

Long-term Opioid Therapy for Chronic Pain and the Risk of Opioid Addiction

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INTRODUCTION

There has been a constant struggle to define the role of opioids in medical therapy, due to their potential for misuse, overuse, and addiction since pain is a completely subjective sensation, not amenable to objective measurement, and is intimately tied to emotion and the patient's psychological well-being. Thus the medical decision to administer an opioid analgesic is an attempt to balance the potential for pain relief, and the reliability of the patient's reporting, against the potential for harm. The decision-making process is less complicated when dealing with acute traumatic injury or surgical trauma. However, with many chronic pain conditions, the etiology or severity of the patient's pain is less obvious. In the majority of situations, a physician does not initiate opioid therapy with the intention of continuing it for months or years, but many patients will continue to seek opioids for relief of pain which becomes chronic.

Until 1990, chronic use of opioid analgesics was widely discouraged, with most physicians trained to taper their patients off opioid medication after an acute treatment trial. The paradigm began to shift as the movement to improve cancer pain treatment became successful with aggressive opioid prescribing. The success of aggressive opioid therapy for cancer pain treatment led to a spill over into chronic non-cancer pain treatment, spurred on by industry-supported continuing medical education programs. As high-dose opioids became more available in the community, it was accompanied by a pattern of escalating drug diversion, opioid misuse, accidental opioid overdose, and deaths that continued to climb through the past decade. (Figure 1)¹ Accidental opiate overdose deaths from prescription opioids began to far exceed deaths attributed to illicit drugs of abuse, such as heroin and cocaine. Nationally, accidental drug overdose deaths surpassed deaths from motor vehicle accidents, reaching a peak of 16,917 deaths from prescription opioids in 2011 (<http://www.cdc.gov/homeandrecreationsafety/overdose/facts.html>). During the period from 2009–12, Rhode Island

Figure 1. Rates of opioid pain reliever (OPR) overdose death, OPR treatment admissions, and kilograms of OPR sold – United States, 1999–2010.¹

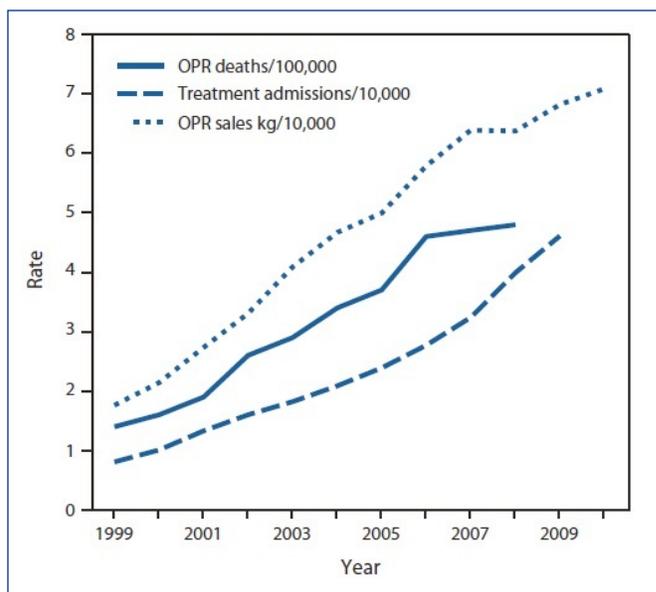
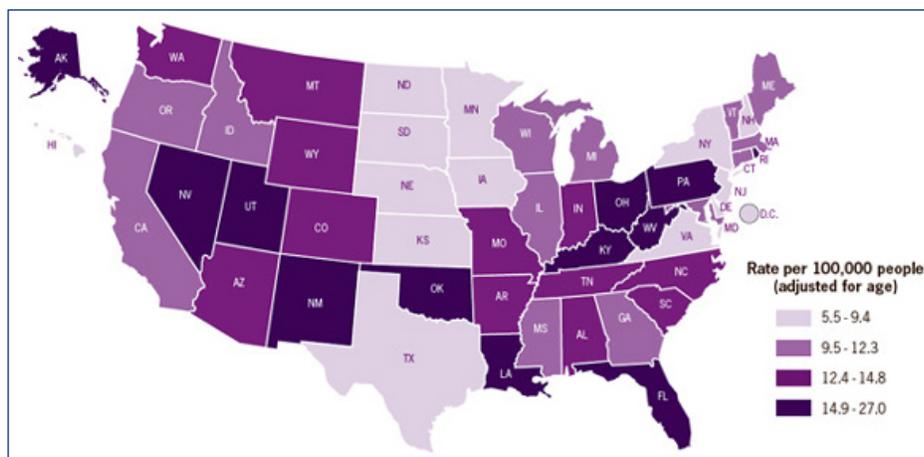


Figure 2. Drug overdose death rate in 2008 and rate of kilograms (kg) of opioid pain relievers (OPR) sold in 2010 – United States.¹

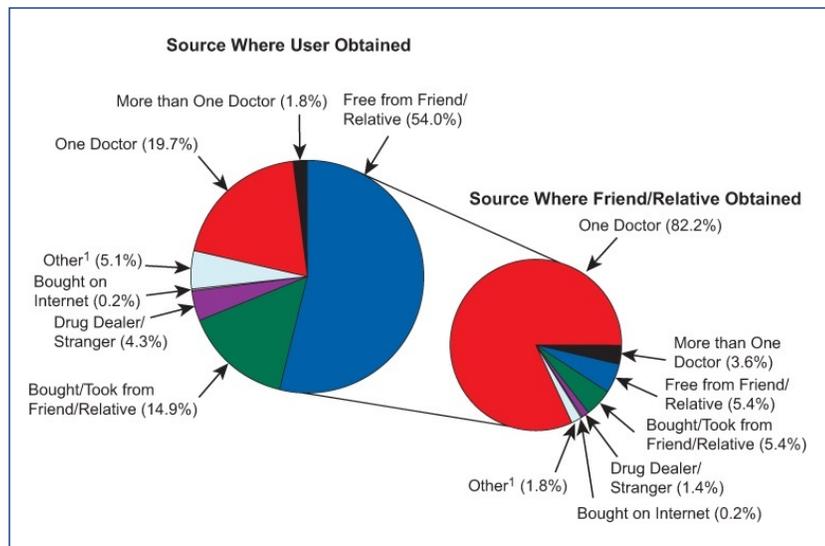


experienced 645 accidental prescription opioid deaths, and in 2008 the state's accidental opioid overdose death rate of 17.2/100,000 people ranked as the sixth highest in the nation. (Figure 2) CDC analysis of opioid prescribing rates

for the year 2012 ranked Rhode Island at 19th nationally, with 89.6 opioid prescriptions per 100 persons; however, this does not imply that 90% of the population are receiving an opioid prescription, as most are repeat prescriptions going to a small percentage of the population. Nationally, the CDC suggests that enough opioid prescriptions are dispensed annually to provide every citizen in the U.S. with a month supply of medication.

What role do prescribing physicians play in this national crisis? CDC statistics have indicated that fewer than 20% of patients dying from accidental prescription opioid overdoses have a legal prescription for the opioid medication involved in their demise. National drug surveys conducted have consistently found that the majority of nonmedical opioid users obtain access to the medication through family and friends, with only a small percentage via drug dealers or Internet sources. (Figure 3) This initially suggests that physicians are a minor source of misused medication; however, when you consider that a physician prescribed the opioids to the family and friends of the unintentional overdose victims, physicians appear to contribute an additional 60% of the misused opioid supply. Overall, physician prescribing provides more than 80% of the misused opioid supply, through their direct intent and through unintended diversion.

Figure 3. Opioid pain reliever sources for nonmedical use among users: 2009–2010. (www.samhsa.gov/data/NSDUH/2k10MH_Findings/2k10MHResults.pdf)



ARE CHRONIC PAIN PATIENTS PRESCRIBED LONG-TERM OPIOID MEDICATION AT RISK FOR ADDICTION?

Despite their documented efficacy in treating acute and cancer pain, there is no strong evidence to support long-term prescribing of opioids for common pain problems, such as low back pain.² Recent efforts by the American Academy of Pain Medicine and the American Pain society to establish

guidelines for opioid prescribing for chronic pain found little high-level evidence of efficacy, and mostly based their recommendations on expert opinion. (http://www.americanpainsociety.org/uploads/pdfs/Opioid_Final_Evidence_Report.pdf) Long-term randomized, controlled trials are difficult, if not impossible to design due to the inherent actions of the opioid class, such as obvious sedative or euphoric effects when administered, the development of tolerance, and the development of withdrawal symptoms when stopped. Even more confusing is the limited evidence of efficacy seen in open trials, where “significant” reductions in pain ratings are limited to 1–2 points on the 10- or 11-point rating scale. The self-reinforcing effects seen with opioid analgesics are often confusing to patients, who may interpret the withdrawal pattern (often manifested as pain and achiness) between doses as evidence of efficacy. Despite patient reports of subjective improvement, global measures of pain relief and improved function are modest or lacking.

Opioid-related side effects and lack of efficacy results in treatment discontinuation by as many as 30% of patients enrolled in opioid trials.³ Another major reason for discontinuation of opioid therapy in clinical trials includes addiction, medication misuse, and suspicion of diversion. Definitions of aberrant drug-related behavior (ADRB) and addiction are quite varied in the literature, and are continually being redefined in the chronic pain setting. Most chronic pain patients treated with long-term opioids will develop evidence of tolerance and physical dependence, a pattern of drug-seeking behavior, craving, and even evidence of continued use despite harm (as in significant side effects). Advocates of long-term opioid treatment have argued that these parameters, typically associated with addiction, are the consequence of inadequate pain treatment and not addiction. Controversy exists over what behaviors should be classified as ADRB. Some of the more widely accepted ADRB's include: lost or stolen prescriptions, early visits without appointments seeking refills, not following the prescribed dosage pattern, seeking medications from multiple physicians, forging prescriptions, use of illicit drugs or detection of non-prescribed opioid medications with urine drug testing, and legal action related

to opioid medications.⁴ Unfortunately, there is no uniformity in defining ADRB's or addiction in the chronic pain literature. Recognizing this difficulty, several structured evidence-based reviews have attempted to examine the risk of addiction in populations treated with long-term opioids.^{4,5} Fishbain et al. reviewed the published literature in 2008, evaluating studies reporting on patients treated with opioids for a period ranging from 2 to 240 months, for an average exposure time of 26.2 months.⁵ After reviewing 67

published reports, they identified 24 studies that measured abuse/addiction, involving 2,507 chronic pain patients, and found an estimated abuse/addiction rate of 3.27%. In studies that excluded patients with a history of abuse or addiction, the rate of reported abuse/addiction dropped to 0.19%. In 17 studies focusing on ADRB, the calculated ADRB incidence was 11.5%, and in patients without a prior history of abuse or addiction, the rate dropped to 0.59%.

A Cochrane Review on long-term opioid management for chronic noncancer pain published in 2010 reported similar findings, with an estimate of opioid addiction of 0.27%, leading the authors to conclude that the risk of iatrogenic opioid addiction is low.⁴ Individual studies have estimated drug abuse/addiction to range between 0-50% of their population. This wide range is due in part to non-standardized definitions of abuse/addiction, as some included any controlled substance, not just misuse or abuse of the prescribed opioid. There is also a built in selection bias depending on the referral pattern of the treatment program. Many pain treatment programs accumulate high-risk patients with a history of substance abuse, or current abuse concerns.

One of the most consistent risk factors predicting opioid abuse/addiction, is a history of opioid abuse (odds ratio of 3.81).⁶ Patients with a history of severe dependence or abuse had an odds ratio of 56 for developing abuse/addiction.⁶ Weisner *et al* surveyed patients receiving long-term opioids in two large group health plans and found that patients with a history of opioid abuse had a prevalence rate of opioid use approaching 50%, compared to patients without a prior opioid abuse history of 2-3%. In their study, patients with an abuse history tended to use higher doses, averaging 100mg of morphine equivalent dose (MED), were prescribed more schedule II opioids, and were prescribed more long-acting opioids.⁷ Gwira-Baumblatt *et al.* identified using more than 100mg MED daily had an adjusted odds ratio of 11.2 for unintentional overdose deaths.⁸

Recognizing the shortcomings of the current literature, and the fact that most long-term opioid trials were conducted over three months or less, it would appear that the risk of developing opioid addiction is low in a prescreened population using low to modest opioid doses. However, in patients with a history of prior substance abuse or high-dose opioid use (≥ 100 mg of morphine equivalent dose), the risk of addiction/abuse is substantially higher.⁹

LESSONS LEARNED

Most data dealing with the benefits and risks of long-term opioid therapy for chronic noncancer pain are based on studies of 8-12 weeks, or deal with highly selected populations. There is a general belief that there is still insufficient evidence to clearly define the safety or efficacy of long-term opioids. Tools for predicting opioid aberrancy and addiction have been studied over relatively brief periods, and are based on testing in at-risk populations, but have only modest

predictive value of treatment success or addiction/abuse when applied to more global pain populations. While some screening tools, such as SOAPP and the Opioid Risk Tool are helpful, they cannot be applied in isolation, are probably most useful as an indicator of who should be more closely monitored, and should not be used to determine who should receive long-term opioids.

Based on current evidence, the following approach to long-term opioid prescribing may be helpful. Most opioid dependent and accidental overdose patients have the following characteristics in common: 1) patients at high risk for overdose or abuse tend to be doctor shoppers, often visiting 5 or more practitioners for opioid prescriptions; 2) accidental overdose deaths are associated with prescriptions of more than 100 mg of MED daily (8.9 fold increase in risk with a 1.7% annual overdose risk); 3) male sex; 4) patients with a history of substance abuse; 5) concurrent psychiatric diagnoses; 6) use of 3 or more different pharmacies.⁶⁻¹¹ Given this, it is critical that any physician intending to prescribe long-term opioids for chronic pain review their state prescription monitoring program (for RI see: <http://www.health.ri.gov/programs/prescriptionmonitoring/>) for evidence of their patient receiving opioids from multiple prescribers or pharmacies. This program is not fool-proof, as patients accessing controlled substances across state lines can avoid scrutiny, but it demonstrates a good faith effort on the part of the physician and due diligence. Careful scrutiny and review of medical records for evidence of a past history of substance abuse will help to identify patients at risk for dependence, misuse, or addiction. A history of addiction does not necessarily preclude opioid therapy; if warranted, but definitely identifies a need for close monitoring. An opioid pain treatment agreement may also be of value, as it clearly defines the expectations for continued opioid treatment parameters, and may serve as a formal informed consent, depending on the design of the document. Finally, avoid prescribing high-dose or large quantities of opioids. The efficacy of prescribing dosages higher than 100mg of MED are associated with a greater risk of diversion, abuse, overdose, and a general lack of efficacy. Unfortunately, there are no completely reliable means to ensure success or failure. Only thoughtful prescribing with an understanding of the risks and benefits can improve treatment success and patient safety.

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