

## Iatrogenic addiction in patients treated for acute or subacute pain: A systematic review

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### ABSTRACT

*We conducted a systematic review of the literature on the evidence for iatrogenic addiction in patients treated for acute and subacute pain. Literature searches yielded 1,943 articles, 53 of which were reviewed in detail, and 41 of which met criteria for inclusion in the review of iatrogenic addiction. Two authors independently reviewed and summarized the findings of each article. Discrepancies of ratings were resolved by discussion. We identified no randomized trials or comparative longitudinal studies. The results of nine studies of low methodological quality suggest conflicting findings. This manuscript discusses some possible mechanisms of iatrogenic addiction and concludes with suggestions for methodologically stronger studies to provide more definitive data regarding the evidence for or against iatrogenic addiction in patients treated for acute and subacute pain. The systematic review of the literature could not adequately answer the study questions; thus, it is not known whether the risk for iatrogenic addiction among patients treated with opioids for acute or subacute pain is relatively high (> 10 percent) or low (< 0.1 percent).*

*Key words: iatrogenic addiction, acute pain, opioids, substance abuse*

### INTRODUCTION

The addiction of a patient to a drug initially prescribed for a medical condition is referred to as an iatrogenic addiction. The postoperative or short-term use of prescription drugs with addictive potential, such as opioid analgesics, increases the risk of iatrogenic addiction. Although a number of studies have examined the rate of iatrogenic addiction in chronic pain patients receiving long-term opioid therapy, few investigations have documented its incidence among hospitalized patients who

receive opioids for acute pain. Results from the Drug Abuse Warning Network (DAWN) indicate that the abuse of prescription opioids rose 71 percent from 1997 to 2002.<sup>1</sup> Given this trend, the issue of iatrogenic addiction among hospitalized patients is a particularly salient topic related to the prescription of opioids.

Epidemiologic data from the National Comorbidity Survey of Psychiatric Disorders in the United States indicate a lifetime prevalence of 7.5 percent for drug dependence (illicit or prescription) and of 14.1 percent for alcohol dependence.<sup>2</sup> In 2003, 2.7 percent of Americans (18 years or older) met criteria for illicit drug abuse or dependence as defined by the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).<sup>3</sup> During this same year, almost 8 percent of the population of the United States met DSM-IV criteria for alcohol dependence or abuse.<sup>4</sup> Among a sample of 363 hospitalized patients, Brown and colleagues found that 21.8 percent had a current addiction disorder to alcohol or illicit drugs.<sup>5</sup>

Addiction is generally understood to be a chronic condition from which recovery is possible; however, the underlying neurobiologic dysfunction, once manifested, is believed to persist.<sup>6</sup> This condition represents a biological susceptibility to addiction to any substance with an addictive potential, even in the absence of any ongoing addictive behaviors or psychological cravings. Therefore, the prescription of opioid analgesics to a patient with a predisposition for, or history of, addiction can initiate an addictive disorder or its relapse. Many patients are discharged from the hospital with prescriptions for long- and short-acting opioid analgesics for postoperative pain without accurate data indicating the probability of their developing an addiction to these medications.

Investigations supported by the National Institute of Drug Abuse suggest that addiction is characterized by destructive motivations and behaviors reinforced and

perpetuated by underlying physiological abnormalities in the brain.<sup>7,8</sup> For certain individuals (6.1 to 16.7 percent of the population), substances of abuse create changes in the brain that “hijack” motivational priorities and lead to a pattern of loss of control, craving, and continued use despite adverse circumstances.<sup>9-11</sup> These individuals are described as having a “switch” in the brain that changes behavior from voluntary to compulsive. Functional changes are thought to occur in the dopamine-mediated reward system, primarily in the left prefrontal cortex and nucleus accumbens. These regions interact with multiple areas of the brain implicated in the pathophysiology of addiction.<sup>12</sup>

## DEFINITIONS

For purposes of this study, we adopted the following definitions accepted by the American Academy of Pain Medicine, the American Pain Society, and American Society of Addiction Medicine.<sup>13</sup> Addiction is a primary, chronic, neurobiologic disease with genetic, psychological, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Physical dependence is defined as a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, or decreasing blood levels of the drug and/or by administration of an antagonist. Tolerance is defined as a state of adaptation in which exposure to a drug induces changes that result in diminution of one or more of the drug's effects over time. Abuse is defined as the use of any drug in a manner other than how it is indicated or prescribed.<sup>13</sup> In one of the first reports of iatrogenic addiction, Rayport<sup>14</sup> described an individual with this syndrome as “One who states that he first received narcotics from a physician to the point of addiction in a disease treatment course.” Finally, acute and subacute pain is defined as short-term pain or pain with an easily identifiable cause and is the body's warning of present damage to tissue or presense of disease.

## STUDY AIM

The aim of this study was to systematically review the relevant literature on iatrogenic addiction. The following questions were addressed:

1. What is the incidence of iatrogenic addiction among persons treated for acute pain?
2. What are the predictive markers for addiction among patients treated with opioids for acute and subacute pain?

3. What steps are currently being taken to treat addiction from short-term opioid use?

## METHODS

We searched PubMed, the National Library of Medicine's literature database, using the following words and phrases (MESH headings): “iatrogenic addiction,” “acute pain and addiction,” “acute pain and opioid abuse,” “acute pain and opioid addiction,” “acute pain and iatrogenic addiction,” “headache pain and opioid abuse,” “acute headache and opioid abuse,” “acute headache and addiction,” “sickle cell pain and opioids,” “sickle cell pain and opioid addiction,” “sickle cell pain and opioid abuse,” and “postoperative pain and addiction.” Articles were included if they addressed issues related to iatrogenic addiction. We excluded redundant studies (i.e., reported identical data), abstracts from conference proceedings, and studies whose design had nothing to do with assessment of iatrogenic addiction.

Two authors independently reviewed each citation to determine whether it might meet our criteria for inclusion in the review. If either author thought that the article might meet the inclusion criteria, two authors then independently reviewed the abstract. If either thought, based on the abstract, that the article might meet the inclusion criteria, two authors then independently read the entire article to make a final decision. Discrepancies in decisions were resolved by discussion, with input from the other authors as needed.

We classified the methodological strength of each study using a scheme previously used by other reviewers.<sup>15,16</sup> Articles were grouped into study design types: I) prospective, randomized controlled trials (RCTs); II) nonrandomized comparative studies with standardized measures, inclusion/exclusion criteria, and follow-up; III) uncontrolled case series with pre- and post-treatment and follow-up; and IV) descriptive studies, case reports, or expert opinion. For each article we attempted to include information on sample, study design, outcomes, and conclusions.

## RESULTS

A search of PubMed with the previously mentioned MESH headings revealed a total of 1,946 articles. Many of these articles were duplicates; 53 were selected for detailed review, and 41 met inclusion criteria. The authors independently reviewed and judged nine articles to be most relevant to the study topic, although other related articles were included for discussion. No randomized or nonrandomized controlled studies were found. Results of the review are summarized in Table 1.

### Studies suggesting high rates of iatrogenic addiction

Selected studies are described here in detail to address

**Table 1. Summary of studies related to iatrogenic addiction**

Authors	Title	Sample	Study design and type	Conclusion
Elander et al. 2004	Understanding the causes of problematic pain management in sickle cell disease	51 adults with sickle cell disease	Class IV; semistructured interviews	Presents evidence that aberrant drug behaviors can begin in the hospital but may not necessarily represent an addiction, and that it may be most appropriate to interpret this behavior as evidence of poorly managed pain
Jamison, et al. 1994	Survey of opioid use in chronic nonmalignant pain patients	112 chronic pain patients from two pain centers who were taking opioids for chronic pain	Class IV; patient survey	63.7 percent of patients expressed some fear of addiction or dependence
Jamison, Kauffman, and Katz, 2000	Characteristics of methadone maintenance patients with chronic pain	248 subjects from three methadone maintenance centers	Class IV: subject interviews	61.3 percent of subjects reported chronic pain; 44 percent of those with pain believed prescribed opioids had led to addiction; most stated that they had always required some substance (alcohol or opioids) to feel normal
Lander, 1990	Fallacies and phobias about addiction and pain	63 staff nurses surveyed/42 staff nurses consulted for case assessment	Class IV; surveys and clinical case assessment	One-third of nurses think that > 5 percent of hospital patients become addicted; 63 percent of nurses rated 5 or higher the likelihood on a 7-point scale that patients could become addicted after 10 days of q4hr meperidine
Marks and Sachar, 1973	Undertreatment of medical inpatients with narcotic analgesics	Physicians of 37 medical inpatients who were taking narcotics for > 48 hr	Class IV; physician survey and case series	40 percent of physicians surveyed stated that the chances were close to 1 percent that a patient receiving 100 mg meperidine for 10 days would become addicted; 22 percent thought chances were > 6 percent; the authors concluded that the probability was < 1 percent that narcotic addicts in the US became addicted while hospitalized and that doctors greatly overestimate the actual chance of iatrogenic addiction
Miller and Jick, 1978	Clinical effects of meperidine in hospitalized medical patients	Record review of 3,634 hospital inpatients treated with meperidine	Class IV; case review estimates	Four of 3,634 subjects showed iatrogenic addiction; two were addicted before entering the hospital
Perry and Heidrich, 1982	Management of pain during debridement: a survey of US burn units	181 physicians and nurses representing 10,000 hospitalized burn patients	Class IV; case series	12 percent of those surveyed knew of a patient who had become a drug abuser upon discharge as a result of receiving narcotics for pain; most patients had a prior history of abuse; 22 were reported to abuse drugs after discharge, but all had a prior history of drug abuse
Porter and Jick, 1980	Addiction rare in patients treated with narcotics	11,882 inpatients who had received at least one narcotic preparation	Class IV; chart review	Four of 11,882 patients with no previous addiction showed addiction after treatment with narcotics while hospitalized
Rayport, 1954	Experience in the management of patients medically addicted to narcotics	277 patients from an addiction unit interviewed; many stated they had become addicted after treatment for their disease	Class IV; retrospective interviews	89 of 1,065 admissions to an addiction clinic suffered iatrogenic addiction; medically addicted patients accounted for 27 percent of inpatients

the study questions. Some studies showed support for a high prevalence of iatrogenic addiction. Pescor<sup>17</sup> in 1939 was one of the first to address the issue of addiction to opioids prescribed for acute pain, reporting that 3.8 percent of a group of 1,036 hospitalized patients “became addicted to morphine given legitimately for the alleviation of a painful or distressing disease” both during and after hospitalization. However, no operational definition of addiction was given in the paper. In a survey study of 1,020 opioid-addicted men consecutively admitted to a hospital, Rayport<sup>14</sup> in 1954 found that the incidence of medical addiction to narcotics was as high as 27 percent and that addiction had begun during treatment of an acute illness in a majority of these patients. These descriptive studies, published 66 and 51 years ago, respectively, leave unanswered how addiction was defined. While the incidence of iatrogenic addiction cannot be relied on in these studies, they do suggest that it can be a consequence of opioid treatment first administered during hospitalization.

More recently, in a study of 363 patients on general medical, surgical, and orthopedic wards of a university hospital, Brown et al.<sup>5</sup> used two standardized measures based on DSM-III-R criteria for substance abuse to determine the rate of abuse among short-term inpatients. The authors reported a lifetime prevalence of 2.8, 10.2, and 25.3 percent for abuse of opioid analgesics, any drug excluding alcohol, and any drug including alcohol, respectively. Given this relatively high incidence of substance abuse, the authors concluded that the probability is high that doctors will administer opioid analgesics for acute pain to inpatients with a history of an addictive disorder.

In a survey study of 112 patients taking opioids for chronic pain, 63.6 percent reported being bothered by the fear of addiction or dependence.<sup>18</sup> In a recent survey study of 248 individuals at three methadone maintenance centers, 44 percent of those surveyed believed that opioids prescribed for pain had led to an addiction.<sup>19</sup> Moreover, many patients receiving methadone maintenance therapy said they had always required some substance (alcohol or opioids) to “feel normal.” The authors suggested that, among persons prone to substance abuse, the treatment of pain with opioids could trigger an addiction disorder, regardless of the treatment setting.

A qualitative study by Elander and colleagues sheds light on how the process of iatrogenic addiction may begin.<sup>20</sup> They performed semistructured interviews with 51 adult inpatients hospitalized in the United Kingdom for a sickle cell crisis, examining issues of analgesic misuse and substance dependence. They found that disputes between patients and physicians or nurses about pain level or the amount of opioids prescribed fueled dissatisfaction over pain treatment, which in turn led some patients to inappropriately manipulate their patient-controlled analgesia pumps, acquire pain medications from

other patients, or use analgesics apart from those prescribed. A portion of these patients continued similar aberrant behaviors after discharge: obtaining analgesic prescriptions from more than one doctor, using analgesics prescribed to another person, using illicit drugs, or injecting oral forms of analgesics.

### Studies suggesting low rates of iatrogenic addiction

Other investigations have suggested low rates of iatrogenic addiction to opioids among patients treated for acute pain. Using data accumulated during the Boston Collaborative Drug Surveillance Program on drug safety in hospitalized patients, Porter and Jick<sup>21</sup> surveyed the files of 11,882 patients who had received at least one narcotic preparation. They found only four cases (0.03 percent) of iatrogenic opioid addiction in patients without a prior history of an addictive disorder. In a similar study, Miller and Jick<sup>22</sup> examined the files of 3,364 hospitalized medical patients who received meperidine. Only four (0.1 percent) patients, two of whom were addicted before entering the hospital, exhibited symptoms of dependence on meperidine. These brief reports support a belief that prescription opioids have minimal potential for addiction when used to treat either acute or chronic pain. Both of these studies, however, only reported on the period of hospitalization, when access to opioids is highly monitored and inappropriate use of opioids would be difficult.

In a study examining how pain is assessed and managed during wound debridement in US burn facilities, Perry and Heidrich<sup>23</sup> analyzed 181 responses to questionnaires sent to the medical staff (one-third of whom were physicians) of various burn units. They calculated that the responders to their survey represented the accumulated knowledge of at least 10,000 hospitalized burn patients. The survey included a question about the rate of iatrogenic addiction to opioid analgesics in burn patients. Twelve percent of the respondents indicated that they knew of a patient who had become a drug abuser on discharge from the hospital as a result of receiving narcotic analgesics for pain. All but one of these iatrogenically addicted patients had a history of drug abuse. The authors concluded that the risk of developing an addiction to opioid analgesics prescribed for pain is low. No information was given about the duration of patients' pain.

Studies examining physicians' fears of creating opioid addiction suggest that the incidence of iatrogenic addiction to opioid analgesics among patients treated for acute pain is less than 1 percent.<sup>24-26</sup> In a survey by Marks and Sachar,<sup>26</sup> physicians were asked about the probability of a hospitalized patient developing an addictive disorder after a 10-day treatment regimen with 100 mg of meperidine intramuscularly every four hours. The majority of

physicians (60 percent) stated that the chances of addiction were less than 1 percent, while only 22 percent stated that they were greater than 6 percent. Based on the physicians' responses, the authors of this survey concluded that the development of addiction to meperidine likely occurs in fewer than 1 percent of patients treated for acute pain.

A study by Zacny et al.<sup>27</sup> offered further support for this position. Under experimental conditions, human subjects with no history of drug abuse reported less opioid reward from a dose of fentanyl paired with a painful stimulus (cold water) than from the same opioid challenge without pain (warm water). The positive psychological effects of fentanyl (e.g., euphoria or elation) were found only when accompanied by warm water, suggesting that the painful stimulus (cold water) abolished this effect. At the same time, studies of the reinforcing effects of drugs in the presence versus the absence of pain in animals showed the opposite outcomes. These studies suggest that pain increases the reinforcing efficacy of opioid analgesia and blunts the psychoaffective effects.<sup>28, 29</sup>

## DISCUSSION

A thorough review of the literature did not produce a single controlled trial devoted to the investigation of iatrogenic addiction to opioids. All articles were classed as Type IV (descriptive studies, case reports, expert opinion), and conclusions were often based on subjective impressions. There were no follow-up studies, and most articles could not answer the question of whether patients develop iatrogenic addiction after taking opioids. Given the recent rise in the prescribing and abuse of opioid analgesics,<sup>30</sup> accurate data on the rate of addiction among inpatients administered opioids for acute pain, although needed, do not seem to exist.

Vanyukov and colleagues<sup>31</sup> argue that some patients have a predisposition for an addiction disorder based on a multifactorial genetic liability. This liability concept is supported by research documenting cross-tolerance for different substances, the cotransmission of substance abuse disorders within families, and addiction to multiple drugs. They conclude that common physiological mechanisms underlie addiction disorders. Clinical studies have documented a high correlation among substance abuse, smoking, and other addictive disorders, such as gambling. It is likely that this relationship is at least partially modulated by characteristics of innate temperament.<sup>32</sup>

Some of the conflict between the results of studies reporting an extremely low risk of addiction for hospitalized patients and the high proportion of substance abuse in the general population can be explained by the unreliable methodology of existing surveys of iatrogenic addiction in hospitalized patients. The studies by Prescor<sup>17</sup> and Rayport<sup>14</sup> can be criticized for being descriptive studies

lacking a rigorous study design. It is also important to note that the studies by Porter and Jick<sup>21</sup> and Miller and Jick<sup>22</sup> were designed to evaluate the clinical effects of opioid analgesics on patients with acute pain, and that findings related to addiction were peripheral to their focus. Furthermore, the authors excluded all individuals with a history of addiction when determining incidence of iatrogenic addiction. As with these surveys, the study by Perry and Heidrich<sup>23</sup> was not specifically designed to assess iatrogenic addiction to opioids but rather to examine the pharmacologic management of burn patients in general. No specific diagnostic criteria, standardized addiction screens, or structured clinical interviews were used. Thus, the rates of iatrogenic addiction to opioid analgesics reported in these studies should be interpreted with caution.

Specific factors in the hospital drug-taking environment might also account for the reported differences. For example, patients in a controlled environment have few opportunities to demonstrate aberrant drug behavior. Once patients are discharged there may be limited coordination of care to identify and follow those patients who may develop iatrogenic addiction.

In sum, a careful review of the studies that assess risk of addiction to opioids in hospitalized patients treated for acute pain show that these studies have methodologic limitations. No well-controlled longitudinal studies on this issue have been reported in the literature. Thus, we do not know whether the risk is relatively high (> 10 percent) or low (< 0.1 percent). The absence of reliable data on the risk of addiction in hospitalized patients is a significant concern because iatrogenic addiction could pose a major public health concern. At present, we do not know whether the expectation of addiction after administration of opioids for acute or subacute pain is exaggerated, and there is no system for closely monitoring the signs of opioid addiction following treatment of acute pain.

Given the current confusion in the literature, we suggest that the following recommendations be considered. First, a simple screen for addiction risk potential based on a history of substance abuse in the family would help patients be aware that they may be at increased risk for medication abuse. Several screening tools currently exist to help identify risk for abuse, including the Screening Instrument for Substance Abuse Potential (SISAP),<sup>33</sup> the Prescription Abuse Checklist,<sup>34</sup> the Prescription Drug Use Questionnaire,<sup>35</sup> the Pain Assessment and Documentation Tool (PADT),<sup>36</sup> the Pain Medication Questionnaire (PMQ),<sup>37</sup> and the Screener and Opioid Assessment for Patients with Pain (SOAPP).<sup>38</sup> Limitations of these measures have been identified.<sup>39,40</sup>

Second, further exploration of different delivery systems that adequately treat pain, while also decreasing the risk for substance misuse, should be encouraged. This includes the development of short- and long-acting opioid

medications that are not easily compromised. Finally, priority should be given to the development of rigorous, controlled, longitudinal studies of patients prescribed opioids for acute pain. A unified call for designated support through federal agencies (e.g., the National Institutes of Health) to fund these studies and help clarify this issue is needed. Future studies in which patients are assessed preoperatively for family and personal history of substance abuse and are followed for more than six months after discharge would help to assess the incidence of iatrogenic addiction. This systematic review of the literature could not adequately answer the study questions.

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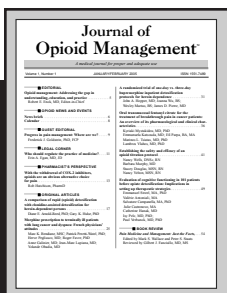
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