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Should we be concerned when COVID-19-positive patients take opioids to control their pain? Insights from a pharmacological point of view

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Abstract. – OBJECTIVE: The purpose of this narrative review is to discuss the available information regarding the currently utilized COVID-19 therapies (and the evidence level supporting them) and opioids for chronic pain with a focus on warnings of potential interactions between these two therapeutic approaches.

MATERIALS AND METHODS: Papers were retrieved from a PubMed search, using different combinations of keywords [e.g., pain treatment AND COVID-19 AND drug-drug interaction (DDI)], without limitations in terms of publication date and language.

RESULTS: Remdesivir is an inhibitor of CYP3A4 and may increase the plasma concentration of CYP3A4 substrates (e.g., fentanyl). Dexamethasone is an inducer of CYP3A4 and glycoprotein P, thus coadministration with drugs metabolized by this isoform will lead to their increased clearance. Dexamethasone may cause hypokalemia, thus potentiating the risk of ventricular arrhythmias if it is given with opioids able to prolong the QT interval, such as oxycodone and methadone. Finally, the existing differences among opioids with regard to their impact on immune responses should also be taken into account with only tapentadol and hydromorphone appearing neutral on both cytokine production and immune parameters.

CONCLUSION: Clinicians should keep in mind the frequent DDIs with drugs extensively metabolized by the CYP450 system and prefer opioids undergoing a limited hepatic metabolism. Identification and management of DDIs and dissemination of the related knowledge should be a major goal in the delivery of chronic care to ensure optimized patient outcomes and facilitate updating recommendations for COVID-19 therapy in frail populations, namely comorbid, poly-medicated patients or individuals suffering from substance use disorder.

Key Words:
COVID-19, Opioids, Drug-drug interaction, CYP450 system.

Introduction

The COVID-19 pandemic is disproportionately affecting individuals living with chronic conditions by posing a significant challenge for patients seeking to preserve their care continuity due to the pronounced polarization of healthcare resources and workforce towards the prevention of SARS-CoV-2 spreading[1,2]. Although during a health emergency, pain is usually deemed a low priority, pain does not stop for a pandemic, it still demands adequate care and may even worsen or exacerbate due to the pandemic-related stressors[3-5]. Mounting evidence[6] indicates that COVID-19 is having a profound effect on patients with pain who, similarly to other frail populations (e.g., cancer patients), are underserved with no (or very limited) access to pain centers and experiencing the massive redeployment of their pain clinicians to other areas of care, thus being at increased risk of suboptimal pain management.

A tight relationship between the immune system and pain has been documented with chronic pain (CP) promoting immunosuppression in some individuals[7]. Although it is unknown whether CP patients are more susceptible to viral infection or the consequences thereof, it has been suggested that the compromised immune response system observed in chronic pain patients could be even further suppressed by factors, such as depression, poor sleep and opioid use, with potential to in-

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crease susceptibility to viral infections, including SARS-CoV-2 infection[3,8]. Consequently, there might be a potential risk for pain patients to more frequently showing adverse outcomes if tested positive for SARS-CoV-2[6]. In line with this, it was observed[9] that comorbidities increase the chances of developing a more severe disease leading to hospitalization in the intensive care unit (ICU) and potentially death. Increasing evidence[10,11] is also suggesting that the long-term consequences of surviving from the most severe manifestation of COVID-19, namely acute respiratory distress syndrome (ARDS), may have an impact on CP occurrence in patients. It has been documented[10] that CP occurs both in COVID-19 patients surviving from ARDS and milder forms of the disease. Taking into account the relevance of neurological complications of COVID-19, it is anticipated that several patients with COVID-19 will develop neuropathic pain within weeks or months or that patients with neuropathic pain will exhibit a deterioration of their neurological complication or exacerbation of their pain. However, no consistent data regarding the prevalence and clinical characteristics of neuropathic pain in patients infected with COVID-19 are currently available[12].

Overall, there are no clear and unequivocal recommendations informing clinical decision in pain patients who are tested positive with SARS-CoV-2 and eventually hospitalized. Furthermore, evidence[13] is poor on whether the rapidly evolving and steadily increasing use of experimental COVID-19 therapies may have potential for drug-drug interactions (DDIs), particularly with drugs used for common comorbidities, such as CP. Thus, it would be of paramount relevance and clinical interest to explore the relationship between the use of analgesic drugs and COVID-19 management, with a focus on the opioids that are generally employed in some CP conditions. The purpose of this narrative review is to discuss the available information regarding the currently utilized COVID-19 therapies (and the evidence level supporting them) and opioids for CP with a focus on warnings of potential interactions between these two classes of drugs.

Selection of evidence

Papers for the present review were retrieved by a PubMed search, using different combinations of keywords (e.g., pain treatment AND COVID-19 AND drug-drug interaction), without limitations in terms of publication date and language. Papers were selected for inclusion according to their relevance for the topic as judged by the Authors and were searched until March 2021. All types of studies were evaluated, including systematic reviews, case studies and clinical guidelines. The references of included studies were also reviewed to identify additional sources.

Covid-19 Treatment Options: A Rapidly Evolving Landscape

Following the fast-evolving understanding of SARS-CoV-2 virology, several potential drug targets are emerging and addressing both host response to the infection and clinical course of the disease[14]. Drugs preventing viral entry by inhibiting TMPRSS2 (i.e., camostat mesylate), targeting spike protein/angiotensin-converting enzyme 2 (ACE2) interactions (i.e., umifenovir), inhibiting viral entry and endocytosis (i.e., cloroquine/hydroxychloroquine) or targeting viral polyprotein synthesis (i.e., lopinavir, remdesivir) were progressively endorsed as potential therapies[14-18]. The immune response was also targeted through IL-6 inhibitors (tocilizumab, sarilumab), corticosteroids and IFN-β[14]. However, although most of them have also been included in ongoing clinical trials, they are not recommended for treatment at this time with only remdesivir being specifically approved by the US Food and Drug Administration (FDA), the UK Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicine Agency (EMA) for the treatment of COVID-19 in adults and adolescents (aged 12 years and over and weighing at least 40 kg) with pneumonia requiring supplemental oxygen therapy[19,20]. Moreover, among the repurposed drugs and experimental therapies that have been employed so far, only dexamethasone has proved to provide a mortality benefit and reduce the duration of hospital stay among 6,425 patients with severe COVID-19[21-24].The rapidly developing field of the new COVID-19 therapeutics demands an up-to-date overview of the clinical evidence supporting current recommendations, as well as an evaluation of the risk/benefit ratio for each available drug, particularly in frail and comorbid populations. Here, we focus our attention on the currently approved medications for COVID-19, as well as the successful example of drug repurposing in conferring mortality benefit (i.e., dexamethasone). A broad summary of their rationale of use and clinical efficacy can assist clinicians who are caring for patients with COVID-19 in seeking safer patient outcomes by means of appropriate therapeutic decisions.

Remdesivir

Originally proposed for Ebola virus treatment, remdesivir is a prodrug showing antiviral activity against SARS-CoV-1, MERS-CoV, and SARS-CoV-2 (for the latter, EC50: 0.77 μM; EC90: 1.76 μM)[23] in a variety of *in vivo* and *in vitro* experiments[25-27]. Remdesivir is converted to the active drug in the triphosphate form (remdesivir triphosphate) within cells[28]. Remdesivir acts by inhibiting the RNA-dependent RNA polymerase, which has a critical role in RNA virus replication and is also essential for the initiation of RNA replication in the host cell, a key step in the RNA virus cycle of infection[29]. Recent *in vitro* studies[26,30] revealed that remdesivir mimics an RNA nucleotide building block and, by a covalent link to the replicating RNA, leads to the premature termination of viral RNA transcription.

Assessment of potential efficacy of remdesivir in COVID-19 patients was initially hampered by the limited availability to compassionate use and the absence of clinical trials in critically ill patients with COVID-19[31] until the final results of the National Institute of Allergy and Infectious Diseases (NIAID) ACTT-1 Study became available providing initial strong evidence for a modest benefit of remdesivir[32,33]. Approximately 1,062 hospitalized patients received remdesivir (200 mg daily x 1 day followed by 100 mg daily x 9 days, up to 10 days total) or placebo in a 1:1 ratio. Patients receiving remdesivir experienced a shorter median time to recovery (10 *vs.* 15 days, RR for recovery 1.29; 95% CI 1.12-1.49, $p<0.001$) and a reduction in 29-day mortality (11.4 *vs.* 15.2%, HR 0.73; 95% CI 0.52-1.03). Furthermore, the observation that a 10-day treatment course had similar improvement in clinical status compared to a 5-day treatment course (10-day *vs* 5-day odds ratio 0.76; 95% CI 0.51-1.13 on day 14)[34,35] led to the National Institute of Health (NIH) recommendations of pursuing a 5-day treatment course of remdesivir when on supplemental oxygen but not mechanical ventilation, while maintaining the 10-day course for those patients on mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Although the initial results with the ACTT-1 trial seemed promising, findings from the international SOLIDARITY trial (with 2,750 patients receiving remdesivir and 4,088 no study drug) indicated no statistically significant reduction in mortality, thus suggesting that remdesivir may have limited utility in curbing mortality rates and that it may have limited efficacy[36]. Furthermore, a recent meta-analysis[37] comparing the effects of treatments for COVID-19 suggested that the impact of remdesivir on mortality, mechanical ventilation, length of hospitalization and duration of symptoms remain uncertain, thus raising further concerns about remdesivir therapeutic potential. Accordingly, the World Health Organization (WHO) recently advised against the use of remdesivir in hospitalized patients with COVID-19, regardless of disease severity[38], while recognizing that more research is needed, especially in certain groups of patients, and supporting continued enrolment in trials evaluating remdesivir. It has been also suggested[39] that the therapeutic window for remdesivir can be very narrow with greater benefit to be observed in individuals at high risk of hyper-inflammation who are diagnosed early during illness (≤10 days) and require supplemental oxygen. Of note, the availability of surrogate markers of infection progression may assist clinicians to better identify the optimal timing for remdesivir administration before further lung damage occurs. Importantly, according to the living WHO guidelines[40] among the key practical issues that clinicians should keep in mind there is the need of monitoring potential DDIs when remdesivir is co-administered with strong inducers or inhibitors of CYP enzymes. Furthermore, transaminase elevations have been observed in the remdesivir clinical trials[31], including in healthy volunteers and patients with COVID-19, thus indicating the need for a close monitoring of liver function in all patients before starting remdesivir and while receiving it as clinically appropriate[41]. In line with this, drug interactions have been identified as an unseen danger of experimental COVID-19 therapies[13], thus further underlining the relevance of DDIs and their time course to achieve an appropriate therapy selection particularly in comorbid or poly-medicated populations. *In vitro* studies have shown that remdesivir is a substrate for esterases in plasma and tissue, drug-metabolizing enzymes CYP2C8, CYP2D6 and CYP3A4, and for OATP1B1 and P-glycoprotein transporters. Furthermore, remdesivir induced CYP1A2 and potentially CYP3A *in vitro*; thus, its co-administration with CYP1A2 or CYP3A4 substrates with a narrow therapeutic index may lead to loss of their efficacy[41]. Finally, *in vitro*, remdesivir is an inhibitor of CYP3A4, OATP1B1 and OATP1B3. Although the clinical relevance of these *in vitro* drug interactions has not been established, as remdesivir may transiently increase plasma

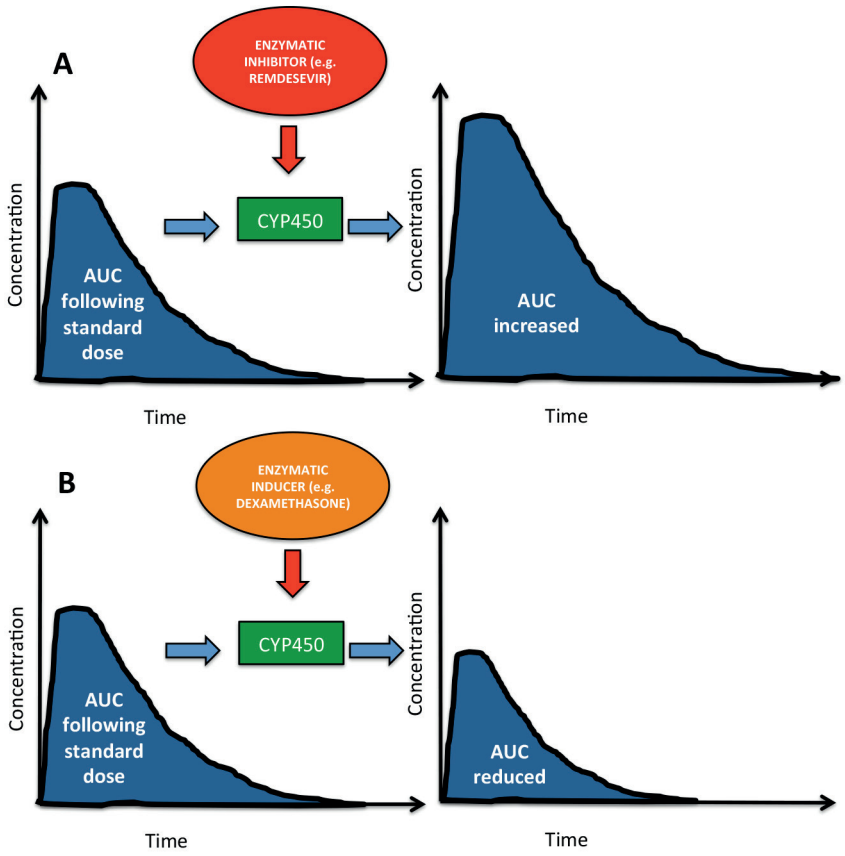

Figure 1. General effect of CYP450 inhibition **(A)** or induction **(B)** on area under curve. An increased AUC does not necessarily mean an increase in drug effect and similarly, a reduced AUC does not always translate into a reduced drug effect. AUC has an inverse correlation with drug effect if a pro-drug is used. Among opioids, tramadol can be considered a pro-drug, being its metabolite M1 up to six-times more potent than the parent drug in producing analgesia, and 200-times more potent in MOR binding. CYP2D6 induction may, indeed, increase the effect of tramadol and produce more adverse events. AUC: area under curve. Graphical elaboration of text in[106].

concentrations of substrates of CYP3A or OATP1B1/3, medicinal products that are substrates of CYP3A4 (e.g., fentanyl, buprenorphine, oxycodone) or substrates of OATP1B1/3 should be administered at least 2 hours after remdesivir[41]. Considering the relevance of the CYP450 system in opioid pharmacokinetics, this information can be of great interest for clinicians caring for COVID-19 patients who require an opioid prescription for pain relief. Figure 1 illustrates the effect of CYP450 inhibition and induction on drug pharmacokinetics.

Dexamethasone

Dexamethasone is a steroidal anti-inflammatory agent, listed in the WHO model list of essential medicines since 1977[42] and is widely employed to reduce inflammation in various chronic conditions amenable to glucocorticoid therapy, including asthma, rheumatoid arthritis and lupus. The anti-inflammatory mechanism and the ability to dampen down the body's immune system provided the rationale for its use particularly during the late stage of COVID-19 infection when the increasing number of infected epithelial cells and cell debrides trigger a massive cytokine release, also known as cytokine storm, with hyper-inflammation and immunosuppression[43]. Nevertheless, the beneficial effects of corticosteroids may also depend on the timing of treatment, the severity and the stage of the disease, as well as the dose administered and any individual characteristics of patients including comorbidity or polypharmacy. Verifying dexamethasone therapeutic potential in COVID-19 patients has been initially impeded based on the previously unsatisfactory data from SARS and MERS outbreaks showing variable

outcomes and higher mortality[44]. Accordingly, in the early stages of the epidemic, there was great uncertainty about the efficacy of corticosteroids in COVID-19[45] with many guidelines including those of the WHO, NIH and the European Society of Intensive Care Medicine and the Society of Critical Care Medicine (ESICM/SCCM) initially recommending routine use only for patients who developed refractory shock or were treated with corticosteroids prior to diagnosis of COVID-19. Recent evidence[40] suggests that dexamethasone did earn its place in the clinical realm as treatment of COVID-19 with a strong recommendation by the WHO in severe and critical COVID-19 patients. Furthermore, the evidence[37] arising from a recent meta-analysis suggests that corticosteroids probably reduce mortality and the need for mechanical ventilation in patients with COVID-19 compared with standard care. Of note, this evidence stems mostly from the RECOVERY trial, which showed a significant decrease in 28-day mortality in dexamethasone-treated patients compared to those receiving usual care (21.6% *vs* 24.6%, RR 0.83, 95% CI 0.74-0.9). Of note, such benefit was documented in patients receiving both invasive mechanical ventilation and oxygen support[46]. To date, there is no clear evidence if the aforementioned benefit may be considered a class effect as suggested by the results from the METCOVID and REMAP-CAP COVID-19 studies, since conflicting and not conclusive evidence was obtained when methylprednisolone or hydrocortisone was employed[47,48]. Overall, dexamethasone stands as a successful repurposed treatment strategy endowed with additional features including a long-lasting effect, allowing for a once-a-day regimen, and relatively low cost. However, clinicians should weigh the risks/benefits ratio that may vary with the severity of the disease, the availability of other treatment substitutes, as well as the incidence of other significant medical issues, particularly comorbidities[49]. To this end, the risk of DDIs should also be taken into account. Dexamethasone is reported to be a moderate inducer of CYP3A4 and glycoprotein P with its induction being dose-dependent and occurring after multiple doses. Thus, coadministration with other medicinal products metabolized by CYP3A4 (e.g., fentanyl, oxycodone) may increase their clearance, resulting in decreased plasma concentration[50]. While the clinical significance of the extent of induction is still uncertain, clinicians are advised to monitor concentrations of other CYP3A substrates if administered in conjunction with dexamethasone[50]. Furthermore, drug interaction studies provided evidence that dexamethasone may also act as CYP3A4 substrate, which is sensitive to competitive inhibition by strong CYP3A4 substrates, such as aprepitant and fosprepitant, thus leading to the recommendation of reducing dexamethasone dosing up to 25-50% when given in association with such molecules[51]. Taking into account that the CYP3A subfamily enzymes metabolize about one-third of clinically used drugs from almost all therapeutic categories, several potentially serious DDIs with corticosteroids in general, and with dexamethasone specifically, can be recognized. Dexamethasone is considered an inducer of other members of the CYP450 family enzymes, although, at least on a laboratory level, such an increase was not statistically significant in human liver slice preparations, owing to a variable response between different subjects[52]. However, the actual extent of the increased activity and the following clinical relevance is unknown. As far as we know, the only report describing a 10-fold *in vitro* increase in CYP2D6 activity, mRNA and protein after exposure to corticosteroids, has been withdrawn later[53]. Beyond the pharmacokinetic interactions, it would be important to keep in mind that dexamethasone may cause hypokalemia, thus potentiating the risk of ventricular arrhythmias if it is given with drugs able to prolong the QT interval. Of note, a risk for QT prolongation has been associated with drugs frequently used in the treatment of pain particularly in a dose-dependent manner, such as methadone, oxycodone or ketorolac[54].

Opioids: A Reason Of Concern When Co-Administered With Covid-19 Therapeutic Options?

Recognized as a major public health problem, severe chronic pain affects an increasing number of patients worldwide and requires a multidisciplinary approach taking into account all the pain dimensions and the related bio-psycho-social issues. Furthermore, some CP conditions are regarded as a disease[55,56] and its management appear particularly challenging in frail populations, including elderly, immunocompromised or poly-medicated subjects. With the aging of the population, the prevalence of chronic pain in older patients poses the burden of multimorbidity and polypharmacy as the elderly usually experience from one up to three comorbidities,

including hypertension, diabetes, depression and cancer[57,58]. As a result, comorbidities are a reason of concern when selecting the appropriate analgesic treatment due to the potential risk of DDIs and the occurrence of untoward adverse events, which may undermine analgesic efficacy. Effective pain management during the COVID-19 pandemic has been particularly difficult to pursue in terms of risks of harm from undertreatment and/or lost continuity of pain care (mostly due to pain therapy centers that shut down), as well as clinical implications arising from interactions between pain medications and the immune system and ultimately the experimental COVID-19 strategies employed so far. The impact of opioid drug treatment on immunity may be a safety concern for the physician although immunosuppression should not be regarded as a common side effect of all opioid molecules[59]. Accordingly, while the immunosuppression induced by morphine, fentanyl and remifentanil have been consistently reported in both animal and human studies, opioids such as tramadol or tapentadol exhibit a lower immunosuppressive activity at analgesic doses[60,61]. Of note, the potential immunomodulatory effects of methadone and buprenorphine can also be of relevance since higher susceptibility to different infections, or worst disease progression is reported in opioid-addicted subjects[62-64]. With regard to the potential interaction between pain medications and the experimental COVID-19 therapeutic options employed so far, a recent cross-sectional and multicenter study assigned a level D (i.e., consider therapy modification) risk for the interaction between oxycodone or fentanyl with the repurposed antiviral combination lopinavir/ritonavir due to an increase of drug concentration due to CYP3A4 inhibition[65]. Nevertheless, the evidence of interactions between opioids and the currently approved COVID-19 treatments in SARS-CoV-2-positive patients is scant, thus leaving uncertainty in clinical decisions. While referring clinicians to a constantly up-to-date database of potential interactions available online at www.covid19-druginteractions.org, here, we discuss the main pharmacological features of opioids that may have a role in DDIs, particularly their peculiar pharmacokinetics, in order to assist pain clinicians for appropriate prescribing in critically unwell patients during the COVID-19 pandemic.

Morphine

Morphine, also known as the archetypal opioid analgesic, is a naturally occurring full agonist of the μ-opioid receptor (MOR), and has in addition some activity on both δ and κ opioid receptors (DOR and KOR)[66]. It is mostly metabolized by demethylation and glucuronidation. Demethylation occurs *via* CYP3A4 and CYP2C8 and produces normorphine. The glucuronidation, the predominant metabolizing pathway, involves two enzymes, UGT2B7 and UGT1A3, with the former producing the 6-conjugate [morphine-6-glucuronide (M6G)] and the 3-conjugate (morphine-3-glucuronide, M3G). While M3G is devoid of any opioid analgesic activity, M6G is 50-fold more potent than the parent drug as an analgesic[67,68]. Importantly, morphine metabolites contribute differently to morphine's immunomodulatory effects, including modulation of innate and adaptative immunity[69]. It has been shown that M3G binds to Toll-like receptor 4 (TLR4) to induce allodynia and hyperalgesia, thus counteracting the analgesic effects of both morphine and M6G presumably via upregulation of pro-inflammatory cytokine IL-1[70]. A recent study[71] investigated whether morphine route of administration (intravenous, epidural or spinal) would impact differently on the immune cell function and cytokine production and found that while all three minimally hinder IL-2 production by CD4+ cells, only IV or epidural morphine injection mostly likely would counteract the IFN-γ production by CD8+ cells. Although coadministration with dexamethasone or remdesivir has not been studied, based on metabolism and clearance a clinically significant interaction is unlikely. In addition, remdesivir does not affect UGTs, thus poorly influencing morphine metabolism.

Fentanyl

Fentanyl is a synthetic opioid, full agonist of MOR, which, depending on the formulation and route of administration, may display a fast onset of action (when delivered as immediate-release forms) and short duration of action. Of note, fentanyl has been for a long time mostly used for the management of pain during surgical procedures. A transdermal fentanyl patch proved to be effective for the treatment of chronic pain while transmucosal oral formulations can be employed to manage breakthrough pain in adults with cancer[72]. Fentanyl is mainly metabolized by CYP3A4-mediated N-dealkylation to inactive metabolite norfentanyl, although some studies[73,74] have suggested that also other CYPs may play a role in its metabolism. Thus, potential inter-

actions may occur when fentanyl is given concurrently with agents that affect CYP3A4 activity. Co-administration with agents that induce CYP3A4 activity may reduce the efficacy of fentanyl, while the concomitant use of fentanyl with strong CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, clarithromycin and nelfinavir) or moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice and verapamil) may result in increased fentanyl plasma concentrations, potentially causing serious adverse drug reactions, including fatal respiratory depression[75]. To date, dexamethasone is a moderate CYP3A4 inducer and may decrease concentrations of fentanyl due to induction of CYP3A4, but this is unlikely to be clinically relevant. Of note, *in vitro*, remdesivir is an inhibitor of CYP3A4 but the evidence supporting meaningful effects upon remdesivir-fentanyl co-administration is lacking[76]. Finally, because fentanyl has an extraction ratio from 0.8-1.0, its rate of hepatic elimination should be more dependent on liver blood flow than on changes in its intrinsic clearance[77].

Hydromorphone

Hydromorphone is a synthetic morphine analogue, endowed with a higher affinity for MOR than DOR and commonly employed for the treatment of moderate to severe acute pain and CP. The oral analgesic potency ratio of hydromorphone to morphine has been reported to vary between 7:1 and 11:1. Hydromorphone is highly water-soluble and such a feature facilitates the development of very concentrated formulations[78]. Hydromorphone shares with morphine a similar metabolism mainly carried out by UGT 2B7 and UGT1A3 enzymes to produce the metabolite hydromorphone-3-glucuronide (H3G). Although very poorly metabolized by CYP450 enzymes, it has been reported the conversion of hydromorphone to dihydromorphone and its isomer named dihydroisomorphone by the enzyme dihydromorphinone ketone reductase[67]. The effect of 2-month treatment with hydromorphone on immune response and competence has been evaluated in patients suffering from chronic pain[77]. No impact on cutaneous-cell immunity, T-lymphocyte subpopulations nor IL-1 and IL-6 production has been reported. Thus, hydromorphone does not display immunosuppressant properties[79,80]. Coadministration with remdesivir or dexamethasone has not been studied but, basing on metabolism and clearance, a clinically significant interaction is unlikely. Hydromorphone is eliminated *via* glucuronidation, mainly by UGT2B7 that was not reported to be affected by remdesivir.

Oxycodone

Oxycodone is a semi-synthetic selective MOR agonist whose affinity for the MOR is less than that of morphine or methadone although it displays a similar antinociceptive effect. Oxycodone efficacy in treating acute, cancer-related, and chronic pain has been documented, thus placing oxycodone as one of the invaluable alternatives to morphine[81-83]. Oxycodone is bio-transformed in the liver by cytochrome into active metabolites (oxymorphone and noroxycodone) with higher MOR affinity that participates in its analgesic efficacy, as well as into several glucuronide conjugates[84]. Oxycodone is metabolized mainly *via* oxidative, but also *via* reductive pathways with only 10-14% being excreted in unchanged or conjugated forms in urine. Oxycodone is mostly a CYP450 3A4/5 substrate, which makes it prone to the interactions with CYP3A inducers and inhibitors with the potential risk of reduction and increase of oxycodone plasma concentrations, respectively. The main oxidative pathway includes N-demethylation to noroxycodone by CYP3A4/5 and further to noroxymorphone by CYP2D628. Approximately 11% of oxycodone is O-demethylated to oxymorphone by CYP2D6, which is further transformed to noroxymorphone by CYP3A4/5 and CYP2D628. Less is known about the role of P-glycoprotein in the transport of oxycodone *via* blood-brain barrier. As dexamethasone is a CYP3A4 inducer and remdesivir appears to inhibit *in vitro* CYP3A4, caution should be exercised if oxycodone is given to patients receiving the aforementioned medications.

Tramadol

Tramadol is an atypical opioid whose pharmacodynamic properties of tramadol distinguish it from classic opioids being a weak opioid (with low affinity for MOR and KOR) that also inhibits the reuptake of serotonin and noradrenaline[85,86]. While structurally related to codeine and morphine, tramadol is 6,000-times less potent than morphine and 10-times less potent than codeine, thus standing as advantageous compared to classic opioids thanks to a limited incidence of side effects and a lower abuse potential[85,86]. Tramadol is extensively metabolized in the liver *via* CYP2D6 and 3A4, to O-desmethyltramadol (M1) and N-desmethyltramadol (M2), respectively,

being the main phase 1 metabolites. Subsequently, both M1 and M2 are further metabolized to secondary metabolites and conjugated with glucuronic acid and sulfate before excretion in urine. The metabolite M1 is the most pharmacologically active, being up to six-times more potent than the parent drug in producing analgesia, and 200-times more potent in MOR binding. Active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite; however, the clinical importance of such an interaction has not been studied. Caution should be exercised if tramadol is given to patients receiving remdesivir although no clear evidence of their interaction has been documented so far.

Tapentadol

Tapentadol is an atypical opioid that acts as both a MOR agonist and a noradrenaline reuptake inhibitor (NRI), approved in the EU as prolonged-release (PR) formulation for the treatment of severe chronic pain manageable only with opioid analgesics[87]. Tapentadol's unique mode of action supports its rationale of use in conditions of both cancer and non-cancer chronic pain. It has been proposed that these two mechanisms synergistically interact with each other to confer analgesic effectiveness for nociceptive (due to its MOR component activity), neuropathic (due to its NRI component contribution) and mixed pains while sparing from opioid-related adverse events, mainly gastrointestinal[87]. Moreover, literature data consistently show that tapentadol PR is associated with improvements in all dimensions of quality of life (with superior results if compared with oxycodone controlled-release (CR) and its association with naloxone), which in turns exerts a positive effect on functional recovery and sleep quality[88,89]. The major metabolic pathway for tapentadol is conjugation with glucuronic acid to produce glucuronides with the major metabolite being tapentadol-O-glucuronide[90]. Thus, this molecule is associated with a low risk of DDIs at the CYP450 level and may, therefore, be used in poly-treated patients[90]. Furthermore, tapentadol exhibits a lower immunosuppressive activity at analgesic doses *vs.* morphine[60,61,91]. The major elimination pathway for tapentadol is conjugation with glucuronic acid mediated *via* UGT mainly UGT1A6, UGT1A9 and UGT2B7 isoforms. Thus, concomitant administration with strong inhibitors of these isoenzymes may lead to increased systemic exposure of tapentadol[92]. Pending further research on the co-administration of tapentadol with the currently recommended therapies for COVID-19, the low risk of DDIs at CYP450 level may support the preferred use of tapentadol over opioids metabolized through the CYP450 hepatic system.

Methadone

Methadone is a synthetic opioid acting primarily at the MOR but also at KOR and DOR. Moreover, it also binds N-methyl-D-aspartate (NMDA) receptor as a weak antagonist and such activity supports its use in neuropathic pain[59]. Methadone stands as a cornerstone strategy for substitution therapy in opioid dependence but also as a valuable option in the management of chronic pain, especially in cancer pain. Studies *in vitro* have shown that CYP2B6 is the main determinant of methadone metabolism, clearance, elimination, and plasma concentrations in humans. Methadone is cleared predominantly *via* N-demethylation to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), which is pharmacologically inactive, and hence secondarily to 2-ethyl-5-methyl-3,3-diphenylpyrroline (EMDP). Importantly, the disposition of methadone, which is dosed as a racemate, is stereoselective. CYP2B6 genetics also influences methadone metabolism and clearance that appear in CYP2B6*6 carriers and increased in CYP2B6*4 carriers; as a result, CYP2B6 genetics can explain, at least in part, interindividual variability in methadone metabolism and clearance. Overall, both constitutive variability due to CYP2B6 genetics, and CYP2B6-mediated drug interactions (i.e., with CYP2B6 inducers, such as ritonavir or lopinavir/ritonavir), can alter methadone disposition, clinical effect and drug safety. Pharmacodynamic variability may also occur, as one-third of well-maintained methadone patients may experience withdrawal symptoms, and adverse events can occur despite normal therapeutic plasma concentrations[93-96].

Of note, inducers or inhibitors of CYP3A4 and CYP2D6 can affect methadone levels thereby modifying its safety profile[97,98].

Methadone shows dose-dependent cardiotoxicity, such as torsade de pointes[99], and can prolong the QT interval of the ECG, an issue of potential clinical significance[100,101]. Thus, co-administra-

tion with medications that prolong QT interval, such hydroxychloroquine, is not recommended. No data are currently available regarding DDIs between methadone and remdesivir and/or dexamethasone.

Buprenorphine

Buprenorphine is an atypical opioid and a semisynthetic thebaine derivative, ~20-fold more potent than morphine, acting as a partial agonist of MOR, opioid-like receptorl (ORL-1) full agonist and KOR and DOR antagonist. The main features of buprenorphine encompass high affinity for the opioid receptors, low intrinsic efficacy and slow receptor binding kinetics. Clinical trials documented buprenorphine efficacy in the treatment of chronic pain and, in some countries, in the maintenance treatment of heroin addiction as an alternative to methadone, as well as its suitability for the sublingual and transdermic mode of administration[102].

Buprenorphine is metabolized by 14-N-dealkylation to norbuprenorphine by CYP3A and by CYP2C8. Of note, both parent molecule and dealkylated metabolite undergo extensive phase II metabolism by UGT, followed by CYP2D6. Norbuprenorphine is a μ (mu) agonist with weak intrinsic activity. Co-administration of buprenorphine with strong CYP3A4 inhibitors, such as ketoconazole, has been shown to increase the C_{max} and AUC of buprenorphine (approximately 70% and 50%, respectively) and, to a lesser extent, of its metabolite norbuprenorphine[102,103]. Thus, patients receiving buprenorphine may require dose reduction if combined with potent CYP3A4 inhibitors (e.g., ritonavir, nelfinavir or indinavir, ketoconazole and itraconazole or macrolide antibiotics). Conversely, concomitant use of CYP3A4 inducers with buprenorphine may decrease its plasma concentrations, potentially in sub-optimal treatment of opioid dependence with buprenorphine. Patients with substance use disorder are more susceptible to develop COVID-19 owing to underlying comorbidities, immune suppression, and social correlates of drug use[104]. To this end, caution should be exercised among subjects with alcohol or opioid dependence and comorbid liver dysfunction when initiating treatment for COVID-19 pending more data on potentially detrimental DDIs between buprenorphine and remdesivir and/or dexamethasone[104].

Table I summarizes the current evidence on the DDIs of concern when opioids are co-administered with COVID-19 therapeutic options.

Conclusions

Multimorbidity and the resulting polypharmacy may bear a risk of DDIs, which should be systematically assessed and monitored when initiating treatment for COVID-19 in patients already receiving chronic treatment in order to anticipate the risk and eventually identify an appropriate therapeutic alternative. Predictors of DDIs encompass administration of drugs with a narrow therapeutic index or able to prolong the QT interval, as well as an extensive drug metabolism, *via* hepatic CYPs[94]. Of note, positive associations have been documented between the occurrence of potential drug interaction and the number of drugs, the length of stay and the characteristics of the administered medications[105]. Although the risk of drug interactions should not necessarily preclude the use of experimental therapies for COVID-19, it is of utmost relevance to recognize potentially harmful drug interactions thus promoting safe prescribing in critically ill patients during the COVID-19 pandemic[76]. Accordingly, although the likelihood of drug interactions reported in *in vitro* studies may not be always predictive of what will occur in people, in presence of scant evidence, a review of the best available evidence and expert opinion may assist physicians in a rapidly evolving clinical scenario. The earlier repurposed therapies, especially hydroxychloroquine and the antivirals (ritonavir/lopinavir), did raise important concerns in terms of DDIs which have been regarded as the "unseen danger" of the experimental COVID-19 therapies although the current recommendations against their use may have shed a different light on DDIs. However, DDIs may occur upon administration of the currently recommended therapies and demand a careful appraisal of the available information to guide clinical decisions. To this end, the clinician should keep in mind the frequent DDIs with drugs extensively metabolized by the CYP450 system and prefer opioids undergoing a limited hepatic metabolism. Furthermore, in the current pandemic scenario, it would be advisable to take into consideration the existing differences among opioids with regard to their impact on immune responses. To this end, *in vivo* studies[79,91] suggested that tapentadol and hydromorphone appear neutral on both cytokine production and immune parameters and may stand as many valuable options. While waiting for further clinical trials and observational studies aimed at providing more concrete data, clinicians need to re-evaluate current treatment recommendations as new data emerges. Overall, identification and management of DDIs and dissemination of the related knowledge

Table I. Drug-drug interaction of concern when COVID-19-positive patients take opioids.

	Dexamethasone	Remdesivir	Notes
Buprenorphine	Interaction possible (CYP3A4 and glycoprotein P induction)	Interaction possible (CYP3A4 inhibitor)	Metabolized by 14-N-dealkylation to norbuprenorphine by CYP3A and by CYP2C8 **Consider therapy modification**
Fentanyl	Interaction possible (CYP3A4 and glycoprotein P induction)	Interaction possible (CYP3A4 inhibitor)	Possible decreased analgesia when DEX co-administration. Possible toxicity when remdesevir co-administered. **Consider therapy modification**
Hydromorphone	Interaction unlikely	Interaction unlikely	Mainly metabolised by glucuronidation, via UGT 2B7 and UGT 1A3 enzymes
Methadone	Interaction possible (CYP3A4 and glycoprotein P induction)	Interaction possible (CYP3A4 inhibitor)	Complex pharmacokinetics. *in vitro* CYP2B6 is the main determinant of methadone metabolism. **Consider therapy modification. Close monitoring for side effects or withdrawal symptoms**
Morphine	Interaction unlikely	Interaction unlikely	Mainly metabolized by glucuronidation, via UGT 2B7 and UGT1A3 enzymes
Oxycodone	Interaction possible (CYP3A4 and glycoprotein P induction)	Interaction possible (CYP3A4 inhibitor)	Possible decreased analgesia when DEX co-administration. Possible toxicity when remdesevir co-administered. **Consider therapy modification**
Tapentadol	Interaction unlikely	Interaction unlikely	Mostly metabolized by glucuronidation, via UGT1A6, UGT1A9 and UGT2B7 enzymes
Tramadol	Interaction possible (CYP3A4 induction)	Interaction possible (CYP3A4 inhibitor)	Mainly metabolized in the liver via CYP2D6 to O-desmethyltramadol (more active than parent drug or other metabolites) and via CYP3A4 to N-desmethyltramadol **Consider therapy modification**

Elaborated from data in[41,50,66,75,84,92,94].

should be a major goal in the delivery of chronic care to ensure optimized patient outcomes and facilitate updating recommendations for COVID-19 therapy in frail populations, namely comorbid, poly-medicated patients or individuals suffering from substance use disorders.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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