Best Practice & Research Clinical Anaesthesiology 34 (2020) 529–537

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

12

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

Filomena Puntillo, MD, PhD, Professor of Anesthesia and Pain Medicine [a], Mariateresa Giglio, MD, Consultant Anesthetist [b], Nicola Brienza, MD, PhD, Professor of Anesthesia and Intensiva Care [c], Omar Viswanath, MD, Professor of Anesthesia [d, e, f, g], Ivan Urits, MD, Professor of Anesthesia [h], Alan D. Kaye, MD, PhD, Professor and Chairman, Anesthesia [g], Joseph Pergolizzi, MD, Professor of Anesthesia [i], Antonella Paladini, MD, PhD, Professor of Anesthesia [j], Giustino Varrassi, MD, PhD, President [k, l, *]

[a] *Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", 70124 Bari, Italy*
[b] *Anesthesia, Intensive Care and Pain Unit, Policlinico Hospital, 70124 Bari, Italy*
[c] *Department of Emergency and Organ Transplantation, University of Bari "Aldo Moro", 70124 Bari, Italy*
[d] *Valley Pain Consultants – Envision Physician Services, Phoenix, AZ, USA*
[e] *University of Arizona College of Medicine-Phoenix, Department of Anesthesiology, Phoenix, AZ, USA*
[f] *Creighton University School of Medicine, Department of Anesthesiology, Omaha, NE, USA*
[g] *Louisiana State University Health Shreveport, Department of Anesthesiology, Shreveport, LA, USA*
[h] *Beth Israel Deaconess Medical Center, Department of Anesthesia, Critical Care, and Pain Medicine, Harvard Medical School, Boston, MA, USA*
[i] *NEMA Res Group, Naples, FL, USA*
[j] *Department of MESVA, University of L'Aquila, 67100 L'Aquila, Italy*
[k] *Paolo Procacci Fdn, Via Tacito 7, 00193 Roma, Italy*
[l] *World Institute of Pain, Winston-Salem, NC, USA*

Keywords:
chronic pain
COVID-19
telemedicine
interventional pain

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

* Corresponding author. Paolo Procacci Foundation, Via Tacito 7, 00193, Roma, Italy.
E-mail address: giuvarr@gmail.com (G. Varrassi).

https://doi.org/10.1016/j.bpa.2020.07.001

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.

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 mi-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, dipyrone), 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 Shenzen 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 form 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

Acknowledgments

Funding: This research has been possible thanks to an unconditional grant provided by the "Paolo Procacci Foundation-ONLUS", Via Tacito 7, 00193 Roma, Italy.

Authorship: All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures: Filomena Puntillo, Mariateresa Giglio, Omar Viswanath, Ivan Urits, Nicola Brienza, Joseph Pergolizzi, Antonella Paladini, and Giustino Varrassi have nothing to disclose. Dr Kaye serves on the Speakers Bureau for Merck, Inc.

References

[1] Merskey HE. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Pain; 1986.
*[2] Bouhassira D, Lantéri-Minet M, Attal N, et al. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain 2008;136:380–7. https://doi.org/10.1016/j.pain.2007.08.013.
[3] Fayaz A, Croft P, Langford RM, et al. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open 2016;6:e010364. https://doi.org/10.1136/bmjopen-2015-01036413.
*[4] Del Giorno R, Frumento P, Varrassi G, et al. Assessment of chronic pain and access to pain therapy: a cross-sectional population-based study. J Pain Res 2017;10:2577–84. https://doi.org/10.2147/JPR.S136292.
[5] Fatoye F, Gebrye T, Odeyemi I. Real-world incidence and prevalence of low back pain using routinely collected data. Rheumatol Int 2019;39(4):619–26. https://doi.org/10.1007/s00296-019-04273-0.
*[6] Latina R, De Marinis MG, Giordano F, et al. Epidemiology of chronic pain in the Latium Region, Italy: a cross-sectional study on the clinical characteristics of patients attending pain clinics. Pain Manag Nurs 2019;20(4):373–81. https://doi.org/10.1016/j.pmn.2019.01.005.
*[7] Langley P, Muller-Schwefe G, Nicolau A, et al. The societal impact of pain in the European Union: health-related quality of life and healthcare resource utilization. J Med Econ 2010;13(3):571–81. https://doi.org/10.3111/13696998.2010.516709.
[8] Goesling J, Clauw DJ, Hassett AL. Pain and depression: an integrative review of neurobiological and psychological factors. Curr Psychiatry Rep 2013;15:421.
[9] Hylands-White N, Duarte RV, Raphael JH. An overview of treatment approaches for chronic pain management. Rheumatol Int 2017;37:29–42. https://doi.org/10.1007/s00296-016-3481-8.
[10] Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020;323(15):1488–94. https://doi.org/10.1001/jama.2020.3204.

[11] Song XJ, Xiong DL, Wang ZY, et al. Pain management during the COVID-19 pandemic in China: lessons learned. Pain Med 2020 Apr 22. https://doi.org/10.1093/pm/pnaa143. pnaa143.
[12] Cousins MJ, Lynch ME. The Declaration Montreal: access to pain management is a fundamental human right. Pain 2011 Dec;152(12):2673–4. https://doi.org/10.1016/j.pain.2011.09.012.
*[13] Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. Pain 2015;156:1003–7. https://doi.org/10.1097/j.pain.0000000000000160.
[14] Basbaum AI, Bautista DM, Scherrer G, et al. Cellular and molecular mechanisms of pain. Cell 2009;139(2):267–84.
[15] Machelska H. Dual peripheral actions of immune cells in neuropathic pain. Arch Immunol Ther Exp (Warsz) 2011;59(1):11–24.
[16] Rittner HL, Brack A, Stein C. Pain and the immune system. Br J Anaesth 2008;101(1):40–4.
[17] Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth 2019;123(2):e273–83. https://doi.org/10.1016/j.bja.2019.03.023.
*[18] Zis P, Daskalaki A, Bountouni I, et al. Depression and chronic pain in the elderly: links and management challenges. Clin Interv Aging 2017;12:709–20. https://doi.org/10.2147/CIA.S113576.
[19] van Hecke O, Hocking LJ, Torrance N, et al. Chronic pain, depression and cardiovascular disease linked through a shared genetic predisposition: analysis of a family-based cohort and twin study. PloS One 2017 Feb 22;12(2):e0170653. https://doi.org/10.1371/journal.pone.0170653.
[20] Barnett K, Mercer SW, NorburyM WattG, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012;380:37–43.
[21] Guthrie B, Payne K, Alderson P, et al. Adapting clinical guidelines to take account of multi- morbidity. BMJ 2012;345:5.
[22] Smith D, Wilkie R, Uthman O, et al. Chronic pain and mortality: a systematic review. PLoS One 2014;9:e99048.
[23] Vos T, Allen C, Arora M, et al. Global, regional, and na- tional incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990e2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1211e59.
[24] Stein C. Opioids, sensory systems and chronic pain. Eur J Pharmacol 2013;716:179–87.
[25] Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. Nat Rev Neurosci 2005;6:521–32.
[26] Liu MM, Reidy AB, Saatee S, et al. Perioperative steroid management: approaches based on current evidence. Anesthesiology 2017;127:166–72.
[27] Plein LM, Rittner HL. Opioids and the immune system-friend or foe. Br J Pharmacol 2018;175:2717–25.
[28] Saurer TB, Carrigan KA, Ijames SG, et al. Suppression of natural killer cell activity by morphine is mediated by the nucleus accumbens shell. J Neuroimmunol 2006;173(1–2):3–11. https://doi.org/10.1016/j.jneuroim.2005.11.009.
*[29] Franchi S, Moschetti G, Amodeo G, et al. Do all opioid drugs share the same immunomodulatory properties? A review from animal and human studies. Front Immunol 2019;10:2914.
[30] Deer T, Sayed D, Pope J, et al. Emergence from the coronavirus disease 2019 pandemic and the care of chronic pain: guidance for the interventionalist. Anesth Analg 2020;10:1213.
[31] Allam AES, Ergonenc T, Garcia Martos A, et al. Ultrasound-guided interventions during the COVID-19 pandemic—a new challenge. Am J Phys Med Rehabil 2020;99(7):580–1. https://doi.org/10.1097/PHM.0000000000001467.
*[32] Cohen SP, Baber ZB, Buvanendran A, et al. Pain management best practices from multispecialty organizations during the COVID-19 pandemic and public health crises. Pain Med 2020 Apr 7:pnaa127.
[33] Shanthanna H, Strand NH, Provenzano DA, et al. Caring for patients with pain during the COVID-19 pandemic: consensus recommendations from an international expert panel. Anaesthesia 2020 Apr 26. https://doi.org/10.1111/anae.15076.
[34] Mao Bei, Liu Yang, Chai Yan-Hua, et al. Assessing risk factors for SARS-CoV-2 infection in patients presenting with symptoms in Shanghai, China: a multicentre, observational cohort study. Lancet Digit Health 2020 Jun;2(6):e323–30. https://doi.org/10.1016/S2589-7500(20)30109-6. Published online 2020 May 14.
[35] Catalist NE. What is telehealth? NEJM 2018;4.
[36] Pron G, Ieraci L, Kaulback K. Medical advisory secretariat, health quality ontario. Internet-based device-assisted remote monitoring of cardiovascular implantable electronic devices: an evidence-based analysis. Ont Health Technol Assess Ser 2012;12(1):1–86.
[37] Our world in data. Availble at: https://ourworldindata.org/technology-adoption#mobile-phone-adoption. [Accessed 30 June 2020].
[38] De Benedictis A, Lettieri E, Masella C, et al. WhatsApp in hospital? An empirical investigation of individual and organizational determinants to use. PloS One 2019;14(1):e0209873.
[39] Fortier MA, Chung WW, Martinez A, et al. Pain buddy: a novel use of M-health in the management of children's cancer pain. Comput Biol Med 2016 Sep 1;76:202–14. https://doi.org/10.1016/j.compbiomed.2016.07.012.
[40] CHOIR. Available at: https://choir.stanford.edu/. [Accessed 30 June 2020].
[41] PAINOUT. Availble at: http://pain-out.med.uni-jena.de. [Accessed 30 June 2020].
*[42] Cravello L, Di Santo S, Varrassi G, et al. Chronic pain in the elderly with cognitive decline: a narrative review. Pain Ther 2019;8:53–65. https://doi.org/10.1007/s40122-019-0111-7.
[43] Martorella G, Boitor M, Berube M, et al. Tailored web-based interventions for pain: systematic review and meta-analysis. JIMR 2017;19:e385.
[44] Slattery BW, Haugh S, O'Connor L, et al. An evaluation of the effectiveness of the modalities used to deliver electronic health interventions for chronic pain: systematic review with network meta-analysis. J Med Internet Res 2019;21:e11086.
*[45] Eccleston C, Fisher E, Brown R, et al. Psychological therapies (Internet-delivered) for the management of chronic pain in adults. Cochrane Database Syst Rev 2014;2:CD010152.
[46] Uscher-Pines L, Huskamp HA, Mehrotra A. Treating patients with opioid use disorder in their homes. An emerging treatment model. JAMA 2020 May 27. https://doi.org/10.1001/jama.2020.3940.
[47] Padroni M, Mastrangelo V, Asioli GM, et al. Guillain-Barré syndrome following COVID-19: new infection, old complication? J Neurol 2020 Apr 24:1–3.
[48] Li X, Wang W, Zhao X, et al. Transmission dynamics and evolutionary history of 2019-nCoV. J Med Virol 2020 May;92(5):501–11. https://doi.org/10.1002/jmv.25701. Published online 2020 Feb 14.

[49] Mao X-Y, Jin W-L. The COVID-19 pandemic: consideration for brain infection. Neuroscience 2020;437:130–1.
[50] Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. Brain Behav Immun 2020 Apr 10. https://doi.org/10.1016/j.bbi.2020.04.017.
[51] Yan Tiantian, Xiao Rong, Lin Guoan. Angiotensin-converting enzyme 2 in severe acute respiratory syndrome coronavirus and SARS-CoV-2: a double-edged sword? FASEB J 2020;34(5):6017–26. https://doi.org/10.1096/fj.202000782.
[52] Cui Ning, Zou Xugong, Xu Lin. Preliminary CT findings of coronavirus disease 2019 (COVID-19). Clin Imag 2020 Sep;65:124–32. https://doi.org/10.1016/j.clinimag.2020.04.042.
[53] Niazkar HR, Zibaee B, Nasimi A, et al. The neurological manifestations of COVID-19: a review article. Neurol Sci 2020 Jun 1:1–5.