Economic Burden of Chronic Pain

Chronic pain poses a significant burden in the United States, as more than 100 million Americans are estimated to be affected by some degree of chronic pain.\textsuperscript{1,2} With chronic pain comes an increased use of healthcare resources. An estimated $635 billion is spent annually on treating and managing chronic pain.\textsuperscript{1,2} In addition, people with chronic pain are estimated to contribute an additional $261 billion to $300 billion in related healthcare needs compared to people without chronic pain. These additional healthcare costs include higher number of emergency department (ED) visits, more hospital expenditures, higher medication costs, and higher psychological costs, such as treatment of depression that can result from the inability to properly treat the pain.\textsuperscript{2}

An analysis from the Institute of Medicine found that, on average, an individual suffering from pain generates healthcare expenditures that are $4,516 higher than a person without pain. Furthermore, an individual with severe pain generates health expenditures that are $3,210 higher than a person with moderate pain.\textsuperscript{1}

To address the treatment aspect of chronic pain, opioids represent an important, if not essential, part of the overall treatment plan.\textsuperscript{3} In recent years, the pain management drug and devices market has grown. It was estimated at $35.4 billion in 2012 and is expected to grow 3.2% each year, reaching $41.5 billion by 2017.\textsuperscript{2,4} Opioid prescriptions have been on the rise. A report from the US Department of Health & Human Services (HHS) and National Institutes of Health (NIH) found that 76 million total opioid prescriptions were dispensed in 1991 by retail pharmacies in the United States compared to 219 million total prescriptions in 2011 and 207 million in 2013.\textsuperscript{5}

Impact of Opioid Abuse

With the increased prescribing of opioids for the management of chronic pain, a subsequent increase in the nonmedical use and abuse of opioids has been on the rise as well.\textsuperscript{6} Nonmedical use of opioids is classified as:

- **Abuse**
  - intentionally taking a drug to produce euphoria

- **Misuse**
  - taking medication in a manner other than prescribed

A total of 2.1 million Americans are reported to be addicted to prescription opioids.\textsuperscript{6} Patients being treated with chronic opioid therapy are 3.27% more likely to abuse opioids or become addicted, and there is a 25 times lower rate of abuse and/or addiction in patients without a prior history of opioid use compared to those who do have a history of opioid use (0.19% vs 5%, respectively).\textsuperscript{9}

The Centers for Disease Control and Prevention (CDC) estimates that more than 16,000 people die each year from overdoses related to pain medications, with 1 in 20 US citizens aged 12 years and older reporting use of prescription pain medication for nonmedical use. According to HHS, “Opioid analgesics were involved in 30% of drug overdose deaths where a drug was specified in 1999, compared to nearly 60% in 2010. Opioid-related overdose deaths now outnumber overdose deaths involving all illicit drugs such as heroin and cocaine combined.”\textsuperscript{7} Similarly, a report from the CDC indicated that the number of drug overdose deaths related to opioids has been staggeringly higher than deaths related to heroin, cocaine, and benzodiazepines.\textsuperscript{8} The CDC also reports that in 2008 there were 14,800 deaths related to prescription painkiller use. For every one opioid-related death there are:\textsuperscript{11-14}

- 10 treatment admissions for abuse
- 32 ED visits for misuse or abuse
- 130 people who abuse or are dependent on opioids
- 825 nonmedical users

In addition to the dangers associated with opioid misuse and abuse, the diversion of opioids has led to an estimated cost of $55.7 billion each year, impacting both healthcare and societal resources. Workplace costs accounted for $425.6 billion (46%), healthcare costs accounted for $25 billion (45%), and criminal justice costs accounted for $5.1 billion (9%).\textsuperscript{2,15}

The primary routes for opioid abuse, other than ingestion, include inhaling, parenteral, and smoking.\textsuperscript{16} In addition, the primary forms of opioid manipulation include crushing or grinding the drug into small particles or powder, dissolving the drug in a solvent, and extraction by exposure to heat or cold (TABLE 1).\textsuperscript{17,18}

A collaborative approach is needed between healthcare providers, patients, state and federal government, and the pharmaceutical industry to address the growing opioid abuse problem. A number of efforts have been put forth to address opioid abuse in the United States, including:
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- Education\(^{19,20}\)
  - Clinical education regarding appropriate prescribing, screening, monitoring, and patient management
  - Patient education on appropriate adherence, storage, and disposal

- Federal guidance\(^{19,21,22}\)
  - Changes of drug scheduling classes
  - Risk Evaluation and Mitigation Strategies (REMS)
  - Changes to opioid labeling

- Increased legislation and enforcement designed to limit abuse at the state level\(^{23-25}\)
  - Prescription Drug Monitoring Programs

Another recent introduction to help mitigate the abuse of opioids is the development of opioids with abuse-deterrence (AD) technology. The US Food and Drug Administration (FDA) has approved three AD opioids since early 2014 and several new technologies and drugs—both branded and generic—are currently under development.\(^3\)

**FDA Guidance to Pharmaceutical Industry on the Development of AD Opioids**

In April 2015, the FDA issued a guidance document that outlines the recommendation for evaluation and labeling of AD opioids. The FDA guidance document was developed to assist pharmaceutical manufacturers in the development of AD opioids in an effort to improve public health and safety. AD is defined as deterring but not preventing abuse, according to the FDA document. The document explains the FDA’s current thinking on:  

- The studies to conduct to demonstrate that a formulation has AD properties
- Detail how those studies will be evaluated
- Identify what labeling statements may be proposed based on the results of the studies

There are seven approaches to AD opioid formulations outlined in the FDA guidance document, including:\(^{16}\)

- **Physical/chemical barriers**
  - Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse (FIGURES 1–3).

<table>
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<tr>
<th>TABLE 1. Primary Routes of Opioid Abuse and Manipulation(^{16-18})</th>
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**FIGURE 1. Crushed gelatin capsule**

**FIGURE 2. Crush-resistant tablet**

**FIGURE 3. Noncrush-resistant tablet**

- **Agonist/antagonist combinations**
  - An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered and released only upon manipulation of the product. For example, a product can be formulated such that the substance that acts as an antagonist is not clinically ac-
With chronic pain comes an increased use of healthcare resources. An estimated $635 billion is spent annually on treating and managing chronic pain.\textsuperscript{1,2} When the product is swallowed, but becomes active if the product is crushed and injected or snorted.

- **Aversion**
  - Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed. For example, the formulation can include a substance irritating to the nasal mucosa if ground and snorted.

- **Delivery system, including use of depot injectable formulations and implants**
  - Certain drug release designs or the method of drug delivery can offer resistance to abuse. For example, sustained-release depot injectable formulation or a subcutaneous implant may be difficult to manipulate.

- **New molecular entities and prodrug**
  - The properties of a new molecular entity or prodrug could include the need for enzymatic activation, different receptor binding profiles, slower penetration into the central nervous system, or other novel effects. Prodrugs with AD properties could provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter the abuse of the parent opioid. New molecular entities and prodrugs are subject to evaluation of abuse potential for purposes of the Controlled Substances Act.

- **Combination**
  - Two or more of the aforementioned methods could be combined to deter abuse.

- **Novel approaches**
  - This category encompasses novel approaches or technologies that are not captured in the previous categories.

In addition, the guidance outlined four categories of studies for evaluating potential AD opioid formulations, including:

1. Laboratory-based manipulation and extraction studies, which aim to evaluate how easily a drug formulation can be manipulated; (2) pharmacokinetic (PK) studies, which evaluate in vivo PK profiles of manipulated versus intact drugs and compare them to competitors; (3) clinical abuse potential/human abuse liability studies, which provide the impact on how likely a drug is to be abused and the appeal to abusers; and (4) postmarket studies, which may determine if the formulation results in lower levels of abuse compared to nondeterrent formulations of the drug.\textsuperscript{16}

For drugs that demonstrate AD properties or the potential to reduce abuse, there are four categories of labeling claims that may align with the clinical studies conducted, including:

1. **Category 1** – those formulated with physicochemical barriers to abuse; (2) Category 1 and Category 2 – those expected to reduce or block the effect of the opioid when the product is manipulated; (3) Category 2 and Category 3 – those expected to result in a meaningful reduction in abuse; and (4) Category 4 – those shown to reduce abuse in the community. These claims would be included in Section 9.2 (Abuse) of the drug's prescribing information based on the results of clinical trials. The categories may help clinicians make the best choices for each patient.\textsuperscript{16}

**The Case for Inclusion of AD Opioids on Formulary**

The inclusion of AD opioid analgesics on formularies may reduce opioid abuse and cut US healthcare costs related to opioid abuse and diversion. The estimated net economic benefit ranges from $1,757 per patient to $4,033 per patient, depending on the differences in price and insurance coverage.\textsuperscript{2} Though AD opioid technology is fairly new, a few studies have shed positive light on the potential economic impact.

A study by Rossiter et al analyzed insurance claims data to estimate changes in rates of diagnosed opioid abuse among continuous users of extended-release (ER) opioids. The researchers also calculated the excess medical costs associated with diagnosed opioid abuse using a propensity score matching approach. The study included patients enrolled in commercial plans, Medicaid and Medicare, and the uninsured population. Data from 2009 to 2011 recorded in the Truven Health Analytics database were included, with the analysis divided into a 6-month pre-reformulation period (February 2010 to August 2010) and a 6-month post-reformulation period (November 2010 to May 2011).\textsuperscript{26}

The researchers found that the introduction of reformulated ER opioid was associated with relative reduction in rates of diagnosed opioid abuse of 22.7% for commercially insured patients ($P<0.001$) and 18% for Medicaid patients ($P=0.034$). A significant change was not found for the Medicare population ($P=0.707$). The AD formulation resulted in annual per-patient savings of $9,456 for the commercially insured, $10,046 for Medicare eligible individuals, and $11,501 for Medicaid patients ($P<0.001$ for all).\textsuperscript{26}
Overall, the reformulated AD ER formulation was associated with an annual medical savings of approximately $430 million. The researchers concluded, “Payers and policy-makers should consider these benefits as they devise and implement new guidelines and policies in this therapeutic area.”

In follow-up commentary from Kirson et al, researchers estimated the percent reduction in abuse-related medical costs associated with reformulated oxycodone ER opioid in order to establish indirect cost savings. The researchers utilized data from the Rossiter et al and Birnbaum et al studies and adjusted costs from 2009 to 2011 US dollars via the Consumer Price Index.

Of the $58.4 billion in annual societal costs associated with prescription opioid abuse, excess medical and drug costs accounted for $24.2 billion (41.4%), criminal justice costs accounted for $5.4 billion (9.2%), and workplace loss of productivity accounted for $26.8 billion (45.9%). The researchers identified lost workplace productivity as premature death, lost wages/employment, excess medically related absenteeism costs, excess disability costs, and presenteeism costs. The researchers concluded that ER AD opioids could substantially impact the annual societal costs associated with opioid abuse.

**State Legislation**

As of May 26, 2015, 33 US states have put forward AD Formulation (ADF) legislation in an attempt to address opioid abuse and misuse in the United States. Of the 33 states, seven states have passed ADF legislation that has been signed by the state governor, five states have had ADF legislation passed by one or both houses of the state legislature, 18 states have introduced ADF legislation, and three states have ADF legislation pending filing. See TABLE 2 for a breakdown of the states’ ADF legislation standings.

The Maryland Senate Bill 606, which was passed and signed into law on May 12, 2015, requires insurers, nonprofit health service plans, and health maintenance organizations (HMOs) to provide coverage for at least two brand name AD opioid analgesic drugs and, if available, at least two generic AD opioid analgesic drug products. The bill also prohibits the insurers, nonprofit health service plans, and HMOs from requiring an enrollee to first use an opioid analgesic product without AD labeling before providing coverage for a specified AD opioid analgesic drug product.
Can you speak to the economic impact that chronic pain poses to the US healthcare system?

Dr. Vogenberg: From a national perspective, the issue of chronic pain has really increased over time. We see it both in worker’s compensation and disability, as well as in the healthcare plan cost—both medical and pharmacy benefits.

Dr. Krakauer: The economic impact is considerable. In addition, there is considerable cost in lost economic productivity.

What are the dangers of opioid abuse and overdose in terms of societal impacts?

Dr. Vogenberg: A lot of the unintended effects of opioid abuse are coming out now, not just [dangers] to the particular patient who may have been prescribed opioids and becomes addicted to them, which has been written on for a long time. But now it has gone beyond that patient to other family members, particularly children, so that has become a broader societal impact of having opioids available. It has exponentially expanded this abuse problem.

Dr. Krakauer: Opioid abuse, in some form, has been known since antiquity. We now have serious problems with drug dependence, with prescription opioid abuse a leading cause or trigger. In addition to cost, this [abuse] results in lost productivity, crime, and more than 16,000 deaths [related to overdose] each year. More than 5% of the US population reports use of pain medication for nonmedical use.

How is AD opioid technology impacting the issue of opioid abuse?

Dr. Vogenberg: I think it is a little too soon to really know. I think there has been some benefit to it and the technology continues to get better. I think we are heading in the right direction.

Dr. Krakauer: AD opioid technology has the potential to ameliorate this problem. Formulations that make abuse difficult create a barrier. Although some products based on this technology are available, it is too early to determine the overall impact. Continued studies of the impact, potential impact, and unintended consequences are necessary and expected.

How would a pharmacy & therapeutics (P&T) committee go about considering and selecting an AD opioid formulation for formulary consideration?

Dr. Vogenberg: From a safety and effectiveness perspective, I think the safety part has been kind of elevated because of this concern around abuse and the availability of deterrent technologies, but then how do you balance that availability of deterrent technologies with the effectiveness? [The health plan will] bring in experts, either from among other staff or experts in their physician networks to give them more insight and information around which particular technology may be better than another or [weigh] the pros and cons of each of the technologies.

Dr. Krakauer: There are several ways a [P&T] committee might address this. While making a reasonable choice of opioids avail-
able for pain is appropriate, there also needs to be a recognition that a minority of the population might be prone to dependence. Since we are not certain these products substantially impact opioid abuse overall, it is not clear that we should globally mandate how they should be prescribed or inhibit attempts to find the most appropriate ways to use or manage their use.

Can you discuss how opioid abuse affects Medicare spending and resources? Is that a problem typically found in this covered population?

Dr. Krakauer: Opioid use is common in Medicare, with 10 million users. Of the half million [users] in the top 5% of Medicare opioid use, 29% obtained opioids from more than four [different] prescribers and 31% from more than three [different] pharmacies. Medicare spends $2.7 billion on opioids, of which $1.9 billion (69%) is attributed to the top 5% of Medicare users, whose monthly opioid bill averages $310.

Currently, 33 states have put forward legislation regarding inclusion of AD opioids on formularies, with seven states that have passed legislation that has been signed into law. Do you think all states should have legislation that mandates the inclusion of AD opioids on formularies?

Dr. Vogenberg: I think the concerns today about the AD opioids has been the cost factor. I think a lot of the push back has been around what is going to happen to the cost of care versus the benefit by using this new deterrent technology. There is some new compelling data being generated about the potential economic benefits of AD opioids and that will need to be assessed on a case by case basis in deciding what products to cover on a formulary. I think there is really a split position out there from a political perspective. And it is hard to say what would happen—I do not think anything is going to happen on the national level with Congress, so I think it is going to end up being more of discussion within the states.

Dr. Krakauer: These products are too new. It is not clear how [these products] can contribute to addressing the opioid abuse problem. Currently, [the cost of AD drugs] can be more expensive than the generic equivalent. We need to see more clinical and economic data to determine the overall cost-benefit of these products and how best to use them and manage their use. It is not clear how legislation might facilitate this.

Is there anything else, in your perspective, that you feel a managed care professional should consider when it comes to opioid AD technologies?

Dr. Vogenberg: I think there has to be some sensitivity to the demographics. Certain states and cities have more problems than others related to opioid abuse. I think looking at things much more collaboratively and interactively is going to be more important. The big concern is [that] you do not take away the drugs—whether it is an AD or not. But this criminalization of opioid use is becoming an issue from a professional perspective. If we are not allowed to prescribe or dispense drugs or it is highly limited, then we are going to create a problem for patient access to these products. And if they are not able to get the products then you are going to have even a bigger economic impact and more societal impacts as well.

“From a national perspective, the issue of chronic pain has really increased over time. We see it both in worker’s compensation and disability, as well as in the healthcare plan cost.”

—F. Randy Vogenberg, RPh, PhD

F. Randy Vogenberg, RPh, PhD, and Randall Krakauer, MD, FACP, FACR, discussed pain management and abuse-deterrence opioid technologies from a managed care perspective. Drs. Vogenberg and Krakauer were compensated for their participation.
REFERENCES


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