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Trading Addiction: An Analysis of Prescription and Non-Prescription Opioid Abuse

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Abstract description: Opioid abuse, addiction, and overdose is a serious public health concern that has plagued the healthcare system for the last thirty years. The compiled research in the following paper explores the rise of the opioid epidemic, the implications of more recent prescription monitoring and pain management programs, the relationship between non-prescription and prescription opioids, and the current face of the epidemic, illicit opioids. Kentucky has, unfortunately, been at the forefront of this epidemic with regard to both prescription and illicit opioids. Policy reformation and preventative action must be taken into consideration in regard to the relationship between prescription and non-prescription opioid use. Addressing the relationship is crucial to ensure by fighting one addiction we are not unknowingly promoting another in order to effectively turn the tide on the opioid epidemic.

Keywords and phrases: Opioid use disorder, overdose, fentanyl, heroin, naloxone, narcotic, analog, injection drug use

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INTRODUCTION

The opioid epidemic has evolved rapidly throughout the last decade. The abuse of and addiction to opioids is a prevalent national crisis, with more than 130 people dying from opioid-related drug overdoses a day (Health Resources and Administration 2020). In the late 1990's healthcare providers began to prescribe these pain relievers at greater rates, which ultimately led to the widespread diversion and misuse of the medications seen today. In 2018, 67,367 drug overdose deaths occurred in the United States, with opioids being involved in 46,802 of the overdose deaths (69.5% of all drug overdose deaths). Two out of three (67.0%) opioid-involved overdose deaths involve synthetic opioids (CDC 2019). An estimated 1.7 million people in the United States suffered from

substance use disorders related to prescription opioid pain relievers, and 652,000 suffered from a heroin use disorder. An estimated 4 to 6 % who misuse prescription opioids transition to heroin, and about 80% of people who use heroin first misused prescription opioids (National Institute on Drug Abuse 2020). In addition to increases in opioid misuse, addiction, and overdose, the opioid epidemic contributes to an increase of neonatal abstinence syndrome due to opioid misuse during pregnancy and the spread of HIV and hepatitis C by intravenous injection.

While these data are alarming, among 38 states with prescription opioid overdose death data, 17 states saw a decline between 2017-2018, and none experienced a significant increase. Addressing overprescribing of opioids through prescription monitoring and improved pain management has been pivotal in combatting the crisis; however, there is still much work to be done. An analysis of the opioid epidemic reveals a challenge facing the healthcare system: illicit opioids, such as heroin and fentanyl, have increased in frequency of abuse and overdose despite the decrease in prescription opioids. The healthcare system should shift focus to combat the new face of the epidemic.

OPIOID PHARMACOLOGY

To better understand the epidemic and create a curative path to combat it, basic opioid pharmacology should be noted. Opioids are a class of drugs that work to produce a variety effects, but primarily pain relief. Opioid pharmacology was born when morphine was first isolated from opium in 1806 by Sertürner. By 1847 the chemical formula for morphine ($C_{17}H_{19}NO_3$) was deduced, which coupled with the invention of the hypodermic needle in 1853 led to more precise and widespread clinical use of morphine for the first

time (Blackmore and White 2002). Morphine is considered the archetypal opioid and consists of a benzene ring with a phenolic hydroxyl group at position 3 and an alcohol hydroxyl group at position 6 and at the nitrogen atom. In addition to morphine, three other naturally occurring alkaloids can also be extracted from *P. somniferum* (Opium Poppy): codeine, papaverune, and thebaine. Chemical manipulations of the opiate alkaloids in the 19th Century began to yield many semi-synthetic opioids, such as diamorphine, dihydrocodeine, buprenorphine, nalbuphine, naloxone and oxycodone, that became useful in the practice of medicine. Following suit, the 20th Century saw the production of a multitude of synthetic opioids. Synthetic opioids can be divided into four chemical groups: the morphinan derivatives (levorphanol, butorphanol), the diphenylheptane derivatives (methadone, propoxyphene), the benzomorphan derivatives (pentazocine, phenazocine) and the phenylpiperidine derivatives (pethidine, alfentanil, fentanyl, sufentanil and remifentanil) (Pathan and Williams 2012).

Additionally, opioids can also be grouped in regard to their effect at opioid receptors. Opioid agonists produce the maximal response by stimulating the receptor. Partial agonists bind to the receptors, but only give a partial functional response (Buprenorphine). Antagonists bind to receptors, produce no functional response, and prevent agonists from binding to that receptor (Naloxone). There are three opioid receptors, DOP (the delta receptor), KOP (the kappa receptor) and MOP (the mu receptor). Each receptor is a G-protein-coupled receptor, controlled by different genes, and are widely distributed primarily within the central nervous system (CNS) and throughout the peripheral tissues. There is a series of endogenous ligands active at the receptors that are derived from parent compounds provided from three pro-hormone

precursors (Trescott et al., 2008). **Table 1** is below detailing opioid receptors and their respective endogenous ligands and precursors.

Receptor	Precursor	Endogenous Ligands
DOP	Pro-enkephalin	Met-enkephalin, Leu-enkephalin
KOP	Pro-dynorphin	Dynorphin-A, Dynorphin-B
MOP	Pro-opiomelancortin	β-endorphin

Table 1. Opioid Receptors Broken Down.

The stimulation of each opioid receptor produces a range of effects, which are dependent on the location of the receptor. Agonists binding to MOP receptors may cause analgesia, sedation, respiratory depression, bradycardia, nausea and vomiting, and a reduction in gastric motility. Additionally, agonists binding to DOP receptors can cause spinal and supraspinal analgesia and reduce gastric motility, while KOP receptor activation can produce spinal analgesia, diuresis, and dysphoria (Trescott et al., 2008).

The chemical structure of opioids can be further subdivided:

- 4,5-epoxymorphinan ring = morphine, codeine, oxymorphone, oxycodone, buprenorphine, hydromorphone and hydrocodone
- Phenylpiperidines = alfentanil and fentanyl,
- Diphenylheptylamines = methadone.

Although these compounds differ in chemical structure, physicochemical properties and in pharmacokinetics, they have one common feature, which is their interaction with the

MOP receptor as the primary target. All opioids used in clinical practice today exert their action at the MOP receptor, with some having additional activity at one of the previously mentioned receptors (Drewes et al.,2012).

THE THREE WAVES

The rise of the opioid epidemic can be divided into three waves. The first wave began in the early 1990s following a significant increase in the prescribing of opioid medications for pain treatment. Prior to this decade painkillers derived from the opium poppy were typically only written as prescriptions for patients with advanced cancer or other terminal conditions. Dr. Russell Portenoy, MD, pain specialist and neurologist, was acclaimed as the "King of Pain" after he became a trailblazer for wider prescription of opioids for pain treatment and management. Portenoy and company hemmed a movement to enhance this group of painkillers. The movement was branded with the proclamation that not treating pain properly amounted to medical negligence and that the risks of opioids were minimal compared to what was believed (Gale 2016). Lectures and writing on the subject often referenced a study published in The New England Journal of Medicine by Dr. Hershel Jick, MD, and graduate student, Jane Porter, in 1980. The study concluded "that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction" with data suggesting four out of 11,882 hospitalized patients who received at least one narcotic and had no prior history of addiction, documented addiction (Jick and Porter 1980). The study was invoked by doctors and pharmaceutical companies to promote to the medical community

that opioids are not very addictive. This reassurance contributed to many healthcare providers writing opioid prescriptions at much greater rates for non-cancer related pain.

Porter and Jick's acclaimed study that sparked the movement was widely misinterpreted as it did not account for patients after their hospital stay (Gale 2016). By 1999, 86% of patients on opioids were using them for non-cancer pain (Leu et al., 2020). The Joint Commission on Accreditation of Healthcare Organizations endorsed this treatment and established new standards in 2001 that held hospitals and physicians responsible for ensuring adequate pain treatment (*Chidgey et al., 2019*). From 1999 to 2014 opioid prescriptions quadrupled and there were more than 165,000 deaths related to opioid overdose (CDC 2016). The second wave of the opioid epidemic began in the following decade marked with a significant increase in opioid deaths involving heroin, increasing by 286% from 2002 to 2013 (Leu et al., 2020). Due to the implementation of a multitude of drug monitoring programs it became increasingly more difficult to obtain a prescription opioid, which shifted the focus to the cheaper and more accessible alternative with similar effects, heroin. Approximately 80% of heroin users first misused prescription opioids before turning to heroin (National Institute on Drug Abuse 2020).

The third wave began shortly after in 2013, this time with a significant increase in overdose deaths involving illicitly manufactured fentanyl. Fentanyl is a synthetic opioid, 50 to 100 times more potent than morphine. The drug is sold as a "powder, dropped onto blotter paper, put in eye droppers and nasal sprays, or made into pills that look like other prescription opioids" (National Institute on Drug Abuse 2020). Illicit fentanyl abuse has continued to consistently increase over the course of the decade. Overdose deaths

involving synthetic opioids, fentanyl and fentanyl analogs, were 12 times higher in 2019 than in 2013 (CDC 2020).

A common theme in opioid literature is attempting to place blame on someone or something for the origin of the opioid epidemic; however, it cannot be pinpointed to one certain movement or only one pharmaceutical company. The healthcare system failed, but with good intentions. The Food and Drug Administration (FDA) approved Oxycontin®, manufactured by Purdue Pharmaceuticals, in 1995. The active ingredient of oxycontin is oxycodone, a semisynthetic narcotic analgesic, used for pain management (Jayawant and Balkrishnan 2005). Purdue Pharmaceuticals led an aggressive marketing campaign that promoted Oxycontin® as "smooth and sustained pain control all day and all night" (Purdue Pharma popular timelines). Additionally, the campaign promoted Oxycontin's® extended-release formulation by claiming that one dose could relieve pain for 12 hours, more than twice the duration of other pain medications on the market at the time. This caught the attention of physicians and patients alike as it would prevent interruption of sleep and daily activities, with promising lower abuse potential since the drug would be absorbed slowly. Oxycontin® produced $31 billion in revenue for Purdue Pharmaceuticals (LA Times**). However, this vision was too good to be true. Purdue Pharmaceuticals' clinical trials conducted for FDA approval reported that many patients given Oxycontin® were asking for more pain medication before their next dose scheduled 12 hours later (Chow 2020). Despite these results Purdue Pharmaceuticals still went to the FDA for approval and went on to produce advertisements in medical journals claiming pain relief in patients can be achieved by the 12-hour dosage regimen. The FDA based its judgment on marketing history of MS Contin, "a similar controlled-release

formulation of morphine used in the medical community since 1987, without significant reports of abuse and misuse (FDA)."

After FDA approval, the number of prescriptions of Oxycontin® increased to over 14 million in 2001, up from 316,000 prescriptions in 1996. This increase in prescriptions saw sales increase to nearly $3 billion, in comparison to the $44 million in 1996 (Van Zee 2009). The commercial success of Oxycontin® was astounding; however, it was followed by increasing rates of abuse, addiction, and overdose. Abusers began to crush the tablets and snort the powder or dissolve them in water and inject the drug for a fast, intense morphine-like high (Jayawant and Balkrishnan 2005). In 2002, federal prosecutors with the Justice Department began an investigation on Purdue Pharmaceuticals after receiving reports pills were being crushed, snorted, and injected, stolen from pharmacies, and sold illegally (NY Times). It was not until 2003 that the media added a spotlight on the investigation. This occurred because Rush Limbaugh, radio host, admitted to listeners on his national radio show that was addicted to painkillers and "would immediately enter a 30-day treatment program" (Bennett and Pacenti 2003). Limbaugh's personal statement came a week after news outlets reported Limbaugh was being investigated for illegally obtain prescription drugs. Limbaugh admitted the origins of his addictions stemmed from when his doctor prescribed painkillers to treat post-surgical pain following a botched spinal surgery. Limbaugh chose to treat the severe pain with prescribed painkillers instead of an additional surgery (Bennett and Pacenti 2003). Limbaugh's personal statement sent the media into a frenzy with headlines focusing on the abuse of Oxycontin®. The growing attention from the media gave even more reason for federal prosecutors to thoroughly continue their

investigation on Purdue Pharmaceuticals.

After the four-year investigation, the officials determined that Purdue Pharmaceuticals was aware of the abuse and addiction reports yet continued to market the drug aggressively. The prosecutors recommended the top three Purdue Pharmaceuticals executives be indicted on felony charges; however, the Justice Department did not follow the recommendation (NY Times). Purdue Pharmaceuticals executives did however plead guilty to misdemeanor charges with a community service agreement in 2007 (NPR 2019).

PRESCRIPTION DRUG MONITORING PROGRAMS

The mere guilty plea did not fix the damage that was already done in regard to opioid abuse and addiction. The DEA recognized this and began developing drug abuse monitoring programs to address the opioid crisis. A prescription drug monitoring program (PDMP) is an electronic database that tracks controlled substance prescriptions at the state level to help mitigate prescription misuse and diversion. These programs were individualized for each state and designed to uphold state laws ensuring access to appropriate pharmaceutical care and deterring diversion. PDMPs facilitate communication among the healthcare system, specifically between pharmacists and healthcare providers, as well as state insurance programs, healthcare licensure boards, health departments, and law enforcement.

PDMPs were established with features that allow healthcare providers to access patients' prescribing histories to inform their prescribing decisions. Additionally, before pharmacists dispense controlled substances, they log the prescription information into the state PDMP—the rate the information is submitted varies from state to state and

pharmacy to pharmacy, ranging from monthly to daily to in real time (CDC 2020). Real-time use maximizes the benefit of PDMPs, as well as constantly managing and evaluating the program as the face of the epidemic changes. Currently, 49 states, the District of Columbia, and the US territory Guam have implemented PDMP legislation. Missouri is the only state without a PDMP, however, Faisal Khan, former head of the St. Louis County Health Department, led a voluntary county based PDMP program in 2017 that now covers other areas of the state (Weber 2019). Based on the experience of PDMPs in the past, those PDMPs implemented more recently have been implemented faster with more innovative resources.

The first PDMP was implemented by New York state in 1918. Drugs, such as heroin and cocaine were allowed to be prescribed by federal and state laws. The legislation was enacted to monitor prescriptions for cocaine, heroin, codeine, morphine, and opium. Pharmacists were required to report prescriptions for cocaine, heroin, codeine, morphine, and opium to the health department within 24 hours of dispensing the drug. The program was only in effect for three years before it was ultimately eliminated; however, it would go to serve as the blueprint for many PDMPs to come (TAG 2018).

California established their own statewide PDMP in 1939 that has been in continuous operation since. California originally placed their administration in a newly created Bureau of Narcotic Enforcement. Hawaii followed their lead in 1943 and many other states followed suit during the 1960's and 70's. In the beginning all PDMPs had the same characteristics that included collecting prescription information on Schedule II controlled substances, requiring multi-copy state issued prescription forms to prescribe and dispense Schedule II substances, and requiring sending prescription information to

the state within 30 days from the time the drug was dispensed. The new wave of monitoring prescriptions was put in question in front of the Supreme Court with Roe v. Whalen 1977 when challenges were raised regarding legality of New York state's Controlled Substance Act. The supreme court ruled that "New York state does have the authority to collect the information as part of its police powers … was not unconstitutional and did not violate patient confidentiality" (TAG 2018). The ruling granted continuation of New York's PDMP, while indirectly opening the door for other states to pass PDMP laws at the start of the 21st Century when opioid abuse, addiction, and overdose reached a new high.

Twenty-seven states implemented PDMPs from 2000 to 2010 (SAMHSA 2017). Oversight of all controlled substances is now recommended including Schedule II through V drugs, as well as controlled non-opioids such as stimulants (D'Souza et al., 2020). Each PDMP is still individual to each state typically following one of the three models. One of these models is operated through non-mandated use, which allows prescribers and pharmacists to access the database voluntarily. A second model involves proactive reporting, which allows prescribers and pharmacists to receive unsolicited reports on patients who are on a combination of controlled medications or a potentially dangerous dose and on patients who receive prescriptions from multiple providers. The third, newer model features mandated use and requires prescribers to review their respective PDMP before prescribing any controlled substance. The mandated use model has now been adopted in Kentucky, Tennessee, New York, and Ohio (D'Souza et al., 2020).

KASPER

Kentucky has, unfortunately, been at the forefront of the opioid epidemic for many years. Between 2000 and 2013, the number of drug overdose deaths in Kentucky rose from 246 (6.1 per 100,000 population) to 1,019 (23.2 per 100,000 population) (American Public Health Association). To address the epidemic Kentucky first implemented Kentucky All Schedule Prescription Electronic Reporting (KASPER) in 1999. Initially KASPER allowed prescribers, pharmacies, and law enforcement to request reports that detailed a patient's controlled substance prescription history. KASPER became fully electronic in 2005 which allowed pharmacists and prescribers to utilize the KASPER reports in real time to make more informed decisions regarding patient care. According to Kentucky's Cabinet for Health and Family Services, when a patient's KASPER report is created, the report will show the following: date range for the report, patient names and date of birth, prescription information such as date filled, quantity, day supply, doctor name and city, drug name and strength, and pharmacy name and city. To evaluate the effectiveness of KASPER an independent study was done in 2010 that revealed "16% of licensed pharmacists and 27.5% of licensed controlled substance prescribers were registered with the PDMP" (Wixson et al., 2015). These statistics were further evidence that overall less than 25% of healthcare professionals access PDMPs to obtain controlled substance reports (Green et al., 2011).

In 2012 the Kentucky General Assembly passed House Bill 1 (HB1). HB1 adopted the PMDP mandated use model and made changes to the prescribing and monitoring of controlled prescription drugs. HB1 included "1) mandatory KASPER registration and use by controlled substance prescribers and dispensers, 2) a requirement

that pain management clinics be owned by licensed physicians, 3) licensure standards for practitioner-owned pain management clinics (a responsibility of the medical licensure boards), 4) licensure standards for grandfathered non-physician-owned pain management clinics (a responsibility of the Kentucky Office of Inspector General), and, 5) prescribing guidelines for Schedule II and Schedule III controlled substances containing hydrocodone (American Public Health Association)." HB1 was intended to assist prescribers in making appropriate treatment decisions, to readily identify patients in need of substance abuse treatment, and to identify "doctor shoppers."

A research team from the University of Kentucky College of Pharmacy published an 88-page report in 2015 evaluating the impact of HB1. Their findings concluded within the few years of HB1 the number of prescriptions dispensed for all Schedules of controlled substances decreased by 4 to 8%. Prescribers registered with KASPER increased by 262%, while pharmacists registered with KASPER increased by 322%. HB1 may have effectively addressed inappropriate prescribing; there was a significant decrease in high dose oxycodone prescribing and patients receiving the medical "holy trinity" decreased by 30%. The "holy trinity" is a concurrent drug therapy that is the combination of an opioid, a benzodiazepine (commonly prescribed medications are Valium and Xanax), and skeletal muscle relaxants, especially carisoprodol. This drug combination has been reported to potentiate the high "through unique interactions with colocalized μ-opioid and $GABA_A$ receptors… inducing a synergistic increase in dopamine in the nucleus accumbens (NAc) and depression of respiration (Horsfall and Spragye 2016)". It should also be noted prescribing of buprenorphine/naloxone for OUD treatment increased by over 40%. Additionally, the study evaluated the possible impact

on “doctor shopping” as it was a key proponent within HB1. For the purpose of consistency, the study defined doctor shopping “as a patient receiving multiple prescriptions from four or more different prescribers and filled at four or more different pharmacies within a three-month period.” There was a decrease by over 50% in the number of patients that met this definition. The evaluation noted “treatment admissions in Kentucky for prescription opioids decreased at a higher rate while treatment admissions related to heroin increased at a higher rate compared to surrounding states. Similarly, hospital discharges and deaths due to prescription opioid overdose in Kentucky declined post-HB1 while hospital discharges and deaths due to heroin overdose increased (Freeman et al., 2015).” The impact of KASPER is notable in reducing doctor shopping and abuse of prescription drugs; however, the statistics paved way for research to be executed investigating the possible role PMDPs may play in shifting the high rates of abuse, addiction, and overdose from prescription opioids to heroin.

In 2018, Dr. Anjali Dhanda published a study examining opioid use in patients presenting for Suboxone® (BUP/NAL) at the University of Louisville Physicians Outpatient Center, Robley Rex VAMC, and two private practices in Louisville, KY. The study determined that after the passage of Kentucky House Bill 1 in 2012 (HB1), there was a significant increase in patients reporting heroin use and opioid agonists in comparison to non-heroin opioids when presenting for treatment. Data were collected from a multi-site chart review study that extended from January 1, 2009 to July 1, 2016. The study included a series of multinomial logistic regressions using Stata version 13 to determine strength of association between Pre-Post HB1, clinical setting, sex, age, and type of substance reported at BUP/NAL intake appointment. Type of substance reported

was used as the dependent variable. This data identified heroin as the most commonly used drug by patients who sought BUP/ NAL treatment after the enactment of HB1 and also a significant increase in use of an opioid agonist. The study defines an opioid agonist as methadone or any buprenorphine containing product. The data also supported a rise in heroin use with the decline in non-heroin opioid use after HB1. Limitations to the study included the small sample size of four locations that could lead to generalized conclusions. Additionally, there was nothing in the article relating to the availability, cost, popularity of heroin from year to year in the region. Even though a causal relationship cannot be supported conclusively, the study raises concerns of trading addiction.

HEROIN

While Kentucky and other Appalachian states are hit hardest by the opioid epidemic (Appalachian counties had an opioid overdose death rate that was 72% higher than in non-Appalachian counties throughout the country; U.S Department of Health and Human Services 2020), there have been studies done across the country investigating the shift from prescription opioid to heroin abuse. Heroin is an illegal opioid that is processed from morphine. Pure heroin is a white powder than can be snorted or smoked, while impure “black tar” heroin is a dark color, resulting from processing methods that create impurities. “Black tar” heroin is most commonly injected into veins or muscles under the skin (National Institute on Drug Abuse 2014). Similar to morphine, the analgesic effects of heroin are enacted when the two active metabolites, 6-O-acetylmorphine and morphine, bind to the mu-opioid receptors of the central nervous system. The mu-

receptors also enact respiratory depression, euphoria, and physical dependence (Hosztafi 2003). The National Survey on Drug Use and Health reported in 2016 that about 948,000 Americans used heroin in the past year. Additionally, the number of people using heroin for the first time in 2016 was revealed to be 170,000—nearly double what it was in 2006 (National Institute on Drug Abuse). There have been many studies conducted in the last decade that reveal there is a potential correlation between PDMPs, the reformulation of Oxycontin®, and the spike of heroin use during the early 2010's.

Given the notable increase in heroin and decrease in prescription opioid abuse, a study published by Dr. Theodore Cicero, PhD et al., at Washington University, St. Louis examined the relationship between heroin and prescription opioids (see Figure 1). Anonymous surveys were completed by 15,227 patients with opioid dependence. The surveys were collected quarterly from January 1, 2008 to September 31, 2014.

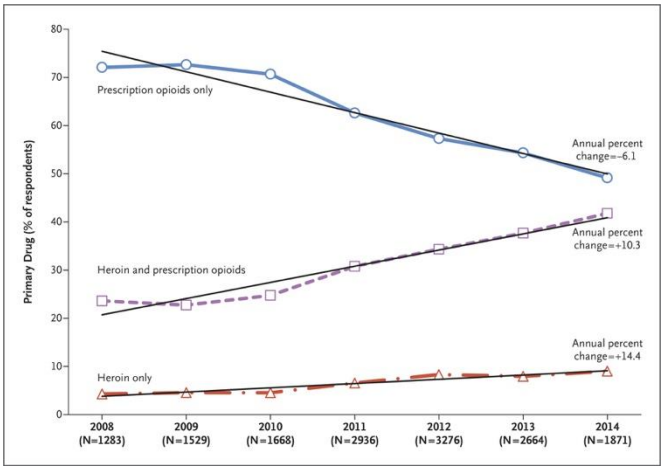

Figure 1: National Rates of Abuse of Opioids among 15,227 Respondents. Adapted from "Shifting Patterns of Prescription Opioid and Heroin Abuse in the United States," by T. J Cicero et al., 2015, *The New England Journal of Medicine, 373,* p: 1789-1790.

Figure 1 illustrates the unadjusted rates of abuse of prescription opioids only, abuse of prescription opioids and abuse of heroin only. From 2008 to 2010 prescription opioid abuse remained consistent at 70%; however, it began to decrease steadily with an average annual reduction of 6.1% to less than 50% in 2014. Although exclusive heroin abuse was low in the study's population in comparison to the other two variables, it more than doubled (from 4.3% to 9.0%) from 2008 to 2014. Abuse of both heroin and prescription opioids contemporaneously revealed an average annual increase from 10.3%, from 23.6% in 2008 to 41.8% in 2014 (Cicero et al., 2015). An online interview was also performed to gather supplemental qualitative information from the patients. While only 267 of the 15,227 agreed to participate, nearly 49% of those participants reported abusing prescription opioids prior to heroin use and 73% gave the rationale of accessibility and cost regarding their transition to heroin (Cicero et al., 2015).

Similar to Dhanda et al.'s study mentioned previously, Branham's study argues that there are unintended effects of the implemented prescription drug monitoring programs (PDMPs). Branham argues that PDMP's may move prescription opioid users to heroin as heroin shares many effects of prescription opioids and is easier to access—making it a good alternative from an addict's perspective. The case study rests on the evaluation of the impact of PDMPs on heroin abuse across twenty-one different states through use of treatment admissions records obtained from the Treatment Episode Data Set. The relationship between heroin admissions and prescription opioid admissions was significant for the average data ($\beta = 0.41$, $p = 0.0017$) and the 5-year data ($\beta = 0.5$, $p = 0.036$), both showing positive associations between heroin and prescription drug admissions in states during the post PDMP implementation period. The data supported

the argument; however, there were some noteworthy limitations, the most prominent being the sample size. The data set used in this study reviewed only those who seek treatment. Therefore, it cannot be concluded with certainty that this information represents the drug abusing population to the greatest capacity.

Further examining the associated rise in opioid dependence and heroin addiction, interview data was collected in King County, Washington at five syringe exchange sites. The study was conducted with intent to determine the proportion of current heroin users who were able to report being "hooked on" prescription opioids before heroin use and determine if there are different characteristics of heroin users based on their history with prescription opioids. The results indicated among the respondents who used heroin in the prior four months, 39% reported abuse of prescription opioids first. Regression analysis revealed those abusing prescription opioids prior to heroin were "significantly more likely to be younger, to have reported recent sedative medication use, and less likely to have reported recent crack use" (Peavy et al., 2012). A notable limitation to the study is the use of convenience sampling the studied followed, which may generalize the population of heroin users in King County, Washington to only the five syringe exchange sites interviewed. Despite limitations, the study illustrated the relationship the can be drawn from heroin and prescription opioid abuse.

Heroin abuse is currently not limited geographically or demographically. Data has revealed that over the last 50 years heroin users entering treatment has evolved from a common urban, minority centered to problem to one much more widespread. More recent heroin users were men and women in their twenties "living in less urban areas (72.5%) who were introduced to opioids through prescription drugs (75.0%; Cicero et. al, 2014)."

The recent users exhibit similar drug use patterns to those who misused prescription opioids. The growing demographic of heroin users may be attributed to the fact that heroin is cheaper and more accessible, and that there is an acceptance of heroin use among those who abuse prescription opioids.

Another factor that potentially helped ignite the transition to heroin is the reformulation of OxyContin®. OxyContin® originally rose to popularity for recreational drug users because the drug offered more of the active ingredient, oxycodone, than other prescription opioids due to its extended release nature. The extended-release formulation releases oxycodone every 12 hours; however, the properties could be easily circumvented through crushing or chewing for uses like snorting or using intravenously for a quick high. In 2010 Purdue Pharma replaced the drug on the market with an abuse-deterrent formulant (ADF) that made it more difficult to abuse the drug in the common fashion (Evans et al., 2019). The FDA acknowledged that ADFs do not eliminate all drug abuse; however, the reformulation was intended to prevent the tablets from being chewed or crushed for sniffing, smoking, or injecting by making it harder, viscous in water, and less "liked" for intranasal abuse (FDA 2020). By the early 2010's there was a growing literature regarding the potential of prescription opioid misuse being key into trajectories into injection drug use and/or heroin. The compiled research raises the question: is the promotion PDMPs and ADFs an effective policy to reduce drug abuse or is it unknowingly promoting non-prescription opioid abuse?

SPREAD OF DISEASE BY INJECTION DRUGS

The significant increase in heroin abuse also brought an increase in spread of blood-borne infections, specifically, hepatitis C (Hep C) and human immunodeficiency virus (HIV) by injection drug use. The primary transmission route for Hep C and HIV is through contaminated needles, syringes, and other injection drug equipment, such as a cooker. This can happen if a contaminated syringe is used to liquefy and apportion the shared drug. A 2005 study conducted by Dr. Stephan Koester, PhD, Jason Glanz, and Anna Barón revealed that among 304 heroin-injecting networks, 82% reported dividing the drug as a liquid, 86% reported using a cooker, 67% reported using a reservoir of water that syringes had been rinsed in to mix drugs (Koester et al., 2005). Injection drug users are at the greatest risk for developing these infectious diseases. Globally, 60% to 80% of injection drug users are Hep C positive (Nelson et al., 2011). In the United States, rates of Hep C infection among current and past injection drug users are 70% to 90% (Wang et al., 2011). Additionally, nearly 300,000 individuals are coinfected with HIV and Hep C—representing 25% to 30% of all HIV infected individuals and 5% to 10% of all Hep C infected individuals (Diaz et al., 2001).

In March 2010 injection drug users in San Diego between the ages of 18-40 who had injected illicit drugs within the previous six months, California were recruited for a cross-sectional study of hepatitis C and HIV infection risk. The survey assessed sociodemographics, drug use history, HIV and Hep C virus risk behaviors and perceptions, and medical history. Additionally, the parent study had questions on prescription-type opioid use to compare prescription opioid use prior to transitioning to heroin with other heroin injection drug users. Out of 123 heroin injection drug users, 49

(39.8%) reported that they had used prescription-type opioids illicitly prior to the first time they used heroin. The primary prescription-type opioids that these individuals were abusing included: Oxycontin®/oxycodone (75.5%), Vicodin™/hydrocodone (69.4%), morphine (34.7%). However, participants also reported using Percocet™ (20.4%), fentanyl (20.4%), Dilaudid™/hydromorphone (16.3%), methadone (14.3%), Demerol™ (8.2%), and other prescription-type opioids (4.1%; Pollini et al., 2011).

Millennials (born between 1981 and 1996) have been at the forefront of the opioid crisis, in both rural and urban areas, as well as the fastest growing generation for those infected with Hep C. Since 2013, the number of Hep C related deaths in the United States has exceeded the number of deaths associated with HIV and 59 other infectious diseases combined (Liang and Ward 2018). A study published in 2019 by Michelle Rose, MBA, et al., further examined the correlation. The argument was supported by partnering with Norton Healthcare and screening all individuals per standard risk-based criteria, except for pregnant women, for Hep C from 2016 to 2018. The data was analyzed for demographic shifts. The data demonstrated 2,615 (3%) of a total of 86,243 individuals screened for Hep C infection tested positive for chronic Hep C. The average age of those infected significantly decreased by an average of 3.7 years annually. The proportion of Hep C positive millennials increased over the three years, while baby boomers significantly decreased over the time period (Rose et al., 2019). The results support that Hep C has become a predominantly millennial disease and correlates with trends seen with the opioid epidemic.

Because most injection drug users who become infected with Hep C do so as young adults, there is a greater risk of chronic Hep C. Chronic Hep C is now typically

curable with oral medications, such as Daklinza, Zepatier, or Mavyret, taken every day for two to six months; however, many infected with Hep C do not know they are infected because symptoms may take decades to appear, until the virus damages the liver enough to cause the signs and symptoms of liver disease (Mayo 2020). Chronic Hep C can cause serious health problems, such as liver damage, cirrhosis, liver cancer, and liver failure (CDC 2020). This chronic condition leads to potential years of health care expenses, as well as the risk of transmitting it to others if continuously left untreated. Additionally, continued substance use among infected individuals raises the risk for developing more serious liver disease (Schulte et al., 2016).

NEONATAL ABSTINECE SYNDROME

In addition to the devastating numbers of addiction and overdose, there are other consequences to the opioid epidemic. One population hit with complications extending from the epidemic is pregnant woman and infants. Neonatal abstinence syndrome (NAS) is a withdrawal syndrome that can occur in newborns exposed to certain drugs of abuse, including opioids, during pregnancy (CDC). These drugs pass through the placenta that connects the child to its mother in the womb causing the infant to form a dependence on the drug. This causes withdrawal to occur as the drug is slowly cleared from the infant's system with symptoms often beginning within one to three days after birth. Symptoms of NAS depend on the type of drug, how much and how often the mother was taking the drug, genetic factors, and whether or not the baby was carried full term. With regard to opioids, symptoms of NAS may include excessive and high-pitched crying, mottling, diarrhea, fever, tight muscle tone, overactive reflexes, rapid breathing, seizures, and

tremors (Medline). Infants exposed to opioids during pregnancy are more likely to be born premature, have poor fetal growth, be born with birth defects, have longer hospital stays after birth, and be re-hospitalized within 30 days after being born. A recent study published in 2018 revealed that "children with a history of NAS were significantly more likely to have a subsequent educational disability (Fill et al., 2018)."

Coinciding with the increase in opioid use among pregnant women, "NAS grew nearly 7-fold from 2000 to 2014" (Jansson and Patrick 2020). Rates of OUD in pregnancy grew substantially from 1999 to 2014 with over 30,000 infants diagnosed with NAS in 2014 (Winkelman et al., 2018). In 2016 the Healthcare Cost and Utilization Project reported "seven newborns were diagnosed with NAS for every 1,000 newborn hospital stays … that is approximately one baby diagnosed with NAS every 19 minutes in the United States, or nearly 80 newborns diagnosed every day" (CDC 2020). A study published in 2019 by Dr. Strahan, PhD and company explored the increasing cost of NAS. The study reported "infants with NAS had a 15.9-day (20.4-day) mean (SD) length of stay and total overall hospitalization costs were $572.7 million. The average cost per infant with NAS was $22,552. Neonatal abstinence syndrome rates were highest among Medicaid-covered births (12.3 per 1000) and those without insurance (7.0 per 1000). Total costs were highest for births covered by Medicaid ($477.0 million; Strahan et al., 2019)."

The consequences and possible complications related to NAS are devastating and warrant an extensive look at treatment. Pregnant women with OUD are recommended to not quickly stop opioid use during pregnancy as it may lead to preterm labor, miscarriage, or fetal distress, and are instead encouraged to use Medication-Assisted Treatment

(MAT) during pregnancy. MAT uses a combination of pharmaceutical treatment and behavioral counseling and therapy (CDC 2020). Methadone and buprenorphine are frequently used for treating opioid dependent pregnant women. Methadone has been recommended as the standard of care for pregnant women with OUD, while buprenorphine was added to the mix in more recent years. Treatment of pregnant women with methadone or buprenorphine improves infant outcomes by stabilizing fetal levels of opioids. The National Institute on Drug Abuse reported women treated with methadone or buprenorphine had infants with "lower risk of NAS, less severe NAS, shorter treatment time, higher gestational age, weight, and head circumference at birth" in comparison to untreated pregnant women (National Institute on Drug Abuse 2017).

Infants born with NAS are treated with non-pharmaceutical methods focused on supportive care, such as swaddling, breastfeeding, rooming in, and skin-to-skin exposure (National Center on Substance Abuse and Child Welfare). Pharmaceutical methods, such as methadone or morphine, are also used when warranted by greater severity of symptoms (Finnegan 2013). Infants are weaned off treatment medication that can extend over three weeks whenever symptoms subside. Pharmaceutical treatment is required for "50 to 70% of infants" and is based on genetic factors, other drug exposures, gestational age, breastfeeding, and practice of rooming-in (a practice where postnatal mothers and infants stay together in the same room for 24 hours a day from the time they arrive in their room after delivery) (Logan et al., 2013). Pharmaceutical treatment is formulated based on the cumulative threshold score, taken from most commonly the Finnegan Neonatal Abstinence Severity Scoring System (nas 2018).

While there are many proactive measures in place that aid in managing NAS, it is important to examine the current research to expand the best possible healthcare available for pregnant women with OUD. Access to contraception is underutilized as nearly nine out of ten pregnancies among women with OUD are unplanned (Hurley et al., 2020). This statistic makes light to the lack of access to contraception and sex education in young adults today. Substance Abuse and Mental Health Services Administration (SAMHSA) also reported about 50% of women in treatment for OUD are using contraception in comparison to about 80% of women in the general population. Expanding access to contraception and discussing family planning options with women with OUD may reduce future unplanned pregnancies and the overall burden of NAS. In addition to promoting access to contraception, addressing underlying causes of OUD and training healthcare professionals to eliminate any preexisting stigma associated with pregnancy and OUD is pivotal for holistic care.

ILLICIT OPIOIDS

Prescription opioids may be directed through resale or theft to illicit markets that are not supplied through the United States healthcare system. Illicit markets were commonly reserved for heroin; however, recently, the illicit market has expanded to most notably encompass synthetic opioids, such as fentanyl. Fentanyl is an opioid that is 50 to 100 times more potent than morphine. The drug is sold as a powder, dropped onto blotter paper, put in eye droppers and nasal sprays, or made into pills that look like other prescription opioids. Fentanyl and its analogs, such as acetyl fentanyl, ocfentanil, and carfentanyl, are widely synthesized in laboratories and adulterated with illicit drugs,

contributing to the exponential growth in the number of drug-related overdose deaths (CDC 2019).

Synthetic opioids are commonly packaged and sold in bulk from abroad to drug trafficking organizations or even as counterfeit pills made to look like popularly diverted prescription opioid medications. Manufactured synthetic fentanyl has many diverse sources. Illicit drugs are often trafficked through complex pathways. One noteworthy pathway being bulk shipments from China to drug trafficking organizations in Mexico, then traveling across the Southwest border (Phillips et al., 2017). Fentanyl and its analogs are most often sold through illegal drug markets and are also often mixed into and/or with heroin, cocaine, methamphetamine, and counterfeit pills (CDC 2019).

Fentanyl in wholesale markets costs about one-tenth as much as heroin, but has been shown to be 10-25 times more potent than heroin (Phillips et al., 2017). The cost is an added incentive to not only transition to fentanyl, but to adulterate other drugs with it. Additionally, the reduced costs contribute to the increase in counterfeit prescription opioid pills laced with or containing only fentanyl.

Knopf's 2016 report published in *Alcoholism & Drug Abuse Weekly* demonstrates there is an increase in opioid overdoses, showing significant increases in heroin and illicit fentanyl. The report states heroin and illicit fentanyl were responsible for most of the increase in overdoses in regard to opioids. The report rests on data from the CDC that demonstrated between 2013 and 2014, shortly after the strict implementation of PDMPs, overdose rates involving methadone were unchanged, but deaths involving opioid pain relievers increased 9%, deaths involving heroin increased 26% and deaths involving synthetic opioids (other than methadone) increased 80%. The majority (approximately

61%) of the drug overdoses in 2014 involved some type of opioid. A noteworthy limitation to the study is the possibility that some overdose deaths were counted more than once. This happens because some deaths involve more than one type of opioid and these deaths were included in the rates for each category (Knopf 2016).

The numbers Knopf reported at the beginning of the third wave of the epidemic have not plateaued. Illicit fentanyl abuse has continued to consistently increase over the course of the decade. The CDC recently reported rates of overdose deaths involving synthetic opioids increased over 16% from 2018 to 2019, overdose deaths involving synthetic opioids were nearly 12 times higher in 2019 than in 2013, and more than 36,000 people died from overdoses involving synthetic opioids in 2019. Additionally, the latest provisional drug overdose death counts through May 2020 suggest an acceleration of overdose deaths during the COVID-19 pandemic (CDC 2020). Opioids accounted for about 75% of all overdose deaths during the early months of the pandemic--about 80% of those included synthetic opioids (Baumgartner and Radley 2021). The recent acceleration is likely due to the nature of isolation and loneliness attributed from the recent pandemic.

CURRENT OUD TREATMENT

There are currently three FDA approved medications used for treatment of OUD: methadone, buprenorphine, and naltrexone. The goals of these medications are to reduce or eliminate withdrawal symptoms, block the effects of illicit opioids, and reduce or eliminate cravings to use opioids. Buprenorphine FDA-approved products for opioid dependence include Bunavail (buprenorphine and naloxone) buccal film, Cassipa (buprenorphine and naloxone) sublingual film, Probuphine (buprenorphine) implant for

subdermal administration, Sublocade (buprenorphine extended-release) injection for subcutaneous use, Suboxone (buprenorphine and naloxone) sublingual film for sublingual or buccal use, or sublingual tablet, Subutex (buprenorphine) sublingual tablet, and Zubsolv (buprenorphine and naloxone) sublingual tablets (FDA 2019). Buprenorphine is an opioid partial agonist. The most common treatment buprenorphine treatment is Suboxone (buprenorphine/naloxone). Naloxone is an opioid antagonist that blocks the opioid receptors. Used independently, naloxone or its brand name Narcan® is used to reverse opioid overdose. However, when combined with buprenorphine, it provides all of the benefits of the stand-alone buprenorphine product, but adds a deterrent to misuse. Suboxone minimizes the risk of overdose and was formulated to have a lower risk of dependency than that of methadone. Other less common FDA-approved medications for treatment of opioid dependence are Dolophine (methadone hydrochloride) tablets, Methadose (methadone hydrochloride) oral concentrate, and Vivitrol (naltrexone for extended-release injectable suspension) intramuscular (FDA 2019).

Randomized clinical trials have concluded methadone and buprenorphine were found to be more effective in reducing illicit opioid use in comparison to no medication. Additionally, methadone and buprenorphine are associated with reduced risk of overdose death (SAMHSA 2018). While there is continued research in place comparing naloxone and buprenorphine with placebos and no pharmaceutical treatment. Individuals may take medication for OUD on a short-term or long-term basis. The most common use of pharmaceutical OUD treatments are maintenance treatment, medication taper, and medically supervised withdrawal.

WHATS NEXT

In 2017 the American College of Physicians (ACP) released a statement calling addiction to be treated as any other chronic condition. The president of ACP, Dr. Damle, MD, MS, MACP stated "substance use disorders are treatable chronic medical conditions, like diabetes and hypertension, that should be addressed through expansion of evidence-based public and individual health initiatives to prevent, treat, and promote recovery." Dr. Damle's quote encompasses the holistic approach that must be taken to create a curative path to effectively treat OUD.

A study published in 2019 by Dr. Chen, PhD et al., projected the future of overdose deaths in the United States. A system dynamics model of the US opioid epidemic projected outcomes of simulated individuals who engage in nonmedical prescription or illicit opioid use from 2016 to 2025 was designed and the analysis was performed by calibrating the model from 2002 to 2015 data from the National Survey on Drug Use and Health and the Centers for Disease Control and Prevention. The study revealed "the annual number of opioid overdose deaths is projected to increase from 33,100 in 2015 to 81,700 in 2025…from 2016 to 2025, 700,400 in the United States are projected to die from opioid overdose, with 80% of the deaths attributable to illicit opioids (Chen et al., 2019)." The projected numbers of significant increases in abuse, addiction, and overdose is not to diminish the vital work that has been done by healthcare professionals over the last two decades; however, implementations of PDMPs, OUD treatment, and reformulation of prescription opioids have only had a modest effect over the opioid epidemic. It is urgent that the current policies in regard to OUD are reexamined to combat the changing course of the epidemic.

With the widespread implementation of mandated PDMPs potential effects on the illicit drug market should be taken into consideration when each state reevaluates their individual program. The increased demand for illicit opioids is noteworthy and appropriate steps must be taken to mitigate those effects. Additionally, more research studies should be invested in to better understand and characterize the relationship between prescription and non-prescription opioid abuse. There is only a small body of literature currently out on the potential of prescription opioids as a precursor to illicit opioids, making it a vital subject to be studied in the future.

In order to potentially reduce the high-risk consequences of injecting opioids, testing for Hep C and HIV should be made more readily available, specifically in low-income areas geographically, such as rural Central Appalachia (West Virginia, Southwest Virginia, Eastern Kentucky, Southeast Ohio, East Tennessee, and Western North Carolina) where the numbers of injection drug use are among the highest rates of use and overdose across the US. The unmatched rates are most likely due to the many barriers to treatment and testing Central Appalachia faces, including a lack of access to health care and lack of health care providers with specialized training (Moody et al.,2017) . More accessible testing could prevent transmission by early identification. Additionally, Hep C and HIV testing could take place in facilities that also administer pharmaceutical OUD treatment and syringe service programs. Population-based screening is another potential strategy for identifying those infected and connecting them to treatment in a clinical environment an individual is comfortable in.

Population-based screening may also work well for pregnant women with OUD, another population with high-risk consequences due to OUD. Continuing behavioral

therapy and counseling after the pregnancy may motivate the women to continue with treatment with the intent of nurturing coping skills and reducing the risk of returning to substance use. More accessible testing for Hep C and HIV and screening women for depression, anxiety, and other mental health diagnoses will create a more in-depth approach that will allow the healthcare provider to better create the best treatment for each individual woman.

In addition to widespread testing and screening, improving access to medications for OUD is another potential strategy. The efficacy of pharmaceutical OUD treatments, such as methadone, buprenorphine, and naloxone, in reducing complications and fatal overdose and improving remission rates has been proven through decades of research; however, universal treatment is lacking (Wakeman et al., 2018). Almost 80% of Americans with OUD do not receive medical treatment (Saloner and Karthikeyan 2013). Access to addiction treatment should be promoted at both primary care offices and pharmacies. It is pivotal to make it easier to obtain OUD treatment than to get illicit opioids.

Healthcare providers and pharmacists should see a shift in curriculum relating to OUD. There is a lack in clarity and consistency throughout medical and pharmacy schools. It is imperative to effectively equip physicians to appropriately prescribe opioids and other addictive substances. Currently opioid prescription training is "a fairly short-term, stand-alone segment of medical education (Singh and Pushkin 2019)." Extending the training and addressing the ethics of the matter to remove any stigma towards OUD will better prepare physicians and pharmacists to deal with ethical implications of opioid prescriptions.

Education on the subject should not be limited to healthcare professionals. It would be greatly beneficial to develop a program on this subject aimed for children. Drug Abuse Resistance Education (DARE) was founded in 1983 and was greatly promoted in school systems. DARE was the youth directed byproduct of America's "War on Drugs." An article published through American Addiction Centers in 2021 revealed in short why the program did not work. One major factor being the hysteria that was ramping through America at the time had the program focus on punitive consequences rather than rehabilitative education (Berry 2021). The struggles of DARE should be noted and used to build a more believable program. Starting the program in school systems in rural areas could potentially be the beginning of another curative path.

The compiled research conveys the changing nature of the epidemic. Addressing overprescribing of opioids through prescription monitoring and improved pain management has been pivotal in combatting the crisis; however, there is still much work to be done as the use of illicit opioids is historically high and only expected to increase. To prevent unknowingly promoting another addiction (and ultimately change the course of, but not eliminate, the epidemic) it will require a multipronged strategy, that consists of the healthcare system overcoming the stigma of OUD and developing innovative ways of delivering related services to those in need.

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