Opioid Use Disorder and COVID-19: Inpatient Considerations for Intersecting Pandemics

Justine Lazatin, DO[1,3,4], Ariana Kam[2], Alesia Cloutier, DO, MS[1,3,4], Grace Chang, MD, MPH[3,4]

1. Harvard South Shore Psychiatry Residency Training Program 2. School of Medicine, Boston University 3. Department of Psychiatry, Veterans Affairs Boston Healthcare System 4. Department of Psychiatry, Harvard Medical School

Background

Increased risk of contracting COVID-19 and developing more severe symptoms

- Patients with a diagnosis of substance use disorder (SUD) within the past year had a higher risk of contracting COVID-19 and worsened outcomes ($p<10^{-30}$)[1].
- People who are fully vaccinated against COVID-19 and have a SUD appear to be at higher risk for breakthrough infections than people without a SUD.
  - Risk of breakthrough infection for vaccinated individuals with opioid use disorder (OUD) was significantly higher (7.1%) than for vaccinated individuals without a SUD (3.6%), ($p<0.001$) [2].
- Patients with a diagnosis of OUD within the past year had the highest risk of contracting COVID-19 of any SUD type and were eight times more likely to develop COVID-19 than those without a SUD diagnosis [CI 8.411-8.997][1].
- Proposed mechanisms for worsened outcomes in patients with OUD include socioeconomic factors, effects of chronic opioid use upon multiple organ systems, immunosuppression, and drug-drug interactions[3,4].
- COVID-19 impacts multiple organ systems that are also impacted by OUD[5].
- Therefore, treatment considerations for patients hospitalized for OUD and COVID-19 may need to be tailored beyond the sum of standard approaches for each illness alone.

Methods

PubMed was reviewed to determine the current evidence regarding management of patients hospitalized for COVID-19 infection in the context of OUD and opioid detoxification. Searches were conducted utilizing key words such as “opioid,” “detox,” “withdrawal,” “COVID,” “COVID-19,” and “Sars-Cov-2.” Relevant articles published from January 2020 through March 2021 were reviewed for inclusion. A narrative review format was deemed appropriate given the scarcity of literature available on this topic.

Results

A. Opioid Use and COVID-19 Complications[5-14]

System	COVID-19 Considerations	Opioid Use Disorder Considerations	Treatment Considerations
Respiratory	Cough, shortness of breath, pneumonia, hypoxia, acute respiratory distress syndrome	Respiratory depression, increased risk of hypoxia	Monitor CBC with differential, monitor pulse oximetry, and obtain chest x-ray and/or additional imaging studies (CT)
Cardiovascular	Arrhythmias, heart failure, myopericarditis, acute cardiac injury	Arrhythmias, coronary artery disease, myocardial infarction	Obtain EKGs with more frequent monitoring, obtain BMP and correct any electrolyte abnormalities
Central Nervous	Headache, dizziness, ataxia, seizures, impaired consciousness, delirium	Cerebral perfusion abnormalities, epilepsy, polyneuropathy, unsafe gait	Monitor mental status, monitor for fall risk, obtain EEG if seizures are a concern
Gastrointestinal	Nausea, vomiting, diarrhea	Nausea, vomiting, diarrhea, abdominal cramping	GI symptoms associated with COVID-19 may overlap with symptoms associated with opioid withdrawal
Renal	Acute kidney injury	Acute kidney injury	Monitor BMP, closely monitor kidney function
Hematologic / Immunologic	Hypercoagulability, hyperimmune response	Dampened immune response	Closely monitor labs and vital signs to detect for signs of decompensation and provide for early intervention

Patients with a diagnosis of OUD within the past one year had the highest risk of COVID-19 of any SUD type.

Patients with a diagnosis of OUD within the past one year were found to be eight times more likely to develop COVID-19 than those without a SUD diagnosis [CI 8.411-8.997].

Individuals with OUD are at higher risk of requiring hospitalization for COVID-19 infection and are at higher risk for death than those without OUD ($p<0.0001$)[1].

Medically managed opioid withdrawal complicated by a COVID-19 infection puts patients at a high risk of numerous complications that should be closely monitored[4-12].

In considering treatment options for OUD and COVID-19, providers should be cautious regarding risks associated with combining multiple QT-prolonging agents. Special attention should also be given to drug-drug interactions that can alter metabolism of buprenorphine and/or methadone.

To our knowledge, this represents the first narrative review discussing the challenges and clinical considerations faced by consultation-liaison psychiatrists responsible for helping to manage patients hospitalized for COVID-19 infection in the context of OUD.

B. Pharmacologic Considerations[14-19]

- A number of recently investigated pharmacotherapies for COVID-19 may result in **QT-interval prolongation** or **altered metabolism** of methadone or buprenorphine[2].
- For COVID-19 patients receiving multiple QT-prolonging agents, the standardization of pre and post-treatment EKG monitoring is key. May consider replacing methadone with buprenorphine[16].
- Of note, the only FDA-approved drug for COVID-19 is remdesivir, an anti-viral agent, which underscores the importance of combining experimental COVID-19 pharmacotherapies and treatments for OUD with caution.
- Naltrexone may be associated with less interactions when considering concurrent COVID-19 therapies.

B-1.) QT-prolonging Medications	B-2.) Altered metabolism of MTD or BUP
Methadone	Methadone + chloroquine (both CYP2D6 substrates, increasing serum levels of methadone when co-administered)
Chloroquine/Hydroxychloroquine	Methadone + lopinavir/ritonavir (L/R) (Lopinavir induces methadone metabolism; methadone concentrations are reduced by 50% by administration of L/R)
Azithromycin	Buprenorphine + favipiravir (favipiravir is a CYP2C8 inhibitor; therefore, co-administration with buprenorphine may increase buprenorphine levels and effects)

Discussion

- While psychiatrists are generally knowledgeable regarding the treatment considerations and strategies for OUD and opioid withdrawal syndrome (OWS), co-morbid infection with COVID-19 may be associated with additional complications.
- It is crucial that primary medicine teams and mental health physicians alike are well-versed in understanding the effects of COVID-19 infection superimposed upon opioid use disorder (including OWS, opioid overdose, and medication assisted treatments for opioid use disorder) across multiple body systems, as well as the potential implications for symptom monitoring, treatment, and management.

References

1. Wang QQ, Kaelber DC, Xu R, Volkow ND. COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States [published correction appears in Mol Psychiatry. 2020 Sep 30:;]. Mol Psychiatry. 2021;26(1):30-39. doi:10.1038/s41380-020-00880-7
2. Wang L, Wang Q, Davis PB, Volkow ND, Xu R. Increased risk for COVID-19 breakthrough infection in fully vaccinated patients with substance use disorders in the United States between December 2020 and August 2021. World Psychiatry. 2021 Oct 5. doi: 10.1002/wps.20921. Epub ahead of print. PMID: 34612005.
3. Schimmel J, Manini AF. Opioid use disorder and COVID-19: biological plausibility for worsened outcomes. Substance use & misuse. 2020;55(11):1900-1901.
4. Baldini A, Von Korff M, Lin EH. A review of potential adverse effects of long-term opioid therapy: a practitioner's guide. The primary care companion to CNS disorders. 2012;14(3)
5. Gavriatopoulou M, Korompoki E, Fotiou D, et al. Organ-specific manifestations of COVID-19 infection. Clinical and experimental medicine. 2020:1-14.
6. Acevedo, R. B., Botelho, B. G., Hollanda, J., Ferreira, L., Junqueira de Andrade, L. Z., Oni, S., Mello, T. S., & Mudfield, E. S. (2021). Covid-19 and the cardiovascular system: a comprehensive review. Journal of human hypertension, 35(1), 4–11. patients. Clinical Infectious Diseases 2003, 37 (4), 476-482.
7. Doshi R, Majmundar M, Kansara T, Desai R, Shah J, Kumar A, Patel K. Frequency of Cardiovascular Events and In-hospital Mortality With Opioid Overdose Hospitalizations. Am J Cardiol. 2019 Nov 15;124(10):1528-1533. doi: 10.1016/j.amjcard.2019.07.068. Epub 2019 Aug 23. PMID: 31521260.
8. Mégarbane B, Chevillard L. The large spectrum of pulmonary complications following illicit drug use: features and mechanisms. Chemico-biological interactions. 2013;206(3):444-451.
9. Paur R, Wallner C, Hermann P, Stöllberger C, Finsterer J. Neurological abnormalities in opiate addicts with and without substitution therapy. Am J Drug Alcohol Abuse. 2012 May;38(3):239-45. doi: 10.3109/00952990.2011.644001. Epub 2012 Jan 20. PMID: 22263960.
10. Pun BT, Badenes R, Heras La Calle G, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study [published correction appears in Lancet Respir Med. 2021 Jan 27:;]. Lancet Respir Med. 2021;9(3):239-250. doi:10.1016/S2213-2600(20)30552-X
11. Roy, S., Ninkovic, J., Banerjee, S. Pharmacol 6, et al. Opioid Drug Abuse and Modulation of Immune Function: Consequences in the Susceptibility to Opportunistic Infections. 442 (2011).
12. Kosten TR, Baxter LE. Review article: Effective management of opioid withdrawal symptoms: A gateway to opioid dependence treatment. Am J Addict. 2019;28(2):55-62. doi:10.1111/ajad.12862
13. Krishnan A, Hamilton JP, Alqahtani SA, A Woreta T. A narrative review of coronavirus disease 2019 (COVID-19): clinical, epidemiological characteristics, and systemic manifestations. Intern Emerg Med. 2021;16(4):815-830. doi:10.1007/s11739-020-02616-5
14. Hsia, B. C.; Greige, N.; Quiroz, J. A.; Khokhar, A. S.; Dally, J.; Di Biase, L.; Ferrick, K. J.; Fisher, J. D.; Krumerman, A., QT prolongation in a diverse, urban population of COVID-19 patients treated with hydroxychloroquine, chloroquine, or azithromycin. Journal of Interventional Cardiac Electrophysiology 2020, 59 (2), 337-345.
15. Mercuro, N. J.; Yen, C. F.; Shim, D. J.; Maher, T. R.; McCoy, C. M.; Zimetbaum, P. J.; Gold, H. S., Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA cardiology 2020, 5 (9), 1036-1041.
16. Behzadi, M.; Joukar, S.; Beik, A., Opioids and cardiac arrhythmia: a literature review. Medical principles and practice 2018, 27 (5), 401-414.
17. Sefidgarmia, M.; Salari, S.; Alaedini, K., QT Interval Prolongation in COVID-19 Patients on Methadone Treatment. Iranian Journal of Psychiatry and Behavioral Sciences 2020, 14(2), e104431.
18. Ghosh, A.; Roub, F.; Bisaga, A., Drug treatment of SARS-Cov2: potential effects in patients with substance use disorders (SUD). Journal of Psychosomatic Research 2020, 135, 110159.
19. McCance-Katz, E. F.; Rainey, P. M.; Friedland, G.; Jatlow, P., The protease inhibitor lopinavir–ritonavir may produce opiate withdrawal in methadone-maintained