Major increases in opioid analgesic abuse in the United States: Concerns and strategies

Wilson M. Compton*, Nora D. Volkow

National Institute on Drug Abuse, 6001 Executive Boulevard, MSC 9589, Bethesda, MD 20892-9589, USA

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Abstract

The problem of abuse of and addiction to opioid analgesics has emerged as a major issue for the United States in the past decade and has worsened over the past few years. The increases in abuse of these opioids appear to reflect, in part, changes in medication prescribing practices, changes in drug formulations as well as relatively easy access via the internet. Though the use of opioid analgesics for the treatment of acute pain appears to be generally benign, long-term administration of opioids has been associated with clinically meaningful rates of abuse or addiction. Important areas of research to help with the problem of opioid analgesic abuse include the identification of clinical practices that minimize the risks of addiction, the development of guidelines for early detection and management of addiction, the development of opioid analgesics that minimize the risks for abuse, and the development of safe and effective non-opioid analgesics. With high rates of abuse of opiate analgesics among teenagers in the United States, a particularly urgent priority is the investigation of best practices for treating pain in adolescents as well as the development of prevention strategies to reduce diversion and abuse.

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1. Background/Identification of the problem

Though abuse and addiction to opioid agents is not a new phenomenon (De Quincy, 1998), new is the scale, range and growth of the problem. Epidemiological surveys of youth in the United States in 2003 indicated that opioid analgesics were among the most frequently abused illicit drugs among secondary students (12th graders), second only to marijuana (Johnston et al., 2004). Further, the past few years have seen a marked increase in the use of opioid medications in the United States and an even greater increase in problems associated with such use (Substance Abuse and Mental Health Services Administration, 2003a,b). This upsurge in use and problems is particularly concerning because it seems to represent an expanded pathway to opioid addiction (Siegal et al., 2003).

Despite these concerning data, there are major limitations to the existing research, the first of which is that the terms misuse, abuse, dependence and addiction are used in idiosyncratic ways. At a minimum, each author should clearly specify their definitions and for this paper, we define opioid abuse as any intentional use of opioids outside of a physician’s prescription for a bona fide medical condition, excluding accidental misuse. It should be noted that our use of the term “abuse” is distinct from the abuse diagnosis specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). On the other hand, “addiction” in this paper is synonymous with the standard DSM-IV diagnosis of dependence which is defined as including compulsive use, impaired control, tolerance, withdrawal and continued use despite physical and psychological problems caused or exacerbated by use (American Psychiatric Association, 1994).

According to recent epidemiological data, 4.7% (i.e. 11.0 million) United States household residents over the age of 12 abused an opioid medication in 2002 and 13.7% of these persons (i.e. 1.5 million) endorsed the symptoms of a DSM-IV opioid use disorder (Substance Abuse and Mental Health Services Administration, 2003b; American Psychiatric Association, 1994). As seen in Fig. 1, the annual...
incidence of opioid analgesic abuse increased from 628,000 initiates in 1990 to 2.4 million initiates in 2001 (Substance Abuse and Mental Health Services Administration, 2004.)

From another perspective, between 1998 and 2002, the number of opioid analgesic drug mentions (i.e. excluding heroin and morphine) in medical examiner cases increased in 28 of 31 reporting areas of the United States (Substance Abuse and Mental Health Services Administration, 2004). Thus, the relationship of prescription opioid drugs to death is of increasing concern. Examining data from emergency departments, mentions associated with opioid drugs, another indicator of problems, increased 135% from 1995 to 2002 and 18.5% from 2001 to 2002 (Substance Abuse and Mental Health Services Administration, 2003b).

The increase in opioid analgesic abuse is especially worrisome since at the doses that these substances are sometime abused they can result in respiratory depression and death. In addition it is particularly problematic for two populations—adolescents because of uncertain implications for future addiction and the elderly because of increased sensitivity to toxic effects. Like other drug-related conditions, opioid analgesic abuse is mostly concentrated in adolescents and young adults (Substance Abuse and Mental Health Services Administration, 2003b); yet, little is known about opioid effects in adolescence. Most of what we know about opioid abuse and addiction has been learned from heroin addiction in 20 to 40-year-old individuals. Given rapid brain development during adolescence, early exposure to opioids may result in neurobiological changes and behavioral consequences that may differ from those we have seen in adults.

Given these concerns, the purposes of this paper are to: (1) describe the patterns of opioid analgesic use that may be particularly related to abuse or addiction; (2) describe possible causes of the recent increases in opioid abuse in the United States; (3) review potential factors that are associated with abuse or addiction compared to safe therapeutic use of these agents and (4) review future directions for research on opioid analgesic abuse and addiction.

2. Patterns of opioid prescription

There are two basic ways that opioid medications are obtained: through medical prescription and through illicit sources. Both of these may be inter-related in that as medical prescriptions increase, more medications may be available for diversion.

Prescription of opioids falls into two major subtypes: treatment of acute pain with brief periods of opioid use and treatment of chronic pain with long-term exposure. Treatment of acute pain conditions with brief, short-term prescriptions of opioid analgesics is rarely associated with abuse or addiction (Porter and Jick, 1980), although extra medication left in a medicine cabinet represents a potential source for family members and others in the home.

In contrast to the rare association with addiction in short-term prescriptions, long-term administration of opioids has been associated with the development of abuse or addiction in 2.8–18.9% of patients (Fishbain et al., 1992; Cowan et al., 2003), paralleling rates of abuse or addiction among opioid users in the general population (Substance Abuse and Mental Health Services Administration, 2003b; Anthony et al., 1994). Thus, given a generally high prevalence of chronic non-cancer pain, the group potentially at risk for addiction as a complication of treatment is significant (Harstall and Ospina, 2003; Gureje et al., 1998). The implications of this observation for prevention are clear: identification of those at highest risk and careful monitoring of patients for early signs of abuse or addiction is reasonable, though little research has been completed to guide this process (Simoni-Wastila and Strickler, 2004).

3. Increasing access to opioids

As we consider potential reasons for the upsurge in opioid abuse, there are several forces apparently driving the increases. First, there have been marked increases in the numbers of prescriptions written for opioids in the United States (Zacny et al., 2003). Thus, one explanation for the increases is as a byproduct of a growing availability of prescription opioids.

Second, internet access to prescription drugs, including opioid analgesics, has opened a new source for access to these drugs and may explain a portion of the increases (National Center on Addiction and Substance Abuse, 2004; Forman, 2003). What this means is that anyone with a credit card can get access to prescription opioids and that these drugs may be taken without the supervision of a physician. It is also recognized that some of the opioid analgesics available over the internet are manufactured by sites that do not have proper quality controls, potentially compounding the risk of toxicity. Although access through the internet is a major problem and may explain some of the marked increases in opioid drug problems, the fact that the same rate of increase has not occurred for other prescription drugs (Substance Abuse and Mental Health Services Administration, 2003).
Mental Health Services Administration, 2003b), such as stimulants, suggests that other factors contribute to the increases.

Third, changes in drug formulation and prescribing practices may have led to greater risk of diversion and abuse of opioid analgesics (United States General Accounting Office, 2003; Hancock and Burrow, 2002). The new pattern of prescribing in the United States includes an emphasis on primary care physicians for care of patients with pain conditions rather than physicians who specialize in pain treatment (United States General Accounting Office, 2003).

4. Variables contributing to the abuse of opioid analgesics

A key observation is that the problems associated with prescription opioids have increased in recent years in the United States. Joranson and colleagues reported that increases in medical use of opioid analgesics were not associated with increases in reported opioid-related problems during the early 1990’s (Joranson et al., 2000), but more recent data contradict this finding (Zacny et al., 2003). The increase in opioid analgesic-related emergency department mentions, which is an indicator of opioid-related problems (Substance Abuse and Mental Health Services Administration, 2003a), does not appear to be solely accounted for by an increase in prescriptions. Indeed, Fig. 2 which is based on the work of Zacny et al. (2003), shows that the rate of increases in problems associated with the opioid analgesics in some instances is equivalent to the rate of the increases for prescriptions (e.g. hydrocodone and morphine) and in others exceeds it (e.g. fentanyl and oxycodone). In the case of fentanyl, emergency department mentions increased more than 50-fold from 1994 to 2002 while the number of prescriptions increased only 7.2-fold. A similar excessive increase in emergency department mentions compared to prescriptions is seen for oxycodone (5.5-fold increase versus 2.5) but not for morphine (2.5 versus 2.3).

In other areas of medicine, there appear to be distinctions between doses utilized therapeutically and dosages that are abused. For example, methylphenidate dosages for attention deficit disorder are typically below the level expected to produce reinforcement (Volkow and Swanson, 2003). However, for opioid agents, the results are less clear. In drug abusers, dosages used for adequate pain control are identical to the dosages used to induce reinforcement (Fischman, 1989) However, in non-drug abusing populations, both pleasant and unpleasant effects of the agents have been noted (Zacny, 2003; Zacny and Gutierrez, 2003). Thus, while the very way that most opioids are prescribed for outpatients is potentially addicting, it is not clear who is at risk for this effect.

Differences in the formulations of the opioids are also likely to affect their reinforcing effects and their desirability for diversion and abuse. Both abuse and analgesic potential of opioids depend primarily on the degree to which they bind to the mu opioid receptor. Thus, for persons with severe pain, the most potent agents must be prescribed, the very agents which put the patient most at risk for abuse or addiction. More malleable issues include route of administration and formulation details. For example, oral opioid agonists with small doses of naloxone (a potent opioid antagonist only active when...
taken by injection) are much less likely to be injected than the same agent without the antagonist (Baum et al., 1987). Further research is needed on formulations, which reduce injection potential and certainly the development of strong analogues with minimal abuse potential is a laudable goal.

For youth, we hypothesize that there may be a social learning aspect, based on modeling of drug use by adults in their families and social networks. Medications may be taken by family members on a routine basis and may be used for a variety of conditions. The increases in marketing for medications in media (especially television) may be related to changed attitudes towards ingestion of psychotherapeutic agents. Moreover, the fact that these drugs are “medication” and endorsed by physicians may give a false sense of safety.

Another major issue in addiction is the expectation that the subjects have of the drug effects and the setting of use of a substance (context of administration). In the case of opioid analogues the expectation is for pain relief. When given for acute conditions, opioids are often given in a medical setting. In contrast, when given chronically, opioids are taken in the context of every day activities. Because opioids, like other drugs that increase dopamine, can lead to conditioned responses, the use of the substance may become conditioned to the activities of daily living. We hypothesize that such use may trigger craving for the drug by environmental stimuli, which could result in problematic use.

5. Scientific questions

Significant increases in the abuse and addiction to opioid analogues provide urgency to research development of effective prevention and treatment approaches. An additional concern is that the extent of opioid analgesic abuse in countries other than the United States is uncertain. Is the situation in the United States a harbinger of problems likely to be seen in other locations? Are there cross-national differences in opioid analgesic abuse, which may help to illuminate the causes of the increases in certain populations? More specific scientific questions relate to developmental neurobiology, natural history of addiction to opiate analogues and the treatment of chronic pain. The main concern for developmental neurobiology is to determine the risk to brain development associated with acute and chronic opioid administration. How does the use of opioids at different stages of brain development impact future reinforcing properties of other substances? Is there a priming effect or, conversely, a diminished responsiveness? That is, does use of opioids early in development increase the likelihood of use later in life, or does early use mean that higher doses might be needed? This type of question implies a need for studies of opioids on the developing brain, using both in vitro and in vivo models. The implications of this research would be far-reaching, even pertaining to the practice of prescribing opioid analogues to adolescent for outpatient procedures, such as dental interventions. Should the same practices used for adults be used for children and adolescent or are there differences in vulnerability to addiction during the different developmental stages?

An important question in the natural history of opioid analgesic abuse is the identification of who is at risk for addiction. Even basic information about the degree of overlap of chronic pain conditions with opioid abuse is lacking. Though it is recognized that individuals who have a past history of drug abuse are the most vulnerable to addiction when treated with opioid analogues, much less is known about the risk of those that have not abused drugs in the past. Monitoring of abuse of these agents is needed as is research that leads to procedures for early identification of problematic opioid use will help clinicians detect early symptoms of addiction before the syndrome is fully developed (Katz et al., 2003). Additional questions include: how are these agents abused (i.e., are they injected or taken orally, are they taken by themselves or in combination with other drugs such as alcohol)? What are the sources for obtaining these agents? There is major black market for these drugs—rivaling or exceeding cocaine and heroin. What are the sources? Where do users obtain their substances? How does the source vary according to the type of user? That is, do youth who have never used non-medical opioids have different sources for obtaining their drugs from experienced heroin users? What about the elderly, who may be particularly vulnerable to the side effects of medications? How do the elderly get into trouble with opioids?

In the area of treatment development, are there non-opioid agents that are strong analogues but do not have an addictive potential? For example, recent work with drugs that act on cannabinoid 2 receptors, which are constrained to peripheral sites, suggest that they could be potentially beneficial for neuropathic pain (Rice, 2001). Or can we develop less abuseable, but still potent, forms of opioid agents? Alternatively are their combinations of medications that can be given to treat pain but to minimize the chances of addiction (Basile et al., 2002). From the treatment arena, how should one treat pain in persons who have a history of addiction or those who already exhibit signs of addiction?

6. Conclusion

Acute as well as chronic pain can be very handicapping to the individual. Opioid analogues are very effective medications and when used properly have many beneficial effects. However, it is important to recognize that a potential side effect from chronic use can be abuse and addiction, and though not frequent, this complication can have devastating consequences. In fact, correct use and abuse of these agents are not polar opposites—they are complex, inter-related phenomena which need to be studied jointly. Because of their reinforcing effects, opioid analogues are also targets for diversion and abuse. Increases in diversion are likely to reflect not only, greater opioid analgesic availability from prescription increases and the relatively easy access via the internet but also access to new more powerful formulations. This sig-
ificant increase in abuse in the United States (and possibly elsewhere) poses an urgent need to expand research on issues related to vulnerability and to the effects of opioid analgesics on brain development, on therapeutic strategies for pain management that minimize risks and help identify early signs of addiction and on the impact that the internet has on this new epidemic.

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