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Review Article

The COVID-19 pandemic and its consequences for chronic pain: a narrative review

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Summary

The COVID-19 pandemic transformed everyday life, but the implications were most impactful for vulnerable populations, including patients with chronic pain. Moreover, persistent pain is increasingly recognised as a key manifestation of long COVID. This narrative review explores the consequences of the COVID-19 pandemic for chronic pain. Publications were identified related to the COVID-19 pandemic influence on the burden of chronic pain, development of new-onset pain because of long COVID with proposed mechanisms and COVID-19 vaccines and pain interventions. Broadly, mechanisms underlying pain due to SARS-CoV-2 infection could be caused by `systemic inflammatory-immune mechanisms´, `direct neuropathic mechanisms´ or `secondary mechanisms due to the viral infection or treatment´. Existing chronic pain populations were variably impacted and social determinants of health appeared to influence the degree of effect. SARS-CoV-2 infection increased the absolute numbers of patients with pain and headache. In the acute phase, headache as a presenting symptom predicted a milder course. New-onset chronic pain was reportedly common and likely involves multiple mechanisms; however, its prevalence decreases over time and symptoms appear to fluctuate. Patients requiring intensive support were particularly susceptible to long COVID symptoms. Some evidence suggests steroid exposure (often used for pain interventions) may affect vaccine efficacy, but there is no evidence of clinical repercussions to date. Although existing chronic pain management could help with symptomatic relief, there is a need to advance research focusing on mechanism-based treatments within the domain of multidisciplinary care.

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Introduction

The uncertainty of the COVID-19 pandemic led to abrupt interruption of treatment for patients suffering from chronic pain in March 2020. Total deaths in the subsequent two years of the pandemic now approach 6 million, despite the development of effective vaccines [1]. Delivery of medical care was transformed as healthcare systems were strained by acutely infected patients and supply chain disruption. This led to cancellation of procedures and other challenges for patients with chronic pain.

Much like the disease itself, the impact of COVID-19 on existing and newly developed pain is complex. COVID-19 and associated lockdowns have exhibited a variable effect on worldwide pain prevalence and morbidity. Globally,

there was an increase in search engine terms that included `pain´, suggesting increased public interest and concern on a global scale [2]. Across many countries, people were burdened by uncertainties regarding their job, physical distancing recommendations and social isolation, all of which could have influenced physiological pain and psychological distress [3, 4]. In North America, opioid-related deaths due to overdose increased during the pandemic, with all US states exhibiting an upward trend in mortality [5].

A preliminary literature search identified a need to report the consequences of the pandemic for chronic pain to help improve understanding and serve the needs of affected populations, both for clinical care and research endeavours. Published reviews or editorials have focused on a combination of post-COVID-19 symptoms [6]; considered only acute pain presentation from the infection [7, 8]; highlighted the potential for the increased rate and the need for rehabilitation [9, 10] or have become outdated [11]. Considering this gap, we set to review the published reports to evaluate the burden, type and progression of new-onset chronic pain after SARS-CoV-2 infection, as well as the influence of the pandemic on chronic pain patients. Additionally, we also reviewed the possible mechanisms underlying pain associated with SARS-CoV-2 infection and treatments being considered to address post-COVID-19 pain.

Methods

This narrative review was informed by a systematic search of the literature carried out in Medline, Embase and Cochrane databases that identified articles reporting on chronic pain or its treatment and COVID-19. The search terms for `pain´ or `chronic pain´ and combined with `COVID-19´ or terms to indicate post-COVID-19 sequelae (long COVID, post-acute COVID-19 syndrome, post-intensive care syndrome) using the OVID interface and the search strategy for Medline is shown in online Supporting Information (Appendix S1). The initial search was carried out on 7 February 2022 and repeated on 12 April 2022. Titles and abstracts were screened for relevant articles. The reference lists of all included citations were hand-searched to identify other additional studies. After removal of duplicates, we considered original English language articles of any study design to inform our results as relevant to our review objectives. Subsequently, selected articles were categorised into sections to summarise pertinent results in a narrative report.

Results

A total of 3859 titles and abstracts were considered. Since pain associated with SARS-CoV-2 infection was reported by a vast number of publications, we only considered articles where the study specifically assessed and reported pain symptoms. Key findings are summarised in Tables 1 and 2. Published literature related to pain after SARS-CoV-2 infection includes survivors with variable severity of illness and a heterogeneous spectrum of symptoms. Hence, pain consequences are described in different terms, such as post-acute coronavirus disease 2019/COVID-19 syndrome, COVID-19 long-haulers, post-acute sequelae of SARS-CoV-2 infection and long COVID [6, 12]. Some consider the constellation of symptoms similar to `post-intensive care syndrome´ [9, 13]. Although there is no established terminology or criteria for diagnosis of post-COVID-19 pain, most consider this to be the persistence of mental and physical health consequences after initial infection, and according to the Centers for Disease Control and Prevention (CDC) the criteria are met if symptoms persist for >4 weeks [14].

Pain as a symptom of COVID-19

Although we do not intend to detail the burden, features and treatment of acute COVID-19-related pain, it is relevant

Table 1 Key findings on pain and headache associated with COVID-19.

Acute SARS-CoV-2 infection can present with pain, commonly as myalgia, joint pains and headache [8]
New-onset chronic pain after SARS-CoV-2 infection is one of the five common features of long COVID. Its prevalence decreases over time and symptoms can fluctuate [25, 27]
Common pain conditions with long COVID include myalgia, fatigue, joint pains and post-intensive care syndrome-like syndrome [9, 12, 29]
Risk factors for developing chronic pain include the following: the need for intensive care, high BMI, female sex, myalgia at hospital admission, loneliness and a perception of increased isolation [12, 21, 28]
Possible mechanisms for pain include sympathetic overactivity, dysregulation of neural activity similar to chronic fatigue syndrome and inflammatory-immune mediators [37, 38, 42, 47]
Headache as a presenting symptom predicts a milder course, but delayed onset along with other neurological symptoms warrants evaluation for secondary causes [19]

Table 2 Key findings regarding the effect of the COVID-19 pandemic on chronic pain patients and the use of steroids for pain interventions.

Across the world, the pandemic increased the physical and mental health burden in chronic pain patients, with some variations based on certain populations and subsets of patients [23, 58, 59]
Risk factors for increased pain included social isolation, lack of psychological support, female sex, lower level of education, reduced physical activity and disabled employment status [23, 77, 79]
Delivery of chronic pain care was affected, but telemedicine was well adapted in most developed countries for any non-interventional patient–provider interaction [120, 121]
Steroid exposure may reduce the efficacy of COVID-19 vaccines, but the existing data are unclear. It is best to consider avoiding steroid injections 2 weeks prior to the vaccine and at least 1 week following the vaccine [101, 122]
Steroid exposure does not seem to affect the SARS-CoV-2 infection rate. However, exposure to chronic opioids might be a risk factor for increased infection severity [29, 117]

to recognise the association of acute pain and COVID-19. During acute infection, generalised myalgia and headache alongside upper respiratory symptoms were noted to be common symptoms. Based on studies published in the first 5 months of the pandemic (n = 12,046), the prevalence of arthralgia and/or myalgia was 15.5% [15]. Most studies originate from China, although studies from Europe reported a higher prevalence of both symptoms. It is not clear whether this difference was based on different strains of the virus or the different times of its effect from one to the other region. A systematic summary of 54 studies evaluating the incidence rate of symptoms noted the most common to be: headache (1.7–33.9%); sore throat (0.7–47.1%); myalgia/arthralgia (1.5–61.0%); chest pain (1.6–17.7%); and abdominal pain (1.9–14.5%) [8]. In a more recent telephone survey of 266 COVID-19 patients from Turkey, pain was reported by 72%, including myalgia (50%), headache (49%), pain with neuropathic symptoms (25%) and polyarthralgia (14%). Simple analgesics were used by 32% of patients and numbness was the most common neuropathic symptom, with a strong association between neuropathic symptoms and headache. Myalgia was significantly associated with female sex, fever, sore throat, headache and polyarthralgia [16]. Headache has been noted to be a common and important symptom during acute SARS-CoV-2 infection as well as post-COVID-19. It was noted to be one of the five most prevalent acute symptoms, with a specificity of 90%, along with the presence of fever, fatigue, myalgia and arthralgia in the early stages of the pandemic [17]. In a meta-analysis assessing the contribution of headache as an acute symptom, it was more prevalent in non-hospitalised (58%) than in hospitalised (31%) patients [18]. Patients presenting with headache typically had a shorter clinical course of SARS-CoV-2 infection with symptoms lasting 23 ± 11.6 days when compared with patients presenting without headache (31.2 ± 12.0 days) [19]. In a multicentre study of patients with severe COVID-19, the two most common pain symptoms were headache (30%) and chest pain (23%). Interestingly, the presence of headache was associated with lower likelihood of ICU admission, when age and sex were controlled, and absence of pain was associated with both ICU admission (OR 2.92) and death (OR 3.49) [20]. Most studies were retrospective reviews of hospital records or cross-sectional patient surveys and were susceptible to incomplete data or bias. However, some observations were consistent across studies, even those conducted in different countries. Importantly, the presence of headache in the acute phase seems to be associated with a relatively better outcome.

Burden of persisting pain in SARS-CoV-2 infection survivors

Studies reporting pain after SARS-CoV-2 infection are primarily surveys carried out at various intervals, either after diagnosis, admission or discharge from hospital [13], with few cohort [12] and case control studies [21]. It is difficult to know the specific number of studies capturing the post-COVID-19 pain burden and characteristics accurately since pain has been captured as one of the symptoms in many studies [22] and as the primary outcome in some [23, 24]. A review that considered studies reporting in German and English language early in the pandemic (up to 10/02/2020) noted a lack of clear data on long-lasting pain symptoms, although it highlighted the increased possibility [11]. The FAIR Health database of over 34 billion private healthcare claim records involving 1,959,982 COVID-19 patients, noted persistent pain in 5.1% of patients and was one of the five most common symptoms lasting 30 days or more after initial diagnosis [25]. Studies early in the pandemic identified an increase in joint pain or chest pain as predominant symptoms, when assessed 2–4 months after infection [22, 26]. In a relatively recent study, patients admitted to the hospital with COVID-19 symptoms had significantly higher prevalence of de-novo pain overall

(65.2%), and de-novo headache (39.1%) compared with inpatient controls (11.0% and 2.7%, respectively, p = 0.001). The prevalence of headache was observed to reduce over time, as indicated in a review and meta-analysis of 28,438 COVID-19 survivors. The overall prevalence of headache at varying periods was 47.1% (95%CI 35.8–58.6%) at onset or hospital admission; 10.2% (95%CI 5.4–18.5%) at 30 days; 16.5% (95%CI 5.6–39.7%) at 60 days; 10.6% (95%CI 4.7–22.3%) at 90 days; and 8.4% (95%CI 4.6–14.8%) at ≥180 days after onset/hospital discharge [18]. New-onset chronic pain (>3 months) had a prevalence of 19.6% in COVID-19 patients compared with 1.4% in controls (p = 0.002), with these differences remaining significant even in patients with no previous pain [24]. In addition, COVID-19 patients who reported anosmia had a remarkably higher likelihood of new-onset pain (83.3%) compared with those with no changes in olfaction (48.0%, p = 0.024). Considering that this is a relatively small cross-sectional study of 46 COVID-19 and 73 control patients and since no other study has observed this association of anosmia and pain, the certainty of evidence of this finding is low. A systematic review and meta-analysis assessed the time course and post-COVID-19 pain symptoms of musculoskeletal origin in 14,639 hospitalised and 11,070 non-hospitalised COVID-19 patients among studies up to May 2021. Approximately 10% reported suffering from musculoskeletal-related post-COVID-19 pain at some time during the first year, with myalgia (5.6%–18.2%), arthralgia (4.6%–12.1%) and chest pain (7.8%–23.6%) noted at different follow-up periods. Interestingly, they observed a decreased prevalence of post-COVID-19 pain from symptom onset to 30 days, an increase after 60 days, but a second decrease >180 days following infection [27]. This review included six preprints, alongside peer-reviewed studies, of which the majority (73%) were cross-sectional in design with only six being longitudinal cohort studies. Rheumatologic and musculoskeletal symptoms have been specifically assessed in a few subsequent studies. In 300 patients with COVID-19, 92.3%, 72.7% and 56.3% reported some musculoskeletal symptom at hospitalisation, 2 weeks and 1 month, respectively. These symptoms predominantly included fatigue (44.3%); back pain (22.7%); arthralgia (22.0%); myalgia (21.0%); low back pain (16.3%); and neck pain (10.3%) at 1 month. Higher BMI was associated with increased odds of persistence of fatigue (OR 1.08, 95%CI 1.03–1.13), myalgia (OR 1.08, 95%CI 1.01–1.14) and arthralgia (OR 1.07, 95%CI 1.02–1.14, p = 0.012) at 1 month [12]. When they followed the same cohort of patients at 3 and 6 months, 74.6% and 43.2% had at least one rheumatic and musculoskeletal symptoms, respectively [28]. At 6 months, common symptoms included fatigue (31.6%), joint pain (18.6%) and myalgia (15.1%). In an adjusted model, female patients were more likely to have fatigue (OR 1.99, 95%CI 1.18–3.34), myalgia (OR 3.00, 95%CI 1.51–5.98) and joint pain (OR 3.39, 95%CI 1.78–6.50) at 6 months. In a study of 738 patients hospitalised for COVID-19, patients with myalgia at admission (n = 369) were more likely to experience persistent musculoskeletal pain (42.5%) compared with patients without myalgia (34.5%) at 7 months post-infection [21]. Patients with myalgia were also more likely to have >3 long-term post-COVID-19 symptoms, the most prevalent of which were fatigue, dyspnoea on exertion, musculoskeletal pain, dyspnoea at rest, hair loss and memory loss. If one considers `worsening of pre-existing musculoskeletal pain´ or `new-onset musculoskeletal pain´, the prevalence of new-onset post-COVID-19 musculoskeletal pain was 73.2% [21]. There is a paucity of evidence regarding long-term opioid therapy and the COVID-19 pandemic. A large retrospective database study indicated worse outcomes in patients on long-term opioid therapy, including increased likelihood of Emergency Department visits, hospitalisations, mechanical ventilation, vasopressor support and mortality; however, investigators were unable to assess effects based on opioid dosing [29]. A more recent review and meta-analysis included five good quality observational studies and reported COVID-19 patients with concomitant opioid use had an increase in mortality (OR 1.72, 95%CI 1.09–2.72, p = 0.02) and ICU admission in adjusted analysis [30]. Although these studies do not differentiate between prescription and other opioid use, the conclusions suggest opioids influence disease severity by multiple mechanisms including immune modulation and respiratory depression.

Patients with critical COVID-19 are predisposed to a range of pain symptoms, similar to those observed in post-intensive care syndrome. Exposure to mechanical ventilation, neuromuscular blockers and steroids leads to increased risk of developing acute respiratory distress syndrome, myopathy and post-traumatic stress disorder [9]. Prone positioning as a ventilation strategy has been reported to add additional risk of peripheral nerve injury with possible weakness and subsequent pain [31, 32]. Early in the pandemic, among 100 patients treated in the ICU, pain was the sixth most common symptom at 48 days after discharge [33]. To address the needs of post-intensive care syndrome, including chronic pain, in COVID-19 ICU patients, Ojeda et al. reported their randomised controlled trial protocol involving early care, therapeutic education and psychological intervention [34] and separately published findings in patients screened for their

randomised controlled trial and surveyed 1 month after discharge. Among 65 patients, 51% had new-onset pain with 44% having pain in >2 body sites and 39% having clinically significant pain (>3 NRS) [13]. Many of them presented with a diffuse pain syndrome associated with fatigue, myalgia and associated post-traumatic stress disorder and depression [10, 35]. Reports after the SARS epidemic in 2010 describe similar symptoms that mirror fibromyalgia or chronic fatigue syndrome [36]. By 6 months following discharge, the majority of COVID-19 ICU admissions were noted to have similar pain rates to the general population, but those with lasting symptoms are often tremendously functionally debilitated [36].

Mechanisms and treatment considerations of COVID-related pain

It is likely that pain associated with SARS-CoV-2 infection has multiple causes [7, 37]. Three main broad categories arise from published literature: systemic inflammatory immune mechanisms; direct neuropathic mechanisms as primary cases; and secondary mechanisms due to COVID-19 pathology or treatment (Fig. 1). The viral infection involves significant inflammatory and immune changes along with the involvement of the nervous system through various routes [38]. The proposed mechanisms could involve neuro-inflammation through direct entry to central nervous system by binding to the neuropilin-1 (NRP-1) receptor at the olfactory cavity or by disruption of the blood–brain barrier (neurotropism) [39], along with systemic infection via angiotensin-2 receptors [40]. Interestingly in a rat model, binding of NRP-1 with the viral spike protein seemed to not only block vascular endothelial growth factor-A and NRP binding, but also demonstrate anti-allodynic properties, suggesting decreased pain symptoms could play a role in increased disease transmission [41]. Nervous system involvement can disrupt homeostatic mechanisms targeting a stress integrator at the hypothalamus, thereby leading to fatigue symptoms similar to myalgic encephalitis or chronic fatigue syndrome [42, 43]. In support of this, ongoing investigations have considered the use of low-dose naltrexone [44, 45] that could also influence the release of pro-inflammatory cytokines [46]. Several reports indicate the involvement of the autonomic nervous system, specifically the sympathetic nervous system [47]. It is not clear if in a subset of patients the sympathetic nervous system is more involved; however, a higher risk of unfavourable outcomes occurs in patients with comorbidities [48]. This could lead to a state of dysautonomia or hyperinflammation [49, 50]. To regulate sympathetic overactivity, stellate ganglion blocks have been considered [48, 50]. However, the rationale for blocking the sphenopalatine ganglion for non-specific headache is not clear [51, 52]. Myalgia is common in other viral disease, mediated by interleukin-6 (IL-6), upregulated in muscle and joint tissues [7]. It is unclear if the accumulation of angiotensin-2 could lead to the possibility of central pain [37]. Admission to ICU can be associated with secondary causes of pain and post-intensive care-like syndrome [9]. Myopathy can be induced by medications and immobility. Positioning for prone ventilation can lead to peripheral nerve and other injuries [31, 32]. Similarly, the known increased incidence of stroke in COVID-19 patients could contribute to higher burden of post-stroke pain in survivors [53]. Considering the diverse physiological and psychological impairments found in COVID-19 patients, treatment focus has been on multidisciplinary interventions to promote physical and psychological rehabilitation [9, 54].

Pandemic influence on patients with pre-existing chronic pain

The pandemic impacted chronic pain patients due to increases in social isolation, anxiety and depression, in addition to disruption of healthcare delivery (Fig. 2). Reports of the impact on pain burden differed internationally. The COVID-19-related lockdowns increased the burden of pain in chronic pain patients in Spain [55–57], the United Kingdom [58], the United States [59], Canada [60], Japan [23, 61], Austria, Germany and Switzerland [62]. One of the largest surveys, of 25,482 Japanese participants conducted in August 2020, observed that 10.4% of patients reported persistent pain during the pandemic, while only 6.3% of participants had pre-existing chronic pain. Loneliness and a perception of increased social isolation during the COVID-19 pandemic were associated with increased prevalence and incidence of all types of pain and pain intensity [23]. In an early European survey involving 719 patients from Austria, Germany and Switzerland, chronic pain worsened in 53% of patients in whom both biological and psychosocial factors were noted to be associated [62]. Similarly, a patient survey across 14 countries (n = 14,975) showed increases in pain symptoms during the pandemic [63], which were more dramatic in certain diseases states, such as systemic lupus erythematosus [64] and fibromyalgia [65, 66]. In contrast, some studies showed improvement in existing pain during the pandemic in pain patient populations [67] or in specific patient groups such as the endometriosis population (n = 285) [68]. Many other reports showed the pain burden did not differ markedly before and after the pandemic [69–72]. A large international study showed no change in pain in five European countries

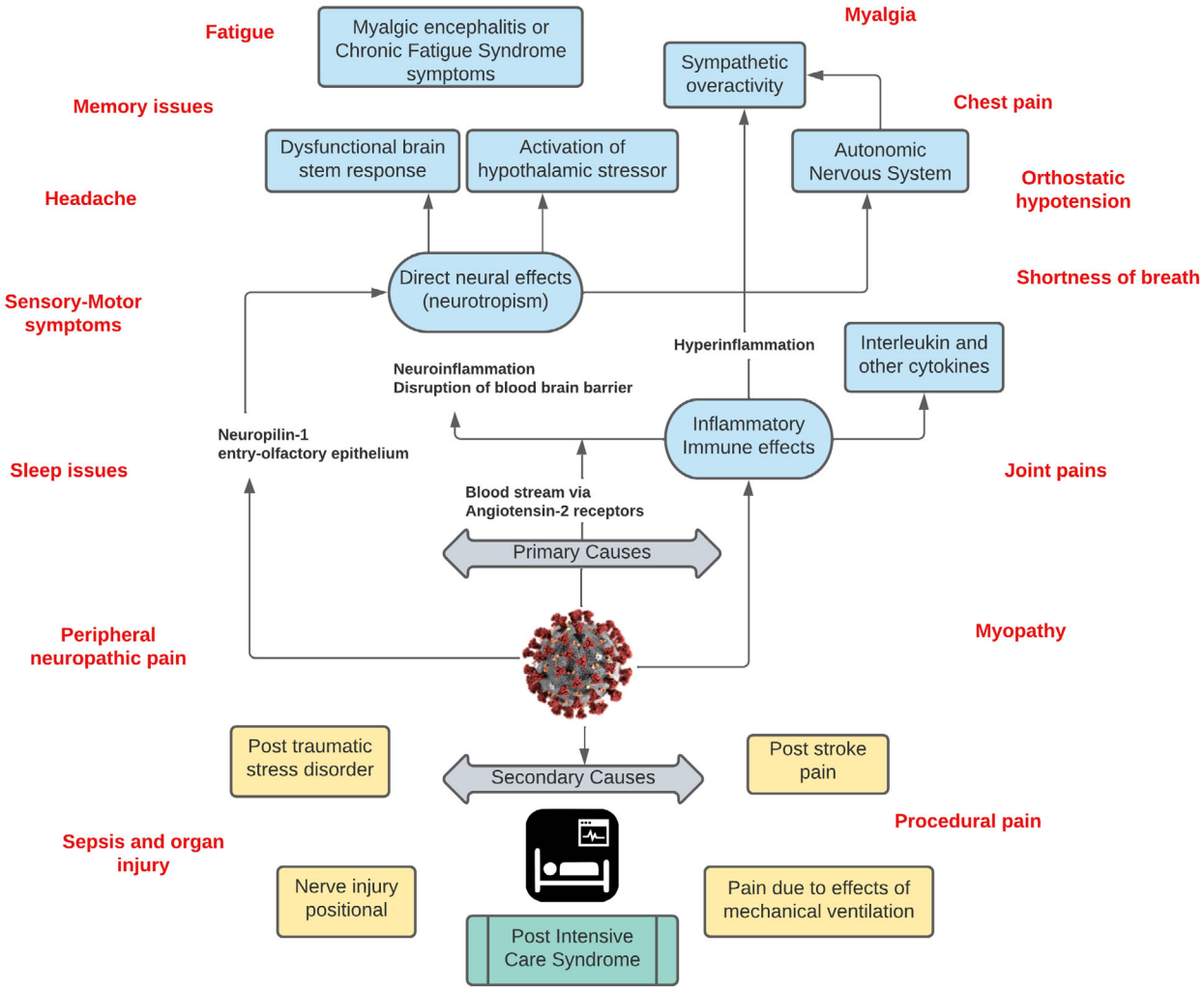

Figure 1 Possible mechanisms of pain and associated symptoms with COVID-19.

during the pandemic but did show increased pain in the Brazilian cohort [73]. Additionally, other studies showed mixed results, with patients reporting increases or decreases in functionality within the same conducted study depending on the survey tool used [74]. Although similar pain scores have been reported in patients pre- and post-pandemic [69, 70], vulnerable populations were more likely to experience increased pain burden due to patient factors influenced by pandemic settings. For example, a study in Texas showed that Caucasian patients reported an improvement in back pain during the pandemic, while Black/African-American patients did not [75, 76]. Risk factors for increased pain burden during the pandemic include the following: female sex; non-white race; lower level of education; and disabled employment status [77–79]. In young people with chronic pain, direct exposure to SARS-CoV-2 infection did not impact pain but economic stress did worsen pain symptoms [80]. In many cases, pain catastrophising or anxiety was linked to greater perceived severity of pain during the pandemic [78, 81]. Although widespread adoption of telemedicine facilitated healthcare access, patients with higher pain burden or level of anxiety were found to be less accepting of telemedicine [82] and patients who also had delays or cancellations of interventions were more likely to report increased pain [83, 84]. There was a substantial increase in opioid overdose deaths in the United States and Canada during the pandemic [5, 85], but it is not clear if opioid prescriptions to pain patients was contributory. Given decreased access of patients to surgical and medical procedures, it is likely that this increase in overdoses or deaths was driven by increased use of illicit fentanyl, fentanyl analogues, methamphetamine and cocaine,

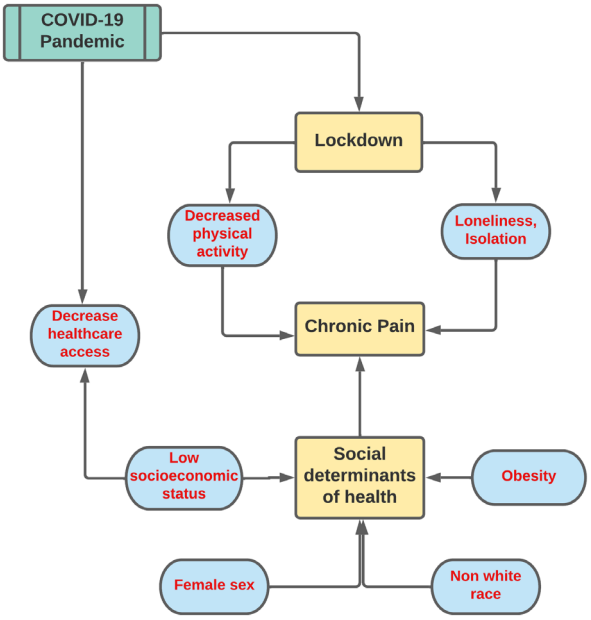

Figure 2 Factors influencing symptoms burden during the COVID-19 pandemic on existing chronic pain patients.

often in combination or adulterated formulations [86]. Data from Europe indicate that there has always (before and during the pandemic) been a wide variability in access to prescription opioids [87]. Although most recent data are not available, a June 2020 report from the European Monitoring Centre for Drugs and Drug Addiction, as well as an independent report from Harm Reduction International, indicates there has been overall decrease in the availability of illegal drugs largely as a result of pandemic-related confinement measures in both Europe and Asia [88, 89]. The pandemic decreased psychological support and reduced ability of chronic pain patients to employ coping strategies for pain [90–92]. Even in studies that showed no increase in pain, other measures of quality of life such as coping, mood and social support worsened during the lockdown [93–95]. Scores of physical and mental well-being seemed to universally decrease in all countries due to the pandemic [63], and introverted patients [96] or those with increased social isolation or loneliness [23] were more likely to experience increased pain. Although the quality of evidence is low, many studies demonstrate a reduction in pain and an improvement in physical function with regular activity or exercise [97]. During the period of lockdown, increased pain intensity was associated with reduced physical activity [98, 99]. Such reduction in physical activity was observed to be mediated by fear avoidance and catastrophising [58]. Intensity of fear regarding contracting COVID-19 was also linked to higher pain intensity and decreased level of function in patients with existing chronic pain [100].

COVID-19 vaccines and chronic pain interventions

Vaccines in circulation for SARS-CoV-2 infection as of March 2022 offer protection via the humoral and cellular immune response pathways, conferred after 14 days following the viral vector AstraZeneca and Johnson and Johnson vaccine and 7 days after the second dose of the mRNA-based vaccines BNT162b2 (Pfizer) and mRNA-1273 (Moderna) [101]. There have been concerns that their efficacy is decreased in patients exposed to steroids [102, 103]. Although the CDC has not made recommendations regarding steroid injection for pain management or the timing of the COVID-19 vaccination, some data exist to drive recommendations. Studies have shown that patients taking corticosteroids have a decreased immune response to hepatitis B [104], influenza [105], pneumococcal [106] and Pfizer and Moderna mRNA-based COVID-19 vaccines [102]. Other studies have shown no reduction in immune response to tetanus toxoid [107] or influenza vaccine [108, 109] after a short course of steroids. Unfortunately, the Pfizer, Moderna and AstraZeneca vaccines were all developed in trials that excluded patients that were taking ≥20 mg.day^{-1} of prednisone steroid equivalent for >14 days in the 6 months prior to enrolment. The Johnson and Johnson vaccine trial (Janssen phase III ENSEMBLE) excluded patients exposed to >2 weeks of daily prednisone in the 6 months prior to the trial [110]. Despite these early restrictions hindering understanding of the effect of steroids on vaccine response, some emerging studies suggest that vaccine effectiveness is reduced in the setting of steroid exposure. The Advisory Committee on Immunisation Practices of the CDC reported that patients on high-dose corticosteroids may have reduced response to the second dose of the mRNA vaccine and therefore require a third dose >28 days after the second [111]. This is supported by the study by Naranbhai et al., which demonstrated lower antibody levels after vaccine in cancer patients using steroids [112]. Similar findings were observed in patients with chronic inflammatory disease taking prednisone. A small study (n = 133) demonstrated a 10-fold reduction in antibody titres and reduced ability to neutralise virus in patients with a mean daily dose of 6.5 mg prednisone [102]. This appeared to be dose independent, as the effect persisted even in patients taking < 5 mg.day^{-1}. These findings should therefore be considered in patients presenting for steroid-based pain procedures. Findings were similar in a study of

patients with rheumatic disease, where patients taking glucocorticoids (n = 130), at a mean prednisone dose of 6.7 ± 6.25 $mg.day^{-1}$, had reduced immunogenic response to the Pfizer mRNA vaccine [103]. However, a Veterans Affairs cohort with inflammatory bowel disease showed no difference in vaccine effectiveness in the steroid exposed or unexposed [113], suggesting that the reduced quantitative titres may not have clinical impact. Increased risk of infection is a well-established side effect of chronic steroid use [114] and known risk factors for breakthrough SARS-CoV-2 infection despite vaccinated status include age >50 y and immunosuppression [Tenforde et al., preprint, https://doi.org/10.1101/2021.07.08.21259776]. Steroids act as immunosuppressive drugs via disruption of inflammatory cytokine pathways and myriad other mechanisms that continue to be a topic of scientific inquiry [115]. However, a retrospective study evaluating IgG antibodies in 443 patients who had received a cumulative total of 504 steroid injections during the pandemic noted no difference in SARS-CoV-2 infection rates [116]. The Advisory Committee on Immunisation Practices reported that live virus vaccines (currently under development for COVID-19) are not contraindicated due to steroid use, provided the therapy is < 2 weeks in duration and low to moderate doses. If these criteria are not met, live virus vaccine administration should be delayed 3 months after cessation of high-dose or longer than 2 weeks of daily steroid therapy [117]. Many studies have noted that in the setting of a live vaccine, if doses of prednisone over 2 $mg.kg^{-1}$ or 20 $mg.day^{-1}$ are delivered for more than 2 weeks, there is a concern for development of infection [118]. This group also stated that the administration of steroid by injection to joint, bursa or tendon would not contraindicate use of live vaccine [119], although they did not make recommendations about the live virus COVID-19 vaccines that are currently under development.

In conclusion, the COVID-19 pandemic continues to increase the burden of pain in most parts of the world, not exclusively in patients with pre-existing chronic pain but also in anyone infected with SARS-CoV-2 and developed enduring pain symptoms. Our review indicates a need for attention to the consequences of persistent pain in patients after any severity of COVID-19, with increased risk of post-intensive care syndrome in patients requiring ICU care. Patients with certain characteristics are more susceptible to pandemic effects, which contribute to increased pain burden in pre-existing chronic pain patients. Treatment for most patients will need multidisciplinary care, and there is a need to advance research focusing on mechanism-based treatments.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1 Search strategy for Medline database.