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Minerva Anestesiologica 2020 Dec 15

DOI: 10.23736/S0375-9393.20.15029-6

Article type: Experts' opinion and Point of view

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Article first published online: December 15, 2020

Manuscript accepted: October 26, 2020

Manuscript revised: September 25, 2020

Manuscript received: July 10, 2020

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Chronic Pain and COVID-19: pathophysiological, clinical and organizational issues

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Target journal: Minerva Anestesiologica (<https://www.minervamedica.it/it/riviste/minerva-anestesiologica/index.php>)

Acknowledgments

Editorial assistance was provided by Luca Giacomelli, PhD, Chiara Degirolamo, PhD and Aashni Shah (Polistudium SRL, Milan, Italy). This assistance was supported by Grunenthal.

Funding

None.

Conflicts of Interest

None declared.

Abstract

During the lockdown phase of the COVID-19 pandemic, a call not to neglect the continuum of care of patients who present with chronic diseases, including pain, was made. In the field of pain, COVID-19 had an impact both from a clinical (i.e., the influence of SARS-CoV-2 infection on pain) and organizational (i.e., how patients with chronic pain should be managed in the post-COVID-19 era) perspective. Furthermore, patients with chronic pain are also frequently frail subjects, affected from multiple comorbidities and hence are at increased risk of infection. On these bases, how the necessity to continue pain therapy will be pursued in the post-COVID-19 era?

In this paper, we comment on the above-mentioned topics, on the basis of available data and our experience as pain therapists.

The coronavirus disease 2019 (COVID-19) pandemic has undoubtedly changed our lives and our approach to medicine, for a yet undefined period of time. Indeed, the severity of the COVID-19 pandemic has required full attention from global healthcare authorities and regulatory bodies, with major modifications of the standard approaches of care to non-COVID-19 diseases.

However, among hundreds of “instant papers” on the COVID-19, only few large, prospective studies, mainly concerning the effectiveness of antivirals or drugs blocking ILs in the most ill patients, have been published until the publication of RECOVERY Trial (Randomised Evaluation of COVID-19 Therapy) ^[1], and therefore clinical decisions concerning treatment of COVID-19 and any other concomitant or ongoing disease were initially based mostly upon the individual clinician’s experience.

Even during this phase, a call not to neglect the continuum of care of patients who present with chronic diseases, including pain, was made ^[2-4]. In the field of pain, COVID-19 had an impact both from a clinical (i.e., the influence of SARS-CoV-2 infection on pain) and organizational (i.e., how patients with chronic pain should be managed in the post-COVID-19 era) perspective. Furthermore, patients with chronic pain are also frequently frail subjects, affected from multiple comorbidities and hence are at increased risk of infection. The increasing number of contributions exploring the current unmet needs in chronic pain management during the pandemic highlights the global efforts the worldwide pain community is placing to unveil unprecedented challenges, to develop strategies aimed at ensuring an optimal pain care provision with the final aim of mitigating the risk of inadequate pain control that may originate from inappropriate pain medication use or treatment discontinuation ^[5-11]. On these bases, how the necessity to continue pain therapy will be pursued in the post-COVID-19 era?

In this paper, we comment on the above-mentioned topics, on the basis of available data and our experience as pain therapists.

COVID-19 and pathophysiology of pain

At present, some very preliminary reports have suggested increased pain in patients with COVID-19 [5-12]. Indeed, infection from SARS-COV-2 may lead to a cytokine storm – the most evident hallmark of pulmonary disease in COVID-19 patients – that may also have systemic consequences beyond pulmonary involvement and lead to increased pain, and, potentially, to the establishment of chronic pain [6,13]. The link between increased expression of pro-inflammatory cytokines and more severe pain in COVID-19 patients is intriguing, but should be better investigated in dedicated studies.

We also believe that hospitalizations due to COVID-19, especially in the Intensive Care Units, may have a major impact on pain over a medium-long term. Indeed, hospitalized patients had not the opportunity to receive early rehabilitation and therefore may carry an increased risk of developing or worsening of chronic pain [5,14]. Epidemiological studies should be performed to investigate this issue. However, while waiting for such studies, analgesic treatment should not be denied both for patients hospitalized for COVID-19 who undergo to rehabilitation and for any patient already suffering from chronic pain, in order to preserve the effectiveness of analgesic treatment and make functional recovery easier [7,14-16]. Remarkably, different analgesic treatments differ in terms of achievement of complete functional recovery. In order to foster the best possible outcomes of the rehabilitation process, a closer cooperation between pain therapists and physiatrists/physiotherapists is of utmost importance. At the same time, proper psychological assistance should be ensured to all patients, since a compromised psychological state can lead to increased severity of perceived pain [15].

Analgesic therapy in the post-COVID-19 era

It is imperative that patients with chronic pain receive analgesic treatment according to their specific needs [7,17,18]. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used analgesic treatments, even if in a limited timeframe, consistent with the appropriateness temporal duration of therapy, also through the use of online prescription if possible. However, it is important to remark that NSAIDs may mask early symptoms of COVID-19 (fever, myalgia) and hence can potentially lead to a delayed diagnosis of the disease. The European Medicines Agency's pharmacovigilance risk assessment committee has recommended updating the product information for drugs containing ibuprofen and ketoprofen to report this warning [19].

Opioids are also widely used for the management of chronic pain and can be prescribed via online prescription. Therefore, they retain a major role in the current strategy of pain treatment. Although some opioids may cause immunosuppression, individual opioids differ in their potential of immunosuppression [20]. Moreover, opioids differ in their metabolism. Indeed, some opioids are metabolized by the cytochrome P450 family and, hence, may cause pharmacological interactions, for example with antivirals, therefore impairing the pharmacological therapy of poly-medicated patients [21,22]. Last, in principle, ongoing treatment with opioids should be continued according to current guidelines, with the aim to avoid undesired and unplanned withdrawal, which may cause physical and psychological harm to the patient [23,24]. Remarkably, any change to opioid scheduling and prescriptions should be performed only after careful evaluation of ongoing treatment and requires the active participation of the patient to achieve an optimal level of care. The availability of analgesic treatment and the monitoring of therapy must be made possible to all patients, with the aim to avoid therapy interruptions and inappropriate drug use, as well as evaluation and monitoring of abuse and misuse risk. Moreover, so far no data regarding opioid use in COVID patients has been published. Similarly, data regarding the use of corticosteroids or anticonvulsants

in COVID patients are scant with limited guidance on how to best use them ^[9]. We acknowledge that exploring the clinical relevance of the aforementioned pharmacological interventions as well as surgical approaches would be desirable; however, its discussion is beyond the scope of our work. Pending further clinical data, we refer the reader to newly released position statements and recommendations for clinical practice ^[9,25,26].

New organizational models in the post-COVID-19 era

Proper management of chronic pain is a major issue from an organizational perspective. In Italy, there is still a lot to do in this field. Indeed, pain management has been extensively affected by the COVID-19 pandemic ^[7,17,18]. Indeed, pain is more frequently reported in frail and elderly patients, who have a higher risk of developing severe COVID-19 infection and therefore should be visited at hospitals only when strictly necessary. Furthermore, some clinical activities and routines usually performed in pain management units can also be performed by correct implementation of telemedicine, keeping in mind that proper communication between the physician and the patient remains necessary ^[27]. These issues have led to the necessity of an extensive reorganization of pain management in the post-COVID-19 era.

First, it must be stressed that continuous monitoring is essential for the management of chronic pain, and therefore re-evaluations of every patient with chronic pain should be performed regularly. When inpatient visits are required, patients, their caregivers and personnel should be screened for symptoms of SARS-CoV-2, prior to the patient coming into the hospital, according to available screening tools and practice. Social distancing and personal protection measures should be taken, in line with the specific regulations issued by healthcare and government authorities.

Triage of patients may be helpful in differentiating those who may be adequately treated by telemedicine and those who need inpatient consultations ^[7]. To this end, factors such as acuity and severity of pain, the presence of psychiatric conditions, occupational and social situation should be taken into account ^[7]. Telemedicine may become a very useful tool for the assessment of patient-reported outcomes ^[27]. In addition, mobile phones equipped with a camera allow for sharing images, for instance of painful areas or assessment of mobility of patients. According to Italian regulations, many drug prescriptions can be performed from remote. Therefore, telemedicine may be preferred over inpatient consultations when only monitoring of patients and treatment, or refilling of prescription are required. Furthermore, telemedicine may allow a more constant interaction between the pain therapist and the patient.

Overall, telemedicine has proved to be well-accepted by patients and associated with a relevant saving for healthcare resources ^[28,29]. However, telemedicine cannot always replace face-to-face visits, especially when a correct diagnosis is yet to be made ^[30]. Moreover, technological and mostly patient-related barriers, including limited access to the internet, poor familiarity with smartphone or computer and psychosocial stressors may hinder an effective use of telemedicine ^[27,30]. When telemedicine can be applied, user-friendly technology should be selected, also keeping in mind the issues of confidentiality of personal health information. Indeed, currently-used applications for telemedicine vary in terms of their control over the content, security, and marketing claims ^[27].

Directions for research

The COVID-19 pandemic has brought unforeseen challenges in the field of chronic pain as well as offered opportunities for improvement (Table 1). Nevertheless, the changes in pain management imposed by the COVID-19 pandemic have left several “grey areas” requiring investigation in the near

future. First, proper assessment of the importance of pain treatment in patients who are rehabilitating from COVID-19 is paramount. Such studies should also investigate the most suitable treatment for these patients. With respect to telemedicine, new organizational models are being developed and should be evaluated by formal approaches, such as pharmacoeconomic and drug utilization studies. In this line, validation of pain assessment questionnaires specifically developed for the telemedicine setting should also be pursued. Last, it would be interesting to implement narrative medicine approaches and tools into telemedicine, with the aim to reach a more comprehensive evaluation and support for patients.

The above-mentioned lines of research are surely of major relevance for the incoming post-COVID-19 era. However, clinicians should ensure that patients continue to receive proper analgesic treatment for chronic pain, without any interruption due to the challenging situation we are facing in daily practice.

Key messages

1. COVID-19 outbreak has heavily impacted on all National Health Services from a structural, organizational and routinely patients' management standpoints.
2. A lot of pain therapists were moved in ICU to manage COVID-19 patients both for respiratory support and to treat their painful condition, with the consequence of deprioritizing in many cases the management of outpatients suffering from chronic pain.

3. Identification and implementation of strategies aimed at ensuring continuity of care provision while mitigating the risk of inadequate analgesic treatment, self-medication with potential risk of adverse events and even treatment discontinuation are crucial.

4. It's imperative that patients with chronic pain receive analgesic treatment according to their specific needs. From an organizational perspective, use of new technologies to follow-up patients are essential, even if not all of them could benefit from the wide range of opportunities such technology may offer.

Authors' contributions

All Authors contributed to the conceptualization of information and the drafting of the manuscript.

All Authors have read and approved the final version of the paper.

References

1. Papes D, Jeroncic A, Ozimec E. Redundancy and methodological issues in articles on COVID-19. *Eur J Clin Invest.* 2020;e13301
2. Van de Haar J, Hoes LR, Coles CE, Seamon K, Fröhling S, Jäger D, et al. Caring for patients with cancer in the COVID-19 era. *Nat Med* 2020; 26(7): 1146
3. Gaur S, Dumyati G, Nace DA, Jump RLP. Unprecedented solutions for extraordinary times: Helping long-term care settings deal with the COVID-19 pandemic. *Infect Control Hosp Epidemiol* 2020; 41(6): 729-30.

4. Wolf MS, Serper M, Opsasnick L, O'Connor RM, Curtis LM, Benavente JY, et al. Awareness, attitudes, and actions related to COVID-19 among adults with chronic conditions at the onset of the U.S. outbreak: A cross-sectional survey. *Ann Intern Med.* 2020; 173(2): 100-9.
5. Clauw DJ, Häuser W, Cohen SP, Fitzcharles MA. Considering the potential for an increase in chronic pain following the COVID-19 pandemic [published online ahead of print, 2020 Jun 3]. *Pain.* 2020;10.1097/j.pain.0000000000001950. doi:10.1097/j.pain.0000000000001950.
6. Shanthanna H, N. H. Strand, D. A. Provenzano, C. A. Lobo, S. Eldabe, A. Bhatia, J. Wegener, K. Curtis, S. P. Cohen and S. Narouzev - Caring for Patients With Pain During the COVID-19 Pandemic: Consensus Recommendations From an International Expert Panel. *Anaesthesia.* 2020;75(7):935-44.
7. Coluzzi F, Marinangeli F, Pergolizzi J. Managing chronic pain patients at the time of COVID-19 pandemic. *Minerva Anesthesiol.* 2020; 86(8): 797-9.
8. Puntillo F, Giglio M, Brienza N, Viswanath O, Urits I, Kaye AD, et al. Impact of COVID-19 pandemic on chronic pain management: Looking for the best way to deliver care. *Best Pract Res Clin Anaesthesiol.* 2020 Jul 17 doi: 10.1016/j.bpa.2020.07.001 [Epub ahead of print].
9. Cohen SP, Baber ZB, Buvanendran A, McLean BC, Chen Y, Hooten M, et al. Pain Management Best Practices from Multispecialty Organizations during the COVID-19 Pandemic and Public Health Crises. *Pain Med* 2020; (doi: 10.1093/pm/ pnaa127)
10. Deer TR, Sayed D, Pope JE, Chakravarthy KV, Petersen E, Moeschler SM, Abd-Elseyed A, Amirdelfan K, Mekhail N; ASPN COVID Workgroup. Emergence From the COVID-19 Pandemic and the Care of Chronic Pain: Guidance for the Interventionalist. *Anesth Analg.* 2020; 131(2):387-94
11. Javed S, Hung J, Huk BK. Impact of COVID-19 on chronic pain patients: a pain physician's perspective. *PainManag.* 2020; 10(5), 275–7

12. Papa A, Salzano AM, Di Dato MT, Varrassi G. Images in Practice: Painful Cutaneous Vasculitis in a SARS-Cov-2 IgG-Positive Child. *Pain Ther.* 2020;1-3. doi:10.1007/s40122-020-00174-
13. Quartuccio L, Semerano L, Benucci M, Boissier MC, De Vita S. Urgent avenues in the treatment of COVID-19: Targeting downstream inflammation to prevent catastrophic syndrome. *Joint Bone Spine.* 2020;87(3):191-193. doi:10.1016/j.jbspin.2020.03.011.
14. Barker-Davies RM, O'Sullivan O, Senaratne KPP, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. *Br J Sports Med.* 2020;bjsports-2020-102596. doi:10.1136/bjsports-2020-102596.
15. Carda S, Invernizzi M, Bavikatte G, et al. COVID-19 pandemic. What should PRM specialists do? A clinician's perspective [published online ahead of print, 2020 May 19]. *Eur J Phys Rehabil Med.* 2020;10.23736/S1973-9087.20.06317-0. doi:10.23736/S1973-9087.20.06317-0.
16. Panella L, Rinonapoli G, Coaccioli S. Where should analgesia lead to? Quality of life and functional recovery with tapentadol. *J Pain Res.* 2019; 12:1561-67.
17. Piraccini E, Byrne H, Taddei S. Chronic pain management in COVID-19 era. *J Clin Anesth.* 2020;65:109852. doi:10.1016/j.jclinane.2020.109852.
18. Driver LC. Ethical considerations for chronic pain care during a pandemic [published online ahead of print, 2020 May 2]. *Pain Med.* 2020;pnaa159. doi:10.1093/pm/pnaa159.
19. Torjesen I. Ibuprofen can mask symptoms of infection and might worsen outcomes, says European drugs agency. *BMJ.* 2020 Apr 22;369:m1614.
20. Franchi S, Moschetti G, Amodeo G, Sacerdote P. Do all opioid drugs share the same immunomodulatory properties? a review from animal and human studies. *Front Immuno.* 2019;10:2914. doi: 10.3389/fimmu.2019.02914.

21. Gudin J. opioid therapies and cytochrome P450 interactions. *J Pain Symptom Manage* 2012;44:S4-14.
22. Ing Lorenzini K, Girardin F. Direct-acting antiviral interactions with opioids, alcohol or illicit drugs of abuse in HCV-infected patients. *Liver Int.* 2020;40(1):32-44.
23. Pergolizzi JV, Varrassi G, Paladini A, LeQuang J. Stopping or decreasing opioid therapy in patients on chronic opioid therapy. *Pain Ther.* 2019;8(2):163-76.
24. Hao J, Lucido D, Cruciani RA. Potential impact of abrupt opioid therapy discontinuation in the management of chronic pain: a pilot study on patient perspective. *J Opioid Manag.* 2014;10(1):9-20.
25. Sorbello M, El-Boghdady K, Di Giacinto I, Cataldo R, Esposito C, Falcetta S, et al. The Italian coronavirus disease 2019 outbreak: recommendations from clinical practice. *Anaesthesia.* 2020;75(6):724-32.
26. Recommendations on Chronic Pain Practice during the COVID-19 Pandemic. A Joint Statement by American Society of Regional Anesthesia and Pain Medicine (ASRA) and European Society of Regional Anesthesia and Pain Therapy (ESRA). Available at: <https://www.asra.com/page/2903/recommendations-on-chronic-pain-practice-during-the-covid-19-pandemic>. Last access on September 14th 2020.
27. Eccleston C, Blyth FM, Dear BF, et al. Managing patients with chronic pain during the COVID-19 outbreak: considerations for the rapid introduction of remotely supported (eHealth) pain management services. *Pain.* 2020;161(5):889-93. doi:10.1097/j.pain.0000000000001885.
28. Edwards L, Thomas C, Gregory A, et al. Are people with chronic diseases interested in using telehealth? A cross-sectional postal survey. *J Med Internet Res* 2014;16: e123.

29. Soegaard Ballester JM, Scott MF, Owei L, Neylan C, Hanson CW, Morris JB. Patient preference for timesaving telehealth postoperative visits after routine surgery in an urban setting. *Surgery* 2018; 163:672-9.

30. Negrini S, Kiekens C, Bernetti A, Capecci M, Ceravolo MG, Lavezzi S, Zampolini M, Boldrini P. Telemedicine from research to practice during the pandemic. "Instant paper from the field" on rehabilitation answers to the Covid-19 emergency. *Eur J Phys Rehabil Med.* 2020. doi: 10.23736/S1973-9087.20.06331-5. [Epub ahead of print].

Table 1. Challenges faced by chronic pain outpatients during COVID-19 pandemic and potential approaches and interventions for the near future

Challenges
Limited access to treatment/difficulty to pain medication refill
Shutdown of pain services and physical therapy/ exercise programs
Failure to receive education or advice to adequately manage chronic pain
Onset or exacerbation of mental health concerns including anxiety, depression
Delayed elective joint replacement procedures that result in functional limitations and increase use of analgesics and opioids
Approaches and interventions for the near future
Telemedicine to connect HCPs with patients and to reduce the risk of exposure
Virtual consultation and electronically medication refill
Development and implementation of triage protocols to provide care according to pain severity and its related clinical implications
Development and validation of pain assessment tools for the virtual consultation setting
Development of online physical therapy programs via video tutorials
Development of educational platforms to both foster patient self-management and develop competences needed to engage with digital tools