Review Article

A Review on Prescription Opioid Abuse - Are Abuse Deterrent Formulations a Solution

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Abstract: Non-medical prescription opioid drug use is a growing problem in India. The development of abuse-deterrent formulations (ADFs) of prescription opioid analgesics is a novel strategy toward reducing abuse and diversion of these medications. However, drug abuse still remains a problem as the addict may switch over to other accessible non abuse-deterrent opioids. Moreover opioid ADFs may themselves be abused via the intended route of administration by increasing the dose or dosing frequency. This review stresses upon the need to further elucidate the risk and benefit of long term opioid therapy and ADFs in the management of chronic non-malignant pain.

Keywords:

The use of Opioid for the management of chronic nonmalignant pain has seen a significant increase In the past 2 decades. Among all pain visits, Opioid prescribing nearly doubled from 11.3% to 19.6% from 2000-2010 in US, whereas nonopioid analgesic prescribing remained unchanged (26%-29% of visits).[1] Chronic pain is the pain which persists past the normal time of healing which may be less than one month, or more than six months. Chronic nonmalignant pain is considered to be of more than three months duration.[2] Various non pharmacological options, such as massage therapy, physical and occupational therapy, biofeedback, guided imagery, and cognitive–behavioral therapy and Interventional therapies, such as nerve blocks, transcutaneous electrical nerve stimulation (TENS), and injectable medications have been used in various situations. However, a therapeutic plan typically employs the use of non-opioid and opioid analgesics to help control the pain.[3]

This increase in usage has led to concerns of misuse and abuse of opioids. Misuse is defined as the intentional therapeutic use of a prescription opioid analgesic in an inappropriate way, but excluding events that meet the definition of abuse. Abuse is the intentional, nontherapeutic use of a prescription opioid analgesic for the purpose of achieving a desirable psychological or physiological effect. In the last decade, non-therapeutic use of prescription medications has increased markedly. The morbidity and mortality associated with non-therapeutic use of opioids are also rising.[4] A study conducted in Bangalore estimated that in 2010 approximately 6.2% of adolescents aged 12 to 17 years and 9.5% of 12th grade students have engaged in the nonmedical use of controlled pain medications; of which opioid analgesics are most likely to be used, misused, and/or abused by this age group.[5]

Such use of opioids can lead to serious consequences, including addiction, physical dependence, overdose, drug-related suicide, drug-related road traffic accidents, spreading of serious infectious diseases via shared drug paraphernalia or death.[6] Although chronic opioid analgesic therapy exposure has been shown to lead to abuse/addiction in a small percentage of chronic pain patients, a larger percentage will demonstrate aberrant drug-related behaviors and illicit drug use.[7] The appropriate use of opioids in treating pain disorders poses a significant clinical challenge and dilemma. A balance needs to be achieved between adequate pain control and managing the risks of these powerful drugs.[8]

In 2016, the Centers for Disease Control and Prevention (CDC) released guidelines for Prescribing Opioids for Chronic Pain attempting to shift the physicians away from an opioid centric

strategy.[9] CDC recommended that benefits and harms should be evaluated within 1 to 4 weeks of starting opioid therapy for chronic pain and every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, other therapies should be optimized and opioids should be tapered to lower dosages or discontinued.[10]

Various strategies to minimize abuse of prescription opioid analgesics have included the educational and regulatory initiatives. The development of novel formulations with abuse-deterrent properties - those properties shown to meaningfully deter abuse, even if they do not fully prevent it - is a relatively new and evolving strategy. Abuse-deterrent formulations (ADFs) have the potential to limit the medical consequences if misused (e.g., if the drug is overingested, crushed or chewed before ingestion, or administered with alcohol) or taken in error.[6]

Such ADFs are being created mainly by two methods. One is to add a pharmaceutical or a chemical component like naloxone to the opioid so as to decrease the user's response to an abused substance or to provide an adverse reaction when the user alters the formulation. Another method is to deter the physical alteration of the drug's original manufactured form to extract the active ingredient through various methods, such as crushing, chewing, or mixing with a solvent, such as alcohol.[3]

Various such formulations are currently FDA approved and carry abuse deterrent labeling. [Table 1][9]

Table 1 Opioid Products with Food and Drug Administration (FDA)–Approved Abuse-Deterrent Labeling

Opioid	Year of approval	Formulation
Oxycodone	2010	Forms a viscous gel on being dissolved that is difficult to inject through a hypodermic needle
Oxycodone	2014	Combination of extended-release (ER) oxycodone along with naloxone; that blocks opiate-induced euphoria and can induce withdrawal
Morphine	2010	Combination of ER morphine with naltrexone at its core; that blocks opiate-induced euphoria on being crushed, chewed but remain sequestered on being swallowed
Hydrocodone	2015	Forms a viscous gel on being dissolved that is difficult to inject through a hypodermic needle
Morphine	2015	Contains inactive ingredients that make the tablet harder to adulterate when subjectedto physical manipulation or chemical extraction.
Oxycodone	2016	Contains inactive ingredients that make the tablet harder to manipulate
Oxycodone	2016	Combination of ER morphine with naltrexone at its core; that blocks opiate-induced euphoria on being crushed, chewed but remain sequestered on being swallowed
Morphine	2017	A polymer matrix tablet technology with controlled-release properties as well as physical and chemical barriers that resist manipulation.
Hydrocodone	2017	Designed to resist drug extraction through the most common routes: oral, intranasal, and intravenous
Oxycodone	2017	Contains inactive ingredients that make the tablet harder to manipulate

But an ongoing debate still revolves around the long-term use of opioids in the treatment of chronic nonmalignant pain. The major dilemma with simply shifting opioid prescribing to ADFs is lack of a strong evidence of efficacy of opioids in treating chronic pain, regardless of their formulation. A Cochrane review in 2010 reviewed 26 studies with 27 treatment groups that enrolled a total of 4893 participants and concluded that there was only weak evidence suggesting effectiveness of long-term opioid therapy for chronic pain and many patients discontinue long-term opioid therapy due to adverse events or insufficient pain relief.[11] A recent review conducted in 2015 also determined that evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and there exists a dose-dependent risk for serious harms.[12] ADFs though have the potential to deter abuse, do not show any increased efficacy in relieving pain than nonopioid medications or nonpharmacologic treatments.[9]

Moreover, ADFs per se are not a treatment for addiction and a risk of opioid addicts to switch to other opioids if their drug of choice was reformulated cannot be overlooked. Many studies

conducted to determine the changes in opioid prescribing and dispensing after the introduction of ADFs in the market have found that though the prescription opioid overdoses decreased substantially after the major change in the pharmaceutical market, the same has not been observed with the comparator opioids. Switching to other accessible non abuse-deterrent opioids might occur resulting in a significant level of residual abuse and particularly, heroin overdose rates have continued to increase.[13,14,15]

ADFs don't prevent patients from taking higher doses than prescribed, which is the most common way opioids are misused. This increases the risk of other dose dependent adverse effects of opioids that extend beyond their potential for abuse. These include immune, endocrine, cardiovascular, gastrointestinal, neuropsychiatric, and respiratory effects.[9] Evidence suggests the higher mortality rate among patients receiving long-term opioid treatment than those not treated with opioids.[16]

Concerns have also been expressed that the potential additional costs associated with opioid ADFs could impede access to these medications for patients with legitimate medical needs.[17]

Considering the evidence accumulated till date, the National Institutes of Health panel recommended further research to improve the understanding of the types of pain, specific diseases and patients that are most likely to be associated with benefit or harm from opioid pain medications; validate tools for identification of patient risk and outcomes; evaluate multidisciplinary pain interventions; estimate cost-benefit and effectiveness and harms of opioid pain medications with alternative study designs; and investigate the effects of risk identification and mitigation strategies on patient and public health outcomes.[18]

Conclusion:

The various types of pain and their treatment options continue to pose challenges in our health care system. There is much yet to be learned about the effectiveness, safety, and economic efficiency of long-term opioid therapy. Abuse continues to remain as a major area of concern among clinicians when opioids are prescribed. Though currently available opioid ADFs have been shown to be associated with significant reductions in rates of abuse of these formulations, this has been accompanied by an increase in rates of heroin abuse and overdose. Hence this stresses the need for various research communities and policymakers to examine the totality of the evidence regarding the benefits and risks of opioids and the ADFs.

Conflict of Interest: None

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