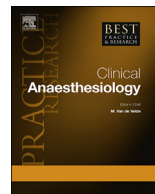




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Impact of COVID-19 pandemic on chronic pain management: Looking for the best way to deliver care

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Although pain treatment has been described as a fundamental human right, the Coronavirus disease 2019 (COVID-19) pandemic forced healthcare systems worldwide to redistribute healthcare resources toward intensive care units and other COVID-19 dedicated sites. As most chronic pain services were subsequently deemed non-urgent, all outpatient and elective interventional

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procedures have been reduced or interrupted during the COVID-19 pandemic in order to reduce the risk of viral spread. The shutdown of pain services jointly to the home lockdown imposed by governments has affected chronic pain management worldwide with additional impact on patients' psychological health. Therefore, the aim of this review is to analyze the impact of COVID-19 pandemic on chronic pain treatment and to address what types of strategies can be implemented or supported in order to overcome imposed limitations in delivery of chronic pain patient care.

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Introduction

Chronic pain is commonly 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 [1]. The overall prevalence of chronic pain in the general population is around 20% [2–6]. Its burden is huge in terms of personal and socioeconomic costs [7]. Disability, emotional imbalances and social isolation are frequently associated with chronic pain often resulting in a vicious circle that compromises the quality of life (QoL) of affected patients [8,9].

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2 (e.g., severe acute respiratory syndrome coronavirus 2), a coronavirus related to the SARS source from 2003. Pharyngodynia, dry cough, and fever are the initial symptoms of a mild respiratory tract infection; however, in some cases, it may rapidly progress to respiratory distress requiring intensive care unit admission and ventilatory support with fatal outcome in 1.8–3.4% of cases [10]. Pain can be an early symptom of COVID-19 infection including myalgias, back pain, and headache [11]. In addition to age, other risk factors for severe COVID-19 disease include smoking, pulmonary disease, congestive heart failure, diabetes, AIDS, and hematological disease.

The outbreak of COVID-19 in the first months of 2020 from Wuhan to Europe and the USA imposed a strategy for infection control consisting worldwide of a ban in gathering, home isolation, and stoppage in all non-essential social services, including non-urgent healthcare. Although pain treatment has been described as a fundamental human right [12], the COVID-19 pandemic forced healthcare systems worldwide to redistribute healthcare resources toward intensive care units and other COVID-19 dedicated sites. As most chronic pain services were deemed non-urgent, all outpatient and elective interventional procedures have been reduced or interrupted during the COVID-19 pandemic in order to reduce the risk of viral spread. The shutdown of pain services jointly to the home lockdown imposed by governments has affected chronic pain management worldwide with additional impact on patients' psychological health.

The aim of this review, therefore, is to analyze the impact of COVID-19 pandemic on chronic pain treatment and to address what types of strategies can be implemented or supported in order to overcome imposed limitations in delivery of chronic pain patient care.

Chronic pain features and therapeutic challenges during COVID-19 pandemic

Chronic pain is a complex multidimensional experience severely compromising the QoL, often limited ability to work, sleep, and affected social interactions with friends and family. According to the 11th International Classification of Diseases (ICD-11), chronic pain can be classified into seven categories: primary, cancer related, post-traumatic and postsurgical, neuropathic, visceral, musculoskeletal, and headache/orofacial [13]. The meaning of chronicity is far beyond the temporal criterion; chronic pain is a real "disease" associated with multiple adaptations in the nervous, endocrine, and immune systems [14–16]. Many factors have been associated with the development of chronic pain including demographic ones (e.g., age, ethnicity, occupational factors), lifestyles (e.g., smoking, alcohol,

physical activity), physical and mental health, genetics, history of abuse or violence, and also coping strategies [17].

With the aging of our population, the prevalence of chronic pain in older patients is increasing [4]. Multi-morbidity is independently associated with chronic pain; up to 88% of patients with chronic pain have other comorbidities such as depression [18], cardiovascular and pulmonary diseases, diabetes mellitus, and cancer [19,20]. Comorbidities increase the risk of side effects of analgesics limiting the applicability of disease-specific clinical guidelines and making it more challenging to obtain good pain control [21]. Moreover, in people with other co-morbidities, chronic pain is an independent risk factor for mortality [22].

Overall, chronic pain is considered the leading cause of disability and is associated with high economic and social burden. In this regard, low back and neck pain are the most frequent syndromes associated with disability, but other chronic pain conditions are identified in the top ten list [23]. As a result of disability, untreated chronic pain can cause job loss, economic problems, depressive mood, and social isolation. Cognitive, affective, and emotional disorders have been found in many chronic pain patients causing complex biopsychosocial interactions [24].

All these features have been even more exacerbated during the COVID-19 pandemic, contributing to make the delivery of effective pain management more challenging. On one side, patients tend to stay away from hospitals due to fear of infection, so that acute pain is largely untreated and can more easily progress to chronic pain, increasing the risk of disability and depressive status. On the other side, social isolation imposed during the pandemic can promote passive coping strategies, with further worsening of depressive mood and increasing suicidal ideation. Therefore, in this global health pandemic, risk factors for pain morbidity and mortality have been amplified.

Several challenges have emerged during the COVID-19 pandemic for pain physicians, in terms of both risks of harm from undertreatment and risks of harm from inappropriate treatment, since interaction between pain medications and the immune system must be considered. Untreated chronic pain can affect the immune system inducing immunosuppression in some patients [25]. Moreover, the association of chronic pain, comorbidities, and older age increases the risk of infection including COVID-19 diseases. Pain treatments can also compromise the immune system in particular with the use of steroids. Oral or injected steroids can induce secondary adrenal insufficiency altering immune response [26]. Opioids, in general, decrease natural killer (NK) cells in a dose-dependent manner, and therefore, they are associated with the progression of infectious states. Opioids can also have immunosuppressive effects interfering with innate and acquired immune responses via directly acting on immune cells (linking μ -opioid receptors (MOR) and Toll-like receptors 4) or indirectly acting on the hypothalamus–pituitary–adrenal axis (producing corticosteroids) and on the sympathetic nervous system (producing noradrenaline). Both corticosteroids and noradrenaline, acting on leucocytes, also negatively modulate the immune response decreasing NK cell cytotoxicity [27].

Morphine can also act via D1 dopamine receptors in the nucleus accumbens shell, increasing the release of neuropeptide Y (NPY) and reducing splenic NK cell cytotoxicity in rodent models [28]. High dosages and long-term opiate therapy increase the risk of immunosuppression even though with different effects according to the type of opioid, fentanyl and morphine being the most immunosuppressive and buprenorphine the least [29]. Fentanyl patches can also increase the risk of respiratory depression in case of fever, and non-steroidal anti-inflammatory drugs (NSAIDs) can mask COVID-19-related fever and myalgias. Moreover, the risk of infection for patients, caregivers, and also physicians should be considered when planning a pain treatment in COVID-19 era in order to restrict hospital entry and the risk of viral diffusion.

Finally, there are some “essential” interventional pain procedures that cannot be postponed: patients with an implantable device for intrathecal infusion need the refill of the pump to avoid abstinence syndrome and patients with neurostimulation implants can need checkup in case of infection or wound dehiscence or lead migration [30,31]. During the COVID-19 pandemic, new therapeutic challenges have been added to the usual ones (see Table 1), and the decision about when and how to treat chronic pain have to be carefully evaluated in any single patient.

A case-by-case decision process has been recommended in order to plan whether to see a patient in person, change the appointment to telemedicine, postpone the visit, or perform a procedure. This process includes not only medical factors, but also logistical circumstances [32].

Table 1

Chronic pain patients' features and challenges of pain treatment outside and during COVID-19 pandemic.

| Features of patients with chronic pain | Usual therapeutic challenges | Challenges during COVID-19 pandemic |
|--|---|--|
| Elderly patient | Pain assessment and treatment Greater risk of side effects with NSAIDs and opioids | Greater risk of infection Caution using opioids or steroids NSAID and non-NSAIDs (paracetamol, dipyrrone), can mask fever and myalgias COVID-19 related |
| Disabled patient | Need of a caregiver to take him to the hospital | Risk of infection for him and his caregiver |
| Multi-morbidity | Risk of side effects or less pain control | Difficulties with multi-disciplinary team' evaluation |
| Multi-treatments | Risk of side effects or less pain control | Drugs prescription and storage |
| Cognitive disorders | Pain assessment and treatment evaluation | Difficulty in remote treatment |
| Emotional disorders | Needing of a biopsychosocial model of pain management. Patient compliance and adherence to therapy | Worsening of emotional disorders Worsening compliance to therapy Adding pandemic-related disorders |
| High dosages and long-term opioids | Risk of endocrine imbalance Risk of immunosuppression Risk of respiratory depression | Drugs prescription and storage Greater risk of infection Greater risk of respiratory depression during lung infection and with fentanyl patch during fever |
| Intrathecal Drug Delivery System (ITDDS) | Programming pump refill to avoid opioid abstinence syndrome. | Need to pump refill to avoid abstinence or to optimize infusion therapy |
| Neurostimulation implants | Periodic checks and programming | Need to change exhausted internal battery or surgery for complications or for stage 2 of implant of external leads |

Recommendations for practice of chronic pain during COVID-19 pandemic have originated by expert panels of pain physicians, psychologists, and researchers from North America and Europe [33] and from the American Society of Interventional Pain Physicians, the American Academy of Pain Medicine (AAPM) jointly with the American Society of Regional Anesthesia and Pain Medicine (ASRA), the American Society of Anesthesiologists (ASA), the World Institute of Pain (WIP), American Academy of Physical Medicine and Rehabilitation (AAPMR), and Nord-America Neuromodulation Society (NANS) [32]. The continuity of care and pain medications were the primary goals of the recommendations which were actually "best practices" for risk mitigation of patients and healthcare providers and for regulating the access to pain services. Key points of the recommendations are shown in Table 2:

New strategies of caring for chronic pain patients during COVID-19 pandemic

The peculiarity of pain services is the delivering of a face-to-face service being an in-person visit imperative at the first consultation, in order to assess pathophysiology of pain referenced by the patient. During the COVID-19 pandemic, the needs to contain coronavirus spread on one side and to guarantee the continuity of care on the other have made it necessary to utilize the remote treating of patients with non-urgent conditions and/or long-term disease.

Telehealth and telemedicine have been suggested as a means for treating chronic pain patients at home in nonemergent conditions, as well as to assure continuity of care of patients after hospital discharge. In China, during COVID-19 pandemic, the Pain Departments of Shenzhen and Wuhan have addressed with telemedicine the problem of outpatients needing pain treatment. Indeed, they have used telemedicine to help patients to administer prescriptions and as guidance for physical at-home exercises for pain relief [34].

Telemedicine is a real-time two-way interactive communication conducted remotely with an audio-visual device. Telehealth is a more modern term referring to all possible health and social care uses of technology including digital communication technology, live video conferencing, mobile apps, and Internet of Things (IoT) devices and has emerged in recent years as a new treatment model in most

Table 2

Recommendations for best practice management of pain patients.

- 1) "Infection control" in healthcare settings according to Center of Disease Control (CDC) recommendations: triage points with body temperature check, social distancing, hand hygiene, face mask and gloves during patient care, and cleaning of surfaces in the patient care environment.
- 2) Triage the risk of COVID-19 screening patients and personnel for symptoms of COVID-19.
- 3) Triage the pain procedures in elective, urgent, and emergent situations: suspend elective cases, proceed with emergent ones, and consider case by case in urgent situation.
- 4) Suspend in-person visits whenever possible. In-person visit remains an option that should be taken into consideration according to several factors, such as acuity and severity of pain, whether or not the patient has comorbid psychiatric condition, occupational consideration (such as whether the patient is also a caregiver or has children), the likelihood of the visit/procedure providing meaningful benefit, the likelihood of the patient to seek emergency services, or be started on opioids, and the need for physical examination.
- 5) Adapt ongoing therapy to reduce the risk on COVID-19.
- 6) Perform urgent procedures with the minimal number of personnel, ideally by a single physician avoiding deep sedation requiring airway support.
- 7) Consider intrathecal pump refill as an emergent interventional pain procedure. In some cases, in-home pump refill can be planned.

fields of medicine [35]. Telehealth has been used for the remote control of patients with diabetes, chronic obstructive disease, and emergency cardiac disease and as an alert system for patients with pacemaker or implantable cardioverter-defibrillator (ICD) [36].

Many technical solutions, with different costs and benefits, have been utilized for remote assessment and treatment of chronic pain. Telephone consultation is the first and low-cost example of telemedicine [37] for remote treatment of pain. Email is routinely used by most pain services for communication with patients related to scheduled visits. Mobile health (mHealth), i.e., healthcare application on smartphone, tablets or laptops, has many applications. Messages and image sharing with instant messaging apps (i.e., WhatsApp, Telegram, or Messenger) between patients and healthcare professionals is growing worldwide, since it does not require a personal computer, even if there are some concerns about privacy protection and data security [38]. Even in pediatrics, mHealth associated with virtual reality has been implemented for procedural pain and for assessing pain in children's cancer pain with the aid of three-dimensional avatars [39].

Web-based systems like Collaborative Health Outcome Information Registry [40] or PAIN OUT [41] have been optimized for people with pain. CHOIR is a platform intended to optimize care and advance real-world research permitting a basic multidisciplinary assessment of the patient before even meeting him or her. PAIN OUT is an international registry project born to improve the treatment of patients with post-operative pain. Unfortunately, the pandemic has stressed the efficiency of these web-based systems.

Moreover, differently from the other vital signs, pain, the fifth vital sign, is inherently subjective, so that the reporting of pain experience is extremely variable between patients. Elderly, disabled patients, and patients with cognitive or emotional disorders including opioid addiction can miss remote control or make it more difficult [42]. These collectively represent challenges for telemedicine to overcome.

As a matter of fact, the evidence on telemedicine efficacy in chronic pain is lacking according to some published systematic reviews [43,44], including a Cochrane review [45]. The effects of psychological therapies delivered via the Internet on pain, disability, depression, and anxiety are promising

Table 3

Use of telemedicine during coronavirus infection pandemic.

Utilities of telemedicine during COVID-19 pandemic

- To provide a safe and effective service
- To triage the urgency of an in-person visit
- To evaluate patients and plan treatments
- To help prescribing opioids
- To resolve patient concern
- To perform a biopsychosocial management of pain
- To assess and treat emotional distress, pain-related or pandemic-related

but come from a small number of trials so that the estimate of the effects remains to be assessed. However, to maximize eHealth effectiveness, there is the need of training not only the patients and also the practitioners accustomed to a face-to-face relationship and the need of a rapid integration of remotely supported pain management services.

The COVID-19 pandemic has strained the importance of a biopsychosocial approach to pain: online self-management programs integrating healthy lifestyles and active strategies of coping, like exercises, can represent a good opportunity. Even though opioid prescription telemedicine represents a useful means to evaluate the opportunity of beginning or continuing opioid prescription, telehealth can also address opioid use disorder (OUD) at home [46]. Another important opportunity for telemedicine is the assessment and treatment of emotional distress related to the COVID-19 pandemic itself. Table 3 displays the possible use of telemedicine during COVID-19 pandemic.

Pain caused by COVID-19: an early symptom and a negative prognostic sign of disease

Physical pain can be an early symptom of COVID-19 infection, as patients can complain low back pain, widespread myalgias, or headache. Other pain syndromes can manifest during the infection, caused by the involvement of cranial nerves or nervous roots like Guillen Barre syndromes [47]. Increasing evidence has demonstrated that SARS-CoV-2 has the ability to invade the nervous system above all in immunocompromised patients [48]. According to recent studies, SARS-CoV-2 infection can cause many neurological diseases including viral encephalitis, meningoencephalitis, ischemic stroke, and hemorrhagic stroke [49,50].

Angiotensin-converting enzyme 2 (ACE2) is considered to be a functional receptor for SARS-CoV-2 invasion [51]. SARS-CoV-2 binds to the host cells' ACE2 and infects the cells. SARS-CoV-2 sheds nucleic acid from the host to spread, similar to influenza virus. Endothelial cells of blood vessels have high expression of ACE2, and SARS-CoV-2 infection can attack endothelial cells in the cerebral blood vessels through the ACE2 receptor and disrupt the blood–brain barrier (BBB), resulting in increased permeability of the BBB, cerebral edema, and intracranial hypertension. In addition to invasion by blood vessels, viruses may enter the central nervous system (CNS) through the terminals of the olfactory nerve. Importantly, axonal transport also supports the rapid spread from neuron to neuron [48]. Moreover, two other mechanisms have been proposed in order to explain neurological damage during COVID-19 pneumonia: hypoxic brain injury and an immune-mediated damage to the CNS. Systemic hypoxia can cause neuronal swelling and brain edema, which ultimately results in neurological damage. In addition, cytokine storm with increased levels of inflammatory cytokines and activation of T lymphocytes, macrophages, and glial cell can cause neuronal apoptosis, while damage to endothelium and activation of complement and coagulation cascade could render patients prone to cerebrovascular events, both thrombotic and hemorrhagic [52].

According to recent studies, more than 35% of COVID-19 patients develop neurological symptoms. Some COVID-19 patients may present neurological symptoms as the initial presentation of the disease. Current published studies have suggested that neurological involvement in the pathogenesis of SARS-CoV-2 does seem to be associated with a more “severe” infection and subsequent mortality [53]. Therefore, during the current context of the COVID-19 pandemic, physicians should be aware of the wide spectrum of neurological COVID-19 signs and symptoms for early diagnosis and isolation of patients. Moreover, all these neurological manifestations could result in different painful clinical pictures, ranging from peripheral neuralgia to post-stroke pain syndrome, that need to be treated and pose further challenges for pain physicians.

Conclusion

The COVID-19 pandemic has stressed healthcare systems worldwide, so that many pain services are no longer open for business. Chronic pain patient populations remain isolated with consequent social and psychological impact. Telehealth represents a good opportunity to avoid “missed care”, helping to triage a single case as urgent or emergent and to address pandemic related emotional disorders. This represents an opportunity for all pain physicians to better point out chronic pain patients' needs and how to care for them.

Practice points

- Although pain treatment has been described as a fundamental human right, the COVID-19 pandemic forced healthcare systems worldwide to redistribute healthcare resources toward intensive care units and other COVID-19 dedicated sites
- The shutdown of pain services jointly to the home lockdown imposed by governments has affected chronic pain management worldwide with an additional impact on patients' psychological health.
- Telehealth represents a good opportunity to avoid “missed care”, helping to triage a single case as urgent or emergent and to address pandemic-related emotional disorders.

Research agenda

- Further studies are needed to elucidate the quality of telemedicine visits compared to traditional clinic patient visits
- Further investigation is needed to see how self-isolation in times of a pandemic can precipitate chronic pain

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