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SHORT COMMUNICATION

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Multiple potential targets of opioids in the treatment of acute respiratory distress syndrome from COVID-19

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Abstract

COVID-19 can present with a variety of clinical features, ranging from asymptomatic or mild respiratory symptoms to fulminant acute respiratory distress syndrome (ARDS) depending on the host's immune responses and the extent of the associated pathologies. This implies that several measures need to be taken to limit severely impairing symptoms caused by viral-induced pathology in vital organs. Opioids are most exploited for their analgesic effects but their usage in the palliation of dyspnoea, immunomodulation and lysosomotropism may represent potential usages of opioids in COVID-19. Here, we describe the mechanisms involved in each of these potential usages, highlighting the benefits of using opioids in the treatment of ARDS from SARS-CoV-2 infection.

KEYWORDS

ARDS, COVID-19, cytokine storm, dyspnoea, immunomodulation, opioids

1 | INTRODUCTION

COVID-19 currently represents an ongoing global threat as the development of ARDS during the course of disease may be observed in more than 40% of patients with pneumonia from SARS-CoV-2 infection.[1] ARDS from COVID-19 requires early recognition and a comprehensive management as it can have worse outcomes than ARDS from other causes. Pulmonary fibrosis, thrombotic microangiopathy, pleuritic pain and worsening of respiratory symptoms appear to be factors of a more severe course of disease from the increased inflammatory responses induced by SARS-CoV-2 infection.[2] While opioids can be used for the subjective perception of ARDS from COVID-19,[3] several other properties of opioids may address the physiopathological mechanisms involved in ARDS development and limit essential steps of the viral infectious cycle. Morphine is an organic heteropentacyclic tertiary amino compound being a morphinane alkaloid with potent

analgesic and psychoactive properties. It is most abundant in opium poppy (*Papaver somniferum* L)[4] and acts directly on the central nervous system (CNS) to alleviate pain. By its chemical structure, morphine derives from a hydride of a morphinan, being a conjugate base of a morphine (1+). Specific opiate receptors for morphine are found in brain and control different functions, including analgesia, euphoria, sedation, anxiolysis and respiratory depression.[5] The opioid receptors have been previously described and are represented by miu(μ), delta(δ) and kappa(κ) receptors. While many of them are involved in the perception of pain and dyspnoea, opioid receptors are also found in the digestive system inhibiting bowel movement and on the surface of immune cells having immunomodulatory effects.[6] Opioids are widely used for treating moderate to severe pain in patients who require potent analgesia, mostly in the setting of acute trauma, childbirth, invasive procedures and chronic end-stage illnesses.[7] While strong opioids are potent analgesics, less strong representatives such as codeine and DHC have more pronounced effects on cough, [8] diarrhoea [9] and dyspnoea.[10]

2 | OPIOIDS AND DYSPNOEA

Opiate drugs have long been known to exert effects on the respiratory system. These include reducing the respiratory response to CO_2,[11] hypoxia,[12] inspiratory flow-resistive loading[13] and exercise,[14] with overdoses being capable of producing respiratory depression.[15] Opioid receptors from various areas of the CNS and the cardio-respiratory systems seem responsible for the mediation of the mechanisms of their antidyspnoeic effects.[16-18] Moreover, in the palliation of dyspnoea, opioids are the only agents with sufficient pharmacological evidence.[10,19,20] These are some of the arguments which led to the usage of opioids in the palliation of dyspnoea, being recommended by European and US therapeutic guidelines.[21,22] Treatment of dyspnoea outside oncological pathology such as the chronic obstructive pulmonary diseases (COPD)[23-25] is emerging as an indication in professional society guidelines such as the GOLD.[26] While special precautions regarding morphine usage in patients with severe renal insufficiency, the dosage and dosage intervals require adaptation to the renal function for all μ-opioids due to their renal elimination.[27-29] In patients without severely impaired kidney function, they can be used in both opioid-naïve and opioid-treated patients without relevant breath depression, impaired oxygenation or increase in CO2 concentration.[30] While dyspnoea and anxiety occur most often as associated events, opioids have been known to reduce the subjective perception of breathlessness, mainly by increasing the amplitude of breaths and limiting hyperventilation and tachypnoea while exerting anxiolytic effects. No opioid is superior to another in treating dyspnoea and oxycodone, and hydromorphone and fentanyl can be used for this purpose, while dihydrocodeine, diamorphine, oral and paranteral morphine have the most evidence for this use.[23,31-33]

Opioid-naïve patients require smaller doses of opioids for dyspnoea than for the palliation of pain. However, patients already on opioid treatment will require increases of the baseline dosage of up to 25%-50% for the palliation of dyspnoea.[34] This is associated with the advantages of significant decrease in the intensity of dyspnoea, tachypnoea and no higher risk of respiratory depression but with the drawback of unwanted side-effects such as initial nausea and constipation.[35]

3 | OPIOIDS AND IMMUNOMODULATION

Opioid receptors are present on various cells of the immune system (eg lymphocytes, monocytes, macrophages and neutrophils) exerting inhibitory effects on lymphocyte proliferation and cytokine release.[6,36] (Figure 1). In vitro and in vivo animal experiments have shown a wide spectrum of effects of morphine such as anti-inflammatory, antifibrotic, antitumour, cardioprotective and renoprotective.[37-39] These effects could counteract the excessive inflammation, fibrosis and cardiac and renal pathology associated with COVID-19 as much of its pathology is associated with the dysregulation of the renin-angiotensin system (RAS) from antagonization of angiotensin-converting enzyme 2 (ACE2).[40] Besides, activation of the inflammasome with subsequent adaptative immune responses and cytokine release syndrome or the cytokine storm is seen in SARS-CoV[41] as well as in SARS-CoV-2 pathogenesis.[42] While a reduced pathogenesis from cytokine release and inflammatory cell infiltration in the lungs has been observed with the immunomodulatory effect of opioids in various viral infections, immunosuppression from extended use is not to be overlooked.[43,44] In COVID-19, the distribution of ACE2 receptors mostly in lung tissue but also in heart, kidney, brain and endothelia makes the respiratory tract carry the most important load of viral-induced pathology and the other organs expressing ACE2 the second most affected by the viral replication and the hosts' response against it. Most of the pathology is induced by the immune response against the invading pathogen rather than the infection itself as the virus uses the replicative machinery of the cell followed by budding for its egress rather than cell lysis.[45] The host cell death can occur if excess Ang II is produced leading to direct apoptosis[46] and when excess protein is produced with endoplasmic reticulum (ER) stress, unfolded protein response (UPR) and subsequent apoptosis.[47] Whether a link exists between the antifibrotic and antiinflamatory effects of the depressor arm of RAS with the ACE2 receptors and the antiinflamatory and antifibrotic effects from stimulating opioid receptors in the immune system remains elusive but could represent a future research direction as both receptors are abundant in the brain and peripheral organs and exert seemingly inter-related effects. This could also support the usage of opioids for addressing neurological manifestations of COVID-19 which are not rare occurrences.[48-50]

4 | OPIOIDS AND LYSOSOMOTROPISM

Most amine drugs are naturally occurring alkaloids or synthesis compounds containing the amino group. Being weak bases, they

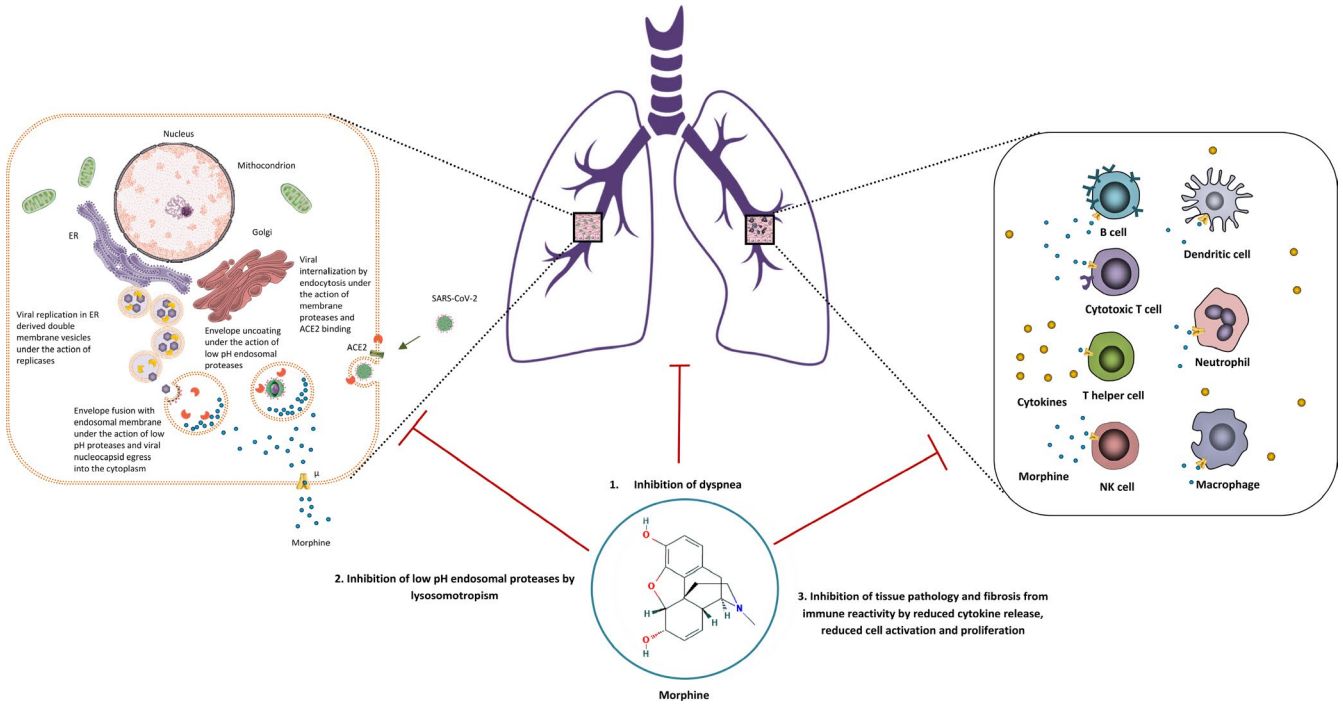

FIGURE 1 Schematic representation of multiple potential targets the opioid morphine in COVID-19

have the ability of lysosomotropism.[51] This translates in the property of accumulating in acidic lysosomes in concentrations several hundred times higher than in the cytoplasm increasing lysosomal pH by becoming trapped following protonation in the ion-trapping process.[51,52] The discoverer of lysosomes, Christian de Duve, who was awarded the Nobel Prize for Physiology and Medicine in 1974 together with George Emil Palade and Albert Claude for their work on the functional organization of the cell, elegantly described in a commentary the theoretical basis for lysosomotropism and physiopathological and clinical implications of this process.[53] In most infections with enveloped viruses, the viral pathogens depend on the low-pH endosomal hydrolases to uncoat their envelope and fuse with the lysosomal membrane, but such processes may be disrupted by aminic drugs that increase the lysosomal pH, exposing the virus to the organelle's degradative enzymes.[54] Since morphine, an aminic drug and the alkaloid of morphinane have long been shown to accumulate in lysosomes having lysosomotropic properties,[55] we may assert that it could have an inhibitory effect on lysosomal acidification along other opioid alkaloids. This is supported by the observations on the lysosomotropic effects of morphine on another enveloped RNA virus the human immunodeficiency virus—HIV-1[56] and of multiple other lysosomotropic drugs on the hepatitis C virus—HCV, an enveloped RNA virus.[57] Moreover, loperamide, an opioid receptor agonist and weak base, was shown to become trapped and increase lysosomal pH being lysosomotropic[58] and inhibiting MERS-CoV and SARS-CoV-2 replication in cell culture.[59-61] The lysosomotropic effect of opiate drugs could therefore be exploited in COVID-19 for the inhibition of viral uncoating in the endosomal internalization pathway as this is a common entry route for coronaviruses[62]

5 | CONCLUSIONS

Triple effects of opioids could potentially be exploited in COVID-19, such as treating dyspnoea, inhibiting the cytokine storm and disrupting lysosomal acidification with effects on both the viral infectious cycle and on the host's response to the infection. Due care should be taken when using opioid drugs as they have a high potential for addiction, with physical and psychological tolerance and dependence often occurring. However, in emergency situations such as ARDS from COVID-19 at the currently indicated dosages for treating dyspnoea, the benefits of using opioids could overcome the unpleasant side-effects, addressing both the viral infectious cycle and the host's response to the viral-induced pathogenesis. These represent arguments to support the perspective of using opioids in addressing the clinical manifestations and pathogenesis associated with the ARDS from the SARS-CoV-2 infection.

CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Andrei Cismaru: Conceptualization (equal); Writing-original draft (equal). **Gabriel Cismaru:** Conceptualization (equal); Writing-review & editing (equal). **Seyed Fazel Nabavi:** Conceptualization (equal); Writing-review & editing (equal). **Seyed Mohammad Nabavi:** Conceptualization (equal); Writing-review & editing (equal). **Mostafa Ghanei:** Writing-review & editing (equal). **Claudia Cristina Burz:** Writing-review & editing (equal). **Ioana Berindan-Neagoe:** Conceptualization (equal); Supervision (equal); Writing-review & editing (equal).

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180:934.
2. Gibson PG, Qin L, Puah SH. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. *Med J Aust*. 2020;213:54-56.e1.
3. Worsham CM, Banzett RB, Schwartzstein RM. Air hunger and psychological trauma in ventilated patients with COVID-19. An urgent problem. *Ann Am Thorac Soc*. 2020;17:926-927.
4. Lal RK, Sarkar S, Singh S, Gupta P, Zaim M. Inheritance pattern and conservative genetics study tool: descriptors on opium poppy (*Papaver somniferum* L.). *Acta Hortic*. 2014;1036:71-86.
5. Valentino RJ, Volkow ND. Untangling the complexity of opioid receptor function. *Neuropsychopharmacology*. 2018;43:2514-2520.
6. Sharp BM, Roy S, Bidlack JM. Evidence for opioid receptors on cells involved in host defense and the immune system. *J Neuroimmunol*. 1998;83:45-56.
7. Morphine: uses, dosage, side effects, warnings - Drugs.com. https://www.drugs.com/morphine.html.
8. McCrory DC, Coeytaux RR, Yancy WS Jr, et al. *Assessment and Management of Chronic Cough*. *Assessment and Management of Chronic Cough*. Agency for Healthcare Research and Quality (US), 2013.
9. Prommer E. Role of codeine in palliative care. *J Opioid Manag*. 2011;7:401-406.
10. Johnson MJ, Hui D, Currow DC. Opioids, exertion, and dyspnea: a review of the evidence. *Am J Hosp Palliat Med*. 2016;33:194-200.
11. Eckenhoff JE, Helrich M, Hege MJ. The effects of narcotics upon the respiratory response to carbon dioxide in man. *Surg Forum*. 1955;5;681-686.
12. Weil JV, McCullough RE, Kline JS, Sodal IE. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. *N Engl J Med*. 1975;292:1103-1106.
13. Kryger MH, Yacoub O, Dosman J, Macklem PT, Anthonisen NR. Effect of meperidine on occlusion pressure responses to hypercapnia and hypoxia with and without external inspiratory resistance. *Am Rev Respir Dis*. 1976;114:333-340.
14. Santiago TV, Johnson J, Riley DJ, Edelman NH. Effects of morphine on ventilatory response to exercise. *J Appl Physiol Respir Environ Exerc Physiol*. 1979;47:112-118.
15. Boom M, Niesters M, Sarton E, Aarts L, Smith TW, Dahan A. Non-analgesic effects of opioids: opioid-induced respiratory depression. *Curr Pharm Des*. 2012;18:5994-6004.
16. Von Leupoldt A, Sommer T, Kegat S, et al. The unpleasantness of perceived dyspnea is processed in the anterior insula and amygdala. *Am J Respir Crit Care Med*. 2008;177:1026-1032.
17. Pattinson KTS, Governo RJ, MacIntosh BJ, et al. Opioids depress cortical centers responsible for the volitional control of respiration. *J Neurosci*. 2009;29:8177-8186.
18. von Leupoldt A, Sommer T, Kegat S, et al. Dyspnea and pain share emotion-related brain network. *NeuroImage*. 2009;48:200-206.
19. Clemens KE, Klaschik E. Symptomatic therapy of dyspnea with strong opioids and its effect on ventilation in palliative care patients. *J Pain Symptom Manage*. 2007;33:473-481.
20. Currow DC, McDonald C, Oaten S, et al. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symptom Manage*. 2011;42:388-399.
21. Kloke M, Cherny N. Treatment of dyspnoea in advanced cancer patients: ESMO clinical practice guidelines. *Ann Oncol*. 2015;26:v169-v173.
22. Levy MH, Smith T, Alvarez-Perez A, et al.Continue NCCN Guidelines Panel Disclosures NCCN Guidelines Version Panel Members Palliative Care 1.2014 Vice-Chair. https://doi.org/10.6004/jnccn.2014.0136
23. Woodcock AA, Gross ER, Gellert A, et al. Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. *N Engl J Med*. 1981;305:1611-1616.
24. Rocker G, Horton R, Currow D, Goodridge D, Young J, Booth S. Palliation of dyspnoea in advanced COPD: revisiting a role for opioids. *Thorax*. 2009;64:910-915.
25. Young J, Donahue M, Farquhar M, Simpson C, Rocker G. Using opioids to treat dyspnea in advanced COPD: attitudes and experiences of family physicians and respiratory therapists. *Can Fam Physician*. 2012;58:e401.
26. Global initiative for chronic obstructive lung disease global initiative for chronic obstructive lung disease pocket guide to COPD diagnosis, management, and prevention: a Guide for Health Care Professionals; 2018. www.goldcopd.org. Accessed August 12, 2020.
27. King S, Forbes K, Hanks GW, Ferro CJ, Chambers EJ. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project. *Palliat Med*. 2011;25:525-552.
28. Murtagh FEM, Chai MO, Donohoe P, Edmonds PM, Higginson IJ. The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother*. 2007;21:5-16.
29. Twycross RG, Wilcock A*PCF4 : palliative care formulary*; 2011. Palliativedrugs.com
30. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012;13:e58-e68.
31. Simon ST, Köskeroglu P, Gaertner J, Voltz R. Fentanyl for the relief of refractory breathlessness: a systematic review. *J Pain Symptom Manage*. 2013;46:874-886.
32. Pang GS, Qu LM, Tan YY, Yee ACP. Intravenous fentanyl for dyspnea at the end of life: lessons for future research in dyspnea. *Am J Hosp Palliat Med*. 2016;33:222-227.
33. Clemens KE, Klaschik E. Effect of hydromorphone on ventilation in palliative care patients with dyspnea. *Support Care Cancer*. 2008;16:93-99.
34. Allard P, Lamontagne C, Bernard P, Tremblay C. How effective are supplementary doses of opioids for dyspnea in terminally ill cancer patients? A randomized continuous sequential clinical trial. *J Pain Symptom Manage*. 1999;17:256-265.

35. Clemens KE, Quednau I, Klaschik E. Is there a higher risk of respiratory depression in opioid-nave palliative care patients during symptomatic therapy of dyspnea with strong opioids? *J Palliat Med*. 2008;11:204-216.
36. McCarthy L, Wetzel M, Sliker JK, Eisenstein TK, Rogers TJ. Opioids, opioid receptors, and the immune response. *Drug Alcohol Depend*. 2001;62:111-123.
37. Dinda A, Gitman M, Singhal PC. Immunomodulatory effect of morphine: therapeutic implications. *Exp Opin Drug Safety*. 2005;4:669-675.
38. Page GG. Immunologic effects of opioids in the presence or absence of pain. *J Pain Symptom Manage*. 2005;29:25-31.
39. Ghiassi-Nejad Z, Friedman SL. Advances in antifibrotic therapy. *Exp Rev Gastroenterol Hepatol*. 2008;2:803-816.
40. Cismaru AC, Cismaru LG, Nabavi S, et al. Game of "crowning" season 8: RAS and reproductive hormones in COVID-19 – can we end this viral series? *Arch Med Sci*. 2020;16. [Epub ahead of print].
41. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol*. 2017;39:529-539.
42. Diao B, Wang C, Tan Y, et al. Reduction and functional exhaustion of t cells in patients with coronavirus disease 2019 (COVID-19). *medRxiv*. 2020. https://doi.org/10.1101/2020.02.18.20024364
43. Salimi V, Hennus MP, Mokhtari-Azad T, et al. opioid receptors control viral replication in the airways. *Crit Care Med*. 2013;41:205-214.
44. Tahamtan A, Tavakoli-Yaraki M, Mokhtari-Azad T, et al. Opioids and viral infections: a double-edged sword. *Front Microbiol*. 2016;7:970.
45. Garoff H, Hewson R, Opstelten D-JE. Virus maturation by budding. *Microbiol Mol Biol Rev*. 1998;62:1171-1190.
46. Zhang H, Zhang X, Hou Z, Deng F. RhACE2 - playing an important role in inhibiting apoptosis induced by Ang II in HUVECs. *Medicine*. 2019;98:e15799.
47. Szegezdi E, Logue SE, Gorman AM, Samali A. Mediators of endoplasmic reticulum stress-induced apoptosis. *EMBO Rep*. 2006;7:880-885.
48. Mao L, Jin H, Wang ME, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77:683.
49. Gklinos P. Neurological manifestations of COVID-19: a review of what we know so far. *J Neurol*. 2020;267:2485-2489.
50. Whittaker A, Anson M, Harky A. Neurological manifestations of COVID-19: a review. *Acta Neurol Scand*. 2020;142:14-22.
51. Kaufmann AM, Krise JP. Lysosomal sequestration of amine-containing drugs: analysis and therapeutic implications. *J Pharm Sci*. 2007;96:729-746.
52. Ohkuma S, Poole B. Fluorescence probe measurement of the intralysosomal pH in living cells and the perturbation of pH by various agents. *Proc Natl Acad Sci USA*. 1978;75:3327-3331.
53. De Duve C, De Barsy T, Poole B, et al. Lysosomotropic agents. *Biochem Pharmacol*. 1974;23:2495-2531.
54. Simons K, Garoff H, Helenius A. How an animal virus gets into and out of its host cell. *Sci Am*. 1982;246:58-66.
55. Liesse M, Lhoest G, Trouet A, Tulkens P. Uptake and intracellular localization of morphine in lysosomes and cell sap of cultured fibroblasts. *Arch Int Physiol Biochim*. 1976;84:638-639.
56. El-Hage N, Rodriguez M, Dever SM, et al. HIV-1 and morphine regulation of autophagy in microglia: limited interactions in the context of HIV-1 infection and opioid abuse. *J Virol*. 2015;89:1024-1035.
57. Gastaminza P, Whitten-Bauer C, Chisari FV. Unbiased probing of the entire hepatitis C virus life cycle identifies clinical compounds that target multiple aspects of the infection. *Proc Natl Acad Sci USA*. 2010;107:291-296.
58. Kannan P, Brimacombe KR, Kreisl WC, et al. Lysosomal trapping of a radiolabeled substrate of P-glycoprotein as a mechanism for signal amplification in PET. *Proc Natl Acad Sci USA*. 2011;108:2593-2598.
59. De Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrob Agents Chemother*. 2014;58:4875-4884.
60. Hoagland DA, Clarke DJB, Moeller R, Han Y. Modulating the transcriptional landscape of SARS-CoV-2 as an effective method for developing antiviral compounds. https://doi.org/10.1101/2020.07.12.199687
61. Jeon S, Ko M, Lee J, et al. Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs. *Antimicrob Agents Chemother*. 2020;64(7):e00819-20.
62. Zumla A, Chan JFW, Azhar EI, Hui DSC, Yuen KY. Coronaviruses-drug discovery and therapeutic options. *Nat Rev Drug Discov*. 2016;15:327-347.

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