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A Social Review of the Opioid Epidemic: The History, Pathophysiology, and Effects on Rural America

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A Social Review of the Opioid Epidemic: The History, Pathophysiology, and Effects on Rural America

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Abstract

One of the more pressing issues in modern day health care is the nationwide health care crisis known as the opioid epidemic. The beginning of this literature review will focus on the history of opioid use and early prescription rates, as well as the summary and definitions of the drugs involved in the current opioid epidemic. The review then shifts to the pathophysiology of addiction involving the activation of opioid receptors and opioid use disorder. The main focus of this literature review is the societal impacts of the opioid epidemic, making special reference to the economic burden and effects on Rural America. The conclusion of this review offers some insight into possible solutions of combating the current opioid epidemic.

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INTRODUCTION

Current State of the Opioid Epidemic

Over the last two decades, opioid abuse and opioid related mortality rates have increased dramatically to reach epidemic levels, leading to a public health care crisis in the United States. This rise in mortality rates due to opioid overdoses can be described in three distinct waves. The first wave began with a rise in prescriptions opioid overdose deaths due to an increase in prescribing rates of opioids, both natural and semi-synthetic, in the 1990s (1). The second wave began in 2010, with heroin being the main contributor to overdose deaths (1). The third and current wave involves synthetic opioids, particularly those involving illicitly manufactured fentanyl (IMF) (2, 3). The current IMF market continues to evolve, and now IMF is commonly found in combination with heroin, prescription opioid pills, and cocaine (2, 3). This continual evolution further contributes to the increasing mortality rates surrounding opioid overdoses and the current health care crisis known as the opioid epidemic (2, 3).

COMPONENTS OF THE OPIOID EPIDEMIC

History of Opioid Use and Prescription Rates

Morphine and heroin were naturally derived in the 1800s from the opium poppy, and were recognized by their medicinal properties (4). These drugs, marketed towards physicians and patients as a safe, efficient, and effective way to treat pain and minor ailments, were used liberally with limited federal and pharmaceutical industry oversight to treat common ailments including cough, diarrhea, anxiety and minor pain (4-6). In 1915 the Harrison Anti-Narcotic Act was implemented with the intention to regulate opioid prescribing and administration practices (7).

Since the passage of the Anti-Narcotic Act, health care providers and patients informed of the possible side effects of opioid use had similar concerns about developing addiction after being placed on such drugs (8). In the 1980s however, attitudes towards opioid safety and pain-management began to shift significantly (6). Opioids had previously been reserved only for severe and impeding cancer pain and end-of-life care (6). However with shifting ideals regarding the underutilization of pharmaceutical opioids, pain specialists along with patient advocacy organizations began to raise awareness and bring attention to concerns regarding the inadequate management and treatment of non-cancer pain (6).

The American Pain Society (APS) introduced an influential campaign regarding pain assessment and management practices by physicians and healthcare persons, resulting in the establishment of the “fifth vital sign”, and by the late 1990s, repeated monitoring and pain intervention was imposed upon health care providers (8). In 2001, The Joint Commissions set new pain management standards, linking patient satisfaction and healthcare quality to pain control (6, 8). Opioid prescription rates were further influenced through training sessions and promotional videos created, supported, and financed by large pharmaceutical companies targeted towards physicians that inaccurately conveyed the danger and risk of addiction from opioid use as “less than one percent” (9).

Opioid prescribing rates peaked in 2010 at 225 million prescriptions dispensed as a result of the widespread marketing campaigns and increased attention on pain management practices (10). Initially propelled by the increased consumption and accessibility of pharmaceutical opioids, a rising amount of opioid overdoses associated with heroin and now illicitly manufactured fentanyl and fentanyl analogs now fuels the current opioid epidemic (6).

Opioids and Opiates

Opioids refer to all natural, synthetic, or semi-synthetic chemicals that interact with opioids receptors and reduce the intensity of pain signaling (11). Opiates refer to opium alkaloids derived directly from the naturally occurring opium poppy including but not limited to morphine and codeine (6, 11). Morphine is a white and crystalline used to treat acute to severe, chronic pain (12). The semi-synthetic opioids include heroin, oxycodone and hydrocodone, while the synthetic opioids include methadone and fentanyl (6, 11).

Fentanyl and Fentanyl Analogs

The fully synthetic opioid fentanyl was first synthesized by Paul Janssen in 1960 with the justification that fentanyl would serve as a highly potent drug with claims of improved receptor specificity, and that compared to morphine would possess a greater adverse effect profile (13). Fentanyl was first approved in the United States by the FDA in 1972 as an option for the treatment of pain, and permitted only to be used in combination with droperidol due to concerns about its property of extreme potency (13, 14). Despite these early concerns about the potential dangers, fentanyl was still an integral part in pain management of for chronic cancer patients and cardiac anesthesia due to its ability to block the body's stress responses induced by surgical stimuli and to provide cardiovascular stability during surgical procedures (13).

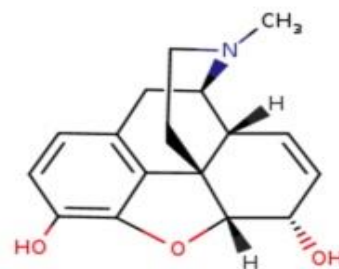


Figure 1. Chemical structure depiction of morphine. U.S. National Library of Medicine. 2016.

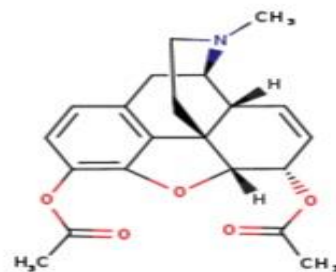


Figure 2. Chemical structure depiction of heroin. U.S. National Library of Medicine. 2016.

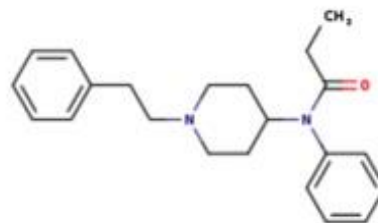


Figure 3. Chemical structure depiction of fentanyl. U.S. National Library of Medicine. 2016.

Up until the 1990s, clinical use of fentanyl was restricted to anesthesia. However, developments and new formulations were created, leading to the introduction non-injectable formulations including but not limited to fentanyl transdermal patches, sublingual tablets, sublingual sprays, and nasal sprays (13). Due to knowledge of its high potency and high potential for abuse, the United States DEA classified fentanyl and a number of other fentanyl analogs into Schedule II of the Controlled Substance Act (13). Decades after its approval and classification, fentanyl abuse reports were relatively low compared to other prescription opioids including oxycodone and hydrocodone (13). Most of the early reports of fentanyl abuse were attributed to abuse either by healthcare professionals that possessed easy access and occupational exposure to fentanyl, or abuse of transdermal patches mainly by patients or persons with substance abuse disorders (15). Prevalence rates concerning the non-medical use of FDA-approved fentanyl and fentanyl analogs remained low.

Despite previous low prevalence rates, in the mid-2000s there was a significant increase in overdose deaths due to illicitly manufactured fentanyl (IMF) (14). In 2006, the Centers for Disease Control and Prevention (CDC) and the Drug Enforcement Administration (DEA) discovered that most of the NFP involved in overdose deaths originated from NPF laced heroin or cocaine intentionally sold as a street drug and for injection purposes (14, 16). The origin of this fentanyl outbreak was attributed to and traced back to one single illegal clandestine laboratory that was developing illicitly manufactured fentanyl; once this lab was shut down, overdose deaths attributed to fentanyl and seizures of NFP promptly declined (13). In 2010 NPF-laced heroin and cocaine re-emerged, and from 2012 to 2014 the number of NPF related deaths more than doubled (17). The rise in circulating NPF has created a significant health crisis. Those exposed are typically

unaware the of addition of NPF, and subsequently are unaware of the alteration of their standard heroin, cocaine, or prescription strength opioid pills (14).

Following the synthesis of fentanyl, numerous fentanyl analogs with chemical structures similar to fentanyl were developed for medical and veterinary use, including but not limited to carfentanil (14). Figure 5 depicts the timeline of events related to select fentanyl and fentanyl analogs (14). Carfentanil first made an appearance in the US

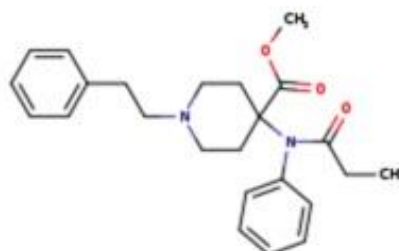


Figure 4. Chemical structure depiction of carfentanil. U.S. National Library of Medicine. 2016.

heroin supply in 2016, with the first outbreak concerning occurring in the Midwest and Appalachian region (14). During this outbreak, the DEA estimated for about 300 overdoses due to consumption of this fentanyl analog (14). In 2016, the CDC estimated that heroin or a synthetic opioid such as fentanyl was involved in over 80% of the opioid overdose deaths in 2016, and saw a 100% increase in deaths due to synthetic opioids from 2015 to 2016 (18).

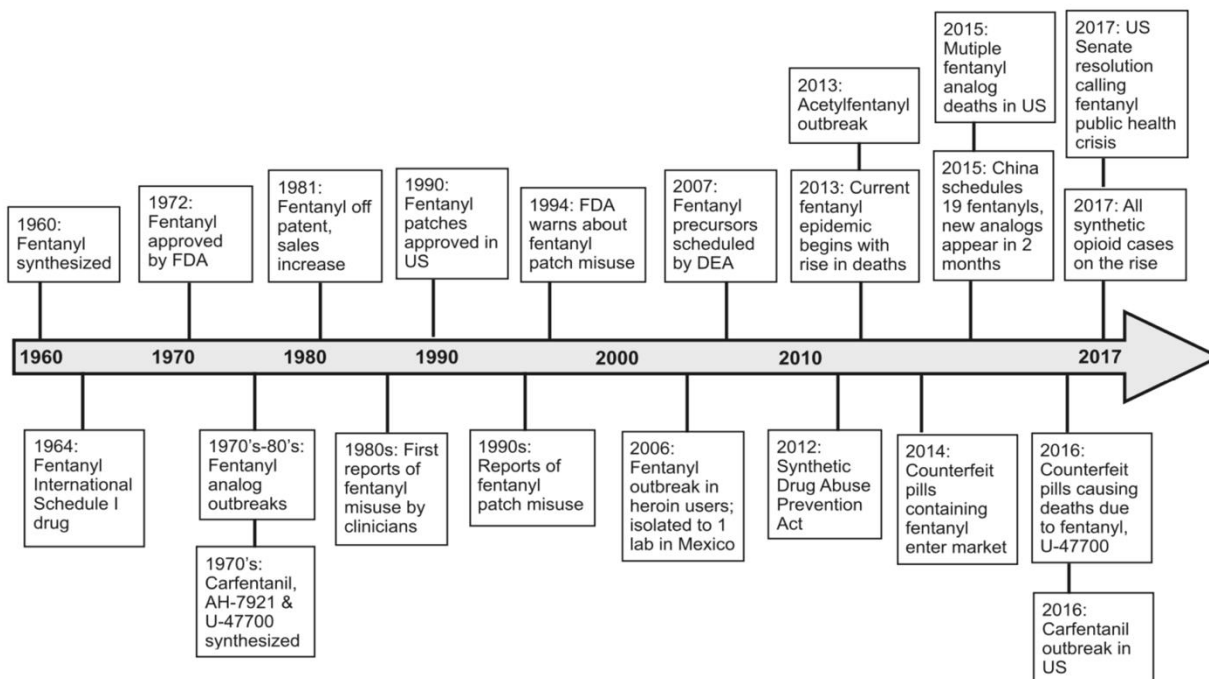


Figure 5. Timeline of select fentanyl events. Armenian et al. *Neuropharmacology*. 2018.

The current opioid epidemic with fentanyl as the main contributor has resulted from multiple fraudulent laboratories with locations worldwide (13). These laboratories manufacture illicit NPF and other fentanyl analogs that would have eluded scheduling by the DEA until very recently, but are now covered under a new derivative law to prevent prosecution evasion (13). The presence and proliferation of fentanyl and fentanyl analogs in the illicit drug market has been a result of several factors including profitability, availability, and the increasing amount of restrictions concerning prescription opioids (14).

PATHOPHYSIOLOGY

Opioid Receptors and Fentanyl Pharmacology

Four types of opioid receptors have been identified to date: mu, delta, kappa, and opioid receptor like-1, and these receptors are classified as G-protein coupled seven-transmembrane signaling proteins (19, 20). Fentanyl, a fully synthetic lipophilic phenylpiperidine opioid, is a full agonist of the mu-opioid receptor (13). This potent opioid produces its pharmacological effects via activation of the mu opioid receptor, and exhibits lower affinity for opioid receptors delta and kappa (13, 21). Fentanyl has a faster onset, shorter duration, and higher analgesic potency compared to morphine (13). Through human and preclinical studies, it was determined that fentanyl is 50 times more potent than morphine via intramuscular route, 150 times more potent via subcutaneous route, and 400 times for potent when administered intravenously; most physicians accept and report that compared to morphine, fentanyl is on average approximately 100 times more potent (13).

Part of fentanyl's enhanced analgesic properties can be attributed to its ability to rapidly cross the blood brain barrier (13). The short duration and subsequent rapid decline of fentanyl

levels in the body is due to the redistribution to other tissues, rapid sequestration into body fat, and in part due to activity of blood brain barrier P-glycoproteins involved in pumping fentanyl out of the central nervous system (13, 22). The lipophilic and solubility properties of fentanyl impact not only the clinical route of administration, but the pharmacology kinetics of its metabolism and elimination within the body (13).

Fentanyl has been identified as a highly effective full agonist of the mu opioid receptor (13). Previous evidence suggested that the primary action of opioid receptors within the nervous system was opioid receptors positively coupling to potassium channels while negatively regulating calcium channel (20). New findings suggest that opioid receptors exhibit effects on ion channel regulation in addition to slower yet robust effects on signal transduction pathways (20).

Opioids most commonly used for the management of pain, such as morphine and fentanyl, act on the mu opioid receptor (MOR) systems (20). Mu opioid receptors contain serine, threonine, and tyrosine residues that are accessible to protein kinases, enabling the phosphorylation of the receptor (20). MOR systems have a seven-transmembrane spanning helical domain that is connected by extracellular and intracellular loops, and this receptor exhibits its effects through interactions with inhibitory heterotrimeric G-protein (13). The interactions between the MOR and heterotrimeric G proteins are responsible for the subsequent opioid related pharmacological effects, including but not limited to euphoria and analgesia (13).

New studies also show that MOR can also produce G-protein independent signaling through utilization of beta-arrestin complexes, and this arrestin signaling has been suggested to be responsible for the respiratory depressive effects that opioids exhibit (13). It is well known that fentanyl, similar to other opioids, yields subsequent respiratory depression primarily due to opioid receptor activations in the pre-Bötzinger complex located in the ventral respiratory group in the

medulla (13). When in combination with other drugs of abuse or central nervous system depressants, fentanyl is likely to engage additional harmful mechanisms, including cardiac arrhythmias, which subsequently lead to mortality (13).

The existing knowledge gap of how fentanyl may contrast from other opioid drugs and receptor agonists is predominantly due to the differences in fentanyl administration practices in clinical settings and the self-administration by drug users for euphoric effects (13). What is known, however, is that mu opioid receptor agonists elicit analgesic effects, are mood enhancers and cause activation of dopamine reward pathways leading to the modulation of euphoria (20). These unwanted side effects of opioid use are major contributing factors to the opioid dependence and addiction.

Opioid Use Disorder (OUD)

Opioids binding to receptors in the CNS illicit euphoric and pain-relieving effects, and after repeated use, dependence, tolerance, and opioid use disorder (OUD) may occur; each condition is represented with distinctive phenomena and characteristics, and markedly distinctive clinical symptoms and implications (6). Opioid tolerance and dependence includes anticipated and physiological adaptations within the body occurring as a result of repeated significant doses of pharmaceutical or illegal opioid substances (6). Dependence symptoms are not unique to opioids and are characterized by signs and symptoms of withdrawal resulting from when the regular dose being administered is reduced or stopped abruptly (23). Tolerance is characterized by a diminished response to a substance as a result of frequent use, and often requires opioid users to increase doses in order to achieve an equivalent analgesic response (23).

Opioid use disorder, unlike dependence and tolerance, is not an adaptive or anticipated response to continual opioid exposure but is instead characterized by problematic patterns of

behavior including irrational and compulsive drug seeking and use despite the detrimental consequences that accompany this behavior due to intense cravings (24). Environmental, social, and genetic factors contribute to the development of OUD, and make some patients more susceptible than others (6). OUD is a complex disease that is currently not fully understood by researchers and clinicians; addiction, a disease of the brain more commonly understood, results from recurrent exposure to substances that alter the brain's structure and function, eventually contributing to the symptoms and characteristics of OUD, particularly drug seeking behavior (25).

Opioid use disorder can be defined as a pattern opioid use that is associated with a wide range of

Table 1 – DSM V diagnostic criteria for opioid use disorder.

- Two or more of the following within a 12-month period:
- Using larger amounts of opioids or over a longer period of time than was intended
 - Persistent desire to cutback or unsuccessful efforts to control use
 - Substantial amount of time spent obtaining, using or recovering from use
 - Craving or strong desire to use opioids
 - Failure to fulfill obligations at work, home or school due to use
 - Continued use despite recurrent social or interpersonal problems caused or exacerbated by use
 - Giving up or reducing social, occupational or recreational activities due to use
 - Recurrent opioid use in situations that may be physically dangerous
 - Continued use despite knowledge of having a physical or psychological problem caused or exacerbated by opioids
 - Tolerance*
 - Development of withdrawal syndrome if use stopped*
- Opioid use disorder severity:
- Mild 2-3 symptoms or signs
 - Moderate 4-5 symptoms or signs
 - Severe 6 or more symptoms or signs

* Tolerance and withdrawal criteria not met if opioids only used under medical supervision and as intended.

physical, mental, social and legal problems; these problems are also associated with increase mortality, clinically significant distress or impairment. The diagnostic criteria for OUD are outlined in Table 1, where an opioid use disorder is the repeated occurrence of 2 or more of the 11 problems within a 12-month period (26). Throughout the clinical course of opioid use disorder, periods of exacerbation and remission occur, however the underlying susceptibility to opioid addiction never disappears. This pattern of OUD is similar to other chronic relapsing conditions,

such as heart disease and diabetes, where complete control of symptoms can be difficult to achieve and patient adherence to treatment is ever evolving and often incomplete (27).

Individuals suffering from opioid use disorder also have increased risk of comorbid conditions, often coinciding with lack of regular health care and the undertreatment of other illnesses (28). The most common comorbid conditions associated with OUD include hepatitis C and HIV (28). HIV management can be challenging due to the multifactorial nature of the disease, including social, physical and economic factors which may disrupt the required continuum of care (29). Effective treatment are available for treatment of hepatitis C but are historically expensive and under prescribed, specifically when pertaining to persons with opioid use disorder (30). Individuals suffering from OUD, particularly those who inject drugs, are more prone and at increased risk of developing infections, both local and systemic (29). Neonatal abstinence syndrome is another notable medical consequence of opioid use disorder, where neonates born to mothers exposed to opioids during the duration of their pregnancy can experience withdrawal symptoms in the first few days of life (31).

Treatment of Opioid Use Disorders

In most cases of opioid use disorder, persons affected present with acute symptoms and in some cases it presents as early opioid withdrawal (28). The period of acute withdrawal symptoms experienced by affected persons depends on the degree or severity of physical dependence and the specific opioid from which the persons with OUD is withdrawing (28). Shorter periods of acute withdrawal symptoms – typically 7 to 10 days – are more closely associated with short-acting opioids, while longer acting opioids are associated with longer periods of withdrawal, lasting up to 14 days or longer (28). Once the phase of acute withdrawal is complete, persons may enter a period of prolonged withdrawal, characterizes by insomnia, hyperalgesia, dysphoria and cravings

(28). The symptoms experienced during both acute and prolonged withdrawal may be a powerful trigger for relapse, but also can be managed symptomatically and can be used as an opportunity for OUD patients to enter treatment (28). The sudden cessation of opioids after long-term use may produce symptoms that result from physiological changes that occurred during extended period of drug use (27). These symptoms may be relieved and managed via medication, and then gradually reduced in order to allow persons suffering from OUD to adjust to the absence of opioids (27).

Three FDA-approved medications – methadone, buprenorphine, and naltrexone – are currently used for the treatment of withdrawal for persons diagnosed with opioid use disorder (6). Methadone and buprenorphine are opioid receptor agonists that provide consistent systemic drug levels due to their long-acting properties (32). This consistent systemic drug level activity has been shown to reduce opioid cravings and prevent withdrawal symptoms, thus making these medications favorable treatments for OUD (27, 32). Naltrexone acts as an opioid receptor antagonist, and therefore is able to block the effects of opioids and can help prevent relapse when taken as directed (6).

Methadone is an oral MOR agonist with a half-life of 15 to 40 hours, and its use in maintenance treatment for persons suffering with OUD has been widely used (27). In the United States, methadone maintenance treatment is only offered through licensed and approved clinics and occurs in approximately three phases (27). The induction and early stabilization phase involve a low dose of methadone administration followed by gradual increases which require daily monitoring; the late stabilization phase involves increased doses as tolerance increase and craving decreases (33). Finally, the maintenance phase involved doses of methadone administered to avoid drug-related euphoria, sedation or cravings (33). Methadone may result in overdoses when given at doses above tolerance level or when used in conjunction with other CNS depressants (28).

Buprenorphine is an analgesic that is available as a monotherapy in sublingual form or in combination with naloxone, and is a partial MOR agonist, an agonist of delta and opioid-like receptor-1, and an antagonist of kappa opioid receptors; this drug has a long half-life of 3 hours, which makes it useful and advantageous in OUD treatment, but can be lethal and lead to overdose when used in conjunction with other CNS depressants (27). A 1 month extended release injection was approved by the FDA in 2017, and another 1-month and 1-week extended release formulations are currently being review by the FDA (29). The number of patients that physicians who are approved to prescribe buprenorphine was increased from 30 to 275 patients in 2016, thus increasing access to treatment (27).

Naltrexone is administered to patients in order to block the effects of opioids, resulting in the maintenance of opioid abstinence (34). As an oral medication, naltrexone is required to be taken daily with effects lasting 24 to 36 hours, or monthly as an extended release injectable medication (27). Adherence to daily dose administration of naltrexone is challenging, and efficacy studies concerning this OUD treatment drug have been contradictory to the improvement of patients and the superiority of the oral route to monthly injections (35, 36). Another concern with patients who use naltrexone for OUD treatment is the increased danger of overdosing due to the discontinuation of treatment using naltrexone only and the resumption of opioid use (37).

By itself, medically supervised withdrawal is usually not sufficient to produce long-term recovery and may increase the risk of overdosing in patients who have lost their tolerance to opioids (30). Treatment of OUD with medication is most effective when administered as a part of a cognitive behavioral approach (27). Patients are also encouraged to minimize relapses through the combination of education, motivational enhancement, and by encouraging lifestyle changes that diminish drug-related problems; persons experiencing substance-abuse disorders are also

encouraged to utilize self-help programs such as Narcotics Anonymous (38). This combination of treatment options encourages patients to change how they think about the effects that opioids have on their lives and to recognize that change is possible (38).

SOCIETAL IMPACTS

Impact on Rural America

Opioid-related mortality rates have continued to increase resulting in a nationwide health concern in the United States. Despite the common belief the “addiction does not discriminate”, there is substantial geographic variation in drug related mortality rates across the United States (39). Opioid-related mortalities, inpatient hospital state, and emergency department visits occur at higher rates in some predominantly rural states such as Maine, Kentucky, and West Virginia (40). However, rates of other largely rural state including Iowa, Nebraska, and South Dakota are among the lowest (40).

Rural areas, when compared to large urban areas, have generally been overlooked by the media, researchers, and national politicians (40). Due to this disparity of coverage, most national studies place their focus on urban areas, and the geographic diversity of the opioid epidemic is obscured (40). Inconsistencies also exist in literature pertaining to the differences between rural and urban opioid use disorders and mortality, and may be a result the national trends distorting important regional and state to state differences due to inconsistent data and coverage (41).

In a study completed by Rigg et al, data from the CDC was utilized in order to avoid inconsistencies and to describe the geographic heterogeneity that exists when determining opioid-related mortality trends and occurrences (40). The authors of this study determined that opioid-related mortalities were the highest overall in urban counties and the lowest the most rural

communities (40). However, the sharpest increase in opioid-related mortalities occurred in more rural than urban areas over the past two decades (40).

Variation also exists within rural areas of each state. Figure 6 depicts opioid-related mortality rates taking into account only the rural counties within each state for 2012-2016 (40). As seen in Figure 6, opioid-related mortalities are the highest in rural central Appalachia,

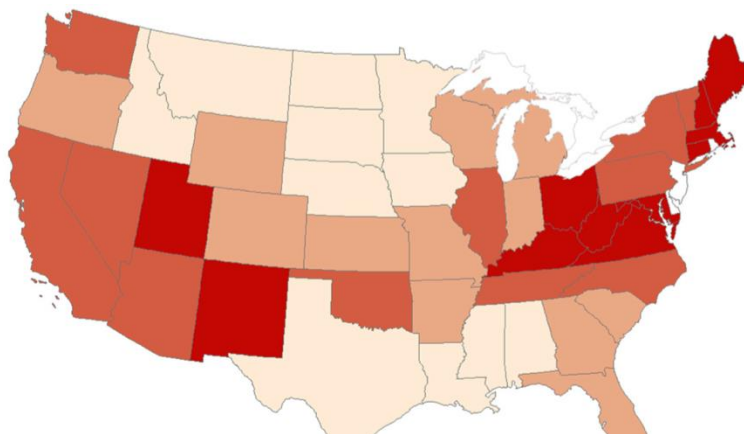


Figure 6. Rural opioid-related mortality rates, by state, 2012-2016. Rates are age adjusted deaths per 100,000 population. **Rigg et al. *International Journey of Drug Policy*. 2018.**

Deaths per 100,000 Population

New England, New Mexico, and Utah; rural counties in West Virginia contributed the highest occurrence of opioid-related mortality rates (40). Largely rural states such as Nebraska, South Dakota, and North Dakota possess low opioid-related mortality rates (40).

Another downfall when determining the geographic differences of the opioid epidemic is the failure to distinguish between the types of opioids involved in opioid-related mortalities. The effectiveness of preventative methods and reduction of opioid overdoses may differ depending on the nature of opioid involved (40). A larger share of rural opioid-related deaths are caused by prescription opioids rather than heroin or synthetic opioids (40). It is however important to note that since 2013, synthetic opioids – primarily illicitly manufactured fentanyl – have contributed to a larger proportion of rural opioid-related mortalities than heroin (40). Using data collected from the CDC, the percentage of all rural opioid-related mortalities age-adjusted per 100,000 population is depicted in Figure 7 (40). Rigg et al worked to determine factors that contribute to the geographic heterogeneity of the opioid epidemic and to the higher prevalence of opioid-related mortality in

some of the hardest-hit rural counties in the United States; they determined three major groups of factors the likely contributed to the diverse distribution opioid-related mortality rates: infrastructural, demographic or socioeconomic, and social (40).

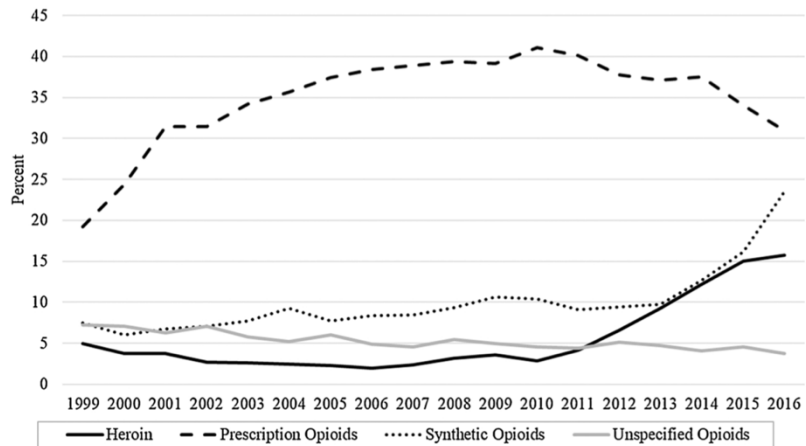


Figure 7. Percentage of all rural drug overdose deaths involving heroin, prescription opioids, synthetic opioids, and unspecified opioids 1999-2016. **Rigg et al. *International Journey of Drug Policy*. 2018.**

Infrastructural factors mentioned by Rigg et al include methods of treatment for persons suffering with opioid-related addiction including but not limited to drug treatment programs and providers, medication assisted treatment (MATs), and the emergence of synthetic opioids (40). Rural clinics and hospitals employing physicians and treatment professionals are often dispersed across sizable geographical areas, making access to treatment difficult (42). The issue of lack of treatment professionals in rural areas is compounded by lower salaries and fewer resources for such physicians (43).

Buprenorphine and methadone are long-acting opioid receptor agonists utilized by medication-assisted treatments (MATs) as potential effective options for treating opioid addictions (27). The uneven geographic distribution of providers of MATs imposes limited access for rural residents, along with long travel times and few options for public transportation (44). Such obstacles can be exceptionally problematic for persons seeking MAT, which often requires frequent and occasionally daily clinic visits (40).

Rigg et al also identified demographic and socioeconomic factors along with social factors that contribute to geographic heterogeneity of the opioid epidemic. Socioeconomic disadvantages

may increase the risk the substance abuse, along with selective out-migration of higher educated individuals due to employment restructuring (45). The movement of livable-wage jobs out of rural areas has resulted in wage polarization, and has led to fewer opportunities and intensified disproportional clustering of multigenerational economic geographic distress in rural communities (46). Such clustering in rural communities may also result in lack on anonymity, which may cause persons suffering from addiction to discontinue or avoid treatment altogether to avoid stigma (47). Although stigma is not only present in rural communities, it can be more pronounced. Treatment specialists in rural communities are more likely to be friend or family members, which further decreases anonymity and can be a powerful deterrent to seeking out treatment (40).

Economic Burden

Unclear explanations for the geographic variation of the opioid epidemic can result in ineffective policy implementation and intervention strategies aimed at preventing the progression of the current opioid epidemic. The prevalence of opioid misuse and abuse has been difficult to determine, and the consequential burden on society due to this misuse has been difficult to quantify (48). This difficulty can be attributed to varied data collection methodologies and varied terminologies associated with persons directly contributing to the opioid epidemic (48). The overall burden of the opioid epidemic has been multifactorial and difficult to quantify, as it manifests itself in numerous ways (49). The financial burden associated with opioid misuse and abuse is particularly significant, particularly when taking into consideration factors associated with healthcare and employers' costs, and the cost of treatment for patients with opioid addiction (50). Determining this total economic burden resulting from the opioid epidemic is an essential component when identifying strategies aimed at prevention (51).

Despite discrepancies throughout findings related to the nonmedical use of opioids, the data collected is in agreeance that the consequence of opioid misuse is significant and continually increasing (48). Estimates of the overall cost to society – taking into account variables such as healthcare, workplace and criminal justice system costs associated with opioid use and abuse – has risen from \$11.8 billion in 2001, to \$55.7 billion in 2007, and \$78.5 billion in 2013 (44, 50, 51).

A recent study was conducted in 2013 by Florence et al in order to estimate the total economic burden caused only by prescription opioid overdose. This study maintained the importance of understanding the distribution of the economic burden created by opioid misuse and abuse in order to inform clinicians, researchers and government leaders; collected data is used by government leaders and healthcare professionals when choosing cost effective methods aimed at addressing the opioid epidemic. This study determined that the total economic burden in 2013 was estimated to be \$78.5 billion (51). This study also estimated that over one third of this estimation was due to increase healthcare and treatment of substance abuse costs, totaling to \$28.9 billion (51).

Florence et al assessed the cost of prescription opioid overdose based on the incidence of deaths contributed to overdose, and the prevalence of opioid abuse and dependence for the 2013 calendar year. This study also took into consideration the cost for persons experiencing overdose or abuse and the costs imposed on society in general, including healthcare costs, the cost of treatment for substance abuse, criminal justice costs, and lost productivity in the workplace (51). The total estimated aggregate costs place a substantial economic burden on local, state, and federal government (51). Although difficult to quantify all costs resulting from opioid misuse and abuse, the costs that are identifiable assist in increasing the understanding of the impacts that this widespread epidemic embodies.

Despite the efforts of numerous cohorts of scientists and economists, the White House Council of Economic Advisors (CEA) has determined that previous attempts to estimate the economic cost of the opioid crisis has been greatly underestimated. The CEA determined that while these previous attempts at informative about certain areas of costs, they only partially account for the damage imposed by this opioid epidemic (52). The main contributor to this underestimation results from the undervaluing of fatalities resulting from opioid overdoses (52).

This estimate completed by the CEA adjusted for the underreporting of opioids in overdose deaths, including those involving heroin-related deaths, which were unaccounted for in previous studies (Florence et al) aimed at determining the economic burden of the opioid epidemic; the nonfatal costs of opioid misuse and abuse were also accounted for by the CEA (52). The most recent estimate completed by the CEA in 2015 put the total economic cost of the opioid epidemic at an estimate of \$504.0 billion, with a total cost estimate range from a low of \$239.9 billion to a high of \$622.1 billion (52).

The CEA recognized and acknowledged the large gap between their estimate of the economic cost of the opioid epidemic and previous estimates completed by other agencies and cohorts. The CEA's reasons for this disparity resulted from their full account for a value of lives lost, the increasing number of overdose deaths in recent years, the focus of previous studies exclusively on prescription opioids, and the adjustment of overdose deaths based on recent research of the significant underreporting of opioid related overdose deaths (52). Estimates completed by individual unverified agencies determining the current values of this economic burden have continued to increase beyond the most recent value determined by the CEA.

COMBATING THE OPIOID EPIDEMIC

Current Solutions

The emergence of the opioid epidemic has been multifactorial, which makes the development of strategies aimed at curbing this epidemic difficult. To date, most of the efforts aimed at addressing the opioid epidemic have been focused on downstream strategies, specifically treatment approaches for persons suffering with addiction and OUD (40). Comparatively, less effort has been devoted to upstream strategies such as prevention and education (40). The lack of medical education on proper opioid prescribing and addiction may have contributed to the increased availability and use of opioids (40). Health care providers should provide education about the disease of addiction and the overdose risk associated with opioids, and should provide patients with information about the dangers of mixing substances and using higher doses than prescribed (28).

An upstream strategy aimed at detecting diversions in prescribing practices is the prescription drug monitoring program (PDMP), which have been established in nearly every state and aim to reduce the availability of opioids and to detect patients with multiple providers (6). Current guidelines set by the CDC suggest the providers review PDMP data prior to the prescribing of any opioids (53). A strategy aimed directly at reducing fatal overdoses resulting from opioid use is the availability of naloxone, an opioid receptor antagonist (54). The effectiveness of naloxone depends on whether overdose bystanders have easy access naloxone, can promptly recognize correct signs and symptoms of overdose, and promptly and effectively administer this medication (6).

CONCLUSION

The opioid epidemic, initially driven by the increased availability of prescription opioids and heroin is now fueled by fentanyl and fentanyl analogs. These opioids act on opioid receptors, triggering downstream effects and may result in addiction and OUD. Medication exists for the treatment of OUD, but access to licensed providers and this medication may be limited due to geographical characteristics, and these characteristics lead to unique barriers and societal impacts, especially in rural America. The opioid epidemic has also caused a significant economic burden, which influences policy implementation and intervention strategies. Current research studies about OUD involving genetics, epigenetics, and pharmacogenetics are being conducted in order to determine risk and susceptibility.

Prospective Research

The regional differences that exists within the opioid epidemic are interesting because a substantial amount of variation exists. It would be interesting to conduct a longitudinal study of the effects of opioids specifically in South Dakota, which is largely a rural state. Understanding these geographical differences that exist in each state would be helpful in fine tuning solutions to address the underlying social and economic factors that are a part of the modern-day opioid epidemic.

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