Controlled Substance Management in Chronic Pain

A Balanced Approach

Peter S. Staats
Sanford M. Silverman
Editors

Springer

Controlled Substance Management in Chronic Pain

Peter S. Staats · Sanford M. Silverman
Editors

Controlled Substance Management in Chronic Pain

A Balanced Approach

Springer

Editors
Peter S. Staats
American Society of Interventional Pain Physicians
Johns Hopkins University
Baltimore, MD
USA

and

Department of Anesthesiology and Critical Care
Premier Pain Centers
Shrewsbury, NJ
USA

and

Department of Oncology
Premier Pain Centers
Shrewsbury, NJ
USA

Sanford M. Silverman
Comprehensive Pain Medicine
Pompano Beach, FL
USA

and

Department of Integrated Medical Science
Charles E. Schmidt College of Medicine, Florida Atlantic University
Boca Raton, FL
USA

and

Department of Surgery
Boca Raton Regional Hospital
Boca Raton, FL
USA

and

Department of Surgery
Broward North Medical Center
Pompano Beach, FL
USA

ISBN 978-3-319-30962-0 ISBN 978-3-319-30964-4 (eBook)
DOI 10.1007/978-3-319-30964-4

Library of Congress Control Number: 2016934191

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

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

Contributors

Gerald M. Aronoff Department of Pain Medicine, Carolina Pain Associates, PA, Charlotte, NC, USA

Jen Bolen The Legal Side of Pain, Lenoir City, TN, USA

Steven Chinn Department of Anesthesiology, Montefiore Medical Center, Bronx, NY, USA

Michael R. Clark Department of Psychiatry and Behavioral Sciences, Johns Hopkins Medicine, Baltimore, MD, USA

Timothy Furnish Department of Anesthesiology, UC San Diego Medical Center, San Diego, CA, USA

J. Gregory Hobelmann Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA

Karina Gritsenko Department of Anesthesiology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

Hans Hansen Pain Relief Centers, Conover, NC, USA

Judith Holmes The Compliance Clinic, LLC, Golden, CO, USA

Kenneth L. Kirsh Clinical Research and Advocacy, Millennium Health, San Diego, CA, USA

Sean Li Premier Pain Centers, LLC, Shrewsbury, NJ, USA

Laxmaiah Manchikanti Anesthesiology and Perioperative Medicine, University of Louisville, Paducah, Louisville, KY, USA

Steven D. Passik Clinical Research and Advocacy, Millennium Health, San Diego, CA, USA

Joseph V. Pergolizzi Department of Medicine, Johns Hopkins University School of Medicine, Bonita Springs, FL, USA

Sanford M. Silverman Department of Integrated Medical Science, Clinical Biomedical Science, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA; Comprehensive Pain Medicine, Pompano Beach, FL, USA; Department of Surgery, Boca Raton Regional Hospital, Broward North Medical Center, Pompano Beach, FL, USA

Peter S. Staats Department of Anesthesiology and Critical Care, Department of Oncology, Johns Hopkins University, Baltimore, MD, USA; President, American Society of Interventional Pain Physicians, Paducah, KY, USA; Department of Anesthesiology and Critical Care, Department of Oncology, Premier Pain Centers, Johns Hopkins University, Shrewsbury, NJ, USA

Andrea M. Trescot Pain and Headache Center, Wasilla, AK, USA

Alicia A. Trigeiro Clinical Research Associate, Millennium Health, San Diego, CA, USA

Mark Wallace Department of Anesthesiology, University of California San Diego, La Jolla, CA, USA

Lynn R. Webster Early Development Services, PRA Health Sciences, Salt Lake City, UT, USA

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

S. Chinn
Department of Anesthesiology, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467, USA
e-mail: schinn@montefiore.org

K. Gritsenko (✉)
Department of Anesthesiology, Montefiore Medical Center, Albert Einstein College of Medicine, Montefiore Pain Center, 3400 Bainbridge Ave, LL400, Bronx, NY 10467, USA
e-mail: karina.gritsenko@gmail.com

L. Manchikanti
Anesthesiology and Perioperative Medicine, University of Louisville, 2831 Lone Oak Road, Paducah, Louisville, KY 42003, USA
e-mail: drlm@thepainmd.com

P.S. Staats and S.M. Silverman (eds.), *Controlled Substance Management in Chronic Pain*, DOI 10.1007/978-3-319-30964-4_1

"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."

References

1. Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definition of pain terms. 2nd ed. Seattle: IASP Press; 1994.
2. Bonica JJ. Definitions and taxonomy of pain. In: Bonica JJ, Loesser JD, Chapman CR, et al., editors. The management of pain. 2nd ed. Philadelphia: Lea & Febiger; 1990. p. 18–27.
3. Turk DC, Okifuji A. Pain terms and taxonomies. In: Loesser JD, Butler SH, Chapman CR, Turk DC, editors. Bonica's management of pain. 3rd ed. Baltimore: Lippincott Williams & Wilkin; 2001. p. 18–25.
4. Manchikanti L, Abdi S, Atluri S, Benyamin RM, Boswell MV, Buenaventura RM, Bryce DA, Burks PA, Caraway DL, Calodney AK, Cash KA, Christo PJ, Cohen SP, Colson J, Conn A, Cordner HJ, Coubarous S, Datta S, Deer TR, Diwan SA, Falco FJE, Fellows B, Geffert SC, Grider JS, Gupta S, Hameed H, Hameed M, Hansen H, Helm S II, Janata JW, Justiz R, Kaye AD, Lee M, Manchikanti KN, McManus CD, Onyewu O, Parr AT, Patel VB, Racz GB,

Sehgal N, Sharma M, Simopoulos TT, Singh V, Smith HS, Snook LT, Swicegood J, Vallejo R, Ward SP, Wargo BW, Zhu J, Hirsch JA. An update of comprehensive evidence-based guidelines for interventional techniques of chronic spinal pain: part II: guidance and recommendations. Pain Physician. 2013;16:S49–283.
5. Henschke N, Kamper SJ, Maher CG. The epidemiology and economics consequences of pain. Mayo Clin Proc. 2015;90(1):139–47.
6. Blyth FM, van der Windt D, Croft P. The global occurrence of chronic pain: an introduction. In: Croft P, Blyth FM, van der Windt D, editors. Chronic pain epidemiology: from aetiology to public health. Oxford: Oxford University Press; 2010. p. 1–14.
7. Tsang A, Von Korff M, Lee S, Alonso J, Karan E, Angermeyer MC, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. J Pain. 2008;9:883–91.
8. Blyth FM, van der Windt D, Croft P. Introduction to chronic pain as a public health problem. In: Croft P, Blyth FM, van der Windt D, editors. Chronic pain epidemiology: from aetiology to public health. Oxford: Oxford University Press; 2010. p. 279–87.
9. Population Reference Bureau: 2013 World Population Data Sheet. http://www.prb.org/pdf13/2013-population-data-sheet_eng.pdf (2013). Accessed 15 Apr 2015.
10. McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. Best Pract Res Clin Rheumatol. 2007;21:403–25.
11. Hoy D, Brook P, Blyth FM, Buchbinder R. The epidemiology of loew back pain. Best Pract Res Clin Rheumatol. 2010;24:769–81.
12. King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, MacDonald AJ. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. Pain. 2011;152:2729–38.
13. Davis M, Glare P, Hardy J. Opioids in cancer pain. 1st ed. Oxford: Oxford University Press; 2005.
14. Institute of Medicine (IOM). Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: The National Academies Press; 2011.
15. Okifuji A, Turk DC, Curran SL. Anger in chronic pain: investigation of anger targets and intensity. J Psychosom Res. 1999;47(1):1–12.
16. Patel KV, et al. Prevalence and impact of pain among older adults in the United States: findings from the 2011 national health and aging trends study. Pain. 2013;154:2649–57.
17. Dionne CE, Dunn KM, Croft PR. Does back pain prevalence really decrease with increasing age? A systematic review. Age Aging. 2007;35:229–34.
18. Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain. 2012;13:715–24.
19. Manchikanti L, Candido KD, Singh V, Gharibo CG, Boswell MV, Benyamin RM, Falco FJE, Grider JS, Diwan S, Staats PS, Hirsch JA. Epidural steroid warning controversy still dogging FDA. Pain Physician. 2014;17:E451–74.
20. Martin BI, Deyo RA, Mirza SK, Turner JA, Comstock BA, Hollingworth W, Sullivan SD. Expenditures and health status among adults with back and neck problems. JAMA. 2008; 299: 656–64. (Erratum in: JAMA. 2008; 299: 2630).
21. Martin BI, Turner JA, Mirza SK, Lee MJ, Comstock BA, Deyo RA. Trends in health care expenditures, utilization, and health status among US adults with spine problems, 1997–2006. Spine. 2009;34:2077–84.
22. Walid MS, Donahue SN, Darmohray DM, Hyer LA, Robinson JS Jr. The fifth vital sign—what does it mean? Pain Practice. 2008;8:417–22.
23. Manchikanti L, Atluri S, Hansen H, Benyamin RM, Falco FJE, Helm S II, Kaye AD, Hirsch JA. Opioids in chronic noncancer pain: have we reached a boiling point yet? Pain Physician. 2014;17:E1–10.
24. Raja SN, Hoot MR, Dougherty PM. Anatomy and physiology of somatosensory and pain processing. In: Benzon HT, Raja SN, Molly RE, Liu SS, Fishman SM, editors. Essentials of pain medicine. 3rd ed. Philadelphia: Elsevier; 2011. p. 1–7.

25. Freye E, Levy JV. Opioids in medicine: a comprehensive review on the mode of action and the use of analgesics in different clinical pain states. 1st ed. Netherlands: Springer; 2008.
26. Stein C, Schafer M, Hansen AHS. Peripheral opioids receptors. Ann Med. 1995;27:219–21.
27. Koob GF. Opioids. In: Koob GF, Arends MA, Moal ML, editors. Drugs, addiction, and the brain. Amsterdam: Elsevier; 2014. p. 133–71.
28. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty four years of experience. Can Fam Physician. 2010;56:514–7.
29. Koob GF. What is Addiction? In: Koob GF, Arends MA, Moal ML, editors. Drugs, addiction, and the brain. Amsterdam: Elsevier; 2014. p. 1–27.
30. Sdrulla AD, Chen G, Mauer K. Definition and demographics of addiction. In: Kaye AD, Vadivelu N, Urman RD, editors. Substance abuse. New York: Springer Science and Business; 2015. p. 1–15.
31. Hser YI, Hoffman V, Grella CE, Anglin MD. A 33-year follow-up of narcotic addicts. Arch Gen Psychiatry. 2001;58:503–8.
32. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic non-cancer pain: a meta-analysis of effectiveness and side effects. CMAJ. 2006;174:1589–94.

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

Alicia A. Trigeiro, Kenneth L. Kirsh and Steven D. Passik

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

A.A. Trigeiro
Clinical Research Associate, Millennium Health,
16981 via Tazon, San Diego, CA 92127, USA
e-mail: alicia.trigeiro@millenniumhealth.com

K.L. Kirsh · S.D. Passik (✉)
Clinical Research and Advocacy, Millennium Health,
16981 via Tazon, San Diego, CA 92127, USA
e-mail: steven.passik@millenniumhealth.com

K.L. Kirsh
e-mail: Kenneth.kirsh@millenniumhealth.com

P.S. Staats and S.M. Silverman (eds.), *Controlled Substance Management in Chronic Pain*, DOI 10.1007/978-3-319-30964-4_2