Controlled Substance Management in Chronic Pain

A Balanced Approach

Peter S. Staats
Sanford M. Silverman
Editors

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To my wife and kids.

To the healthcare workers who come to work each day attempting to help patients with chronic pain.

To the patients with chronic pain. Hopefully, this will help your doctors work with you to have a thoughtful and safe approach to managing your pain.

To the patients with addiction disorders, or who may develop problems with addiction in the future. We hope this book provides insight into minimizing the risks of addiction.

And to the families of patients with pain.

—Peter S. Staats

To my wife, children and office staff, who have all put up with me over the years and have seen what an interesting trip this has been.

To my patients with chronic pain and those with addiction; both are suffering, even the abusers and misusers.

To those families that have lost loved ones to prescription drug abuse, hopefully we can help prevent this from happening to others.

To the patients with chronic pain who have to deal with collateral damage of the new gauntlet of state and federal laws governing how we prescribe controlled substances which ultimately limit your access to them.

Hopefully we can right some of the wrongs and reduce the suffering and, most importantly, educate our fellow physicians to do the same.

—Sanford M. Silverman

Preface

Medicine is a forever changing field. The field of pain management is by some accounts the oldest field of medicine, while others would consider it quite new. Ancient Egyptian Kings are known to have been buried with poppy seeds. The use of controlled substances has waxed and waned over the decades, if not centuries. Prior to the controlled substance act of 1914 patients could freely use opioids for the treatment of a variety of maladies, from exhaustion and rheumatism to the management of pain. Undoubtedly, many patients were effectively treated for their pain using home remedies that included laudanum, or tincture of opium.

Unfortunately, problems with substance abuse did exist that required the passage of the Harrison controlled substance act. Between 1914 and 1970, 50 additional regulations were placed in the controlled substance act of 1970. In the 1970s there was grave concern with regard to opiates, leading to a great national restraint on their use. Nancy Reagan's well-intentioned campaign to stop the use of illicit drugs ("Just Say No") also led to the drive that no patients should receive opiates for the management of non-cancer-related pain.

In the 1980s, the pendulum began to swing back to pro opiates in certain settings. The cancer community noted that patients with cancer were dying with uncontrolled pain that could be potentially effectively managed with opiates, and encouraged the liberalization of their use of opiates. In the 1990s it was noted that patients with non-cancer pain may also benefit from the use of opiates. I heard questions like "Why should I have to get cancer in order to get control of my pain?" Studies were broadly quoted indicating that addiction was exceedingly rare. Prominent pain societies drafted guidelines indicating that it was appropriate to use opiates in certain settings. Physicians were told that the risk of addiction was extremely low in chronic pain patients. Pharmaceutical companies marketed the use of opiates as a means of controlling pain. Literally, hundreds of millions of dollars were spent on marketing to patients and physicians, and billions of dollars in profits were generated by sale of opiates for patients with non-cancer-related pain. However, we were all mistaken in underestimating the potential for abuse and misuse of prescription opioids.

In spite of the enormous costs, chronic pain remains one of the greatest healthcare crises affecting the world today. It costs the American people more than cancer and heart disease combined. The Joint Commission on Hospital Accreditation listed pain as the fifth vital sign. Hospitals are now reimbursed (among other things) on patient satisfaction, which includes the management of pain. Many employed physicians' salaries are also tied to patient satisfaction surveys. Poor pain control would potentially decrease reimbursement to hospitals and group practices. This in turn may have led to overprescribing of controlled substances by well-intentioned physicians who are improperly trained to manage pain. Unfortunately, clear guidelines on the management of pain do not clearly state how to manage the pain, or when to use opioids. In fact, quality evidence is lacking on the use of opioids in chronic non-cancer pain.

The combination of pressures from the government pushing pain control, pharmaceutical companies marketing opiates, the enormous size of the pain problem, and poor understanding of when to use opiates and how to use them safely has led to an explosion of deaths related to the use of prescription controlled substances.

In this text we have asked many world experts to contribute, specifically related to the area they have great expertise in. We hope to provide a balance and a framework for discussion on the appropriate use of opiates. Clearly, some patients require opiates for uncontrolled pain. But how do we do that safely? How do we keep both ourselves and our patients out of trouble? What are the limitations to the use of controlled substances, and what are some reasonable alternatives? We hope that this book and several others frame the discussion and where opiates fit in with pain management. It is our aim to help healthcare providers balance the discussion around appropriate opiate prescription, provide alternative strategies, minimize abuse diversion, addiction, and the unintentional deaths known to be associated with controlled substances.

Peter S. Staats
Sanford M. Silverman

Contents

1 Scope of the Pain Problem 1
Steven Chinn, Karina Gritsenko and Laxmaiah Manchikanti

2 Scope of the Problem: Intersection of Chronic Pain and Addiction 13
Alicia A. Trigeiro, Kenneth L. Kirsh and Steven D. Passik

3 Evidence-Based Treatment for Chronic Pain with Opioids 29
Sean Li and Peter S. Staats

4 Opioid Pharmacology and Pharmacokinetics 45
Andrea M. Trescot

5 Pharmacogenetics 63
Andrea M. Trescot

6 Benzodiazepines, Alcohol, and Stimulant Use in Combination with Opioid Use 75
J. Gregory Hobelmann and Michael R. Clark

7 Marijuana and Cannabinoids for Pain 87
Timothy Furnish and Mark Wallace

8 Adjuvant Agents in Chronic Pain Therapy 111
Joseph V. Pergolizzi

9 Complications of Opioid Therapy 135
Gerald M. Aronoff

10 Risk Mitigation Strategies 163
Lynn R. Webster

11 Naloxone Treatment of Opioid Overdose 181
Sanford M. Silverman and Peter S. Staats

12 From Patient Evaluation to Opioid Overdose Prevention: Ten Steps to Make the Law Work for You and Your Patients 187
Jen Bolen

13 Treating the Difficult Patient 227
Hans Hansen and Judith Holmes

14 Controlled Substance Management: Exit Strategies for the Pain Practitioner 251
Sanford M. Silverman

15 Alternatives to Opiates in the Management of Non-cancer-related Pain 281
Peter S. Staats, Sean Li and Sanford M. Silverman

Appendix A: American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-cancer Pain 297

Appendix B: Sample Opioid Agreement/Informed Consent 299

Appendix C 305

Appendix D 307

Appendix E 309

Appendix F 311

Index 315

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Chapter 1
Scope of the Pain Problem

Steven Chinn, Karina Gritsenko and Laxmaiah Manchikanti

"Pain" is an entity which can mean different things to different people. It is, at the same time, a subjective and objective sensation. For the patient experiencing the pain, it is an unpleasant sensation that causes undue suffering. For the diagnostician, pain is a *symptom* or *sign*, the characteristics of which may help to elucidate where in the body the disease process is taking place. For the surgeon, acute pain at the incision may be an untoward postoperative side effect of performing the surgery; and for the pain medicine physician, pain is a complex multidimensional problem. Therefore, "pain" exists along the full spectrum of a disease process, from diagnosis to treatment. But regardless of its many presentations and etiologies, *pain* has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage," according to the International Association for the Study of Pain [1]. This definition is kept broad, so that it can encompass multiple sources, including (1) actual unpleasant sensory input (i.e., nociception) to pain receptors of the body, (2) but also the modulation of this input within the central and peripheral nervous systems by neurohumoral responses, (3) and the perception of the input by cognitive and psychological responses created by the brain. Just as a small amount of tissue damage may

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"snowball" into a massive response in one patient, it is equally plausible that massive tissue damage may elicit little more than a wince from another patient.

Consequently, chronic pain is a complex and multifactorial phenomenon characterized by persistent and/or long-lasting pain. Chronic pain has been described using multiple definitions, with pain persistent 6 months after an injury, pain beyond the usual course of an acute disease [2], or pain that extends beyond the expected period of healing [3]. A comprehensive definition has been provided by the American Society of Interventional Pain Physicians which defines chronic pain as, "a complex and multifactorial phenomenon with pain that persists 6 months after an acute injury and/or beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal, that is associated with chronic pathologic processes that cause continuous of intermittent pain for months or years that may continue in the presence or absence of demonstrable pathology and may not be amenable to routine pain control methods with healing never occurring [4]."

Determining the prevalence and incidence in the USA and globally has been difficult, because of multiple factors, including the subjective nature of pain and the lack of consensus regarding diagnoses. Difficulty in recalling the first, true "episode" of a recurrent pain condition makes determining incidence difficult, as well as the inability to discern between pain conditions with constant, chronic pain and those states with recurrent, episodic courses. There is a continuum, rather than absolute states [5]. Historically, another hindrance had been the dearth of morbidity data prior to the 1980s. Until then, mortality data had driven research into the general health status of populations, which in turn drove research into more established conditions such as cardiovascular disease and cancer. However, chronic pain conditions such as musculoskeletal disease and lower back pain do not contribute much to mortality trends, and therefore, its trends and statistics have not been trended in the past [6]. Furthermore, the identification of pain conditions has been hampered by ambiguous case definitions and lack of population disease registries or other patient databases for pain statistics [5]. Luckily, there is evidence of increased reporting of chronic pain in the past few decades; this likely represents an increase in self-reported pain, taken from general health surveys and pain-focused studies [6].

Self-reported data from general health surveys provide important information about the frequency of chronic pain and the global burden of disease. According to the WHO World Mental Health Surveys, prevalence of chronic pain is 37 and 41 % for developed and developing countries, respectively [7]. This "composite" percentage falls within the range of other prevalence statistics for individual developed countries such as Denmark, Norway, the Netherlands, Sweden, Israel, and Scotland, with the range being 20–55 % [8]. Using the Population Reference Bureau's world population data from 2013, these prevalence numbers represent approximately 461 million and 2.42 billion people who have chronic pain in developed and developing countries, respectively [9].

The global burden of chronic pain is a very useful metric to measure, because it illustrates the need for the medical community to approach chronic pain from a public health perspective and apply epidemiological techniques to analyze it, just as

with more well-defined diseases such as obesity, diabetes mellitus, and cardiovascular disease. But from a clinical perspective, it serves to characterize chronic pain into more specific divisions and determine the individual prevalence and incidence statistics, because it may have diagnostic and prognostic value. Pain conditions can be stratified along numerous different lines: body site, adult versus pediatric, acute versus chronic, single site versus multisite, nociceptive pain versus neuropathic pain, and cancer versus non-cancer pain.

Among adults, spinal pain is extremely common with a lifetime prevalence of 51–84 % [5, 10]. The 1-year incidence of any lower back pain is reported from 1.5 to 38 % according to some estimates, with recurrence rates at 1 year of 24–80 % [11]. Again, the wide spread of estimates from multiple studies highlights the heterogeneity of authors' definition of "episodic" or "recurrent."

Looking into the pediatric and adolescent population, there have been few longitudinal studies following the trends and risk factors associated with the development of chronic pain. Again, the lack of data stems from a lack of consistency in case definitions for pain conditions, which preclude useful comparisons between different studies. However, in a large epidemiological review of 41 studies since 1991, the authors determined that headache was the most common single pain reported in studies with a 23 % prevalence rate. Back pain, abdominal pain, and musculoskeletal pain were also common. Subject risk factors included female sex, anxiety, depression, and low self-esteem, while environmental risk factors included parental education, mental health status, socioeconomic status, type of residence, and amount of time allowed watching television. From the earliest age through the later adolescent years, they found increasing prevalence for headache, back pain, and musculoskeletal pain, but interestingly, a decrease in recurrent abdominal pain [12]. Other studies have corroborated these rates. In Henschke et al., the 1-month prevalence of chronic lower back pain ranges from 18.0 to 24.0 %, while 1-year incidence rates for lower back pain ranges from 11.8 to 33 %. The 1-month prevalence of headaches and stomachaches are estimated as high as 69 and 49.8 %, respectively [5].

What about cancer pain? There are many similarities between cancer and non-malignant pain. Anatomically, physiologically, and biochemically speaking, there is no difference. The ultimate impact of pain is related to severity, which negatively affects function, but may have no relation to cause. Both cancer and non-cancer chronic pain patients can have comorbid anxiety and depression. But several important aspects differentiate them. Cancer patients will experience cachexia, dyspnea, anorexia, or symptoms resulting from organ dysfunction [13]. Some estimates report 36 % of non-metastatic cancer patients with pain, while 59–67 % of metastatic cancer patients suffer from chronic pain [8].

On the individual level, the consequences of pain can affect multiple facets of a subject's life. For example, poorly treated acute pain following surgical procedures can reduce quality of life, increase recovery time, and increase cost of hospital stays and insurance expenditures. The most feared complication from acute pain is the development of chronic pain; subjects eventually suffer reduced mobility, loss of strength, disturbed sleep patterns, and immune impairment. These effects, again,

reduce the quality of life and functional status even further, causing a downward spiral [14].

On an emotional level, feelings of anxiety, anger, and depression are commonplace. In a vicious cycle, negative emotions can increase the intensity and perception of chronic pain, which then begets more negative emotions. This leads to increased disability, loss of social functioning, and increased isolation. Parents, spouses, and caretakers are unable to fulfill their duties. In fact, 40–50 % of chronic pain patients have a concomitant mood disorder. Anger is also fairly common among chronic pain sufferers. In one study by Okifuji et al., 96 chronic pain patients were surveyed about the frequency and intensity of their anger. 62 % reported anger toward healthcare providers, while interestingly, 74 % of them expressed anger toward themselves, which was significantly associated with depression in a multivariable comparison [15].

A good illustration of the effects of chronic pain on disability is in the older adult and geriatric population. Among older adults, pain is the number one symptom underlying disability, which is the inability to complete basic and instrumental activities of daily living. Again, prevalence rates of chronic pain in the older population have wide distributions depending on the study, but have ranged from 24 to 72 %. In the National Health and Aging Trends Study (NHATS), over 8200 adults beyond the age of 65 were surveyed in regard to their health status; one of the aspects studied was the presence of pain. There was an approximate 52.9 % prevalence of any type of pain. Disability was 70 % more common in persons with pain than those without; and furthermore, this was magnified with subjects who reported multiple sites of pain [16]. Interestingly, this study and other studies have shown that as age increases, there is an increased prevalence of severe back pain, while that of mild severity lower back pain decreased [17].

Taking all of these studies into account, there seems to be several clear messages regarding chronic pain; that musculoskeletal pain, notably back and joint pain, is the dominant single type of chronic pain, but that most people with chronic pain have multiple sites of pain.

Economically speaking, the yearly cost of chronic pain in the United States is estimated to be at least $560–$635 billion per year. However, these data from the Institute of Medicine [14], based on Gaskin and Richard [18], have been shown to be inaccurate [19]. This also showed that approximately 100 million Americans suffer with chronic pain. This study, out of Johns Hopkins [18], defined persons with pain as follows:

- Persons who reported that they experienced pain limiting their ability to work, which is appropriate and includes 43.9 million of the total 100 million being estimated and discussed here with 21.3 million suffering with moderate pain and 22.6 million suffering with severe pain.
- However, the number 2 category is persons who were diagnosed with joint pain or arthritis, which is estimated to be 123.7 million.
- Finally, they also included 24.7 million persons who had a disability that limited their ability to work that had nothing to do with pain.

Consequently, multiple conditions, unrelated to chronic non-cancer pain were not only repeatedly counted, but also included, very costly arthritis and functional disability, which are not related to chronic non-cancer pain. A liberal estimate would be approximately 30 million requiring therapy for chronic non-cancer pain, either with interventional procedures, physical therapy, surgical interventions, or chronic opioid therapy. Two studies by Martin et al. [20, 21], in assessing the effect of chronic spinal pain on the US economy, found that costs were approximately $86 billion, with an increase of 65 % between 1997 and 2005, and a 49 % increase in the number of patients seeking spine-related care. In 2008, federal and state agencies, such as Medicare, Medicaid, and the Department of Veterans Affairs paid out approximately $99 billion in payments related to pain.

With the rising prevalence of chronic pain reaching epidemic proportions, as illustrated previously, the role of treating chronic pain began to take center stage. The public health management of pain reached the forefront of multiple regulatory agencies including the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), the American Pain Society (APS), and the Center for Medicare/Medicaid Services. In 1995, the APS coined the term "pain: the fifth vital sign" and in 1999, JCAHO officially declared pain as "The Fifth Vital Sign," with the hope that monitoring and treating pain became as important as treating and monitoring high blood pressure. However, studies have been equivocal in determining how effective utilizing pain as a vital sign has been in improving the quality of pain management [22]. There have been multiple claims that this aspect in conjunction with multiple other liberalizations strategies has led to escalation of opioid use leading to the epidemic [23]. Nonetheless, this movement has spurred other agencies, such as the Veterans' Health Administration to adopt systematic practices to monitor and reduce pain.

From a treatment standpoint, there are different goals for each group. Rehabilitation and restoration are primary goals for non-cancer chronic pain, while relief and balance of side effects are goals for cancer patients. A cancer pain management plan will have more psychosocial support and increased polypharmacy. A more "liberal" use of opioids is acceptable in the cancer pain management arena, without addiction being a major issue. Why is it acceptable to give sedative doses of opioid medication to cancer patients? Yet, fear of addiction to opioids and other analgesics represents a huge barrier to treatment for non-malignant chronic pain patients; even if it may be warranted. In reality, the treatment of cancer versus non-cancer pain is along a continuum, utilizing the same medications in different dosages and for different indications [13]. Without a doubt, opioid medication prescribed by all physicians, not just pain medicine physicians, represents a major player in the armamentarium for pain of all types: acute, chronic, and cancer-related. Utilizing opioids for extended use in a chronic pain regimen represents a slippery slope with many potential benefits and risks inherent to the nature of opioids' mechanisms of action.

Clearly, this chapter is not meant as a review of the anatomy, physiology, and biochemistry of somatosensory or pain processing, but to fully understand pain as a disease, we must have a firm grasp of all these aforementioned principles and structures.

Somatosensation is a process where physical stimuli activate neural substrates leading to the perception of touch, pressure, and pain. Nociception is the process of activating receptors and neural loops by physical stimuli that may actually damage tissue. In contrast, the sensation of pain is a conscious response, which results from the addition of potential psychosocial factors to afferent neural activation. In turn, pain can lead to suffering, which takes into account a multitude of other considerations, including social isolation, disability, and comorbid mood disorders [24].

The recognition of stimuli as painful can be summarized in four stages: transduction, transmission, modulation, and perception. Transduction represents the conversion of physical "energy," in the form of heat or mechanical, to specific patterns of electrical energy at the terminus of an afferent neural pathway. Pain receptors represent the *vehicle* for this conversion. Next, transmission represents the conduction of the action potentials throughout the peripheral and central nervous systems. Usually, this course involves three orders of neurons. Dorsal root ganglion (DRG) cells transmit action potentials to the spinal neurons, which ascend the spinal cord in established tracts and pathways in order to transmit the electrical activity to the thalamus and brainstem nuclei. Lastly, neurons originating in the brainstem transmit the impulses to the somatosensory cortical areas. The third stage involves modulation of stimulus transmission anywhere along its path. The dorsal horn of the spinal cord is a major site, where weakening or enhancement of the pain signal occurs. The final stage represents cognition and the subjective sensation of pain, processed by the somatosensory cortical areas [24].

Where do opioids exert their effects? Opiates and opioid peptides exert their effects via a family of receptors. In the 1960s, clinical studies looking at the effects of nalorphine and morphine led to the discovery of distinct receptors and the classification of mu and delta opioid receptors. Delta opioid receptors are selective for enkephalins, which are endogenous opioid pentapeptides. Activation of delta receptors results in anxiolysis and analgesia, but not respiratory depression, as with the other types. Mu receptors have high selectivity for morphine and its related synthetic compounds. Furthermore, subtypes of the mu receptor, specifically mu_1 and mu_2, differentiate the analgesic effects of opiates and their major side effects, respiratory depression, and constipation. Kappa receptor activity results in modest analgesia, dysphoria, disorientation, miosis, and mild respiratory depression. Endogenous dynorphins show preferential affinity for kappa receptors [13, 25]. These receptors are located throughout the peripheral and central nervous systems. They can be found at nerve terminals, within the dorsal horn of the spinal cord. Immune cells may even produce endogenous opioids and possess opioid receptors themselves; this may explain the concept of stress-induced analgesia. Clinical applications include peripheral use of opioids in wounds and inflammatory conditions [26].

Within the spinal cord, opioid receptors are located mostly within lamina I and II; mu receptors account for over 70 %, followed by delta (24 %) and kappa receptors (6 %). Supraspinally, mu receptors are found within the amygdala, nucleus accumbens, thalamus, and limbic structures. Here, opioids modulate the

emotional components of pain. Within the brainstem, high densities of mu receptors exist in the periaqueductal gray matter, locus coeruleus, and rostral ventromedial medulla. These structures orchestrate a descending modulatory system that inhibits dorsal horn pain signaling [13].

What is the history of opioid use? What is their historical reference and has their role been in modern Western medicine? Opium, a natural extract from the leaves and fruits of the *Papver somniferum* plant go all the back to third century B.C. in ancient Greece. It has also been described in use during the Middle Ages throughout Europe. The large-scale trade of opium into Europe and the Orient follows a course originating in the Middle East. The British traded opium for tea from China. When the Chinese realized the addictive properties of opium, they attempted to halt the trade, resulting in the Opium Wars of the 1840s. Ultimately, the British won and was ceded Hong Kong. The opium trade was legalized and eventually brought into the USA via Chinese laborers [25, 27].

Morphine was isolated from opium in 1804 for use as an analgesic by Friedrich Serturner, named after Morpheus, the God of Dreams, from Greek mythology. Codeine was isolated from opium in 1832 by Robiquet and used as an all-purpose tonic for multiple ailments and problems; and heroin was developed by the Bayer Company in 1898 as a cough suppressant [27].

"Opiates," including morphine and codeine, refer to any natural or semisynthetic derivative of opium with morphine-like effects. However, the term "opioid" has been used to define all drugs contain that morphine-like qualities and bind to opioid receptors, whether they are natural, semisynthetic, or synthetic. The term also includes the endogenous opioid peptides found in the body, such as enkephalins, dynorphins, and endorphins.

The World Health Organization issued its well-known 3-step "analgesic ladder" in 1986, to be used as guidelines for the treatment of cancer pain. Taking a significant role in this ladder are opioid medications. Step 1 involves the use of non-opioid medications, such as acetaminophen and nonsteroidal anti-inflammatory medications to treat mild pain. Subsequently, step 2 adds a "weak" opioid, such as codeine or oxycodone, to the regimen for treating moderate pain. Finally, step 3 involves adding a "strong" opioid, such as morphine or hydromorphone for severe pain. In all 3 steps, the WHO also advocates for the possible inclusion of other adjuvant therapies, which may include corticosteroids, anti-epileptics, tricyclic antidepressants, and neuroleptic medications [25]. Though it was created specifically for the management of cancer pain, the WHO analgesic ladder has found significant applicability to other types of pain, namely acute pain and chronic non-cancer pain. Proposed modifications have been made to reflect advancements since 1986, including newer opioid agents and new treatment modalities (i.e., neuromodulation), to keep the ladder valid; but the essence of the original ladder remains [28]. Opioids are part of an established armamentarium for the treatment of cancer pain and chronic non-cancer pain.

The WHO analgesic ladder represents a set of guidelines, but not a "one-size-fits-all" set of rules. The extent to which chronic pain responds to opioid analgesics varies depending on patient characteristics and the etiology of the pain.

The patient receiving opioids for chronic pain must be monitored closely, in order that dosages can be titrated quickly and appropriately to address the pain. If the patient presents with severe enough pain levels, then starting at step 2 or step 3 may be warranted.

The anatomy of pain processing and neurochemistry of opioid action was briefly illustrated previously, but how does the binding of an opioid to its receptor translate into its behavioral mechanism of action? Each type of opioid has different behavioral effects that relieve pain and suffering. Opioids also relieve emotional pain, which make them one of the classic drugs of addiction, because of their actions in lessening the threatening effects of rage and aggression [29].

Non-medical use of opioids has been described in 3 modes: controlled users, marginal abusers, and compulsive users with addiction predilections. Controlled users limit their use of the drug to amounts that do not interfere with social functioning; their pattern of use would not be defined as addictive. At the other end of this spectrum, compulsive users may exhibit the classic signs and symptoms of addiction, including withdrawal and craving. They will likely meet the criteria for substance use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Marginal users exhibit behavior somewhere in between that of controlled users ad compulsive users [29].

What is addiction? According to the previous edition of the DSM, the DSM-IV, addiction encompassed two separate, but related constructs, drug *abuse* and drug *dependence*. The DSM-IV actually avoids the use of the term *addiction* because of its negative connotations. The meet the criteria for addiction, a patient must have had to manifest at least 3 of the 7 criteria for "dependence" and at least 1 of the 4 listed criteria for "abuse," both within a 12-month period. However, this choice of semantics has created confusion among clinicians, because of dual use of the term *dependence* to refer to both the physiological sequelae and compulsive behavior aspects, when in fact, these two are separate entities [30]. The DSM-5, which was published in 2013, merges the concepts of "abuse" and "dependence" into a general continuum of "substance use disorders." The new definition for addiction now requires meeting at least 2 of the newly categorized 11 criteria on the "substance use disorder" scale.

As pertains to the addiction cycle, opioid addiction can remain remarkably stable over decades, despite repeated cycles of remission and resumption of use. A prior longitudinal study of heroin addicts in an addiction treatment program followed 581 users over the course of 33 years from 1962 through 1997. During 1995 through 1997, 21 % of subjects tested positive for heroin, while another cumulative 24 % either refused testing or were incarcerated [31].

According to the National Survey on Drug Use and Health (NSDUH) from 2012, enough opioids were prescribed to medicate every American every 4 h for an entire year. Approximately 23.9 million subjects, aged 12 years or older, were current illicit drug users, representing 9.2 % of the US population in that year. In 2001–2002, the 12-month and lifetime prevalence rates of an opioid-use disorder were 0.4 and 1.4 %, respectively [30].

Opioid intoxication for an addicted individual has been described in 4 stages: "rush," "nod," "high," and "being straight." The "rush" describes a short period of intense pleasure and euphoria, which is resistant to tolerance. Next, the "nod" represents a detached state of consciousness, when subjects are detached and calm. Third, the "high" is a general feeling of well-being that may last several hours; but this state is vulnerable to tolerance. Lastly, "being straight" represents the time until withdrawal symptoms appear [27].

Opioid withdrawal syndrome consists of a constellation of symptoms and signs, including yawning, lacrimation, rhinorrhea, perspiration, pupillary dilation, tremors, restlessness, insomnia, weight loss, elevated blood pressure and tachycardia, just to name a few. Piloerection, or "goose bumps" are common, and interestingly, is the origin of the term "quitting cold turkey." Accompanying these somatic and autonomic changes is a characteristic negative emotional state with depressive-like symptoms. Purposeful symptoms, such as craving, pleading, and complaining, start to appear; these actions are goal-oriented toward obtaining more opioid medication. As far as a time course for withdrawal is concerned, purposeful behavior begins 6–8 h after the last dose of heroin, peaking at 36–72 h. The aforementioned autonomic signs also appear 8–12 h after the last dose, peaking at 72 h. The physical withdrawal syndrome can carry on for 7–10 days further, which then marks the end of the acute withdrawal syndrome. The time course for methadone is somewhat longer, while the time course for meperidine withdrawal is significantly shorter. Generally, shorter acting drugs produce a withdrawal syndrome that is shorter onset and of shorter duration.

Lastly, tolerance can be defined as a "state of adaption in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time," according to Freye and Levy [25]. Tolerance to opioids develops to the analgesic, euphorogenic, and depressant effects, although certain autonomic effects, such as constipation or miosis, may be resistant to tolerance. Tolerance develops from pharmacodynamic changes that are neuroadaptive in nature. There are extensive mechanisms for tolerance, involving changes in the receptors, transduction systems, and neuroplasticity. Desensitization of opioid receptor activity and internalization of receptors occurs [13].

Opioid-induced hyperalgesia has been observed in previously addicted opioid users. They display a heightened sensitivity toward pain for up to 6 months after they begin their abstinence. This pain leads to recurrent craving, leading to more relapses to addiction. Therefore, poor pain tolerance may be a significant risk factor for opioid addiction. What are some other risk factors? Genetic factors certainly play a significant role in predisposing certain individuals toward addiction to opioids; they may have increased pain sensitivity because of up-regulation nociception or down-regulated inhibitory modulation pathways. Environmental factors allowing for the subject to gain access to the drugs are another important risk factors. Personality plays a huge role in addiction; risk takers and "adrenaline junkies" may be more apt to experiment with opioids thinking they have enough self-control to stop whenever they simply choose to. However, once they get on the slippery slope

of "controlled" drug use, momentum might carry them into addiction. "Allosteric load" is another theoretical construct that may explain how childhood experiences predispose an individual toward drug abuse. People who have had to adapt to multiple stresses during childhood, such as those who are poor, uneducated, or are abused, have exhausted their coping mechanisms by adulthood. This leads to increased overall morbidity, including painful conditions such as arthritis, musculoskeletal disease, and angina [14].

Despite all of these dangers and pitfalls of prescribing opioids for chronic pain, they still remain one of the most commonly prescribed analgesic medications, with enough opioids prescribed in 2012 to medicate every American every 4 h. So, they represent a double-edged sword for chronic pain patients and their healthcare providers. As detailed in the Institute of Medicine's blueprint for relieving pain in America, they declared the overall effectiveness of opioids as analgesic medication was found to be, surprisingly, inconclusive [14]. The report cites a meta-analysis looking at short-term opioid use in older adults; there were reductions in pain intensity and improvements in functioning, but decreased mental health. In another meta-analysis, looking at studies treating non-cancer pain in over 6000 patients, "weak" opioids were found to be equivalent to other drugs in relieving pain. Only "strong" opioids were outperformed the two other groups [32].

At the same time, chronic pain patients and healthcare providers should not fall prey to the multitude of misconceptions and myths surrounding the utilization of opioids, which is that they always lead to significant cognitive impairment; that doses require continual escalation; and most prominently, that a person in pain must be "drug seeking" if the "standard" dosage of a opioid they are receiving is not enough to control the pain [25]. As all the evidence seems to point toward, pain is not only a symptom that is just linearly associated with the severity of some underlying disease. Chronic pain has multiple components including the physical, cognitive, and the emotional, which make it much more complex than any one simple number on a numerical rating scale can adequately describe. Pain truly is a "condition in itself."

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Chapter 2
Scope of the Problem: Intersection of Chronic Pain and Addiction

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Introduction

The prevailing medical and societal view of opioids is a pendulum, swinging between opiophobia and opiophilia. Like this image, the intersection between pain and addiction is a moving target. Various stakeholders have attempted to find a balance between addressing the crisis of chronic pain in society, while not exacerbating the problem of substance abuse. We need to balance the benefits and harms of opioids and other controlled substances with the risks of addiction.

Over the past 15–20 years, there has been a call to re-evaluate the role of opioids in the management of chronic, non-cancer pain. This has led to a dramatic expansion in legitimate prescribing of opiates. The rhetoric that accompanied this expansion tended to overstate the benefits and trivialize the risks of improving access to prescription opioids. As a result of improved availability, prescription drug abuse has been amplified. This appropriate concern makes physicians and caregivers much more cautious about opioid prescribing. The pendulum thus appears to be swinging from opiophilia back to opiophobia.

Physicians are concerned that opioids have long-term limited efficacy, that hyperalgesia may occur for those taking long-term opioids, and that addiction and abuse are real concerns that physicians need to be concerned with. On the other

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hand, some practitioners believe that these drugs, like many other classes of drugs, have benefits as well as risks. To derive the benefits and contain the risks takes time, expertise, assessment and reassessment, along with open, honest and detailed doctor–patient communication. Opioids cannot be used in a one-size-fits-all fashion. Patients who are treated with opioids need to be adequately assessed and triaged to the appropriate level of care. Significant time and decision making are required to safely prescribe opiates.

There is a general agreement that opioids are only first-line in certain situations (postoperative; severe acute; end-of-life care). However, the risk–benefit ratio is relatively low for an older person with arthritis or other medical comorbidities that contraindicate the use of nonsteroidal anti-inflammatory drugs. It is reasonable to prescribe opioids in some settings, as long as coordinated and monitored care is provided.

While opioid medications do have potential abuse, the risk of addiction shows significant patient variability. This depends upon the patient's history of addiction, psychiatric comorbidities, environmental stressors, and the way in which opioid therapy is delivered (with or without the appropriate level of safeguards for their level of risk). The epidemic of prescription drug abuse is not simply the result of the drugs being "powerful and highly addictive" but is also related to a failure to assess risk, match the use of appropriate safeguards, and then employ the safeguards and monitor the patients in a manner necessary to ensure safety. When a high-risk patient is treated as if they have a low risk, this can lead to abuse diversion or addiction.

There are several risk factors for addiction delineated below:

The agent must be

- Readily available;
- Relatively low cost;
- Rapidly enter the CNS;
- Demonstrate efficacy as a rewarding agent.

Environment must be

- Occupation;
- Peer group;
- Culture;
- Social instability.

Host must be

- Genetic predisposition;
- Familial problems;
- Coexisting psychiatric disorder.

Opioid pain therapy means there will be such an exposure. Identifying the latter two issues requires time and assessment.

People with pain are almost inevitably evaluated at a vulnerable time. Frequently a person with chronic pain begins medical treatment after a prolonged period of

time, and the pain may be considered chronic in nature (6–12 months). During this time, they start to relinquish pleasurable activities, restorative sleep is disrupted, libido is reduced, depression develops, they cannot work, and there may be financial stressors.

If there is an exposure at a vulnerable time and the person has any of the known vulnerabilities—younger age (85 % of the addictions in the world are manifested by the age of 35, so an exposure in a young person is results in greater risk than in an older person), male gender, personal or family history of addiction, current psychiatric problems such as major depression, post-traumatic stress disorder (PTSD), panic disorder etc., history of sexual trauma, and a history of smoking. When these vulnerabilities are unassessed or unaccounted for in the context of an opioid exposure, this may lead to problematic behavior. However, when appropriate safeguards are instituted, these treatments can be successful. There are settings in which monitoring can be less frequent or intense. For example, the older person with arthritis, no personal or family history of addiction, and no current psychological problems (and not surrounded by friends, family members, or others who might "borrow" some of their medicines) can probably be seen monthly and manage a 30-day supply of opioids without problem. On the other hand, a traumatized, 27-year-old coal miner in southeastern Kentucky with a history of PTSD, depression, marijuana use, and cigarette smoking will be more complicated. He may need treatment for his psychological problems, an alteration in the medical regimen (our team might well have used a long-acting opioid such as a 24-h, once-per-day morphine preparation doled out in small supplies, such as 7 tablets, and see the person weekly), and the provision of tools to help in coping. He will need tools to safeguard his medication supply, and we may also choose to employ certain longer-acting medications, perhaps even one that has an abuse deterrent formulation to deter crushing or altering the formulation so as to help deter misuse. A 30-day supply of short-acting opioids (possibly 120–240 tablets) prescribed to this man without safeguards and monitoring is likely to be problematic.

Key Definitions

Unfortunately, the intersection of pain and addiction is clouded by several overlapping, poorly defined terms and phenomenologically difficult to separate concepts. Thus, we start with a definition of terms.

Addiction

Addiction is a relapsing brain disease characterized by compulsive and overwhelming involvement with the use of a drug, despite harmful consequences [1]. It begins with a voluntary decision to use a drug; however, control over usage

decreases radically over time due to recurrent drug use. The behavioral pattern of substance abuse is generally thought to be chronic, and recovery is possible but is a lifelong process. The transition from voluntary user to addict happens through changes to the structure or wiring of the brain from repeated drug exposure. An individual who continues to use the drug despite physical, psychological, and social harm is considered to have an addiction problem. Addiction implies loss of control and is often confused with physical dependence, which is actually a different phenomenon [2].

If a physician believes that their patient is suffering from addiction, they should evaluate the 4 Cs—compulsive use, continued use despite harm, loss of control, and cravings. These must be assessed as part of an evaluation of addiction.

Physical Dependence

Physical dependence is characterized by the manifestation of physical withdrawal symptoms when a drug is discontinued or the dose is reduced. It can also lead to pseudo-addictive behaviors when a patient requires a drug in order to function normally [3]. Behaviors such as aggressively complaining about the need for higher doses or occasional unilateral drug escalations, which appear to be addicted on the surface, may be indications that the patient's pain is not well managed [4].

Tolerance and physical dependence on a drug can develop for both pain relief and the euphoric effects of a drug and can be produced by psychological and pharmacological factors. Withdrawal symptoms, such as sweating, anxiety, and insomnia, can occur when a patient has developed dependence on an opioid, and the drug is discontinued. It is thought to be caused by rebound at the central adrenergic nuclei [5]. Withdrawal symptoms can lead patients to seek opioids from both legitimate and illegitimate sources. While the current DSM-5 excludes tolerance and withdrawal from the diagnostic criteria for substance-use disorder during medical drug treatment, it should be noted that pain patients who are treated continuously with opioids may not manifest any aberrant behaviors.

A law in the state of Washington came into effect in 2012 that attempts to limit the amount of opioids that can be prescribed for those with chronic pain without consultation from an expert. This law was passed in response to high death rates from prescription opioid overdoses in the state. In some cases, some physicians began to taper patients who were using high-dose opioids who had for years. Several patients experienced reemergence of anhedonia and severe pain, both of which were likely to be effects of withdrawal. In this setting, tapering patients' high opioid doses may have destabilized them, leaving them with constant cravings and aberrant behavior [5].

Many clinicians confuse physical dependence with addiction. Physical dependence has been suggested to be a component of addiction, and it has been proposed that patients who seek to avoid withdrawal symptoms construct behaviors that reinforce drug-seeking behavior. However, these assumptions are not supported by

experience acquired during opioid therapy for chronic pain. Animal models have provided indirect evidence for a fundamental distinction between physical dependence and addiction through opioid self-administration. This demonstrates that in the absence of physical dependence, drug-taking behavior is allowed to persist. However, clinical observation also fails to support the conclusions that analgesic tolerance plays a significant part in the development of addiction [2].

Tolerance

Tolerance occurs when an individual becomes habituated to a drug and needs the dose increased to maintain the same effect as an earlier dose. There has been a long-standing basic definition of tolerance as a pharmacologic property highlighted by the need for increasing doses to maintain effects. Tolerance and physical dependence are both common occurrences among patients taking opioids for chronic pain and are unrelated to true addiction [1].

The widely accepted 2001 definition by the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine makes it clear that such a definition is too narrow. Their consensus document states that tolerance "is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time" [6]. Opioids are usually begun at a low dose in order to minimize side effects, and are increased as tolerance develops to the side effects. Early upward dosing is therefore expected. In addition, pain relief is often accompanied by an increase in physical activity, and the increased activity in itself often requires additional medication to provide adequate pain relief. This in itself can explain why early dose escalation is so frequently found. Delayed dose escalation may also herald the appearance of a progressive painful lesion or the development of new pains. In the absence of tolerance, the greatest need for opioid titration occurs during the first 3 months for most patients, and thereafter, further dose escalation may be gradual and minimal unless a mitigating event like disease progression or new injury occurs [2].

Withdrawal

Withdrawal symptoms occur due to the cessation or decrease in the amount of drug that an individual has been taking. The individual must first have developed a physical dependence to the drug in order to experience withdrawal symptoms. Withdrawal symptoms such as nausea, muscle aches, diarrhea, and insomnia can develop within minutes to several days after the reduction in opioid use that had previously been heavy or prolonged [7].

Opioid-Induced Hyperalgesia

Opioid-induced hyperalgesia (OIH) has been suggested as an explanation for the decreased analgesic efficacy of opioids in some patients requiring high doses. Chronic opioid use may increase sensitivity to specific pain stimuli but not others and does not produce allodynia [2]. It has been shown that opioids can cause nociceptive sensitization, can aggravate existing pain, or potentially cause new pains [8, 9]. The mechanisms and signal transduction pathways that mediate OIH are very similar to those of neuropathic pain and opioid tolerance. Hyperalgesia should be considered when patients have unexplained pain that is unassociated with the original pain or increasing levels of pain when their dosage of opioids has also increased. Treatment of hyperalgesia generally includes reducing the opioid dosage or utilizing NMDA receptor antagonists [9, 10].

While hyperalgesia clearly exists in animal models, there is inconsistent evidence to support or refute the existence of opioid-induced hyperalgesia in humans in clinical settings. However, animal models have limitations for accurately predicting human opioid pharmacology [11]. There is significant evidence in the animal literature to suggest that rodents exposed to very low doses of opioids showed signs of hyperalgesia, whereas those exposed to larger doses resulted in a reduction in sensitivity to painful stimuli. There are no animal studies, however, that examine hyperalgesia in chronic pain, so one should be careful in attributing increased sensitivity to pain to hyperalgesia since the evidence supporting it is somewhat thin [12].

Hyperalgesia, or at least decreased opioid effectiveness, also might be explained by low testosterone (hypogonadism) caused by long-term opioid use. Passik and colleagues [13] have recently shown that low testosterone lowers the pain threshold and triggers decreased pain tolerance in men undergoing androgen ablation. Perhaps treating these patients with hormone replacement therapy could help treat their pain sensitivity and restore efficacy of their regimen in the absence of opioid dose escalation or taper. Certain types of people also could be predisposed to this problem as well, such as those with a personal or family history of addiction [14].

Chemical Coping

Chemical copers occasionally use their medications in non-prescribed ways to cope with stress. A major hallmark of chemical coping is the fixation on the procurement of drugs for pain and the inflexibility about non-drug components of care. Medication use becomes central to life, while other interests become less important, and as a result, chemical copers in treatment often fail to move forward toward stated psychosocial goals. They are typically uninterested in treating pain or coping with pain non-pharmacologically. It should be noted, however, that while all addicts are chemical copers, not all chemical copers have addiction disorders.