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Covid-19 Pandemic and Opoid Overdose Increase

Awal Hussein G, Teyib Abafogi A and Sufian Abdo J*

Department of Veterinary Medicine, College of Agriculture and Veterinary Medicine, Jimma University, Ethiopia

***Corresponding author:** Sufian Abdo Jilo**,** Department of Veterinary Medicine, College of Agriculture and Veterinary Medicine, Jimma University, Ethiopia, Tel: +251912753947, E-mail: sufianabdojilo@gmail.com

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ABSTRACT

The newly emerged pandemic poses several socioeconomic crises as globally. Among social crisis drug overdose is increased during pandemic COVID-19 in different parts of the world. These paper reviewed issue related to the effect of corona virus on increament of opoid overdose mortality. Although the health consequences of the pandemic remain unclear evidence suggests there have been challenges in maintaining substance use disorder treatment and a recent content review of COVID-19 and addiction suggests risk of increases in prevalence of withdrawal symptoms and addictive behaviors including relapse. A quick action to prevent the crisis should be implemented as globally.

Keywords: Crisis; Coronavirus; Opoid epidemic; Overdose

Introduction

The nation's COVID pandemic made the nation's drug overdose epidemic worse. This issue brief highlights media and other reports showing increases in drug overdose mortality and other concerns relating to access to evidence-based care for substance use disorders, patients with pain as well as harm reduction services (AMA, 2021) [12]. Individuals with mental health and substance use disorders (SUDs) are particularly susceptible to negative effects of the coronavirus disease 2019 (COVID-19) pandemic. The collision of the COVID-19 pandemic and the drug overdose epidemic has highlighted the urgent need for physicians, policymakers and health care professionals to optimize care for individuals with SUDs because they may be particularly vulnerable to the effects of the virus due to compromised respiratory and immune function and poor social support (Volkow, 2020) [183]. Persons who use opioids may be at elevated risk of harm from the coronavirus disease 2019 (COVID-19) pandemic, yet few data currently exist that can be used to examine this risk (Parker *et al.,* 2021) [105]. Major disasters long have been associated with substantive adverse outcomes, including anxiety and substance use (Galea *et al*., 2020) [63]. Similarly, the coronavirus 2019 (COVID-19; Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) pandemic is likely to pose serious problems for persons with opioid use disorder (OUD) (Henry, 2020) [77]. Persons with substance use disorders, such as OUD, are likely at greater risk of worse COVID-19 outcomes (Holloway *et al*., 2020, Volkow, 2020) [81, 183] . A growing body of literature has also focused on the "collision" of the COVID-19 pandemic and opioid epidemic (Khatri and Perrone, 2020, Becker and Fiellin, 2020) [86, 20], with attention to persons with psychiatric comorbidities. Finally, there is preliminary evidence of an increase in opioid overdoses during the early months of the pandemic, compared to a pre-COVID period (Ochalek *et al*.., 2020, Slavona *et al*., 2020) [128, 169]. Amidst the ongoing pandemic, data remain sparse (Mallet *et al*., 2020) [104], and there has been little research to assess whether COVID-19 has affected opioid use and motivation to stopusing opioids. Preliminary studies show some increases in opioid use through drug testing data (Niles, *et al*., 2020, Morin *et al*., 2021) [127, 121].

Mechanisms of opoid drugs and side effects of opoid

Our brains evolved a dopamine reward system to encourage behaviors linked to survival: eating, procreating, interacting socially and others activities. Our reptilian brain's tiny Amygdala organs trigger "fight or flight" response when we sense pain/fear. Prescription opioid drugs (i.e. Oxycodone, Hydrocodone, Vicodin) and heroin work through same mechanisms of action – brain eventually becomes"hijacked," rewiring it and changing its physical structure (plasticity). Opioids reduce perception of pain by binding to natural opioid receptors, which "mimic" your own neurotransmitters found in the brain and other cells in the body. The "reward regions" of the brain (Nucleus Accumbens) are activated through Dopamine Pathways (promotes desire) and Serotonin (satiety and reduced inhibition) releasing immense, pleasurable reinforcers of Endorphins; thus promoting huge potentiation for repetition. With overdoses, deeper brain regions become impaired resulting in drowsiness, respiratory depression and arrest, which can lead to death. Synthetic opioids desensitize the body's natural opioid system, making it less responsive over time. Repeated administrations inhibit production of own"endogenous opioids" (endorphins), leading to tolerance and severe withdrawal pattern. Addiction occurs when opioids are used only to avoid horrific withdrawal; pleasurable feelings/high no longer occurs (Suzanne and Quenne, 2021) [177].

Historical wave of opoid crisis

The ongoing opioid crisis in the U.S. can b e viewed as having occurred in three waves. The first stage reflected massive increases in the use of prescribed opioids and dates from the mid-1990s through 2010. This wave occurred during a period of loosening restrictions on the prescribing of opioid painkillers and extensive marketing of them to both healthcare providers and consumers. The second wave, from 2010 to 2013, was distinguished by extensive growth in heroin use and associated deaths, although problems related to prescribed opioids remained substantial during this period. The current wave (through the time of writing), beginning in 2013, has been characterized by surging deaths and problems related to the use of synthetic opioids, particularly fentanyl and its analogs. The first wave of the opioid crisis is thought to have begun shortly after the 1996 approval and release of Purdue Pharma's soon-to-be blockbuster drug OxyContin. Prior to the mid- 1990s, opioid prescribing was surrounded by a culture of 'opia-phobia,' as opioid painkillers have a long history of misuse in the U.S. reaching back to the Civil War (Macy, 2018) [99].

Through most of the 20th century, physicians were reluctant to prescribe opioids for pain management, even to cancer patients and to the terminally ill (Quinones, 2016; Hill, 1993; Paice *et al*., 1998; Weissman, 1993) [147, 78, 132, 185) . In 1996, Purdue Pharma introduced a new generation of opioids with the launch of OxyContin, an oxycodone product with an extended-release mechanism that was originally designed to reduce addiction. More specifically, healthcare providers were required to incorporate pain into patient assessments and, where appropriate, encouraged to treat pain symptoms medically, including through the use of prescription opioids. These actions played an important role in the emerging lax culture of opioid prescribing that characterized the first decade of the 2000s: by 2012, 259 million prescriptions for opioids were dispensed and approximately one in four Americans were prescribed an opioid medication each year (Kilby, 2016; Mallatt, 2019) [87 101]. There were an estimated 3,442 deaths involving prescription opioid poisoning (not counting synthetic opioids or heroin) in 1999; this number increased to approximately 15,000 overdoses at the beginning of the second wave of the crisis in 2011. Similarly, rates of substance use disorder (SUD) grew by a factor of six between 1999 and 2009 (Paulozzi *et al*., 2011) [136]. The crisis then evolved to a second wave where deaths and other adverse consequences associated with heroin use dramatically increased. Alpert et al. (2018) [9], and Evans *et al*. (2018) [57] show that this transition was, in part, fueled by a reformulation of OxyContin in August of 2010. The reformulated medication was crush-resistant and therefore harder to snort or inject. Additional government policies targeting the supply of opioid prescriptions also led to rising heroin use (Mallatt, 2020b) [103]. Heroin overdoses tripled between 2010 and 2013, whereas prescription opioid overdoses not involving heroin plateaued or subsided slightly. The overall effect of these market and policy changes was to increase the total number of fatal opioid overdoses. There are differences across the U.S. in terms of the source of heroin. This heterogeneity in source has important implications for policy efforts aimed at curbing use of this substance, and suggests that there are disparities in the type, and potentially harmfulness, of heroin consumed across the country. On the East coast, heroin has historically been imported in white powder form from South Asia while consumers on the West coast generally obtained black tar heroin sourced from Mexico (Abouk *et al*., 2019) [1]. Cutting agents and fentanyl are more easily incorporated into powdered heroin in the East and are more dangerous than pure heroin. Subsequently the East coast has suffered disproportionately from a large spike in synthetic opioid overdoses beginning in 2014. Fentanyl is an extremely potent synthetic opioid that offers several advantages over heroin to suppliers. In particular, fentanyl is relatively cheap to produce, and easier to transport and smuggle since smaller quantities are required. The production of heroin necessitates the relatively expensive, time-intensive, and conspicuous growth of opium poppies. In contrast, fentanyl and its chemical analogues are completely synthesized from ingredients in a lab. Many input components are imported from China to Mexico, where the drug is then synthesized in labs and smuggled across the U.S. border (United States Department of Justice, 2018b) [181].

Demographic Trends in Overdose Mortality

The opioid crisis has not affected socio economic and demographic groups equally. Here we summarize some broad patterns related to gender, race, and age. Overall drug overdose death rates are higher among men than women; about two thirds of opioid overdoses occur among males. However, women are relatively more heavily represented among prescription opioid deaths, with men making up only 59 percent of these fatalities. Non-Hispanic white Americans suffer disproportionately from prescription overdoses, with a death rate of 17.5 deaths per 100,000 populations in 2016 (Scholl *et al*., 2019) [165]. American Indians and Alaska Natives have the second highest rate of opioid overdose deaths, but data on these demographic groups are sparse (Scholl *et al*., 2019; Rudd *et al*., 2014) [165, 152] . Black and Hispanic Americans have traditionally been somewhat less affected by the crisis, perhaps due to under-treatment of pain within these groups, which may have inadvertently protected them from opioid initiation and overuse (Alexander *et al*., 2018; Frankt and Monkovic, 2019) [5, 61]. However, fatal overdose rates are rising among Blacks in more recent years as fentanyl is increasingly concentrated in urban areas, where Black Americans are disproportionately likely to reside. From 2015 to 2017, opioid mortality rates rose especially quickly among Blacks aged 45 to 64 years in large metro areas (Lipp old, 2019). From 2011 to 2016, the age-adjusted rate of overdose deaths involving fentanyl grew the most in the Black population, reaching 140.6 percent per year, while this rate rose 108.8 and 118.3 percent annually for non-Hispanic whites and Hispanics (Spencer *et al*., 2019) [174]. Older populations report far less opioid misuse (McCance-Katz, 2018) [109] and lower rates of opioid overdose deaths corroborate these survey responses, where as individuals aged 18 to 59 suffer relatively higher opioid fatality rates (Centers for Disease Control and Prevention, 2020a) [35]. The risk of opioid overdose is also positively correlated with a myriad of other demographic characteristics, including being disabled, unmarried or widowed, unemployed, uninsured, incarcerated, having low

education, being a citizen (in comparison to a non-citizen), renting rather than owning a home, residing in a non-rural area, and having a low income. Residents of South Atlantic states and Mountain states have relatively high rates of overdose.

Policy Responses to Prescription Opioid Misuse

Governments at all levels have undertaken a range of policy approaches in attempts to curb the opioid crisis. The nature of these policies has changed over time, corresponding to some extent with the types of opioids targeted, and as the character of the crisis has shifted from prescription to illicit opioids. While some localities have departed from the general trend, early policies tended to focus on interventions designed to curtail the supply of prescription opioids, or raise the financial or time costs of accessing these substances. More recent policies have typically emphasized demand-side factors, such as the ability to obtain prescriptions from multiple healthcare providers, and harm reduction efforts, such as naloxone access laws. Which type of policy response is more likely to be more effective is unclear *ex ante*. There are also potentially synergies between policies, suggesting gains to implementing multiple complementary efforts.

Prescription Drug Monitoring Programs

One of the earliest policies implemented by states, and currently by far the most common, is the prescription drug monitoring program (PDMP). PDMPs were adopted as early as1939, in California, and were designed to reduce the misuse of prescription medications generally, not specifically opioids (Holmgren *et al*., 2020). A PDMP is a centralized database containing patient scheduled prescription medications. PDMPs are designed to increase information available to healthcare providers related to patients' history with medically obtained prescription opioids. By 2017, all states had a PDMP in operation (Holmgren 13et al., 2020) [80]. Conceptually, healthcare providers (e.g., physicians who prescribe medications and pharmacists who dispense them) enter information into the database when patients are prescribed or dispensed prescription medications, including opioids. Healthcare providers then have the ability to access the patient's historical use of opioids and other controlled substances. The hope is that healthcare providers will then identify individuals who are potentially misusing opioids and limit access of the drugs to these individuals, thereby curbing misuse without reducing access to medications for legitimate patients. For example, doctor shopping can be identified and prevented by reviewing patient histories. Similarly, and ideally, implementation of a PDMP should not curtail access to prescription opioids for patients who use the medication appropriately (e.g., to manage acute pain). For PDMPs to reduce opioid misuse, healthcare providers must actually use the database, both by entering information after they prescribe or dispense controlled substances and by checking the patient's history before doing so. Several features of the earliest PDMPs may have stifled their effectiveness. Importantly, these PDMPs were voluntary: pharmacists were required to enter controlled substance histories into the centralized database but healthcare providers were not required to check the database at the time of prescribing or dispensing medications. Since many healthcare providers contend that the act of checking or entering information in the database is burdensome, prescribing providers often did not engage with PDMPs. Early PDMPs were not electronic, adding to the administrative burden of using the system. Given this backdrop, some healthcare providers have pushed back on PDMP adoption because of the hassle of utilizing them, such as difficulty in obtaining logins, the database not being accessible (i.e., the platform being 'down'), and incomplete data (Haffajee *et al*., 2015; Young *et al*., 2017; Lin *et al*., 2017) ([74], [192, 93]. Beginning in 2007, several states adopted arguably stronger PDMPs. In particular, this more robust policy approach often involved adding' mandatory access' provisions requiring prescribers to use the database. Conceptually, such mandatory access PDMPs should have more impact than voluntary systems as healthcare providers are legally bound to query the system. In addition to changes in direct effects on opioid use, recent research suggests that mandatory PDMPs reduce crime (Dave *et al*., 2018; Deiana and Giua, 2018) [44, 47], improve children's birth outcomes and decrease NAS (Gihleb *et al*., 2020; Ziedan and Kaestner, 2020) ([68], [193]) and reduce foster care admissions (Gihleb *et al*., 2019a) [66]. The assumed mechanism is that reduced opioid use leads to these improvements. A full consensus has not yet been reached, with some studies showing opposing findings. For example, Mallatt (2018) [100] finds that PDMP adoption leads to increased heroin-related crime in counties with high rates of opioid use. There may be a feedback loop induced by PDMPs whereby pharmaceutical companies reduce prescription opioid promotions following a mandatory PDMP which, in turn, lowers demand for these medications (Nguyen *et al*., 2019b) [125]. PDMPs also appear to directly decrease healthcare provider prescribing of opioids. Using rich health insurance claims data, Sacks et al. (2019) [159] show that opioids dispensed to opioid-naive users decline post-PDMP. Since the databases will contain relatively little information on new users, these results suggest that PDMPs instead reduce prescribing for other reasons, the most likely being hassle costs of using the system (Bachhuber *et al*., 2018) [14].

Using unique data from Kentucky, Alpert Note, however that some states are able to provide risk scores of all patients in PDMPs; e.g., seehttps://apprisshealth.com/solutions/narxcare/ (last accessed November 9th, 2020).15et al. (2020) similarly suggest that reductions in physician opioid prescribing may be at least partially attributable to the hassle costs associated with using the PDMP. Using claims data, Mallatt (2019) [101] shows that PDMPs target users displaying signs of opioid misuse. While studies establish that mandatory PDMPs reduce prescription opioid use and improve some associated outcomes, there could be positive or negative spillover effects on the use of other prescription medications, addictive substances, or non-drug pain therapies.

Whether substitution improves or worsens public health will be determined by the relative harms of the involved drugs. Several studies provide evidence of such substitution. For example, Grecu et al. (2019)[70] show that opioid-related admissions to SUD treatment programs decline following adoption of a mandatory PDMP, and that there are also decreases in admissions for cocaine and marijuana use, which could be economic complements to opioids. However, Mallatt (2020b) [103] finds that consumers substitute to heroin following the establishment of PDMPs, with particularly strong evidence in localities with high prior levels of prescription opioid use. This result is concerning if heroin use is more harmful than the consumption of prescription opioids; we may expect heroin to be more dangerous because of the method of consumption (e.g., injection rather than swallowing pills) or if users are less able to monitor the potency of the dose they are ingesting. Some researchers argue that PDMPs need not be mandatory to reduce prescription opioid use. Wang (2020) [184] shows that PDMPs (whether voluntary or mandatory) reduce opioid misuse when they are adopted in combination with a state-level health integration technology policy that promotes the sharing of health records electronically. Kaestner and Ziedan (2019) [85] find that adoption of a mandatory PDMP reduces sales of scheduled prescription drugs. However, when also controlling for whether the PDMP is electronic, the authors find that the coefficient estimate on the mandatory PDMP variable becomes statistically indistinguishable from zero. They interpret these results to imply that the salient feature of the PDMP is whether the database is electronic, not whether healthcare providers are mandated to check it. Overall, we note that while there are many studies on PDMPs, the literature has not yet reached full consensus on the importance of PDMP implementation and design, leaving10The PDMP may also have a direct effect by reducing the prescribing of other scheduled drugs, such as sedatives or stimulants. scope for future work in this area. There is also opportunity for new research studying how supply-side restrictions affect substitution towards other non-drug medical therapies and how to ensure that policies do not pose undue burdens on underrepresented minority populations (Substance Abuse and Mental Health Services Administration, 2020) [176].

Other Supply-side Policies

There are a number of less studied state-level supply-side interventions. One important category is pain management clinics laws (PMCL), which establish minimum requirements that pain management clinics must meet in order to dispense prescription drugs. Broadly, PMCLs are organized to prevent the emergence or operation of 'pill mills' – medical clinics that knowingly and willingly dispense prescription drugs, including to illegitimate consumers. Pill mills were especially notorious in Florida, which was considered the epicenter of the opioid crisis in the early 2000s. By preventing the ability of nefarious clinics from emerging or allowing authorities to shutter such clinics, the PMCLs reduce both the overall supply of prescription opioids and the extent of diversion to illegitimate users. PMCLs involve many separate requirements for clinics and doctors' offices, with variation in the specific stipulations across states. Each set of laws specifies which facilities are classified as pain management clinics, typically citing prescribing patterns or advertising practices that are characteristic of pill mills. The packages of laws then add more requirements aimed at reducing prescribing within these clinics or shutting them down altogether. Twelve states have passed legislation targeting pill mills. These policies appear to be effective in reducing prescription opioid use. Using government data on sales of scheduled prescription medications, Ziedan and Kaestner (2020) [193] document 15 to 50 percent declines in prescription opioid sales after implementation of a PMCL. Early evidence from Florida and Texas suggest these targeted efforts are effective at curbing prescribing and reducing harmful secondary outcomes like overdoses (Chang *et al.*, 2016; Lyapustina *et al.*, 2016; Mallatt, 2020b; Meinhofer, 2016; Rutkow *et al.*, 2015) [37, 95, 103, 115, 158]. Meinhofer (2016) [115] shows that the substantial crackdown in Florida caused the number of active pain clinic licenses to fall from 988 in 2010 to 407 in 2012. Additionally, quantities of prescribed opioids decreased by 59 percent, opioid-related admissions to drug treatment facilities increased by 33 percent and overdose rates declined. Florida was also unique in that the DEA arrested many offending prescribers during that state's crackdown on pain clinics, whereas pill mill laws in other states did not include a substantial law enforcement component. Chang et al. (2016) [37] find that, prior to the pill mill legislation, the top four percent of opioid prescribers in Florida were responsible for 67 percent of total opioid prescriptions in the state. After the pill mill legislation and law enforcement efforts were implemented, the high risk providers saw fewer patients and pre-

scribed fewer opioids. Lyapustina et al (2016) [95] indicate that the Texas pill mill law reduced opioid prescribing by between eight and 24 percent. Many states have recently passed laws limiting the length of initial prescriptions for opioids (typically to seven days). In considering the impact of these policies, Sacks et al.(2019) [159] unexpectedly show that such policies increase the overall amount of opioids prescribed to new users. This contrary result is driven by the reduction in the length of prescriptions that is more than offset by increases in the frequency of short prescriptions. Determining whether the net effect is harmful or beneficial depends on the relative risks of growth at the extensive margin (frequency of prescriptions) versus reductions at the intensive margin (length of prescriptions). An important private policy that substantially altered the supply of prescription opioids within the U.S. was the August 2010 reformation of OxyContin by Purdue Pharma. From its introduction to the market in 1996 through early August 2010, OxyContin, an extended release version of oxyco done that was often prescribed in high doses, was one of the most commonly misused prescription opioids (Cicero et al., 2005) [40]. One problem with the original formulation was that consumers often crushed or dissolved the pills and then inhaled or injected the drug an a more intoxicating form, thereby circumventing the extended release mechanism occurring with oral ingestion. Under pressure from the Food and Drug Administration, Purdue Pharma released a re-formulated version of Oxycontin that was more difficult to crush or dissolve. The company also quickly (within days) discontinued the original version, thereby abruptly shutting off access to the previous, easy-to-abuse formulation of OxyContin. There were high hopes for the potential of misuse-deterrent reformulations to reduce the injection, snorting, crushing, or chewing of prescription opioids (White *et al*., 2009) [190]. However, the Oxycontin reformulation had unintended spillovers into markets for illicit drugs. While the exogenous and sudden supply shock markedly reduced the use of this opioid, there was substantial and rapid substitution to heroin by consumers. Alpert et al. (2018) [9] conclude that areas with high underlying rates of OxyContin misuse realized large increases in heroin deaths after the reformulation, and that the reformulation explains up to 80 percent of the rise in fatal heroin overdoses after 2010. Similarly Evans et al. (2018) [57] find that each foregone prescription overdose death prevented by the OxyContin reformulation was offset by an additional death from heroin overdose. Further, because heroin is commonly injected and consumers often share needles, this drug-to-drug substitution led to increased transmission of hepatitis B and C (Powell *et al*., 2019; Beheshti, 2019a) [2, 21]. Evans et al. (2020) [29] find additional negative spillovers taking the form of increased child removals in areas with worse opioid outcomes, and Park and Powell (2020) [135] find negative spillovers to lab or force participation, finding increases in disability claiming. The longer-term effects of these policies are not yet well understood. For instance, new initiation into medications for opioid use disorder might decline such that, in steady state, there would be fewer individuals who misuse opioids under the reformulation than there would have been in its absence. However, recent research by Powell and Pacula (2020) [144] suggests the opposite outcome. In particular, the authors uncover evidence of more deleterious effects in the long-run because the reformulation spurred development of illicit drug markets. States and the federal government have also used the Controlled Substance Act (CSA) as a tool for addressing the opioid crisis. Two changes in CSA, targeting rival products and introduced separately, have allowed economists to study whether there are competitive spillovers to prescription products when one but not another product is regulated. In August2014, the U.S. federal government added tramadol, the second most popular opioid medication at the time, to the CSA (entering this medication at level V, which involves restrictions onrefills). Twelve states implemented the identical policy prior to federal action, providing an opportunity to compare effectiveness of the same opioid policy at state versus federal levels. Seven weeks after tramadol's scheduling, the leading opioid form on the market, hydrocodone combination products, was moved from level III to the more restricted level II (where no refills are allowed). Gupta et al. (2020) [73] find that the tightening of these prescribing restrictions decreased their use, but also caused some increases in prescriptions of close competitors. As a result, there was no statistically detectable short-run reduction in total number of opioid prescriptions. In addition to supply-side policies, states adopted doctor-shopping laws (DSL). This represents one of the few policies that have been used at a federal level requiring patients to rep ort to their healthcare professional previous prescriptions and, in a broad manner, prohibiting patients from obtaining medications through fraud, deceit ormisrepresentation. Popovici et al. (2018) [141] show that DSLs reduce opioid overdose deaths and opioid-related admissions to SUD treatment. Prescription opioids and marijuana may b e substitutes along at least some dimensions. For instance, marijuana may sometimes serve as an alternative treatment for chronic pain. Several studies suggest that patients substitute marijuana for opioids following the adoption of a state medical marijuana law (MML). In particular, these studies use health insurance claims data and show that prescriptions for opioids decline post-law (Bradford and Bradford (2017, 2018);Bradford et al. (2018); McMichael et al. (2020)[26, 113]. Recent work suggests that recreational marijuana laws (RMLs) may have a similar impact on the utilization of prescription opoids (Wen and Hockenberry, 2018) [186]. Moreover, reported chronic pain among older adults (Nicholasand Maclean, 2019), and both health-related work absences (Ullman, 2017) and Workers' Compensation benefit receipt (Ghimire and Maclean, 2020) [65] decline (chronic pain is a common ailment among those receiving Workers Compensation benefits), suggesting that the use of marijuana may sometimes

be effective in reducing chronic pain and other work-impeding ailments. Dispensaries, venues in which consumers can legally purchase marijuana, appear to b e particularly important in the relationship between marijuana and opioids. Powell et al. (2018) [145] show that the opening of legal medical marijuana dispensaries reduces opioid related admissions to SUD treatment facilities by 15 percent and opioid fatalities by 16 percent. Similarly, Smith (2020) indicates that deaths from prescription opioid overdose fall percent after a medical marijuana dispensary opens. These effects are concentrated among non-Hispanic white males. However, the benefits of expanded access to marijuana through state laws on chronic pain do not appear to extend to all populations. For example, Maclean et al. (2020) show that applications for Social Security Disability Income and Supplemental Security Income increase following adoption of an MML or RML. The authors hypothesize that individuals applying for disability post-law may have weak lab or market attachment or marginal disabilities that are not improved by marijuana use.

Enforcement of Illicit Drug Prohibitions

Now that the crisis has transitioned towards illicit drugs such as heroin and fentanyl, a discussion of the literature on law enforcement crackdowns during past illicit drug crises is potentially useful. A 2014 review by Pollack and Reuter (2014) [140] summarizes many studies of the effect of such enforcement efforts on drug prices; they do not find solid evidence that raising the risk of arrest or the increasing the length of drug sentences affects street prices. Cunningham and Finlay (2016) [41], and Dobkin and Nicosia (2009) [49] examine the effects of government efforts to make the precursors of methamphetamine less available. Moreover, as fentanyl became more prevalent over this period, its price fell. In 2014, the international law enforcement initiative 'Operation Onymous' shut down darknet drug markets and resulted in the arrests of dark net market administrators, sellers, and customers. However, this intervention caused only a small and temporary price increase in fentanyl which was overwhelmed by the general downward trend during the same time period. Miller (2020) [118] shows that while Chinese efforts to limit the illegal manufacture and export of various fentanyl analogues did flatten the downward time trend in fentanyl prices, the resulting prices remained strikingly low at the wholesale level. On the other hand, Mulligan (2020) [121] argues that reduced law enforcement efforts after 2013, due to the 'Holder memo,' played an important role in the emergence of illicit fentanyl. See Griswold et al. (2018), [72] and Peiper et al. (2019)[137] for examples of fentanyl precursors sourced abroad and mailed to the U.S. In the Holder memo, then Attorney General Eric Holder directed federal lawyers to stop prosecuting nonviolent drug crimes. However, the reformulation of Oxycontin and other regulatory measures, noted above, over this time period may preclude clean identification of Holder memo effects.

Harm Reduction Policies

Since there is little evidence that intensifying enforcement has significant potential for decreasing misuse or raising street prices of illicit or diverted drugs, much of the recent policy response emphasizes harm reduction strategies aimed at reducing fatal overdoses and other problems related to the misuse of opioids. Harm reduction policies include, but are not limited to, naloxone access laws (NALs), Good Samaritan Laws (GSL), and syringe exchange programs (SEP). NALs provide legal immunity to healthcare providers prescribing or administering naloxone, a medication used to reverse opioid overdoses; GSLs grant immunity or mitigated sentencing to individuals who call 911 in the case of an overdose; and SEPs simplify the act of obtaining new, clean syringes for injection drug users, and may include the availability of supervised injection sites or other safety measures (e.g., test strips used to determine if heroin contains fentanyl). Evidence on the effectiveness of NALs is mixed. Doleac and Mukherjee (2018) [50], emphasizing concerns about possible moral hazard, find that online searches for naloxone increase by seven percent and for opioid-treatment fall one percent post-NAL; opioid-related possession arrests, sales, and emergency department visits increase by 17 percent, 27 percent, and 15 percent, respectively, with no change in opioid-related mortality. Conversely, Rees et al. (2019) show that NAL adoption leads to a nine to ten percent reduction in opioid-related mortality and with consistently negative, but less statistically significant, reductions associated with the passage of GSLs. Abouk et al. (2019) [1] highlight the importance of the specific features of NALs, finding that those granting direct authority to pharmacists to distribute naloxone reduce fatal overdoses, whereas other types of NALs do not. An important challenge for all research on this topic is that the enactment of NALs has occurred over a short time period that coincides with the explosion of fentanyl. This confluence of rapid policy adoption and changes in substances used implies that uncovering causal effects using standard quasi-experimental methods is difficult, and even more so if the exact timing of when these policies become effective (which may differ from formally legislated dates) is not well understood.

Price Elasticities, Health Insurance, and Treatment

Examining the evolution of the opioid crisis from prescription to primarily illicit drugs, the role of the price elasticity of demand for opioids is important to consider. Factors that reduce the price of opioids, including insurance expansions such as those due to Medicare Part D, could increase their use (Powell *et al*., 2018) [9]. Soni (2019) [173] uses price variations in Medicare Part D to identify important heterogeneity in elasticity of demand for prescription opioids. Soni also presents evidence that non-prescription pain killers are substitutes for prescribed opioids. However, the local average treatment effect is identified off of individuals at the spending margin of the donut hole; these patients are likely sicker than the typical Medicare Part D beneficiary or younger opioid user. A related issue relevant for this discussion is insurance coverage for drug treatment. This coverage is often incorporated with broader changes in the healthcare delivery system, rather than specifically targeting the opioid crisis. While numerous treatment options are available including medications such as methadone, buprenorphine, and naltrexone, alongside behavioral interventions like counselling (Murphy and Polsky, 2016) [122] – most SUDs, including opioid use disorder, remain untreated. Recent estimates suggest that only one in ten individuals with OUD receive medication for treating it in a given year (Substance Abuse and Mental Health Services Administration, 2019) [175], although there have been recent expansions in availability of DEA-waivered providers of buprenorphine (Dick et al., 2015) [48]. While there are many reasons why individuals do not receive treatment – including strong psychological barriers to treatment and stigma – commonly stated causes include inability to pay and lack of insurance coverage (Substance Abuse and Mental Health Services Administration, 2019) [175]. Thus, increasing the generosity of insurance, both in terms the number of individuals eligible and the services included in plans, may facilitate treatment uptake and health improvements. Research on the effects of health insurance on opioid use disorder frequently uses legal changes resulting from the Affordable Care Act (ACA) as a source of identifying variation. One important modification under the ACA is that SUD treatment (including for OUD) became listed as an essential benefit that must be covered by most plans (McLellan and Woo dworth, 2014) [112]. In addition, Medicaid, the primarly public health insurance system for low income Americans, jointly funded by the states and federal government, is the largest insurance payer for SUD treatment (McLellan and Woo dworth, 2014) [112]. Under the ACA, Medicaid coverage was expanded to include all adults with incomes up to 138 percent of the federal poverty line. However, in 2012 the Supreme Court ruled that the federal government could not compel states to expand Medicaid and not all states elected to do so. Several studies have exploited this variation across states to test the impact of expanding Medicaid and show that this had important implications for opioid use disorder treatment access and outcomes. For instance, Meinhofer and Witman (2018) [116] find that ACA Medicaid expansion increased prescriptions for medications used to treat opioid use disorder by over 100 percent, raised admissions to specialty drug treatment, and increased the probability that opioid use disorder treatment providers accepted Medicaid as a form of payment. Cher et al. (2019) [39] corroborate this finding for OUD treatment medications. This latter finding is particularly important as insurance has historically played a minor role in financing SUD treatment Mark et al. (2016) [106]. To date there is limited evidence that this expansion has led to changes in opioid-related deaths (Averett et al., 2019; Abouk et al., 2019) [13, 2] . However, the dependent coverage mandate in the ACA (which guarantees that children can remain on their parent's health insurance plans up to age 26) is associated with reductions in opioid fatalities among young adults impacted by the policy (Wettstein, 2019) [189]. A concern with any insurance expansion is its potential to induce moral hazard. In the context of the opioid use crisis, this would take the form of insurance reducing the out-of-p o cket prices of prescription opioids, and potentially spurring misuse and opioid use disorder within the population. Powell et al. (2020) [135] leverage the plausibly exogenous variation in prescription drug coverage offered by the introduction of Medicare Part D in 2006 and find that a ten percent increase in the supply of medical opioids leads to a seven percent increase opioid deaths among individuals likely ineligible for Medicare. This finding suggests that some of these prescribed opioids are diverted to other users.

Effects of the COVID-19 Pandemic on Clients

The pandemic is just one more huge crisis that a person suffering from addiction has to deal with. There is such a large decrease in access to treatment; residential treatment centers have reduced the numbers of clients they can admit due to physical distancing restrictions. Many clients whose conditions warrant residential treatment are now forced to only receive virtual, out-patient services. These clients tend to do very poorly and often attend out-patient phone or virtual group counseling while under the influence as they continue to self-medicate and remain in agony. As a result, there has been a sharp rise in overdoses and suicides. These cases are largely overlooked due to the pressing worldwide focus on the horrific pandemic. So too, incredible social unrest in the United States, economic/job losses, corrosive/divisive politics, natural disasters, unemployment, businesses closed, and inconsistent messaging

have only added to overwhelming distress for people. Opioid epidemic uniquely American problem. 'Pain cannot be tolerated,' societal/cultural norms, over-prescription/abuse of pain medications by "Big Pharma," reduced belief in natural, alternatives and increase trust in doctors *not the same* in Europe, rest of world and United States: 5% of world population; uses 80% of prescription opioids. Centers for Disease Control – surveyed over 5,000 persons in June 2020, 40% reported increased struggle with mental health issues: 37% increase in anxiety/depression; 26% increase in trauma/stress related symptoms 13% increase in substance abuse; 13% seriously considered suicide (doubled from previous year!). Accumulated distress serves as relapse trigger. Isolation has become deadly for those addicted. Many, harm-reduction programs have lost employees, shut down, reduced offerings of needle exchange programs; reduced access, Borders shut down, so fewer drugs coming in good thing! But, dealers just cut Heroin with more Fentanyl; much more deadly (Suzanne and Quenne, 2021) [177].

Conclusions and Directions for Future Research

As the opioid crisis has emerged as a major public health concern, so has a large and rapidly growing body of economic research analyzing this crisis. Regulatory and p olicy approaches have played a role in mitigating these initial harms resulting in spillover effects to the consumption of illicit opioids and the incresase of mortality related to overdoses of opoid drugs and Covid 19. Generally, states have played a more active role than the federal government in these policy efforts. Other policy approaches (e.g., day limits to prescribing, CSA advisories, and most harm reduction policies) have received much less attention. In all opioid policy areas, researchers can benefit from the creation of taxonomies that reduce barriers to studying impacts of the policies (Grant et al., 2020) [69], and from considering the power and appropriateness of the statistical methods chosen (Griffin et al., 2020) [71]. As of this writing, the U.S. and many other countries are in the midst of the COVID-19 pandemic which has lead to over 200,000 American deaths. Although its implications for the opioid crisis are unclear, preliminary data indicates that COVID-19 is being accompanied by another increase in opioid-related mortality (Centers for Disease Control and Prevention, 2020b) [36]. Therefore, assessing the causal toll of the pandemic for opioid use and opioid use disorder will be important. In particular, we need to better understand how opioid problems have been affected by other changes related to COVID-19 such as: reduced willingness to seek healthcare, the growth in telehealth, and other non-medical factors such as isolation, strain, uncertainty, economic recession, a large-scale but short-lived government stimulus package, loss of friends and family members to COVID-19, and general disruptions in daily life. Finally, efforts will be needed to determine the most effective policies to address opioid outcomes in the post-COVID19 setting.

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