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Combating the Opioid Epidemic: Are Abuse-deterrent Formulations the Answer?

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Opioid misuse and abuse in the United States (U.S.) has dramatically increased over the past two decades with an estimated 4.5 million people using opioids for nonmedical reasons in 2013.[1] Increases in opioid misuse and abuse is directly correlated with increases in opioid prescribing, emergency department (ED) visits for opioid overdose, inpatient and substance treatment admissions, and opioid-related death.[2–4] Nationwide death rates from accidental opioid overdose now exceed death rates from suicide and motor vehicle accidents combined.[3] Of great public health concern are the number of women of reproductive age on opioids, most of which are enrolled in Medicaid programs, considering the well documented adverse neonatal outcomes associated with opioid use.[5]

Oregon currently leads the nation in nonmedical use of opioids for all age groups.[6] More than 900,000 Oregonians received an opioid prescription in 2012. Of the 1,500 hospitalizations related to drug abuse, nearly one-third were due to opioids. Opioid-related deaths in Oregon mirror national rates with a slight decline in 2012; however, death rates remain 2.5-times higher than rates in 2000.[7]

The risk of unintentional opioid overdose appears to be higher with long-acting (LA) opioids compared to short-acting (SA) opioids. In a population of U.S. Veterans, those prescribed a LA opioid were 2.5-times more likely to experience an unintentional overdose. The risk of unintentional overdose was greatest during the first two weeks following initiation when risk with LA opioids was 5-times higher than SA opioids.[8]

Actions to Address Opioid Misuse and Abuse

In response to the opioid epidemic, many interventions at the state and federal levels have been implemented. In 2012, the Food and Drug Administration (FDA) implemented a risk evaluation and mitigation strategy (REMS) for LA opioid products. In 2014, FDA Draft Guidance was released to assist industry in developing abuse-deterrent opioids and a Public Advisory Committee recommended changing hydrocodone products to Schedule II under the Controlled Substances Act.[9] Subsequently, the Drug Enforcement Agency accepted the recommendation with the rule taking effect last October.[10]

According to the FDA, an important step toward controlling opioid abuse is to formulate opioids in abuse-deterrent formulations (ADF) to overcome known or expected mechanisms of abuse.[11] Two properties of ADFs on the market include physical barriers to crushing, chewing and extraction, and opioids sequestered with opioid antagonists. Table 1 identifies the five opioids with ADFs currently approved to contain labeling describing the product's abuse-deterrent properties consistent with the 2014 FDA draft guidance.

Table 1. Current Long-acting Opioids with Abuse-Deterrent Formulations

Drug	Abuse-Deterrent Properties
OxyContin[12] (oxycodone)	Upon tampering, forms a viscous gel when crushed or dissolved that resists passage through a hypodermic needle
Targiniq ER[13] (oxycodone and naloxone)	Upon manipulation, naloxone will block the euphoric effects of oxycodone
Embeda[14] (morphine and naltrexone)	Upon manipulation, naltrexone will block the euphoric effects of morphine
Hysingla ER[15] (hydrocodone)	Upon tampering, forms a viscous gel when crushed or dissolved that resists passage through a hypodermic needle
Zohydro ER[16] (hydrocodone)	Upon tampering, forms a viscous gel when crushed or dissolved that resists passage through a hypodermic needle

At the state level, Prescription Drug Monitoring Programs (PDMPs) have been implemented to collect dispensing data on opioids and other controlled substances. Currently, 48 states have an actively operating PDMP.[17] The goals and requirements of individual PDMPs vary by state, but in general are designed to help identify sources of prescription diversion, inappropriate prescribing and dispensing, and provide practitioners, law enforcement and public health officials with applicable information.[17,18]

The Oregon PDMP requires pharmacies to submit data weekly for all schedule II-IV controlled substances and is accessible to prescribing health care professionals, pharmacists and their delegated office staff in Oregon and neighboring states.[19] To obtain further information regarding the Oregon PDMP or to apply for access, visit orpdmp.com/health-care-provider/.

Additional interventions have been implemented at the institutional level. In accordance with the guidelines developed by the American Pain Society (APS) and the American Academy of Pain Medicine (AAPM)[20], many clinicians now include use of risk assessment tools, informed consent, opioid management plans and urine drug screening in their practice.[20]

It remains unclear which interventions, if any, are making an impact so far. A recent systematic review found inconsistent evidence regarding the use of risk assessment instruments for predicting opioid abuse or misuse and found no studies evaluating the effectiveness of risk mitigation strategies such as the use of PDMPs.[21]

Evidence for Decreased Abuse and Misuse of LA Opioids

The evidence for effectiveness of ADFs to limit abuse in real world populations is limited. Most information available comes from observations, surveys and expert opinion,[22–26] many of which are conducted by the pharmaceutical industry. Indeed, a review of data submitted to the FDA reveal evidence for "drug-liking" and "drug highs" in non-dependent recreational opioid users are limited to single-dose studies.

Purdue Pharma, the manufacturer of the reformulated OxyContin, utilized the National Poison Data System (NPDS) and found rates of intentional opioid abuse decreased by 36% (95% CI, -40 to -23%) the first two years after the product was introduced to market, but at the expense of a significant increase in cases of intentional heroin abuse.[27] A similar study utilizing data from Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) systems also found rates of heroin-related deaths increased from 2011 to 2013 and was inversely related to opioid availability.[28]

A subsequent study utilizing data from the RADARS system in conjunction with data from Poison Center and Drug Diversion programs, found similar results with regard to abuse exposures and therapeutic errors. The study found diversion reports declined 53% (95% CI, -63 to -41%). Additionally, the study determined the street price of OxyContin fell 22% (95% CI, -33 to -9%) after abuse-deterrent reformulation of OxyContin.[26]

Implications to Practice

Chronic non-cancer pain is common and increasingly treated with opioids.[21] However, there is low-quality evidence to support their use long-term.[20] A recent systematic review funded by the Agency for Health care Research and Quality (AHRQ) was unable to find a single study evaluating the outcomes of long-term opioid therapy on pain, function, or quality of life and concluded there is insufficient evidence to determine the effectiveness of long-term opioid therapy for chronic pain. The AHRQ review was able to find a plethora of low-quality studies evaluating the harms associated with opioids used for the treatment of chronic non-cancer pain. Use of opioids was

associated with significant increases in opioid overdose, opioid abuse and dependence, bone fractures, myocardial infarction, and increased use of medications to treat sexual dysfunction.[21]

Treatment of chronic pain should include a stepwise approach first utilizing non-pharmacologic therapies before progressing to non-opioid drugs and only progressing to opioid therapy if clinically appropriate and necessary.[29] The joint guideline developed by APS and AAPM aims to promote the safe and effective use of chronic opioid therapy for chronic non-cancer pain and includes multiple recommendations with regard to risk stratification, initiation, titration and monitoring and therapy discontinuation.[20]

Conclusion

The development of ADFs is a public health priority for the FDA though robust data evaluating strategies to deter opioid abuse are lacking. Clinicians should not be misguided to assume opioids are now safe. ADFs will only be effective in persons engaging in very high risk behaviors such as snorting, crushing or shooting up. Most overdoses are likely accidental when too high a dose is consumed without engaging in these high risk behaviors. There may be some progress, however, as rates of opioid overdoses and deaths have declined since 2011.[27,28] It is unlikely ADFs are solely responsible for this favorable trend as the institution of PDMPs, REMS, and increasing media coverage may also create awareness of this epidemic. Unfortunately, increased use of heroin may be the unintended consequence, a concerning trend that requires further investigation.

There is still a lack of quality evidence regarding the long-term effectiveness of LA opioids for the management of chronic non-cancer pain. LA opioids may be the best option for a subset of patients with chronic pain, but alternative effective treatments for many patients are available.[29] LA opioids use should be based on the benefits to patient functioning and quality of life compared to the risk of treatment. If opioids are necessary, using SA opioids at the lowest effective dose should be a consistent goal of therapy.[8]

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