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A thorough literature review of PubMed and the latest statistics from the Centers for Disease Control and Prevention (CDC) was performed for the most relevant and updated data regarding overdose deaths.

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Conflict of Interest Statement

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ARTICLE

A New Wave of the Overdose Epidemic Arises During the COVID-19 Pandemic

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1. Introduction

The Coronavirus disease 2019 (COVID-19) has been responsible for over 896,496 deaths in the United States (U.S.)[1] and has temporarily eclipsed the nation's other public health crisis, the overdose epidemic. Overdose deaths in the U.S. are attributed primarily to opioids, but they also include deaths related to stimulants (cocaine and methamphetamine), sedative-hypnotics, other medications, and non-medical substances. The most recent CDC data revealed that 106,699 Americans died from drug overdose during 2021.[2] This was a 51.1% increase since 2019.[2] COVID-19 has created uncharted challenges across the entire healthcare system including an inevitable shift away from the treatment of other conditions, including substance use disorders (SUD).

It can be hypothesized that the increase in overdose deaths during the COVID pandemic has been caused by a multitude of factors, such as lack of accessibility to healthcare, social isolation from lock downs, unemployment, financial hardships, COVID itself, global supply chain issues, as well as other factors. The largest number of deaths from overdose occurred in April and May 2020, when the shutdown mandates were most strict.[3] This was associated with a dramatic shift in critical prevention services for people who inject drugs or temporary shutdown of methadone/buprenorphine clinics, closing approximately 25% of facilities due to social isolation rules and disrupting the distribution of addiction services and the lifesaving reversal medication, naloxone. This paper aims to highlight how the pandemic exaggerated the opioid epidemic in order

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to better prepare and manage SUD if in case similar circumstances arise in the future.

2. Mechanism of Action

Opioid addiction, or opioid use disorder (OUD), is a result of both biological and environmental factors, with genetic factors contributing significantly to the risk of onset and progression. Genetic factors interact with multiple environmental influences, many of which may have shifted during the COVID pandemic. Environmental causes of addiction related to the COVID pandemic include such factors as social isolation, unemployment, and lack of resources available to patients with a SUD. The global social problems associated with the pandemic have serious implications for mental health, due to stress as a result of altered daily habits, loneliness, and financial insecurity. Fear and anxiety already heightened by the health threat were further exacerbated by information and misinformation spread by social media.

3. Causes of Death

The primary drivers of overdose deaths during 2000−2009 were prescription-type opioid analgesics, but illicit opioids came to dominate after 2010.[2,4] More recently, overdoses involving illicit stimulant drugs have increased as well.[2,4] Within the category of illicit opioid use, an initial wave of heroin use was followed by increases in both deliberate and unintentional use of even more potent synthetic opioids (i.e. illicitly made fentanyl and its analogs). Marked increases in overdose deaths involving these synthetic opioids began in about 2013. Synthetic opioids are now almost twice as commonly involved in overdose deaths as prescription opioids or heroin. In 2021, the most recent full year with available data, there were 9173 heroin-related overdose deaths, 13,618 related to natural and semi-synthetic opioids, 3678 related to methadone, 32,537 related to stimulants such as methamphetamine, 24,486 related to cocaine, and 70,601 deaths related to synthetic opioids such as fentanyl and related compounds (note that these numbers represent non-exclusive categories and if multiple agents are implicated, deaths are included in multiple categories).[2] Total deaths in 2021 were 106,699, 75% of which involved prescription and illicit opioids[2]. Of note, 2021 final data show marked increases in overdose deaths, particularly those related to synthetic opioids whose potency and lethality are notable[2,5].

The reduction in trade and transport during the pandemic are likely to have effects on illegal drug supply. Precursor chemicals and other synthetic products are brought from Asia by commercial cargo.[6] Prior drug supply disruptions caused prices to increase, purity of substances to decrease, increased numbers of users to enter treatment, and increased death if left untreated. Shortages seen with heroin or fentanyl can increase the demand for methadone and buprenorphine, requiring the expansion of access to medication therapies and getting individuals into the drug treatment programs.[7] Short-term interruptions in the supply chain are expected to have minimal effect on the availability of synthetic drugs but could have implications for the way drugs are supplied and used as drug trafficking organizations resume operations and trade rebounds.[8] It seems clear that the serious issue of synthetic opioids has not abated during the pandemic.

4. The "Fourth Overdose" Wave

There are several factors that resulted in the increases seen in 2020 may represent a "fourth wave" of the overdose epidemic attributable to the challenges affecting patients with SUD that were exacerbated during the COVID pandemic. During the first three months of the COVID pandemic, social media users, such as through Reddit, Twitter, Facebook were used to described challenges in obtaining medications for OUD, according to one study by El-Bassel et al.[9] For example, through Reddit's anonymous posting, drug users accessed opioid-related subreddits to communicate how COVID-19 influenced their addiction experiences, such as availability of drugs and identifying information and support on obtaining drug treatment within this new environment.[9] Concerns expressed included fear about attending overcrowded methadone clinics, job loss resulting in withdrawal of health insurance, diversion, self-dosing, and self-treatment of withdrawal symptoms by combining over-the-counter and prescription medications. This study demonstrated the utility of social media for addiction clinicians to learn about the challenges and experiences of people using drugs, since such platforms allow anonymity and thus facilitate open discussion among people who use drugs.

Data from the CDC's National Center for Health Statistics document a 30.0% increase in drug overdose deaths in 2020 compared to 2019, with a further increase of 16.2% from 2020 to 2021.[2] Increases from 2019 to 2020 and from 2020 to 2021 were highest for those attributed to synthetic opioids (55.4% and 24.9%, respectively) and stimulants such as methamphetamine (47.4% and 36.5%, respectively).[2,10]

At the beginning of the COVID pandemic, the prevalence in overdose related cardiac arrests rose sharply starting in April 2020 where rates were found to nearly double from April 2020 to May 2020. The 2020 National EMS Information Services (NEMSIS) database revealed increases in overdose related cardiac arrests, approximately 74.1 per 100,000 EMS activations since March 15th, 2020 until June 2020.[11] Since the height of the COVID pandemic, mobility (cell phone-based mobility score − a measure of social distancing) remained lower than baseline, indicating that overall there was a decrease in EMS call volume for other issues during the pandemic, as overdose related cardiac arrests throughout August 2020 remained high. A CDC Health Alert Network Advisory published in December 17th, 2020 revealed that overdose death rate increases were driven by synthetic opioids primarily (based on overdoses through June 2020). A 38.4% increase in opioid deaths was attributed to synthetic opioid overdose deaths across the United States,[12] with continued increases during the rest of 2020 as well.

An analysis of over 500,000 definitive urine drug tests have been performed from January 1st, 2019 through May 16, 2020, where COVID-19 was declared a national emergency on March 13, 2020. Results confirmed a sharp rise of illicit and prescription drug use after the start of the COVID pandemic, including a 31.96% increase in use of non-prescribed fentanyl and a 19.96% increase in use of methamphetamine.[13] Fentanyl is much more potent than heroin and is more likely to cause overdose deaths.

An analysis of non-identifiable electronic health records of 73 million patients in the U.S., demonstrated higher COVID-19 susceptibility and worse outcomes for those with SUD.[14]. According to the study, the risk of COVID-19 was strongest for individuals with OUD followed by individuals with tobacco use disorder, with a greater incidence in the African American population[14]. Providing additional evidence for a possibly increased risk of COVID-19 in people who use substances, an online survey of adolescents and young adults aged 13−24 conducted in the month of May of 2020 assessed the relationship of COVID-19 symptoms, testing, and diagnosis with cigarettes and electronic cigarettes. A total of 4351 participants completed the online survey, and data demonstrated that a diagnosis of COVID-19 was five times more likely in users of e-cigarettes and seven times more likely among users of both e-cigarettes and cigarettes.[15] Both cigarette and e-cigarette use damage the respiratory system, which potentially increased the risk of experiencing exacerbated COVID-19−related symptoms and outcomes.[15]. Researchers found that people who smoked cigarettes for 3 years later after an initial interview were about 1.5 times more likely to use drugs and twice as likely to have SUD at follow-up than those who quit smoking.[16] Among initial nonsmokers who later started to smoke during the study were found to be approximately 5 times more likely to report substance use versus those who did not smoke.[16] Therefore, these studies suggested that smoking increased the risk of SUD; as well as contracting COVID.

5. Limitations of Resources During the Pandemic and Subsequent Psychological Effects

The requirements of social distancing during the pandemic placed a strain on the delivery of healthcare and limited its accessibility. Resources to treat patients with SUD shifted from in-person to virtual, presenting challenges for those depending on opioid treatment centers and other needed services including peer-support groups. Access to psychologist, psychiatrists, therapist, and support groups resulted in hardships for patients at the height of the pandemic. These crucial support services are mainstays in the treatment for majority of patients with depression, anxiety, and SUD, the inability to maintain access to these services during the pandemic pressed on the vulnerabilities of patients affecting mental and physical wellbeing.[17]

Furthermore, job losses, homelessness, and housing instability adds to the psychosocial and environmental factors that may predispose patients to relapse and fall back into SUD. The prevalence of psychological distress among adults in the USA was higher during the COVID-19 pandemic. A psychological distress survey was conducted from April 7−13th, 2020 using the Kessler 6 Psychological Distress Scale and results demonstrated 13.6% of US adults reported serious emotional distress during the pandemic, relative to 3.9% in 2018.[18] Among the subgroups examined in the study, symptoms of emotional distress were highest among young adults aged 18−29 years old and those with lower household income of less than $35 000 per year.[18]

Additionally, global supply chain issues resulted in long-term consequences, which are being further restrained by the war in Ukraine and will likely persist. According to Institute of Supply Management, about 75% of the companies reported supply chain disruptions, 80% expected some kind of disruptions in the near future, 62% reported delays in receiving products due to COVID.[19] More than five million companies

were impacted by the pandemic a lone.[19] With the healthcare industry accounting for nearly 20% of the United States economy, the supply limitations have also translated into a scarcity of medical supplies; which increased treatment expenditures, cancelled or delayed therapies all together.[20] As a result of the pandemic, studies have been pursued to investigate challenges, explore supply chain disruptions, security issues and future sustainability.[19]

The COVID pandemic has had severe financial impacts globally. During the month of April 2020, 23.1 million individuals filed for unemployment in the USA, corresponding to 14.7% of Americans.[21] Financial stress has twice the likelihood to correlate with clinically significant depression.

Reductions in prescription dispensing of intramuscular extended-release/long-acting naltrexone during the early pandemic (March 2020 to May 2020)[22] suggest challenges for patients needing this medication. Inaccessibility was due to healthcare office closures and the lack of providers administering these medications. However, buprenorphine and naloxone prescribing were above the forecasted levels in March 2020 and met the forecasted levels from April 2020 to May 2020. The increased use of telemedicine and establishment of mental health hotlines reduced some barriers toward patients care. The deployment of virtual support meetings, the expanded support of take-home medications for OUD, and buprenorphine prescribing by telehealth were mandated by the federal state, and local levels to facilitate continued access.[22]

6. Pain Medicine

The sudden and overwhelming burden to the healthcare system as a result of COVID-19 has resulted in numerous changes to current practices. One example is chronic pain and perioperative medicine. The pandemic forced the reallocation of anesthesiologists from the outpatient realm to the increase demands in the intensive care units, emergency departments, medicine floors, and intubation teams for COVID airways. It has forced anesthesia residents and other anesthesia care team members to step out of their conventional role, which resulted in the deprioritization of chronic pain management and the perioperative setting. As most chronic pain services were globally deemed non-urgent, all outpatient and elective interventional procedures were limited and interrupted, negatively impacting patients' psychological and overall health[23]. Social media has facilitated this by enabling anesthesiologists to collaborate and share information, advice, and support.

Pain is the number one cause for patients seeking medical attention, and the COVID pandemic has changed the practice of pain management in treating chronic pain. Low back pain is among the leading causes for years lost to disability in U.S., and data demonstrate strong correlations between chronic pain, suicide, and decreased life expectancy.[24] During public health emergencies, patients must be offered access to the care of pain specialists and Cohen et al. describe an ideal framework for physicians in mitigating risk, conservation of resources, and access to pain management services. These include strategies for triaging high risk patients requiring procedures, implementing telehealth to the practice, and managing opioids prescriptions, while minimizing risk exposure.[25] In-person office visits and elective procedures were at a standstill for the majority of the pandemic until state mandates and CDC guidelines permitted the safe delivery of non-emergency and non-urgent healthcare. Telemedicine enabled continuity of care, and with the use of electronic prescribing, the delivery of care to patients in chronic pain was continued until office-based procedures and elective cases in the operating rooms could proceed. Every patient undergoing elective procedures required rapid COVID antigen tests within 72 h of the procedures. Entering hospitals required strict mask policies, social distancing, and temperature checks for employees and non-employees.

7. Anesthesiology- Guidelines in the Curtailing COVID-19

Anesthesiologists were called to the COVID-19 front lines for a vital and dangerous role along with global shortages of medications and medical supplies. The French Society of Anesthesia and Intensive Care (SFAR) assembled a group of experts to deliver pragmatic and logical considerations to the safe delivery of anesthesia and critical care while reducing the transmission of COVID-19.[26] In the face of personal protective equipment (PPE) shortages, anesthesiologists were able to understand the mechanism of transmission of COVID-19, and allocate resources to acquire N95 masks, face shields, and power air purifying respirators to the staff involved in securing the airway in patients who are confirmed positive. There is a substantial risk of becoming infected during airway management of COVID-19 patients. Anesthesiologists being extensively trained in airway and intraoperative management, were naturally prepared to treat unstable COVID-19 patients requiring procedures and/or intubations through various anesthetic techniques

aimed to reduce aerosol exposure. Under these high-risk circumstances, the SFAR proposed various airway management strategies, such as having the most experienced anesthesiologist perform rapid sequence inductions in infected patients.[26] Therefore, with anesthesiologists, time sensitive cases were more safely conducted while reducing exposure to healthcare providers and patients.

Furthermore, anesthesiologists are directly combating the opioid epidemic by reducing the patients' dependence on opioids. Perioperative care and chronic pain management have undergone a paradigm shift with the encouraged use of multimodal analgesia reducing opioid requirements and dependency, such as through the use of Enhanced Recovery After Surgery (ERAS) programs.[27] ERAS is a multimodal, multidisciplinary, evidence-based approach to care of the surgical patient that aims to optimize perioperative management, outcomes and reduce the response to surgical stress.[27] Furthermore, in 2020, the collaboration of the European Society of Regional Anesthesia and American Society of Regional Anesthesia constructed guidelines to perform surgeries under regional anesthesia to avoid aerosolization of infectious particles.[28] Following these guidelines, studies demonstrate that when a multimodal approach to pain management is implemented rather than using opioids alone, there was a decrease in opioid use, opioid prescriptions, and common opioid-related complications.[29] With lower opioid and prescription use, the multimodal approach can lessen the number of overdose morbidity and mortality. Patients who underwent total hip replacements with multimodal analgesia had a 18.5% decrease in opioid prescriptions after surgery.[29] Moreover, multimodal analgesia aims to combat inadequate pain management in the acute postoperative period thus reducing the development of chronic pain and further opioid usage.[30]

In addition, during the COVID-19 crisis, SFAR experts encouraged telemedicine as an alternative to in-person consultation to reduce exposure and improve general access to care to vulnerable populations.[26] According to Valley et al. (2020), telemedicine preoperative evaluation has been studied in a variety of patient populations and suggest that a majority of visits (excluding high risk surgical cases and patents with many comorbidities) can be successfully be performed with telemedicine evaluation.[26] For example, select patient populations underwent successful telemedicine preoperative evaluations before oral and maxillofacial surgery with no complications, highlighting this patient population as one in whom remote evaluation may be beneficial.[26] Therefore select vulnerable populations, such as those who depend on regular pain management appointments can greatly benefit from telemedicine visits-saving travel costs, time, and reducing potential viral exposure. In fact, a pilot study by Peng et al. (2006) illustrated follow-up consultations for chronic pain patients are feasible and more cost-saving versus conventional visits. Patients and anesthesiologists were highly satisfied with telemedicine consultation.[31]

In summary, expert proposals on providing anesthesia in the context of COVID-19 were established for patients to still acquire their needed care and procedures, as well as to reduce the risk of opioid dependency in new and current patients through the use of multimodal analgesia. Institutions were also encouraged to tailor their protocols to their specific needs, constraints and local incidence of COVID-19 infection in order to provide the most effective care with the resources at their disposal.[28]

8. Conclusion

As Americans continue to battle the fluctuating incidence of COVID-19 infections, overdose deaths (especially opioid-related) have risen in tandem and fueled by the pandemic, primarily attributed to synthetic opioid overdoses. Mental health, substance use, and overdose have worsened starting in March of 2020. This "fourth overdose epidemic wave" has been attributed to a number of challenges faced during the pandemic, including psychosocial stressors (anxiety and depression), financial trouble, and SUD. This intersection of the COVID-19 pandemic and the overdose epidemic will transform health outcomes for many years and continue to demand urgent public health action. Both crises have disproportionate impact on vulnerable, underserved racial and ethnic minority populations. From 2017 to 2018, drug overdose deaths were on the decline, but from 2019 to 2021 drug overdose deaths have increased by over 50%.[2] Lessons learned from the rise in deaths are to note the scarcity of resources in the unexpected presence of natural disasters including pandemics.

Given multiple factors influencing the U.S. overdose epidemic, including those related to the COVID-19 pandemic, reducing mortality will require multiple efforts.[32] The federal government has implemented an Overdose Prevention Strategy that emphasizes four domain – primary prevention, harm reduction, evidence-based treatment, and recovery support.[33] Within these domains, it will be critical that efforts focus on clinician barriers and

systems-level improvements that support models of care that integrate and connect behavioral health services, pay for care through payment changes, increase the addiction workforce, and reduce clinician, patient, and institutional stigma. Learning from the impacts of the COVID-19 pandemic may help to strengthen the focus on multiple social factors that were impacted during the pandemic. While these disasters are unavoidable, healthcare requires a delicate balance of resources with secondary plans in place to maintain innovative accessibility to resources to mitigate current healthcare issues such as SUD.

Conflict of interest

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Disclaimer

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