NEWS

When 1 + 1 = 3: the COVID-19 and addiction syndemic

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The COVID-19 pandemic has renewed interest in syndemic theory [1]. Traditionally with syndemics one epidemic primes the conditions to accelerate another existing epidemic, in other words the epidemics synergize. Developed to explain how the epidemic of addiction, especially when it entails injection drug use, primed the spread of HIV [2], syndemic theory has been applied widely; although mostly to intersections of social determinants of health and disease (e.g., the poorly coined "diseases of despair") [3]. For example, the excess in drug-related mortality in American Indian populations may be explained, in part, through an interaction between the epidemics of opioid use, poverty, racism, and historical trauma to cause a disproportionate number of deaths compared to White populations [4].

Prior to and throughout the COVID-19 pandemic, the United States has been in the midst of an opioid epidemic with annual overdose deaths exceeding 70,000 in pre-pandemic 2019 and 100,000 presently [5]. While this trend of increasing overdose deaths was present before COVID-19, modeling studies show that the pandemic appears to have accelerated this trend with currently observed overdose deaths exceeding those predicted [6]. Mass isolation, economic uncertainty, decreased access to healthcare caused by the pandemic likely synergized with the opioid epidemic to fuel this increase in deaths. This synergy also seems to work in reverse such that people who use drugs, especially those with an opioid use disorder, who are disproportionately affected by poverty, reliance on public transportation, multiple medical comorbidities, etc. are at increased risk for COVID-19 infection and for covid-related mortality [7].

From the earliest days of the pandemic we have heard about the interaction between various biological states and COVID-19 (think old age, obesity, pulmonary disease, diabetes, immunocompromise, etc.). In these instances, one disease plus another equals two diseases where the underlying biological and/or social contexts are interacting to amplify the impact of the other. But what happens when one plus one equals three, where two disease states appear to interact creating an opening for a third disease to develop? In *Molecular Psychiatry*, Wang et al. recently found an association between opioid and cocaine use disorder, COVID-19, and the risk for endocarditis, a bacterial infection of the heart valves often caused by injection drug use [8]. First, they show that the increasing prevalence of endocarditis in people with opioid and/or cocaine use disorder during the opioid epidemic accelerated after the start of the pandemic while the prevalence of endocarditis in people who do not use drugs remained unchanged. They next show that the risk for endocarditis in those with opioid and/or cocaine use disorder is greater in those who have had COVID-19.

That people who use drugs are at increased risk for COVID-19 should come as no surprise and we have known for decades that people who use drugs are at increased risk for endocarditis. The news here is that even after controlling for several variables such as demographics, underlying comorbidities, medications that can contribute to the risk of infection (e.g., the use of corticosteroids such as dexamethasone in the treatment of COVID-19), and social determinants of health, people with opioid and/or cocaine use disorder who had COVID-19 were at greater risk for endocarditis than people with opioid and/or cocaine use disorder who did not have COVID-19. Wang et al. had access to an enormous electronic medical record database comprised of nearly 110 million unique patient records, over 1 million of which had an opioid or cocaine use disorder diagnosis. The vast power to control for multiple variables in a sample size this large is a great strength of this study despite known lacuna in electronic medical records when it comes to diagnosing substance use disorders and documenting social determinants of health [9].

So why did this happen? It may be due to pandemic-related increases in drug use, decreases in access to safe injection supplies, and decreased access to healthcare. There may also be synergy between disease processes. There has been significant attention paid to understanding the immune response to COVID-19 infection including the so called "immune storm" of severe COVID-19. There is also a long and perhaps underappreciated literature on the effect of drugs on both innate and adaptive immune function, which may predispose to certain infections [10]. For example, the Veterans Aging Cohort Study found higher incidence of bacterial pneumonia in veterans taking certain opioids [11]. That this was not a finding for all opioids decreases the chance that general factors seen with all opioids such as suppressed respiratory rates and decreased cough reflex explain this finding and point toward potential interactions between specific opioids with immunologic effects and pneumonia incidence. In the case of opioid (especially fentanyl) and cocaine use disorders and COVID-19 it is plausible that combined immune effects synergize to increase susceptibility to endocarditis. We already have reports of impaired endothelial function and altered immune response increasing cardiovascular pathology in those with COVID-19 [12]. We will need significant laboratory and basic clinical research to confirm a biological basis to findings such as those of Wang et al. As with all science, replication is important and replicating associations between opioid and cocaine use disorders as well as other drugs such as methamphetamine, COVID-19, and endocarditis in other datasets, preferably international datasets to evaluate the findings outside of the United States

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sociopolitical context, is something that can be accomplished in the immediate future.

By necessity, many careers pivoted in response to the public health crisis caused by COVID-19. It is almost certain that for years ahead entire careers can be devoted to better understanding the correlates of COVID-19 and disease. We are just at the beginning of a period of discovering disease-disease synergies. While large datasets have allowed identification of these syndemics, it will require basic and clinical research to confirm and explain them. Our ability to respond to and perhaps prevent the next syndemic relies on this.

REFERENCES

1. Mendenhall E, Kohrt BA, Logie CH, Tsai AC. Syndemics and clinical science. Nat Med. 2022;28:1359–62.
2. Singer M. A dose of drugs, a touch of violence, a case of AIDS: conceptualizing the SAVA syndemic. Free Inq Creative Sociol. 2000;28:13–24.
3. Park JN, Rouhani S, Beletsky L, Vincent L, Saloner B, Sherman SG. Situating the continuum of overdose risk in the social determinants of health: a new conceptual framework. Milbank Q. 2020;98:700–46.
4. Ivanich JD, Weckstein J, Nestadt PS, Cwik MF, Walls M, Haroz EE, et al. Suicide and the opioid overdose crisis among American Indian and Alaska Natives: a storm on two fronts demanding swift action. Am J Drug Alcohol Abus. 2021;47:527–34.
5. Ahmad F, Rossen L, Sutton P. Provisional drug overdose death counts: National Center for Heatlh Satatistics; 2022.
6. Cartus AR, Li Y, Macmadu A, Goedel WC, Allen B, Cerdá M, et al. Forecasted and observed drug overdose deaths in the US during the COVID-19 pandemic in 2020. JAMA Netw Open. 2022;5:e223418.
7. 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. Mol Psychiatry. 2021;26:30–9.
8. Wang L, Volkow N, Berger N, Davis P, Kaelber D, Xu R. Association of COVID-19 with endocarditis in patients with cocaine or opioid use disorders in the US. Mol Psychiatry. 2022. https://doi.org/10.1038/s41380-022-01903-1.
9. Truong HP, Luke AA, Hammond G, Wadhera RK, Reidhead M, Joynt Maddox KE. Utilization of social determinants of health ICD-10 Z-codes among hospitalized patients in the United States, 2016-2017. Med Care. 2020;58:1037–43.
10. Eisenstein TK. The role of opioid receptors in immune system function. Front Immunol. 2019;10:2904.
11. Edelman EJ, Gordon KS, Crothers K, Akgun K, Bryant KJ, Becker WC, et al. Association of prescribed opioids with increased risk of community-acquired pneumonia among patients with and without HIV. JAMA Intern Med. 2019;179:297–304.
12. Bavishi C, Bonow RO, Trivedi V, Abbott JD, Messerli FH, Bhatt DL. Special Article—Acute myocardial injury in patients hospitalized with COVID-19 infection: a review. Prog Cardiovasc Dis. 2020;63:682–9.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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