## Introduction

In late December 2019, a new disease of unknown etiology appeared in Wuhan (1), China. On January 30, 2020 the World Health Organization general director declared it as a Public Health Emergency of International Importance. The appearance of this new virus, SARS-CoV-2, known as COVID-19, caused a fracture in the way of living and working around the world, with effects in the future that are still unknown.

The outbreak in Wuhan (China), spread to Europe and America, imposed some strategies to contain the infection, such as social isolation, the absence of interpersonal relationships, cessation of commercial activity and non-essential services.

The high level of attention required by the number of patients affected by COVID-19 forced the redistribution of health resources, with the suspension of non-urgent activity. Although the right to health implies the right to adequate pain treatment (The Spanish Constitution of 1978, in its article 43, recognizes the right to health protection and therefore the right of citizens to receive health care adequate) and the World Health Organization (WHO) determined that pain relief is a fundamental right (2), under which circumstances it was considered a non-urgent procedure, so that the follow-up and treatment of chronic pain was decreased or interrupted during the pandemic. This fact has affected both treating patients and mental health.

The objective of this review was to analyze the impact of COVID-19 on chronic pain through bibliographic reviews. Systematic reviews and extension of meta-analyses have been selected for scope reviews (PRISMA-ScR). The databases consulted were PubMed, Scopus, UpToDate, Embase and the Cochrane Library. The unpublished literature search included: sites for pain organizations, the World Health Organization (WHO). The articles that met the inclusion criteria were those on the management of patients with chronic pain during the COVID-19 pandemic published after the pandemic (December 2019). All primary research studies, reviews, meta-analyses, guidelines and texts published on the sites were considered. There was no language restriction.

## COVID-19 as a factor involved in pain

In late December 2019, an outbreak of pneumonia cases of unknown etiology in the city of Wuhan in Hubei province, China, was announced and reported to the World Health Organization (WHO). It was quickly identified as a new betacoronavirus and linked to SARS-CoV and several other SARS-like coronaviruses transmitted by bats.

The initial symptoms to recognize the disease have been mainly fever, dry cough or dyspnea, although pain has also been an early symptom of this respiratory condition (sore throat, myalgia, low back pain, headache) (3,4). But this disease has shown a more dramatic side, some patients have suffered and suffer a torpid evolution, with ARDS (respiratory distress syndrome) that requires admission to the ICU and mechanical ventilation, resulting in death in 1.8-3.4 % of the cases (5).

Among all the symptoms we will focus our attention on pain. The IASP (International Association for the Study of Pain) defines pain, and especially chronic pain, as that persistent or recurrent pain for more than three months despite the resolution of tissue damage (6).

A good point to start this review is to remark that chronic pain, is the result of the interaction of biological, psychological and social factors,  and the COVID-19 infection seems to involve  each of them.

We know the relationship between acute viral disease (flu, SARS) with symptoms such as myalgia, fatigue, and general symptoms (7,8). After the SARS epidemic, patients with chronic fatigue syndrome, myalgia, depression and persistent sleep disorder up to 1-2 years after infection (9) have been observed.

Patients affected by other pathogens (Ros River Virus, Coxiella Burnetti and Epstein Barr virus) also experienced postviral fatigue syndromes, memory loss, and pain for more than a year (10).

Regarding SARS-CoV2, there are recent studies that specially focus on “the bradykinin storm” (11) and show a relationship beteween virus infection and inflamation.  Bradykinin is not only envolved in  the pro-inflammatory state but also sensitizes the sensory fibers, which produces hyperalgesia (12). These inflammatory and immunological changes could explain why the elderly who are immunosuppressed and obese (increased inflammatory response) may have had a greater impact due to COVID-19. Additionally, COVID-19 infection may include encephalopathy, and structural changes in the brain and spinal cord like others viral infections (13).

The high number of cerebral complications in patients afected  with SARS-COV2, suggested that their neurotropism could cause neurodegenerative problems with an inflammatory basis (14). As shown above for other SARS-CoV infections, a mechanism of spread through the cribriform plate of the ethmoid bone, from the nose to the olfactory epithelium, has been proposed, where ACE2 receptors are highly expressed. This viral neurotropism through the olfactory bulb could be especially responsible for the frequently reported anosmia in these patients (15), SARS-CoV-2 can also reach deeper parts of the brain, including the thalamus and the brain stem, potentially contributing to respiratory failure (16) and to painful symptoms as well (Figure 1).

Brain PET metabolism was analyzed in comparison with healthy subjects throughout the brain, and the findings were confronted with the hypothesis of SARS-CoV-2 spread from the olfactory bulb to other limbic structures and possibly to the brain stem. Therefore, the hypometabolism of the radiopharmaceutical FDG could be considered a quantitative biomarker of this condition. However, cohort studies are needed to specify the relationship between hypometabolism and possible persistence of cognitive, emotional disorders, residual respiratory symptoms or painful complications (17).

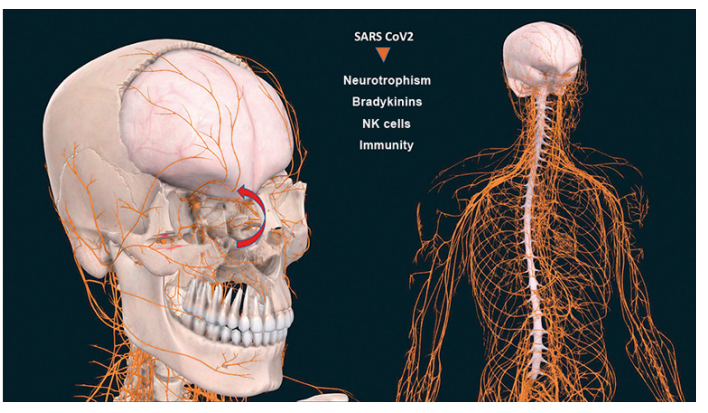


**Figure 1.**

In addition to the direct action of the virus, there are multiple factors that act or increase the painful symptoms. Chronic pain is associated with comorbidities and advanced age, which increases the risk of infections (including COVID-19). On the other hand, whether patients with chronic pain are more susceptible to infection is not yet entirely clear, although the interaction between pain and the immune system must be taken into account, since it has been shown that the persistence of pain and the absence of treatment induces immunosuppression (18).

Some treatments used to relieve pain can depress the immune system. Steroids that induce secondary adrenal failure (19). There are some studies that indicate that opioids decrease the natural killer (NK) cells, a dose-dependent effect, and interfere in the cellular response innate or indirectly by acting 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 NK (20) cells. Morphine and fentanyl cause greater depression than buprenorphine (21). In animal models it has been shown that morphine can also act through the D1 pathway (dopamine receptors in the striated nucleus) (22).

Many patients who have been in the ICU have had long-term functional limitations, psychological disorders, and chronic pain. This suggests that patients who have been in the intensive care unit affected by this

coronavirus will not behave differently (23).

This pandemic also has associated social aspects such as confinement, cessation of routine activities, financial impact, ... that have influenced the entire population. Isolation, limitation of interpersonal contact, fear of illness, uncertain future, economic ruin, etc., have increased the rates of fear and anxiety (24). Persistent stress can lead to varieties of severe mental illness (anxiety, depression, sleep disorder, or thoughts of suicide) (25).

It is important to recognize that thoughts and emotions are closely related to physical pain. Thus, the psychosocial consequences of COVID-19 can influence physical pain and most likely vice versa as well. In other words, those patients who already had chronic pain will likely have a negative impact related to the infection, while those who did not previously have chronic pain can be added to this group (11) (Table I).

| Table I. |
|---|
| 1. Encephalopathy and structural changes in the brain and spinal cord could be included in Covid-19 infection |
| 2. The neurotrophism of SARS-CoV-2 infection could cause neurodegenerative problems with an inflammatory base |
| 3. Bradykinins contribute to pro-inflammatory state and also sensitize the sensitive fibers, leading to hyperalgesia |
| 4. SARS-CoV-2 could contribute in the thalamus and brainstem to respiratory failure and painful symptoms |
| 5. There are important interactions between pain, drugs and the immune system |

## Treatment during COVID-19: how we have changed

Patients with chronic pain require long-term multidisciplinary treatment even during a pandemic. They are mostly elderly with multiple comorbidities and are more susceptible to morbidity and mortality from COVID-19. It is necessary to review pain management practices during the COVID-19 era with respect to resource reallocation measures, community collaborations and the use of analgesics (steroids, opioids) and pain interventions. The patient with chronic pain faces a potential risk of functional and emotional deterioration during a pandemic, which can increase the long-term health burden (26).

During the pandemic lockdown, all elective pain consultations and interventional pain procedures were canceled or postponed (27). This interruption has had serious consequences, as it has led to an increase in pain, a psychological worsening and a decrease in the quality of life in these patients.

Compared to the general population, patients with chronic pain suffer from increased anxiety, stress and depression (28), which in turn increase the risk of chronic pain. Similarly, the relationship between sleep disturbance and pain is also bidirectional. Pain disturbs the quality of sleep and lack of sleep further exacerbates pain. Anxiety and sleep disturbance in confinement have increased uncertainty, worry and fear of illness, loneliness, and severe depressive symptoms. Aggravated by the fact that the isolation and closure of many services (rehabilitation, physiotherapy, psychological support groups etc.) have limited the mechanisms that many patients have been using to control pain.

Confinement has led the population, especially vulnerable patients with chronic pain, to reduced physical activity and exercise (caused by fear of leaving home and closure of sports centres), a change in diet (with increased consumption of “comfort” caloric foods and the absence of home help.

We can assure that all these changes have led to worsening comorbidities and chronic pain and that the interruption of treatment have had alarming consequences not only for individuals but for the health system and the whole society in both the short and long term.

In this scenario, telemedicine, which includes such diverse means of communication as telephone, video, email, fax, etc… has emerged as a key technology for efficient communication and a sustainable solution to provide essential health care services (Figure 2).

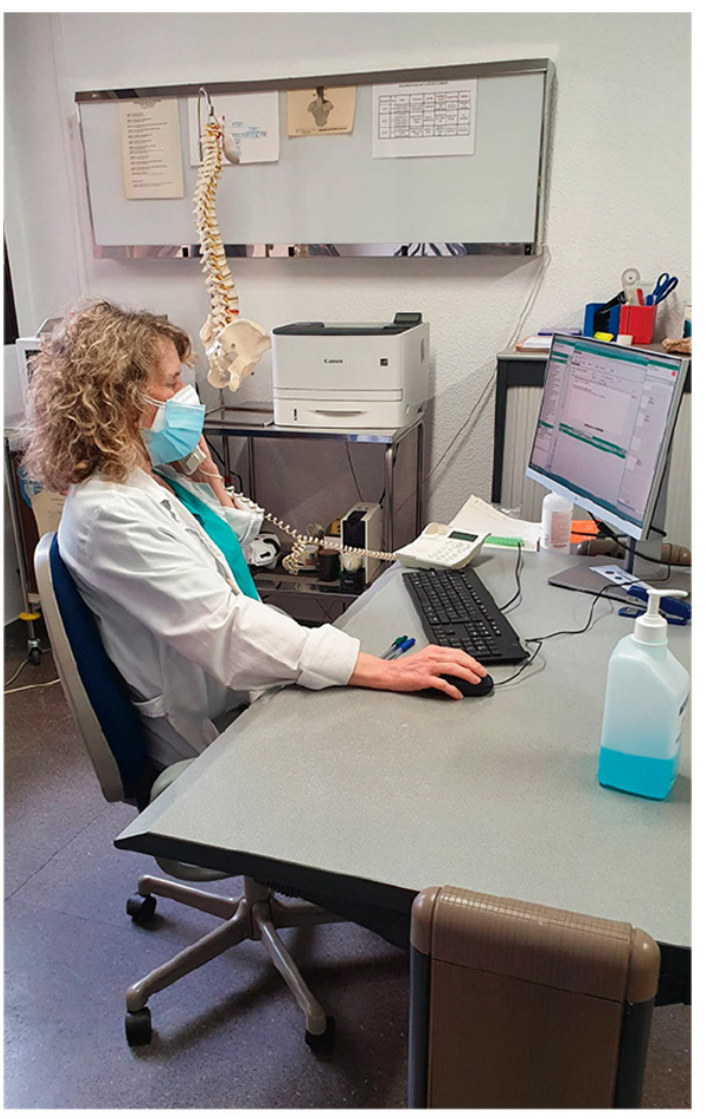

**Figure 2.**

### Telemedicine a new tool

Chronic pain management requires frequent visits to the physician for both pharmacological and non-pharmacological treatment advice. Due to confinement, movement restrictions, social and physical distancing requirements, or the fear that health-care facilities may be infected, we have prevented patients from going to health-care facilities in person. This is where telemedicine has played a major role in helping patients to have a medical consult (29).

In accordance with clinical guidelines, recommendations, and practices, telemedicine should be considered whenever possible (30,31).

Telemedicine services offer many advantages, especially in routine or non-urgent care. Unnecessary and avoidable exposure of those involved in the provision of healthcare can be avoided. The need for personal protective equipment (PPE) is reduced leading to reduction in resource consumption. They improve access to health care and reduce media use across the already highly stressed health infrastructure during the current pandemic, all of which can provide substantial financial savings at all levels (32,33).

Regarding the disadvantages currently there is a lack of clarity about the legal implications of its use. The use of technology cannot replace clinical medicine based on the in-person medical consultation and physical examination of the patient. Also, the possibilities of misdiagnosis and inability to carry out diagnostic radiological investigations are other limitations.

### What evidence do we have of its use in chronic pain?

The large-scale use of telemedicine in the treatment of chronic pain is rare and has generally focused on psychological interventions, exercise, stress reduction therapies etc. Several systematic reviews in adults report pain reduction, of disability, depression and anxiety in intervention groups compared to control groups (34,35). In contrast, psychological therapies performed via the Internet or mobile applications have shown only a small beneficial effect in children and adolescents with mixed chronic pain (36).

Chronic pain management is based on a good evaluation and medical many questionnaires for the evaluation of patients with chronic lumbar pain have shown good reliability and moderate validity (38). The anxiety, depression and sleep questionnaires can also be collected electronically, so it is possible to perform a detailed pain assessment and history online.

The physical examination is the cornerstone of chronic pain management. A thorough physical examination is essential. Therefore, the first consultation should at least preferably be a face-to-face one, although in these special circumstances the patient must be made to understand that sometimes a complete physical examination cannot be performed. An important aspect of chronic pain management is non-drug treatment, such as ergonomics education, physical activity, lifestyle modification, counseling and coping skills, etc. And all these components can be easily delivered through telemedicine.

### Is telemedicine coming to stay with us?

One of the questions we should ask ourselves is whether telemedicine is a temporary tool in times of a pandemic or is it coming to be installed.

Although, according to the evidence, the beneficial effects of telemedicine are very promising, there remains substantial uncertainty surrounding many aspects of the studies conducted around it. These include small sample sizes, methodological defects, limited benefits, insufficient long-term evaluations, little collection of adverse events (39), etc. It is also necessary to explore the satisfaction and acceptance of patients, as well as studies of damage (produced in these) and desertions of this type of care.

If telemedicine is here to stay, which is highly likely, we must develop new clinical guidelines to apply in our medical practice. These guides should include general principles and a practical framework. The general principles should be common to all future guidelines, while the practical framework should mainly address the current scenario of the COVID-19 (40) pandemic (41,42). Among others, it should clearly specify the terms of the first consultation, follow-up consultations, patient management, consents, medications that can be prescribed through teleconsultation (43) etc. and the professionals who use this route must maintain the same ethical and professional standards as those observed in traditional face-to-face consultations.

## COVID inheritance

As far as we know so far there is not much data available on the impact of the COVID-19 pandemic and isolation measures on patients with chronic pain. What is clear is that the COVID-19 disease itself is associated with painful symptoms, including myalgia, arthralgia, abdominal pain, headache and chest pain, even in patients not admitted to the ICU (44). And survivors could have long-term effects, such as pain, that require our attention and management (45).

According to recent studies, more than 35 % of COVID-19 patients develop neurologic symptoms (46). All these neurological manifestations could lead to painful conditions, from peripheral neuralgia to post-traumatic pain syndrome, which must be diagnosed and treated, a challenge for doctors.

The study by Nieto et al. (47) on the impact that confinement has had on patients with chronic pain has shown changes in pain from the beginning of confinement, correlating pain intensity and disability scores and confirmed an increase in pain intensity, the frequency of episodes of pain, interference of pain (in daily activities, ability to work and leisure activities), distress caused by pain, and the effects of pain on sleep and physical activity. Specifically, when respondents were asked about changes (not necessarily related to pain), the mean scores showed a worsening in physical activity, social activities, work activities, emotional state, and overall well-being. These data highlight the importance of paying attention to people with chronic pain during health crises, as their pain problem and their overall health can worsen, as experts have pointed out.

Headache is the most common brain symptom, with a variable prevalence of 6.5 % to 23 % and an average prevalence of 8 % in different studies (48). Persistent daily cephalea has been observed even weeks after recovery (49). Patients had a holocranial, oppressive cephalea that began after 2 weeks after the recovery of respiratory symptoms, with no physical cause (venous thrombosis). The pathogenesis of persistent daily cephalgia is widely known, some studies believe that pain may be due to cytokine production and persistent glial activation, responsible for precipitating the clinical picture (50), also responsible for neurological disorders in COVID-19 (as we saw above).

Specific diseases, such as fibromyalgia, peripheral neuropathy or chronic migraine, have shown clinical modifications. Fibromyalgia has shown worse results in the evaluation tests (quality of sleep, fatigue, pain, rigidity) in patients suffering from COVID disease 19 (51). Later studies will confirm whether the worsening is due to the hypersensitivity of the disease. The study by Consonni and collaborators (52) observed during the pandemic that despite similar complaints about changing habits and concerns about the COVID-19 pandemic, patients with peripheral neuropathy and chronic migraine had different reactions. While, in patients with migraine, it affected behavior, mainly with psychological fragility. This suggests the need to personalize patient care based on their chronic pain conditions.

In conclusion, it takes time to confirm some of the data obtained in the few studies regarding the impact of COVID-19 disease on chronic pain. Fundamentally confirming a physical basis, since the psychological aspect seems clearer, since even in people with a diagnosis of chronic pain not directly affected by the coronavirus, the pandemic outbreak and the subsequent blockade have been important stressors (53). Therefore, interdisciplinary interventions should be designed in which psychologists and health care staff work together to minimize the psychological distress of patients with chronic pain syndromes. These syndromes could increase the demand for medical care at an extremely difficult time. In this situation, telemedicine is an excellent option for patient management.

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