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# Opioids – The Danger of Abuse and Overdose

While there are what seems like an infinite number of public health crises facing our society, the current surge in unintentional drug overdose deaths is one of the most heartbreaking. It would be rare to encounter one life that hasn't been affected by substance abuse in some form. Addiction impacts the lives of everyone around the addict, not just the individual with the disease. Too often, these stories end in tragedy when an unintentional overdose takes a life, and the lives of their loved ones will never be the same. A single substance related death is one too many. Healthy People 2020 recognized this problem and created several objectives surrounding substance abuse, including "SA-12 Reduce drug-induced deaths".[1] Unfortunately, since the objective was written in 1999, the rate of drug induced deaths per 100,000 has only continued to rise, from 6.8 to 20.8 in 2016.[1] According to the CDC, this rate increased by 21.5% between 2015 and 2016 alone, with 66.4% of those deaths involving opioids.[2] Therefore, opioids make up the majority of substances involved in overdose. But what makes opioids so dangerous, and why are they such a problem now? While these drugs have been around several decades, the "opioid epidemic" has been in the news for the last few years due to this surge in unintentional overdose deaths and a correlated increase in opioid prescriptions, subsequent misuse and addiction, and synthetic opioid production. As these and other important contributing factors are identified, it comes down to education efforts for providers, patients, and the general public about the dangers to move towards more responsible prescribing patterns and the primary prevention of addiction.

First, it is important to understand the mechanism of action of opioids and why they cause the various desired effects as well as side effects in the body. An opioid is any natural or synthetic substance that binds to one of the opioid receptors in the body: mu, delta, or kappa. The classic effects are represented by Mu receptor agonists. When bound to the receptor, opioids cause analgesia as well as euphoria, which is why there is a potential for abuse. Opioids can also be incredibly habit forming by enhancing the reward pathway in the brain, and the phenomenon of tolerance leads to increased dosages in order to produce the same effect. Long term use leads to physiologic dependence and severe withdrawal symptoms when the drug is stopped. They are also one of the most dangerous classes of analgesics by nature the high risk of respiratory depression and death.[3]

There are many contributing factors to the "opioid epidemic" including prescribing practices, the potential for abuse and diversion, and the increased use of synthetics like fentanyl in the production of counterfeit pills. There has been an emphasis on data collection in order to better outline the problem and better understand how to combat it. Martins et al. discusses 169 relevant articles comparing worldwide data about unintentional drug overdose in a systematic review published in *The American Journal of Public Health* from 2015. Most notably, across the literature, the review supports the data previously presented from the CDC which demonstrates an increase in overdose deaths in recent years as well as more of them occurring from opioids, specifically prescription opioids.[4] Additionally, this review clearly states, "the increase in overdoses caused by prescription opioid use in the United States parallels the increase in the availability of prescription opioids since the early to mid-1990s in the United States".[4] From 1999 to 2016, overdoses involving prescription opioids has increased five-fold.[2] The prescribing rate in the U.S peaked in 2012 at 80.3 prescriptions per 100 persons.[2] Although not enough to claim causation for certain, the systematic review demonstrates the resounding conclusion of dozens of studies linking prescribing patterns with overdose. More specifically, Bohnert's cohort study showed a clear

association between a higher dose opioid and overdose deaths, and Miller demonstrated an association between opioids with a longer duration of action and overdose.[5,6] In a 2017 article in *Anesthesia and Analgesia*, Clark and Shumacher discuss the epidemic within a supply and demand framework and challenge both providers and pharmaceutical companies to focus on the supply side of the epidemic with safer formulations that may reduce the risk of abuse and diversion, as well as continued effort to better understand pain and appropriate applications for this drug class.[7] Education for providers and patients remains the focus of the demand side of this epidemic, to caution of the dangers and "avoid unnecessary exposure to these drugs".[7] The fields of dentistry, orthopedic surgery, and anesthesia are in a particularly influential position to adjust their prescribing practices and decrease the public's exposure to opioids, specifically adolescent's exposure, who may be encountering this drug class for the first time. Dautremont et al. describe current recommendations for adolescents following outpatient orthopedic surgery, and after a systematic review concluded that there is a lack of evidence supporting current opioid prescribing practices in the adolescent population. Current dosing is largely based on adult regiments, which in recent studies may show overprescription of opioid medications.[8] While opioids remain the gold standard to manage postoperative pain, there is no evidence-based protocol for their use in the adolescent population, and it is possible that the dose and quantity of opioid medications dispensed after outpatient dental and surgical procedures may be far more than is necessary to adequately manage pain.[8] Additional randomized control trials targeting adolescents are necessary in order to inform guidelines and minimize unnecessary exposure to opioids, in hopes of preventing future abuse and dependence, risk factors for overdose.

After considering the importance of prescribing practices and the availability of opioids, it is critical to reflect on other contributing factors to substance abuse, such as mental illness. Several studies have demonstrated the connection between adolescents with depression and the likelihood of drug abuse, particularly opioids.[9,10] Boyd, Young,

and McCabe performed a statistical analysis on 2,627 adolescents comparing characteristics and symptomology between groups of high school students who had never used opioid analgesics, those who were medical users, and those who were nonmedical users, then divided into self-treating versus sensation-seeking subgroups. When compared to nonusers, medical users were more likely to have symptoms of anxiety and depression and have been prescribed another medication for depression, sleep, or anxiety. Additionally, "the prevalence of ADHD was higher in all groups of opioid users".[9] The article raises an another important question of future study: "The role medical use plays in adolescents' nonmedical use".[9] Many nonmedical users illegally obtain opioids from medical users, although this study doesn't identify this number. However, both medical and nonmedical users demonstrated a higher likelihood of drug abuse problems, indicating that medical users may contribute to the larger epidemic. Edlund et al., in a 2015 article in *Drug and Alcohol Dependence*, used cross-sectional data from the National Survey on Drug Use and Health (NSDUH) and the Substance Abuse and Mental Health Services Administration (SAMHSA) to examine a large sample size of adolescents over 5 years, investigating the association between a major depressive episode (MDE) with nonmedical prescription opioid use (NMPOU). The total percentage across all adolescents was 8% and 6% respectively in the past year, with NMPOU usually preceded by a MDE. 15% of those reporting NMPOU reported opioid abuse/dependence and 20% reported MDE.[10] This association is an important risk factor for patients and providers to consider when treating pain with concomitant mental illness, with the hope that adequately treating depression in the adolescent population may prevent future substance abuse, specifically opioid abuse.

After addressing the accessibility of opioids and the risk factors for abuse and addiction, it becomes vital to understand one of the most dangerous components of the overdose epidemic, illicitly manufactured fentanyl. Fentanyl-contaminated drugs are becoming increasingly common and pose serious risk to opioid users.[11] Park et al. attributes the dramatic increases in overdose deaths "to the rise of synthetic opioids in

the illegal drug market".[11] Fentanyl is a synthetic opioid one hundred times more potent than morphine with a rapid onset and a short duration of action most often used medically during the administration of anesthesia or acutely in the postoperative phase. Outpatient, the preparation primarily transmucosal or transdermal and restricted to the treatment of breakthrough pain in cancer patients tolerant to opioids.[3] Park cites data from the DEA that demonstrates "although pure pharmaceutical fentanyl can be diverted from medical use, fentanyl is often manufactured illicitly, and is found in street drugs... thus increasing the lethality of these drugs".[11] In a 2018 article published in the *American Journal of Public Health*, Seth et al. describes data obtained by law enforcement on confiscated drug products that tested positive for fentanyl between 2013 and 2014. The presence of fentanyl in the samples went up by 426% in one year. Seth states, "the increases were strongly correlated with increases in synthetic opioid deaths but not with pharmaceutical fentanyl prescribing rates, suggesting that the increases were largely due to IMF (illicitly manufactured fentanyl)".[12] It is hypothesized that the addition of fentanyl to various street drugs and counterfeit pills is a cost effective way for dealers to increase the potency of the drug and extend their supply, but the dose is difficult to calculate. Park et al. goes on to explain that "most people who use drugs who test positive for fentanyl are unaware that their drugs contain fentanyl".[11] This is an extremely important point to focus on when educating on the dangers of overdose. There is no guarantee or verified ingredient label on illicit substances, some made to look like pharmaceutical grade opioids. Fentanyl has also been found in other drugs of abuse including cocaine.[11] According to a recent report from the National Institute on Drug Abuse, more than half of all overdose deaths from 2016 involved fentanyl.[13] Even chronic users tolerant to opioids may encounter a lethal dose of fentanyl laced into what they believed to be a safe or typical dose for them. This may be the key aspect of the epidemic that requires the most immediate study and attention from federal agencies and law enforcement, but the fight against unintentional overdose must begin with education of the user.

A public health outreach framework is necessary to effect change in order to combat the surge of unintentional overdose deaths. While there are many necessary interventions, the primary and most successful strategy that has been used to combat this epidemic is education. Perhaps the first and most measurable intervention to date tackles the availability and indications for prescription opioids. In 2016, the CDC developed new guidelines for opioid prescribing, excellently summarized by Bredemeyer in an article from the *American Academy of Family Physicians*. The guidelines prioritize managing chronic pain with nonpharmacologic therapy or non-opioid medications primarily, conducting a thorough risk/benefit discussion with patients taking opioids, starting at the lowest dose possible when initiating an opioid, and treating opioid use disorder appropriately.[14] Theses new guidelines are frequently referenced in the literature and emphasized as necessary education for healthcare providers in order to prevent overdose. According to the CDC, the national prescribing rates have declined since 2012 to the lowest they have been in 10 years in 2017 at 58.7 prescriptions per 100 people. Oregon sits just about the national average at 66.1 per 100 people.[2] This single intervention has been objectively beneficial for the supply side of this epidemic as well as encouraging a dialogue between patients and providers about the dangers of opioids. The guidelines also encourage the use of state-level interventions, such as Prescription Drug Monitoring Programs (PDMPs) to track prescriptions and ensure safe use. Clark's article discussed earlier, outlines these options as well as other priorities for intervention: targeted education for providers regarding pain management and opioid use disorder, including the new guidelines and PDMPs, creating abuse deterrent formulations, reducing diversion, treatment of opioid use disorder (OUD), reduction of opioid reduction peri-surgically, continued research, and lastly, education of the general public regarding pain, OUD, addiction, and overdose.[7]

There is a need for education for the opioid naïve about dangers, education for prescribers about the trends of overdose and the CDC's guidelines on responsible prescribing, and education for those struggling with addiction about how to get help. A group of maturing adolescents who could potentially fit into all 3 of three categories

would make an ideal audience. According to Healthy People 2020, young adults age 18-44, have the second highest rate of drug-induced death after adults 45-64, and have the sharpest rate of increase over the past several years, with a rate of 24.7 deaths per 100,000 in 2015.[1] Targeting 17 year-old high school seniors is an attempt to make an impact on this age group. This high school is a private school located in Washington county, but students commute from many surrounding counties including Multnomah county. These 2 counties have the first and third highest rates of drug overdose deaths across Oregon with 152 and 372 deaths per 100,000 respectively, across all drug classes in 2018.[15] The Portland metropolitan area is a hub for access to prescription and illicit drugs, so both the age and location of this student population makes them an ideal target audience. An influential group of high school students can shift the paradigm of their school, community, a maybe even a generation. In addition to the emotional argument as it relates to personal stories of overdose that have impacted this community, an evidence-based argument may encourage behavior change or act as primary prevention for this population.

While the data supports targeting this population for educational efforts, there are several other reasons the impact on this audience may be more meaningful. Experimentation with substances for many adolescents begins in high school. Their first exposure to opioids may occur in a medical setting, possibly in the context of athletic injury, orthopedic surgery, or dental surgery as noted previouslly. Educating a class of high school seniors, particularly ones taking an anatomy and physiology elective with future goals in health care, should be particularly receptive to the physiology of opioids and addiction and hopefully provide a primary prevention education before their first exposure. These students would be in a stage of contemplation-preparation. There is also a high correlation of depression and mental illness and documented opioid abuse in the adolescent population.[10] Education about these risk factors will bring an important awareness to mental health issues and the fine line between experimentation and addiction. The students can take the information and resources provided to their friends and family who may be struggling, as well as have an orientation to responsible

prescribing practices for their future careers. They should be open to the pharmacology and evidence-based medicine model as pre-health students, and may have personally witnessed or have loved-ones who have battled with opioid abuse.

In conclusion, the opioid epidemic and increase in unintentional overdose deaths continues to be a public health issue. The primary intervention at this time is focused on educational efforts for prescribers, patients, and the general public. An audience of pre-health adolescents in Oregon's Multnomah county is an appropriate and opportune target for an evidence-based argument. The learning objectives presented here and directed at this audience are the same goals and priorities of the CDC, NIDA, OHA, SAMHSA, and HP2020. It is imperative for the general public to understand the risk of overdose and the increasing prevalence of fentanyl-contaminated drugs, as well as how the culture of pain management and prescribing patterns has contributed to the epidemic. It is also important to stress how common depression and other forms of mental illness are in the adolescent and young adult populations, and how untreated mental illness is a risk factor for opioid abuse. Lastly, the presentation should provide the students with resources where they can find information for family or friends, treatment opportunities, and the appropriate places to dispose of excess opioids they have been prescribed.[16-18] While there is what my seem like an endless, uphill battle ahead that will require a full arsenal of researchers, biomedical engineers, pharmaceutical companies, psychiatric and medical practitioners, law enforcement, and state and federal government agencies, the fight against this epidemic and the tragedy of unintentional overdose must begin with education of the public. This is a responsibility of every healthcare provider and one that should be honored every day.

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