COVID-19: BEYOND TOMORROW

The Hidden Epidemic of Opioid Overdoses During the Coronavirus Disease 2019 Pandemic

An unexpected tragedy of the coronavirus disease 2019 (COVID-19) pandemic is increased opioid and fentanyl overdoses, since many factors could have reduced opioid use disorder (OUD) and overdoses during this pandemic. Another tragedy is that both epidemics depend on vaccine development, but antifentanyl vaccine support includes no pharmaceutical and only 3 government investments, while industry and government support more than 120 COVID-19 vaccines. This discrepancy in support reflects stigma against those with OUD and failure of approved treatments to decrease overdoses.

The factors expected to reduce overdoses include disruption of drug markets, reduced access to illicit drugs, and improved access to care. We expected better care access from telemedicine for direct home visits, including office-based care with buprenorphine, loosened federal restrictions on take-home methadone, more hotlines for emergencies, and proliferation of virtual community support meetings. Instead, the exponentially rising epidemic of fentanyl overdoses grew in early 2020. The Overdose Detection and Mapping Application Program showed 16% more overdoses in February 2020 than February 2019, escalating to 42% more in May 2020 compared with May 2019.1 Kentucky, which has led the US in opioid overdoses, reported a 17% increase in overdoses transported to an emergency department (ED) in their emergency medical services during the 52 days before and after the COVID-19 state of emergency declaration.2 More critically, they reported a 71% increase in runs with refused transportation and a 50% increase in runs with deaths at the scene from overdoses. Elsewhere, from March to July 2020, compared with 2019, opioid overdose ED admissions more than doubled (from 102 to 227), while other ED admissions dropped by 29%.3

Both epidemics need vaccines because of new threats: the severe acute respiratory syndrome coronavirus 2 and fentanyl. Fentanyl is driving overdose deaths, and the most widely used OUD treatments, buprenorphine and methadone, do not block fentanyl, but a vaccine will. These agents block by binding to the brain’s μ-opioid receptors as full or partial agonists. Maintenance treatment with them reduces opioid use and deaths from most opioid overdoses but not fentanyl. Buprenorphine, the most commonly prescribed OUD medication, can block fentanyl doses that induce respiratory distress at blood levels greater than 5 ng/mL,4 but this level is almost 10 times greater than the trough blood levels of 0.67 ng/mL when taking a standard dose of sublingual buprenorphine. Even at twice the highest US Food and Drug Administration–approved dose of 24 mg/day, the blood level is 1.7 ng/mL, almost 3-fold lower than is required for blocking fentanyl. While the new depot buprenorphine, at 300 mg monthly, appears to create blood levels sufficient to attenuate respiratory depression from therapeutic doses of fentanyl, this buprenorphine dose is triple the recommended dose of 100 mg and ineffective for fentanyl overdoses. Thus, we need new approaches.

A rapidly developing intervention is an antifentanyl vaccine, which blocks lethal fentanyl doses in animals.5 The National Institutes of Health and Department of Defense are supporting optimization of these antifentanyl vaccines, but at less than one-thousandth the level of COVID-19 support. We established the prototypes for these vaccines 50 years ago by chemically coupling heroin or fentanyl derivatives, which are too small to induce antibodies, to antigenic carriers, such as tetanus or diphtheria toxoids, and injecting this combination to produce antibodies against fentanyl within about 6 weeks. These antifentanyl antibodies then bind any fentanyl that might be used later and prevent the fentanyl from getting out of the bloodstream and into the brain or any other organ until excreted by the kidney. The vaccines reduce brain fentanyl levels by 50% to 80% depending on the dose of fentanyl taken, and functionally they completely block lethal fentanyl doses of 50 μg/kg in rats. More importantly, more than 1000 patients have taken anticocaine and antinicotine vaccines over the past 20 years with no major adverse events and good efficacy. The fentanyl vaccines promise better efficacy than earlier cocaine and nicotine vaccines and continued safety in humans. The tiny amounts of fentanyl required to produce overdoses is the basis for this vaccine’s superior efficacy against fentanyl compared with heroin, cocaine, or nicotine. An antifentanyl vaccine needs to produce less than 1% of the amount of antibody required for blocking these other drugs, and the more potent fentanyl derivatives (eg, carfentanil) require fewer antibodies for blocking. Finally, these vaccine-induced polyclonal antibodies bind most all of the fentanyl derivatives because these derivatives have similar chemical structures.6

With 50 years of scientific success and extensive human safety, why is support so meager for antiaddiction vaccines? Several perceptions may contribute to poor support during this COVID-19 pandemic. First, antiaddiction products historically provide limited profits for the pharmaceutical industry. Second, individuals with OUD have medical comorbidities leading to a limited life expectancy, especially during this COVID-19 pandemic. A recent national review of more than 73 million patient records found that patients with COVID-19 infection and substance use disorders had greater hospital...
Social distancing in Kentucky has increased unwitnessed overdose spread, meaning no one was present to give naloxone to reverse the overdose. Kentucky’s overdose clusters also have increased in rural areas, where emergency medical services help and time to get to EDs can be significantly longer.

Fourth, substance use disorder treatment also is poorly available to implement new interventions, such as vaccines. Ochalek et al\(^3\) reported that among those patients who reached the ED and survived an overdose, only 3% in 2020 accessed treatment at the outpatient clinic after overdosing, compared with 10% in 2019. While 10% rates of outpatient follow-through are dreadfully poor, why might they fall by 3-fold during the COVID-19 pandemic? The emergency medical services report\(^2\) from Kentucky, which also captured the volume of individuals with opioid overdoses who never made it to the ED, suggests that those experiencing overdose themselves contributed to reduced treatment access. Patients refusing interventions is a fifth contributor to limited support for anti-addiction vaccines. The number of individuals refusing transport to the ED after reversal of their overdose doubled during the COVID-19 pandemic and was associated with fear of COVID-19 infection at the hospital but also stigma shown by health care professionals.

Poor vaccine support also reflects a sixth factor of health care professionals expressing stigma about addiction. Health care professionals’ triaging of patients for continued care is based on their perceived need for care during this pandemic, and they typically place addiction treatment low on the list. Ochalek et al\(^3\) reported that only half of the patients received a naloxone prescription to take with them, even after their overdose, and only 4% of patients with overdoses who were admitted to the hospital for inpatient care received an addiction consultation before discharge.

The central points about prejudices against antifentanyl vaccine investments begin with understanding the limitations of the existing OUD treatments to prevent fentanyl opioid overdoses but also extend to health care professionals’ need to confront the stigma that these patients face. We need to return our attention to this hidden epidemic that was very much in the public eye before the COVID-19 pandemic struck and that COVID-19 appears to have worsened.

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**References**


