

Chapter 2

The Epidemiology of Pain and Opioid Abuse

Jermaine D. Jones and Sandra D. Comer

2.1 The Epidemiology of Pain and Opioid Abuse

The medicinal and psychoactive effects of the opium poppy (*Papaver somniferum*) have been known for thousands of years [1]. Several major alkaloids in opium that have been isolated, including morphine (8.0–17.0 %) and codeine (0.7–5.0 %), are used therapeutically as analgesics, antitussives, and antidiarrheal agents [2, 3]. Our knowledge of the structure of natural *opiates* (morphine, codeine, and thebaine) led to the development of synthetic and semi-synthetic *opioids* (e.g., hydrocodone, oxycodone, hydromorphone, and fentanyl) with varying analgesic potencies and durations of action [4]. The therapeutic diversity of opioid analgesics has made them one of the clinician's most valuable tools to treat moderate-to-severe acute and *chronic pain*. Chronic pain has been defined by the American Society of Interventional Pain Physicians (ASIPP) as, “pain that persists 6 months after an injury and beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal” [5, 6].

Unfortunately, the immense medical utility of opioids is tempered by their potential to be abused. In addition to analgesia, many opioid drugs produce robust euphoric effects. Both properties of opioids are commonly attributed to their actions upon the mu (μ) subtype of opioid receptors ([7, 8, 9]). The intensely pleasurable subjective effects produced by opioids can encourage nonmedical use leading to addiction. Several different types of investigations, from global and national epidemiological studies [10, 11, 12] to controlled laboratory research [13–16], have confirmed the potential for these drugs to be used for nonmedical purposes. As such, the abuse liability of this drug class creates a dilemma as chronic pain and opioid abuse are two major public health concerns. Recent market research indicates that

J.D. Jones, Ph.D. (✉) • S.D. Comer

Division on Substance Abuse, New York Psychiatric Institute and Columbia University Medical Center, New York, NY, USA

e-mail: JonesJe@NYSPI.Columbia.edu; ComerSa@NYSPI.Columbia.edu

more than 1.5 billion people worldwide suffer from chronic pain [17]. In the US, it has been conservatively estimated that there are over 100 million chronic pain sufferers, with annual direct (e.g., medical expenditures) and indirect (e.g., loss of productivity) costs of over US\$560 billion [18].

The epidemiology and cost of prescription opioid abuse is just as striking. According to the World Health Organization (WHO), the annual global prevalence of opioid abuse was estimated at between 28 and 38 million users [World Drug Report, 2014, heroin (diacetylmorphine) and prescription opioids were not distinguished]. Figures from the US National Survey on Drug Use and Health (NSDUH) place the number of current (within the past month) nonmedical users of opioid analgesics at 4.5 million [19]. Meanwhile, the annual societal costs (direct + indirect) of prescription opioid abuse have been estimated at US\$57 billion [20]. Greater than the economic burden of opioid abuse is the mortality and morbidity resulting from fatal and non-fatal overdoses. The number of unintentional overdose deaths from prescription opioids in the United States has more than quadrupled in the first decade of the twenty-first century [19].

Healthcare clinicians are therefore tasked with balancing adequate pain management using opioids with the risk of patients developing abusive patterns of use. In spite of this concern, the use of long-term opioid therapy has increased dramatically over the past two decades [6, 21, 22]. Nowhere has this increase been more dramatic than in the United States where the total number of opioid pain reliever prescriptions has risen from around 76 million in 1991 to nearly 207 million in 2013 [23]. The United States is easily the largest global consumer of opioid analgesics. Though Americans constitute only 4.6 % of the world's population, we consume 80 % of the global opioid analgesic supply [24–27].

Increased availability of opioid analgesics combined with other factors such as greater social acceptability of using these medications and aggressive marketing by pharmaceutical companies are believed to have led to a substantial rise in the incidence of prescription opioid abuse ([6, 28]; Fig. 2.1). In the last few years, policy-makers have become increasingly interested in provisions for better pain management, while at the same time reducing opioid analgesic diversion and abuse [29].

Because of the risk of *iatrogenic* abuse (attributable due to medical treatment) as a result of exposure to opioids for pain management, there has been substantial interest in their comorbidity. However, determining the frequency of abusive patterns of opioid use among chronic pain patients has proven difficult. Variability in defining “opioid abuse” operationally has led to substantial inconsistency across estimates of their co-occurrence. Terminologies such as “abuse,” “aberrant use,” “misuse,” “addiction,” “pseudo-addiction,” and “nonmedical use” have all been employed in attempts to define the same disease state. The *abstracting* (filtering and selecting the relevant aspects of a concept of interest for research purposes) of criteria defining the problematic use of opioids has also been variable and imprecise, encompassing many combinations of behaviors such as:

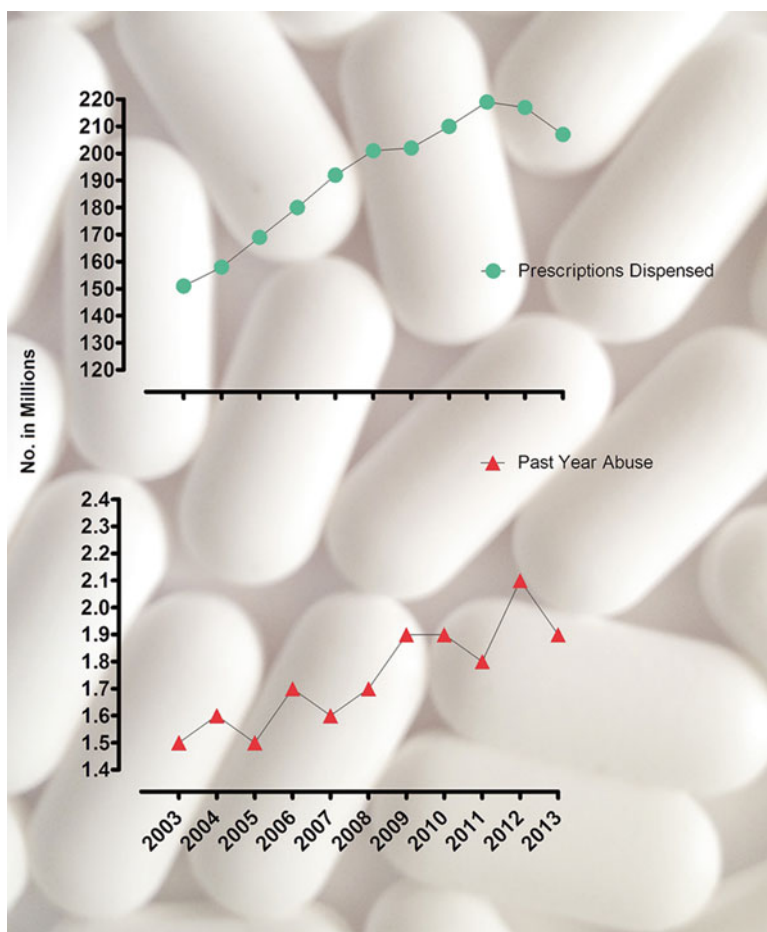


Fig. 2.1 Rates of opioid analgesic prescribing and abuse

- Intravenous and intranasal use
- Using more than prescribed
- Unsanctioned dose escalations
- Obtaining opioids from friends or family
- “Doctor shopping” (obtaining opioids from several medical sources)
- Purchasing opioid medications off the street

An additional challenge is that there are no commonly accepted study design metrics to determine rates of opioid analgesic abuse among chronic pain patients. The methodologies used to quantify the co-epidemiology of pain and opioid abuse have ranged vastly. Internet analyses have been used to capture target keywords from search engines and drug forums to evaluate the frequency of opioid use for nonmedical purposes [30]. Online surveys have also proven to be a rapid method of

providing insight into individuals who use prescription opioids non-medically [31, 32]. Structured examinations of clinical notes and chart reviews of pain patients' medical records have also been used to assess abusive patterns of use [33–41]. Similarly, forensic studies utilizing data from prescription monitoring programs [42] and urine toxicology testing [43–49] have been used as ways of gathering information on aberrant opioid use. On a larger scale, population-based assessments have obtained these data using self-report surveys [50–53]. Other population-based data have come from clinical reports of emergency department visits [54] and treatment center admissions [55–59]. In addition to data from events involving health-care utilization (see also [60]), events involving interaction with law enforcement [61] and adverse events reporting [62–64] have also been used to examine the rates of comorbid pain and opioid abuse.

All of these methods have inherent limitations, examining diverse populations using different endpoints. Accordingly, rates of problematic opioid use among pain patients have ranged broadly (>1–81 %) across studies [65]. Review articles, which combine data across multiple studies, are therefore more likely to provide valid estimates. Portenoy [66] was one of the first to perform an evidence-based, *structured review* (employing an explicit description of what types of studies to be included, to limit selection bias) on this topic. This investigation described and assessed “aberrant drug-related behaviors,” which were operationalized as those indicative of the development of “addiction” [67, 68]. He concluded that the literature indicated that the psychological, social, and physiological vulnerability to addiction was uncommon among chronic pain patients, and therefore the risk of abuse was low. However, no rates of comorbidity were reported due to a lack of studies and other technical issues.

There have since been a number of reviews that have attempted to pool data on the risk and rates of opioid abuse among chronic pain patients. Wasan et al. [69] reviewed nine articles they determined were related to iatrogenic addiction in patients treated for acute or subacute pain. They concluded that they could not adequately answer the study question, and that the risk and prevalence of addiction among patients treated with opioids could not be determined. Bartleson [70] also performed a structured review of 11 reports addressing addiction as a result of opioid treatment. They concluded that opioid therapy is associated with a low risk of abuse or drug addiction, as only two of the studies reviewed indicated the development of abuse/addiction to have been a problem. A *narrative review* (an unstructured, unsystematic critical analysis that describes and discusses the state of a topic from a theoretical and contextual point of view) by Aronoff [71] came to a similar conclusion. Another narrative review by provided one of the first detailed rates of comorbidity [72]. Following their review of 25 studies, they concluded that the prevalence of “addiction” among chronic non-malignant pain patients (patients prescribed opioids for cancer pain are typically distinguished and excluded from this research) varied from 0 up to 50 %. In yet another narrative synthesis, Martell et al. [73] placed estimates of current substance use disorders and aberrant medication-taking behaviors at 5–43 %.

It is commonly believed that these wide-ranging estimates are the result of the limited scientific rigor of these previous reviews (mostly attributable to the lack of primary data on the topic), along with inconsistent operationalization of abuse and addiction [33, 74]. More recent reviews have addressed both these limitations. Integrative literature reviews provide the most scientifically rigorous assessments of the current state of knowledge on a topic [75, 76]. An *integrative review* not only summarizes, but also critiques and synthesizes the representative literature an integrated way. Fishbain et al. [77] performed one of the first integrative reviews of research studies aimed at determining the rates of opioid “abuse/addiction and/or aberrant drug-related behaviors” among patients exposed to chronic opioid therapy. An initial literature searches yielded 79 papers on the topic. Study characteristics were extracted and independently evaluated by two raters according to 12 quality criteria, and a quality score was calculated. Studies were not utilized in the final assessment unless their quality score (from both raters) was greater than 65 %. Sixty seven reports were included in the final analysis. They found that the rate of opioid abuse/addiction among patients with pain (e.g., drug problems, drug seeking, psychological dependence, craving, etc.) was slightly higher than the general population (3.27 % versus 1.7 % among Americans aged 12 or older; [12]). In comparison to rates of abuse/addiction, their estimates of the rate of aberrant drug-related behavior (e.g., aggressively requesting medications, unsanctioned dose escalations, etc.) and inconsistent urine toxicology findings (e.g., the presence of opioid medications that are not prescribed) were higher at 11.5 % and 20.4 %, respectively.

Although the data provided by Fishbain et al. [77] are compelling and informative, recent attempts at standardizing terminology concerning opioid misuse and abuse have greatly aided comparisons across studies. A multidisciplinary group of academic, industry, clinical, public health, and regulatory experts in pain and addiction was convened by the Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks (ACTION; <http://www.action.org>). This panel reviewed existing definitions of misuse, abuse, and related events from consensus efforts, review articles, and major institutions and agencies. Their goal was to develop mutually exclusive and exhaustive consensus definitions of opioid analgesic misuse, abuse, and related events (MARES) to inform clinical trials, post-marketing research, and clinical care [78].

This consensus statement has provided a much better framework for evaluating problematic opioid use in chronic pain patients. Accordingly, Vowles et al. [65] conducted a comprehensive and elegant integrated review aimed at defining rates of problematic opioid use among chronic pain patients. The clinical and scientific literature related to this topic was searched using Science Direct, Google Scholar, PubMed, and PsychINFO/PsycArticles databases. Each potential study identified in the literature search was read in full by two study team members to determine eligibility. In total, data from 38 studies were included (shown below in Fig. 2.2).

The following data were extracted from studies that met inclusion criteria:

- Participant demographics
- Pain details (i.e., sample size, gender, age, pain duration)

Table 2**Characteristics of included studies.**

First author (year)	Sample size (country)	Design	Setting	Method of assessment	Rate (%) of problematic use, %			Quality
					Misuse	Abuse	Addiction	
Adams et al. ^{1,*}	4278 (USA)†	Prospective	Not specified	Q	—	—	4.9	7
Banta-Green et al. ⁵	704 (USA)	Retrospective	Primary care	SI	—	8	13	8
Brown et al. ^{8,*}	561 (USA/Puerto Rico)	Prospective	Primary care	CJ, Q, UDS	2-6	—	—	6
Butler et al. ¹¹	95 (USA)	Prospective	Pain clinic	CJ, Q, UDS	46.3	—	—	5
Butler et al. ¹⁰	226 (USA)	Prospective	Pain clinic	CJ, Q, UDS	34.2	—	—	3
Chelminski et al. ¹²	63 (USA)	Prospective	Primary care	CJ, UDS	32	—	—	2
Compton et al. ¹⁴	135 (USA)	Prospective	Pain clinic	CJ, UDS	28	—	—	5
Couto et al. ^{15,*}	938,586 (USA)	Cross-sectional	Toxicology laboratory database	UDS	75	—	—	0
Cowan and Wilson-Barnett ^{16,*}	104 (UK)	Retrospective	Pain clinic	SI	—	—	2.8	7
Edlund et al. ^{18,*}	9279 (USA)	Cross-sectional	Community database	Q	3.3	—	0.7	5
Edlund et al. ^{17,*}	46,256 (USA)	Cross-sectional	Not specified	INSUR CL	3.2	—	—	5
Fleming et al. ^{20,*}	801 (USA)	Cross-sectional	Primary care	SI	—	—	3.8	8
Fleming et al. ^{21,*}	904 (USA)	Cross-sectional	Primary care	SI	—	—	3.4	6
Højsted et al. ^{23,*}	207 (Denmark)	Cross-sectional	Pain clinic	CJ	—	—	14.4-19.3	7
Ives et al. ^{25,*}	196 (USA)	Prospective	Pain clinic	CJ, UDS	32	—	—	4
Jamison et al. ²⁶	455 (USA)	Prospective	Pain clinic	CJ, SI, UDS	24.0-37.1	—	34.1	4
Jamison et al. ^{27,‡}	110 (USA)	Cross-sectional	Pain clinic	Q	46.4	—	—	1
Katz et al. ^{29,*}	122 (USA)	Retrospective	Pain clinic	CJ, UDS	43	—	—	4
Manchikanti et al. ³⁶	100 (USA)	Retrospective	Pain clinic	CJ	24	—	—	6
Manchikanti et al. ^{35,*}	500 (USA)	Retrospective	Pain clinic	CJ	9.4	—	8.4	4
Manchikanti et al. ^{34,*}	200 (USA)	Cross-sectional	Pain clinic	UDS	3-12	—	—	1
Manchikanti et al. ^{33,*}	500 (USA)	Prospective	Pain clinic	CJ	9	—	—	5
Manchikanti et al. ^{30,*}	500 (USA)	Prospective	Pain clinic	UDS	9	—	—	3
Meltzer et al. ⁴⁰	238 (USA)	Cross-sectional	Primary care	SI	11	—	—	4
Meltzer et al. ³⁹	264 (USA)	Cross-sectional	Primary care	CR	—	—	23	8
Morasco et al. ⁴²	127 (USA)	Cross-sectional	Primary care	Q	78	—	—	1
Naliboff et al. ⁴³	135 (USA)	Prospective	Pain clinic	CJ, UDS	27	—	—	5
Passik et al. ⁴⁵	1160 (USA)	Retrospective	Clinical database	CJ	—	—	6-11	7
Portenoy et al. ⁴⁶	219 (USA)	Prospective	Clinical trial registry	Q	2.6	—	—	3
Reid et al. ⁴⁷	98 (USA)	Retrospective	Primary care	CJ	24-31	—	—	7
Schneider et al. ⁴⁹	184 (USA)	Retrospective	Pain clinic	CJ, UDS	—	—	15.7	7
Sekhon et al. ⁵⁰	797 (USA)	Retrospective	Primary care	CJ	22.9	—	—	5
Skurtveit et al. ^{52,*}	17,252 (Norway)	Prospective	Prescription database	CJ	0.08-0.3	—	—	3
Vaglienti et al. ^{57,*}	184 (USA)	Retrospective	Pain clinic	CJ, UDS	25.5	—	—	5
Wasan et al. ⁵⁹	455 (USA)	Cross-sectional	Pain clinic	CJ, Q, UDS	34.1	—	—	7
Webster and Webster ⁶¹	183 (USA)	Prospective	Pain clinic	Q	56.3	—	—	6
Wilsey et al. ⁶²	113 (USA)	Cross-sectional	Emergency department	Q	81	—	—	2
Wu et al. ⁶⁵	136 (USA)	Prospective	Pain clinic	CJ, UDS	27.9	—	—	3

* The primary study aim was assessment of prevalence of opioid misuse, abuse, or addiction.

† Adams et al.¹—only data from the group taking hydrocodone used.

‡ Jamison et al.²⁷—only baseline data used (i.e., patients who screened as "high risk" on questionnaire).

Method of assessment: CJ, clinical judgment (including chart review); INSUR CL, Insurance Claims Database; Q, questionnaire.

SI, structured interview; UDS, urine drug screen; USI, unstructured interview.

Quality: possible range 0 to 8; higher scores indicate higher quality (quality criteria adopted from Chou et al.¹³).

Fig. 2.2 Rates of problematic opioid use behaviors among pain patients determined by systematic review and synthesis

- Primary objective (e.g., assessment of prevalence, medication safety/efficacy)
- Design (i.e., cross-sectional, prospective, retrospective)
- Setting details
- Methods of assessing problematic opioid use (i.e., structured/unstructured clinical interview)

Fig. 2.3 ACTTION
committee consensus
definitions of problematic
opioid use behaviors



Problematic opioid use behaviors from the selected articles were then coded using the terms defined in the ACTTION statement (Fig. 2.3): misuse, abuse, and addiction [78]. Average prevalence rates were calculated and weighted by sample size and study quality. Their investigation found that rates of opioid analgesic misuse averaged between 21 and 29 %, while rates of addiction averaged between 8 and 12 %. Abuse was reported in only a single study.

In conclusion, determining the rate of comorbid opioid abuse and misuse among patients with pain has proven to be challenging. However, it is clear that particularly in the U.S., there should be increased scrutiny regarding who is a suitable candidate for opioid treatment, and what are suitable precautions [79]. Greater prescribing of opioids in clinical practice also increases the likelihood that they will be diverted to the illegal market. Furthermore, anecdotal reports and news media suggest that individuals who begin abusing prescription opioids may transition to using heroin. Although causality cannot be determined, increases in the numbers of new heroin users (between 2002 and 2011) parallel rises in prescribing and abuse of prescription opioids [80].

The increased focus on how opioid prescribing contributes to the growing “opioid abuse epidemic” has allowed the field to identify patients who are most at-risk of misusing and abusing prescribed opioids. More specifically, patients with a personal or family history of substance abuse and psychosocial comorbidity may need more carefully structured and monitored opioid treatment [81]. Better understanding of all the psychological, social, and genetics risk factor should help circumvent

the development of addiction [82–84]. These issues are discussed in greater detail in a later chapter of this text, so we will not elaborate upon them here.

Much of our thinking on drug abuse is derived from our knowledge and experience with illicit drugs. In contrast, assessment of abusive patterns of prescription opioid use must be placed in the context of a population with germane medical needs and adjusted accordingly. It is a concern that misunderstanding of these behaviors and labeling of patients as “addicts” could lead to unnecessary withholding of medications and undertreatment of pain [85]. Clear and empirical definitions of aberrant opioid analgesic use behaviors will hopefully lead to increased reliability and validity across studies and more scientific consensus to better inform clinical care.

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