.g., paracetamol) and non-steroidal anti-inflammatory drugs (NSAIDs) as the first choice for acute treatment, followed by combination preparations that include caffeine. Triptans have been considered as acute therapeutic options [72, 74]. Some data report benefits of glucocorticoids for the treatment of long COVID headache, in terms of reduction of headache frequency and symptom intensity [77, 78].

Neuropathic Pain

COVID-19 often causes peripheral or central neurological complications and induces post-viral immune syndrome. Accordingly, it is anticipated that a considerable number of the chronic pain complications of COVID-19 will be neuropathic in character [79]. The most common peripheral lesions responsible for neuropathic pain include acute or chronic polyneuropathy, Guillain–Barre' syndrome, chronic inflammatory demyelinating polyneuropathy, or ganglionopathy, while, central nervous system lesions responsible for neuropathic pain include transverse myelitis, encephalomyelitis, and stroke [80].

A recent meta-analysis estimated that the frequency of post-COVID neuropathic pain ranged between 0.4 and 25% [81]. Another study reported the prevalence of "de novo" post-COVID neuropathic pain in almost 25% of previously hospitalized COVID-19 survivors. The presence of neuropathic pain was associated with more anxiety, kinesiophobia, and the duration of post-COVID pain [82].

There is preliminary evidence supporting that neuropathic pain at early post-COVID can be associated with serum levels of neurofilament light chain (NFL) as a potential biomarker

[83], while secondary analysis found no association between serological biomarkers at the acute phase of COVID-19 and the development of long COVID neuropathic pain symptoms at 6 months and 1 year after infection [84, 85].

The high expression of angiotensin-converting enzyme-2 (ACE2) receptors within nervous system cells such as neurons and microglia of the spinal cord could explain the neuro-invasive potential of the COVID-19-associated neuropathic symptoms [86].

Neuropathic pain as a complication of COVID-19 is difficult to treat. The mainstay of treatment is represented by gabapentoids, antidepressants, tramadol, and topical agents (lidocaine plasters, capsaicin patches or botulinum toxin). Strong opioids may be considered in refractory cases. Non-pharmacological treatments include invasive or noninvasive neurostimulation techniques [87, 88].

Musculoskeletal Pain

All types of pain may occur after COVID-19, such as nociceptive, neuropathic, and nociplastic pain—especially in critical care survivors [37]. Nociceptive pain is more prevalent than neuropathic pain. Musculoskeletal pains have been noticed to be a prominent complaint among COVID-19 patients (30%) and other musculoskeletal complaints have been described in 15–36% of cases [89–91]. The prevalence of musculoskeletal pain syndromes among post-COVID-19 patients was also reported in a meta-analysis that included over 25,000 patients (outpatients and previously hospitalized patients) at 4 weeks, and persistent musculoskeletal symptoms were present, including myalgia in 5.7%, arthralgia in 4.6%, and chest pain in 7.9% of patients. The prevalence of post-COVID musculoskeletal pain increased at 60 days, but decreased later on after 180 days [42, 67, 92].

Post-COVID musculoskeletal pain includes a higher prevalence of a generalized widespread pain as well as localized pain syndromes such as cervical pain and lower extremity pain, followed by lumbar spine and upper extremities. A higher prevalence of musculoskeletal pain was also reported in non-hospitalized patients than hospitalized patients [61, 93]. After COVID-19 infection, there are four patterns of musculoskeletal involvement, including myalgia 37.5%, arthralgia 5.7%, new-onset backache 6.8%, and generalized body ache 50%. Musculoskeletal pain may occur three different ways: first, de novo musculoskeletal pain following COVID-19; second, exacerbation of preexisting musculoskeletal pain after COVID-19 infection; third, increasing musculoskeletal pain in non-infected individuals as a result of COVID-19-associated factors, e.g., lockdown, isolation, unreachable medical services [94].

Chest Pain Persistent chest pain is one of the most common symptoms among patients with long COVID-19. A huge number of patients were seeking medical advice because of chest pain [95]. Chest pain persists in 12–22% of patients for few months after acute COVID-19 infection [96–98]. The prevalence of chest pain in non-hospitalized patients was 14.7% compared to 9.1% in hospitalized patients 99 (104). Patients with long COVID-19 present with a wide range of symptoms, ranging from mild to severe chest pain and tenderness. In some patients, it may be so severe that it significantly impairs the ability to perform everyday activities. In post-COVID patients, detailed history-taking and investigations, including blood testing, CT scan, and MRI, were essentially needed to differentiate between cardiac and pulmonary sources of chest pain [96–98].

Following COVID-19 infection, chest pain may be due to underlying cardiac causes such as myocardial injury, coronary artery disease, or myocarditis [100]. Coronary micro-vascular ischemia could be the mechanism of persistent chest pain in patients that have recovered from COVID-19 [101]. Those patients require cardiac referral, proper evaluation, and urgent interventions in other cases [100].

Patients who present with post-COVID persistent chest pain should be thoroughly investigated for pulmonary emboli. It has also been proposed as a potential mechanism for post-COVID chest pain, particularly when accompanied by shortness of breath [102]. Mechanisms of micro-vascular disease in COVID-19 include endothelial injury with endothelial

dysfunction and micro-vascular inflammation, and thrombosis [103, 104].

Mild cases of chest pain may resolve following recovery from acute COVID-19 and not requiring further treatment. For persistent chest pain, a short course of non-steroidal anti-inflammatory drugs or paracetamol may be required. Chest tightness and bronchospasm can be treated by inhaled bronchodilators.

Myalgia Muscle pain is one of the most common complaints during both the acute stage and post COVID-19. It has been reported in 21–62.5% of the patients according to different meta-analysis studies [67, 105, 106]. The prevalence of myalgia was higher in hospitalized patients (22.7%) compared to in non-hospitalized patients (16.8%). Sex differences were not consistent among different reports. Some studies showed a higher prevalence of both myalgia and arthralgia in males compared to females [12], while a significant number of studies showed the opposite [107, 108]. Myalgia was commonly experienced at the acute phase and persists as a component of long COVID in some patients [61, 109]. In addition to the widespread viral-induced myalgias, the most common areas for myalgia are the lower leg, arm, and shoulder girdle [43]. Weakness of the lower limbs has also been reported as suggestive of a motor peripheral neuropathy in post-COVID-19 infection [110, 111].

Myositis is muscle inflammation caused by metabolic abnormalities, which may be triggered by COVID-19 infection. Painful myositis numbers are escalating in long-COVID-19. The affected patients complain of muscle pain, tenderness, fatigue, and weakness [43, 67, 110, 111].

Arthralgia Arthralgia is pain in one or more of a person's joints. COVID-19 is considered as a current trigger in some patients. Viral arthritis is the inflammation of the joints caused by a viral infection. The most common regional areas for arthralgia are the knee joint, ankle joint, and shoulder joint [12]. Although arthralgia is less common compared to myalgia, which is more commonly described, arthralgia is associated with more severe pain [9, 67, 89]. COVID-19-associated viral arthralgia was a novel clinical entity that did not appear to be typical of a viral prodromal or of a reactive arthropathy, and had distinct characteristics from the other musculoskeletal presentations of COVID-19 [89, 90].

Fibromyalgia Fibromyalgia consists of widespread pain and tenderness on palpation at well-defined locations on the neck, trunk, and extremities. Characteristics that occur in more than 75% of fibromyalgia patients include muscle tenderness, chronic fatigue, stiffness, headaches, and sleep disturbance. Fibromyalgia has been suggested to be related to deficient immune regulatory mechanisms and this indicates a prolonged immune system impact in patients with long-COVID-19 [67, 112]. There is an association between chronic pain comorbidities and psychiatric disorders with fibromyalgia [113].

Fatigue Chronic fatigue syndrome is a medical condition that lasts at least 6 months or more. This syndrome may impair a person's ability to perform daily activities and is associated with sleep disorders. Fatigue is one of the most major symptoms associated with COVID-19 infection [114]. It may resolve after the acute phase of COVID-19. However, fatigue and weakness can persist for a few months or longer, particularly among ICU patients. Fatigue is most commonly prevalent among women of middle age and older patients [115]. Long COVID-19 syndrome with the associated psychological and immune stresses may affect the underlying nervous system negatively, leading to worsening symptoms in persons with chronic fatigue syndrome, myofascial pain, and fibromyalgia [67, 92, 115].

How COVID-19 Changed the Management of Chronic Pain

The unprecedented pandemic has created a new "face" of chronic pain post COVID. It leads to rapid and significant changes in the management of chronic pain and the medical practice in general. The COVID-19 pandemic not only had negative effects on medical health systems

but also make changes and created new services in the medical practices.

– The "COVID lifestyle" created what is called "the lockdown lifestyle". People stopped exercising, getting fresh air and sunshine, and socializing, which led to anxiety, depression, isolation, and fearfulness. Vitamin D deficiency is pretty widespread and was made worse during the lockdowns. All of these things exacerbate chronic pain.
– More emphasis on program-directed self-management, rehabilitation, and physical therapy.
– Increased awareness by the pandemic, methods of infection control for the general populations.
– Increased awareness of health care providers by the infection control, use of PPE.
– Triaging of the patients according to the urgency of the medical condition, severity of pain, and the infectious status.
– The development of telemedicine, eHealth, app-based solutions, and remote care.
– Rapid growth of telemedicine and eHealth for effective communications, evaluation, assessment, as well as management of the chronic pain.
– New methods for drug prescription, refill of medications and delivery of controlled medications such as "mobile opioid clinics".
– Warning the health care services by the weaknesses and deficiencies during the hard times such as the pandemic and how to prioritize the services according to the available resources.
– Development of new clinical practice guidelines for the diagnosis, management, medical and interventional pain therapy.
– Expansion of the pain procedures that exclude steroids due to their immune-suppressant effects such as radiofrequency ablations, regenerative injections (e.g., platelets-rich plasma "PRP", bone marrow extracts and stem cells injections). Also, the injections of high volumes with lower concentrations of local anesthetics only without steroids.

– Proper utilization of the opioids depending on those with the lowest immune-suppressant effects.

TELEMEDICINE

Telemedicine, or eHealth, has emerged as a unique technology to facilitate efficient communication to provide essential health care services during the pandemic. It is the most immediate way to enable physicians to continue treatment of patients. The role of telemedicine has declined after the pandemic but is still used by some health institutes for selected patients [9, 116].

The International Association for the Study of Pain (IASP) recommended the rapid introduction of eHealth services for chronic pain patients during the COVID-19 pandemic [3].

Several forms of eHealth services have been rapidly promoted during this crisis, with differing levels of effectiveness [116]. Also, the Medical Council of India along with National Institution for Transforming India (NITI Aayog) released "Telemedicine Practice Guidelines" enabling registered medical practitioners to provide healthcare using telemedicine [22].

The long-term benefits of telemedicine have been evaluated after 1 year post-COVID. The study evaluated the impact of a completely digital program in patients with chronic musculoskeletal pain. Results showed that participants included in the program reported significantly higher improvements in pain and function in comparison to the control group of non-starters at 1-year follow-up [117].

Modalities of telemedicine: different modalities of telemedicine have been introduced including virtual visits via video, phone, or chat, as well as remote patient monitoring and technology-enabled modalities such as using smartphone apps to manage disease [22, 118].

Benefits

– Telemedicine plays an important role in consulting physicians and health care providers without unnecessary exposure [9, 16].

- Telemedicine can decrease the risk of exposure to COVID-19 for both chronic pain patients as well as HCWs "health care workers" [9, 16].
- Improved access to care even for patients living in areas remote from the clinic through saving the resources and reducing costs at all levels by minimizing the use of PPE, transportation, and traveling [16, 22].
- It facilitates the communications with those coming from long distances, physically unfit patients with multiple comorbidities, or already-infected patients [22, 117].
- Some non-pharmacological and physical tools such as patient's educations, psychological support, medical instructions, exercises, and posture or lifestyle changes can be easily implemented through telemedicine [22, 117].
- Telemedicine can ease the workload on the already-burdened health care system and HCWs [16, 116].

Scope of the Services by Telemedicine

- To triage the cases according to the urgency of the medical condition [9, 16].
- To triage the cases according to the risk of infection [9, 16].
- To evaluate patients, assess pain, and plan treatment of chronic pain [30].
- To prescribe and refill pain medications including opioids [60].
- To resolve patient concern and offer patient's education [16, 22].
- To assess and treat emotional distress of chronic pain patients [22, 117].
- To perform a bio psychosocial management of pain [22, 117].

Limitations

- No updated clinical practice guidelines to accommodate the rapid changes of the health care services in response to the pandemic [16].
- The medico-legal issues for the use of telemedicine such as description of controlled medications, refill of opioids and identification of the patient or caregiver, as well as obtaining consent [22, 117, 118].
- Not suitable in some areas, such as rural areas and developing countries with restricted facilities [9, 30].
- Telemedicine is not suitable for patients with advanced diseases or low level in using technology [9, 30].
- Telemedicine does not replace clinical practice and the need of face-to-face consultations and patient's examination, especially for new patients, rapid changes of the patient's condition, or those with associated multiple comorbidities [22, 60, 117].
- Telemedicine is potentially less accurate in evaluation of the patient's condition compared to the conventional in-person visit [16, 22].
- Telemedicine needs some infrastructure changes [22, 117].

Future Plan of Telemedicine

The use of telemedicine may be declining after the pandemic, with a return to 'normal life and improved access to care even for patients living in areas remote from the clinic. However, the pandemic time has created a new window for the introduction of such new services to reduce the risk of exposure and facilitate easy communications after the pandemic [16, 60].

- Changing the practice from face-to-face consultations to telemedicine or mixed services needs more comprehensive work and evidence before replacing the current practices [22, 117].
- Telemedicine technology is a promising tool of communications when used in selected patients under certain conditions, such as post-COVID-19 pandemic [116, 117].
- This newly introduced communication technology needs comprehensive program-directed education and training for both the HCWs and the patients to develop the competences needed to engage with digital tools [116, 117].

– Long-term effects, comparison with face-to-face visits, implementations in normal situations after the pandemics and patient's satisfaction all still lacking evidence and need further evaluation [117].

– Program-directed training for self-management, rehabilitation, and physical therapy should be created and available via video tutorials and applications for smartphones [116–118].

– An updated pain assessment tools including simple pain scales, neuropathic pain scales, and the Pain Catastrophizing Scale (PCS) should be developed and validated to be implemented for the virtual consultation setting [116, 117].

– Build new hybrid, integrated models for chronic pain management to ensure that patients receive the right care at the right time in the best format to meet their clinical needs.

– The financial costs for both systems should be compared and addressed thoroughly [18, 116].

Mobile Opioid Treatment Program

Mobile opioid treatment programs are designed to make the treatment of patients with opioid use disorder as easy and accessible as possible, even for the marginalized, who lack reliable transportation, live in chaotic situations, rural communities, and hard-to-reach populations [119]. For decades, mobile methadone clinics have used vans or other vehicles to bring methadone maintenance programs into the community. They may offer the opioid agonists methadone or buprenorphine treatment [120].

The mobile narcotic program uses technology, such as smartphone apps or online resources, and may allow mobile patients to benefit from counseling as well. The programs have policies and procedures to store, transport, deliver, account for, reconcile, and dispose of opioid waste and would be subject to audit. A mobile opioid program is an important service of particular value to underserved communities [120]. This program can be updated and used in hard times such as the pandemics to make treatment available and beneficial for such people during COVID as well as post-COVID era.

Practical Tips for the Management of Post-COVID Chronic Pain

Management of post-COVID chronic pain should be directed to involve post-COVID pain syndromes, persistent pain and discomfort, pain-associated treatment, intermittent procedural pain and tenderness from multiple types of pain conditions, as well as preexisting chronic pain issues [67, 121].

General Management

– Continuous monitoring and evaluations are essential for every patient before the management of post-COVID chronic pain and should be performed regularly [7, 16].

– Patients who are recovering from COVID-19 require proper assessment to determine the most vulnerable group and investigate the most suitable treatment for such patients [7, 18].

– The presence of psychiatric conditions, mental health problems, and occupational and social situations should be taken into consideration during the management of post-COVID pain [25].

– Mild-to-moderate pain associated with post-COVID symptoms can be relieved with simple analgesics such as acetaminophen and NSAIDs [9, 16].

– Patients with moderate-to-severe pain, opioids with minimal immune-suppression effects (e.g., buprenorphine, tramadol, or oxycodone) are recommended. For neuropathic pain symptoms, gabapentoids are suitable options [9, 121].

Infection-Control Guidelines Should be Followed

– The infection-control precautions according to the WHO recommendations should be followed (5).

– When patient visits are required, patients and their caregivers should be screened for

symptoms of COVID-19, according to available screening tools and practice [7].

– Patient's triaging according to the risk of COVID-19 infection with social distancing and isolations should be applied when required [16, 121].

– Personal protection measures such as hand hygiene, face mask, and gloves during patient care, and cleaning of surfaces in the patient care environment should be taken according to the local regulations by healthcare authorities [16, 121].

Pain Management and COVID-19

– **Medications that reduce post-COVID-19 syndrome:** A warning by a European agency that NSAIDs can mask the symptoms and signs of COVID-19 infection, and this may delay the diagnosis of the disease [7, 56].

– **Medications and immune system:** Medications used to relieve pain can depress the immune system. Some opioids may cause immunosuppression while corticosteroids may induce secondary adrenal failure in addition to the immunosuppressant effect [24, 60, 75].

– **Corticosteroids:**

o Corticosteroids are immuno-suppressants and have been linked to increased risk of infection [24, 48, 60].

o The American Association of Interventional Pain Physicians (ASIPP) and many other international associations state that more selective action should be taken in the administration of corticosteroids [9, 24, 60].

o In immune-compromised patients, epidural injection with the lowest dose of steroids or without steroids should be considered.

o In addition, some studies showed a strong correlation between the epidural volume and pain relief irrespective of the steroid dose [24, 75].

o Randomized controlled trials (RCT) have shown that epidural steroid injection doses exceeding 40 mg methylprednisolone, 20 mg triamcinolone, and 10 mg dexamethasone provide no recognizable pain relief difference compared to lower doses. No additional benefits for doses greater than 10 mg triamcinolone or 4 mg dexamethasone were observed [122, 123].

o There is a strong correlation between the epidural volume and pain relief irrespective of the steroid dose [124].

o There are publications reporting that radiofrequency denervation is a safe practice in the treatment of interventional pain during the pandemic [125].

o Alternatively, regenerative injections (e.g., protein-rich plasma "PRP", bone marrow extracts "BME", and stem cell injections are applicable and preferred compared to degenerative injections (e.g., steroids) especially during the pandemic [48, 125].

– **Opioids:**

o Opioids and corticosteroids used in the treatment of chronic pain and are known to have immunosuppressive effects [9, 20, 125].

o However, pain itself may have an immunosuppressive effect. With that in mind, it is possible that the use of opioids to relieve acute and chronic pain may actually enhance immune response [48, 125, 126].

o In opioid-tolerant patients, opioids are linked to infections like pneumonia [9, 127].

o International pain associations have warned physicians in guidelines published during the pandemic that patients may be more susceptible to COVID-19 and other secondary infections while using opioid analgesics [20, 127].

o Opioids decrease the natural killer cells, a dose-dependent effect, and interfere in the cellular response by acting directly on the hypothalamic–pituitary–adrenal axis (producing corticosteroids) or in the sympathetic system (producing adrenaline). Both act on lymphocytes by negatively modulating the response of natural killer cells.

o Various opioids differ in their effects on the immune system, with morphine and fentanyl having the greatest immuno-suppressive action [126].

o Opioids with lowest immunosuppressive characteristics may be reasonable options in such situations, e.g., buprenorphine is highly recommended while tramadol and oxycodone can be used as a second option [9, 48].

o Dose escalation and before increasing the dose, it is important to differentiate between disease progression from other opioid drawbacks, e.g., tolerance and hyperalgesia.

o Special precautions for the transdermal opioids formula, the elevated temperature associated with COVID-19, may increase absorption from transdermal patches and could increase opioid side effects [9].

Interactions Between Opioids and Antiviral Treatment

Interactions between opioids and antiviral treatments may interfere with the treatment outcomes through different mechanisms, e.g.,

– **Decreased metabolic pathways:** Anti-viral medications, e.g., lopinavir/ritonavir inhibiting CYP3A4, and this may inhibit the metabolic pathway of some opioids (e.g., oxycodone) resulting in increased plasma levels, with possible increasing the risk of overdose and respiratory depression [126, 128, 129].

– **Increased metabolic pathway:** the concomitant use of lopinavir/ritonavir with methadone may significantly decrease the plasma levels of methadone, possibly due to an induction of methadone metabolic clearance, involving either or both (CP450 3A and CYP450 2D6) [129, 130].

– **Enzyme inducers:** Induction of other enzymes, such as intestinal glycoprotein P-450, could also contribute to decreases in drug levels, with possible precipitation of withdrawal symptoms [130].

– **Medications not affected by the antiviral medications:** Morphine, buprenorphine, and tapentadol are not dependent on CYP450 enzymatic activity and can be used safely with antiviral therapy [130, 131].

Pain Medications and COVID-19 Vaccine

– Glucocorticoid injections for pain procedures and musculoskeletal pain may interfere with the potency and efficiency of COVID-19 vaccines. They are generally accepted at 1 week before and after COVID-19 vaccine administration, considering the duration of action, during COVID-19 vaccine administration [26, 75].

Pain Interventions

– **Triage the pain procedures:** [7, 9, 16]

o **Elective:** Patient normally could wait more than 4 weeks and no significant harm is anticipated with postponement of the procedure.

o **Semi-urgent:** Where a delay of the procedure for more than a few weeks could potentially lead to worsening of the patient's condition.

o **Urgent:** These procedures are time-sensitive; a delay in proceeding would result in significant exacerbation and worsening of the condition.

– **Pain procedures for suspected cases:** [7, 11, 16]

– Perform urgent procedures with the minimal number of personnel, to minimize the risk of exposures.

– It is recommended to avoid deep sedation that requires airway support or manipulation.

– **Pain procedures for high-risk patients:** [9, 11, 16]

– Procedures should be limited to urgent cases.

– The procedure should be conducted in a negative pressure room.

– Physicians should be adequately protected and PPE is highly considered.

– After the procedure, the patient should be monitored in the same room
– Then, they can be transferred to an appropriate isolation area.

Hospital Visit Versus Telemedicine

– Patient's triaging the according to the type and severity of pain may be helpful in differentiating those who may be adequately treated by telemedicine from those who need face-to-face consultations [7, 11, 19, 41].
– Stable opioid-tolerant patients have permitted opioid prescriptions via telemedicine to reduce the risk of withdrawal [11, 16].
– Patients at risk of opioid withdrawal should be scheduled for an in-patient visit [16, 19].
– Patients with severe exacerbation of chronic pain: a short-term electronic prescription after evaluation via telemedicine is reasonable. Then arrange for a visit to the pain clinic [22, 41, 60].
– Patients need opioids for longer durations: an inpatient visit is recommended to identify patients who might be candidates for opioids or other interventions [7, 41].
– For implantable intrathecal pumps, an inpatient or clinic appointment is required for refill of opioids [11, 16].

FUTURE DIRECTIONS

Continuation of pain management protocols is highly recommended to avoid the negative impacts on the patients with more suffering, disability, and psychological stresses. Several researches are focused on prevention and treatment interventions for post-COVID-19 syndrome. The following examples are based on exercise, antioxidant supplements, and other pharmacological approaches. An exercise-based rehabilitation program showed change of maximum oxygen uptake [56], while hyperbaric oxygen treatment patients will be subjected to 100% oxygen by mask for 90 min with 5-min air. It showed improvements in memory, attention, and information process with post-COVID-19 symptom. Clinical findings assessed

the role of vitamin D2 and vitamin D3 supplementation and showed significantly reduced risk of COVID-19 infection and death within 30 days. Therefore, the researchers believe vitamin D3 supplementation could be a valuable strategy for limiting the spread of COVID-19 infection and related death and racial differences in COVID-19 outcomes [132].

For specific post-COVID symptoms, a low-dose of naltrexone and NAD "nicotinamide adenine dinucleotide" is used for one group of patients compared to a corresponding placebo tablet and patch for 12 weeks. Results showed improvements of fatigue, well-being, and quality of life [133]. Another technique by using transcutaneous vagus nerve stimulation "TVNS" in the treatment of long COVID chronic fatigue syndrome. The study results suggested that non-invasive stimulation of the auricular branch of the vagus nerve is a possible therapeutic modality for treating long COVID with at least a third of the patients showing improvement, although it is possible that the positive result was simply a placebo response to treatment in the absence of a control group for comparison [134]. There are many trials with the main goals to optimize the patient's symptoms, improve the function, and enhance the quality of life. Furthermore, any successful treatment protocol should include a clear plan based on the patient's symptoms, underlying cause, and associated comorbidities. Physical fitness, rehabilitation programs, and mental health care should be taken into considerations when needed. Continuity of treatment with regular follow-up is essential for post-COVID chronic pain [9, 122].

SUMMARY AND CONCLUSIONS

The COVID-19 pandemic has had unforeseen impacts on the health care services. It has changed our lives and our approach to medicine. COVID-19 is also having a profound effect on chronic pain patients. A significant number of patients infected with COVED-19 developed post- or long COVID-19 symptoms with more burden on patients with chronic pain. Post-COVID-19 is associated with worsening of

previous pain or appearance of de novo pain. Delaying or stopping treatment for patients who are suffering from severe pain will have negative consequences, including increases in pain, disability, and depression.

The management of chronic pain associated with long COVID seems easier compared to that during COVID pandemic with less barriers or restrictions and moving to near-normal life. The post-COVID era is characterized by increased awareness of the infection-control guidelines. Availability of screening tests as well as different vaccinations with millions of people became vaccinated. The use of new technology such as telemedicine showed great advances, more orientation, specifically oriented tools for the assessment and management of chronic pain, as well as published guidelines for the use of telemedicine in pain management. A huge number of publications covering all aspects are now available. Many evidence-based guidelines by different international pain societies with a clear plan for the management of different types of chronic pain were created. However, more research is needed to understand the actual problem of post-COVID pain, the possible pathophysiological mechanisms, and the target-directed prevention and management of post-COVID chronic pain.

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