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Editors

Deer's Treatment of Pain

An Illustrated Guide for Practitioners

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This book is possible due to the support and love of my wife Missy, who has been by my side for many wonderful years. I also dedicate this book to God, who has blessed me through grace well beyond my greatest expectations. I also thank my children, Morgan, Taylor, Reed, and Bailie, for inspiring me in so many ways. Lastly, to our patients, I am eternally grateful for your trust and am hopeful that my work will impact your life in a way that is meaningful.

Timothy R. Deer, MD, DABPM, FIPP

To Emily, my wife, CHRO, and partner. Thank you for your unwavering support, grace, and the selflessness through the many years we have spent together. I love you more than words can express and humbled by your hard work you put in every day for our family and our practice. We are together in all adventures.

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To my entire Evolve Restorative Center family. Thank you for your willingness to help patients and going the extra mile to make sure our patients are cared for and supported. We are building something great.

To Timothy Deer, my brother, thank you for your friendship, support, advice, and partnership. We will continue to work towards globalization of pain care to improve safety and outcomes. We are not victims of circumstance.

To Springer, for their continued work in making this text edition a reality.

Finally, thank you to God, for making all things possible.

Jason E. Pope, MD, DABPM, FIPP

To my wife Halena, my best friend, advisor, and counselor. Your love, support, and companionship are so cherished and appreciated by me. And to our amazing children, Olivia, Tyler, Elizabeth, and Allison. We are so grateful for your love and watching you grow into the wonderful and exceptional young adults that you have all become is the most important and inspirational part of our lives.

To my patients, whom I have had the honor and pleasure of caring for over the past 30 plus years. I have learned more from you than all of my 30 plus years of training and education.

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Tim J. Lamer, MD

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To all my previous educators. Without your guidance and instruction, I would have never acquired the knowledge required to pursue this project.

Finally, to our patients. It is an honor to help you deal with the challenges of pain. I continue to learn from these experiences daily.

David Provenzano, MD

Foreword

I am honored to write this foreword for *Deer's Treatment of Pain: An Illustrated Guide for Practitioners.* As an interventional pain management specialist, I have devoted my career to the treatment of patients with pain and share Tim Deer's passion for patient care, clinical research, and education of the next generation of pain physicians. I have known Dr. Deer for two decades as a friend and colleague and have watched with admiration and respect as he has become among the most highly regarded figures in the field. His leadership in interventional pain is internationally recognized, and he is directly responsible for much of the sentinel work in many areas of pain therapy, particularly neuromodulation and intrathecal drug delivery.

Dr. Deer is an accomplished triathlete. His charitable work with the Ironman Foundation exemplifies the generosity and integrity he brings to all that he does, including the publication of this important textbook, which establishes a new standard reference for our field. This comprehensive resource includes over 100 chapters written by today's thought leaders in every area of pain treatment. It provides the reader with the basic science, anatomy, physiology, and practical treatment considerations necessary to successfully navigate the ever-increasing complexity of interventional pain management.

A recent study by the National Institutes of Health's National Center for Complementary and Integrative Health indicates that nearly 50 million American adults experience significant chronic pain or severe pain [1]. Because pain is one of the most common reasons patients seek help from healthcare providers, it is critical that physicians are well versed in its diagnosis and management. I commend Timothy R. Deer and his colleagues, Jason E. Pope, Tim J. Lamer, and David Provenzano, for assembling this comprehensive volume which details the current understanding of both pain and its treatment. Sections address both pharmacologic and interventional approaches to pain control, as well as neuromodulation, intrathecal drug delivery systems, regenerative therapies, and minimally invasive structural surgeries. Well-placed illustrations and other graphics serve to enhance the text, further increasing the book's value. In summary, the expertise presented in *Deer's Treatment of Pain* provides us with an authoritative reference work that belongs on the desk of every student, clinician, and scientist involved in the study and treatment of pain.

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Preface

Chronic pain is an international issue that impacts the well-being of all nations for numerous reasons. In the past decade, we have come to the realization that the opioid epidemic is a tremendous challenge and has taken a huge toll on society. In that same complex setting, we also have the challenge of an aging population, traumatic injuries, disease progression, and sports-related ailments all of which cause chronic pain syndromes that require solutions. It is in this complicated time that we feel new guidance is needed for the physician or healthcare provider who is attempting to do an optimal job in treating this patient population. This is the environment that created the need for *Deer's Treatment of Pain*.

This textbook has been created with a number of committed physicians who are striving to improve therapeutic efficacy, patient safety, and ethical medical treatment. This is intended to merge a comprehensive text with an atlas feeling where you can visually learn best treatment options for your patient. The physician who embraces these options of an algorithmic treatment approach based on best evidence, expert opinion, and clinical experience will enhance their ability to provide optimal care to those who suffer and seek a remedy.

In developing this educational material, I had the honor of working with Tim Lamer, MD; David Provenzano, MD; and Jason E. Pope, MD. This team of dedicated physicians has created a group who shaped the contents, edited the materials, suggested additions, and used the highest standards to make a commitment to creating an optimal learning experience for the reader.

I wish each of you the best of success as you raise the standard of care in your community by continuing to strive to learn new options and methods. It is my belief that by working together, we can truly offer solutions that will better the human experience.

Charleston, WV, USA — Timothy R. Deer

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Part I

Introduction

The Disease-Based Treatment of Pain

1

Andrew So and Karina Gritsenko

Introduction

The concept of pain has been an implicit variable in the equation of human life for many centuries. As one of the oldest universal phenomena, pain and its effects have asserted varying degrees of influence on religion, philosophy, and politics over time. Most notably, however, the phenomenon of pain has challenged physicians in their treatment planning and methodology; despite its ubiquitous existence, pain has never been universally understood due to its differing definitions across societies, beliefs, and contexts. Subsequently, medical professionals have been continuously tasked with redefining the phenomenon of pain.

Today, pain is one of the leading motivations for patients to seek physician treatment, as it is a component of many disease states; some would even argue that pain has evolved into a disease state in and of itself. This designation is the product of centuries of research that have resulted in various theories attempting to define pain as a complex biological process integrating the roles of anatomy, function, and external experience. With each new theory, the scope of pain's definition has expanded, and physicians have created new approaches to treatment.

As medical professionals' definition and understanding of the pain phenomenon has changed over time, treatment methods have evolved into multimodal approaches designed to attack the various components of this complex disease pathway. To better understand today's pain management techniques, it is important to familiarize oneself with the historical theories of pain, the current pain model, and the available treatments that have crafted the current approach.

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Background and Historical Perspective

As it is regarded today, pain has not always been considered a biological phenomenon. In the prehistoric times, pain was thought to be a means of punishment that arose from an external experience of the spiritual world. In Ancient Chinese philosophy, pain was believed to be an imbalance between the vital forces of yin and yang, the complementary/opposing forces of life.

Early Greek philosophers also had their own postulations on the sensation of pain, as evident in the text of the *Iliad* by Homer (eight century to mid-fourth century BC), who used terms such as *penthos* and *algos* to describe different forms of physical and moral pain. The philosopher Aristotle designated the heart as the center of pain and sensation and believed that pain stemmed from the sensitivity of human organs.

Religion has also been used to explain the concept of pain, particularly in the Middle Ages. With the spread of Christianity, there seemed to be a preoccupation on the crucifixion of Christ and therefore a greater emphasis on bodily suffering. From this preoccupation emerged the idea that pain was a form of divine retribution, as demonstrated with martyred saints and the concept of purgatory.

The Shift to the Anatomical Basis of Pain

Over the centuries, the concept of pain slowly registered a paradigm shift from a philosophical and theological ideology to a more anatomical explanation. The works of Herophilus and Galen contributed to this pivotal shift. Herophilus studied the anatomy of the brain in the third century and laid early foundations in the understanding of the human nervous system and its anatomy. Approximately 1500 years later, the works of the physician Claudius Galen (130–201 AD) would suggest the existence of two sets of nerves with different roles: motor and sensation. Galen also demonstrated that the complete transection of the spinal cord caused sensory and

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motor deficits and theorized that the spinal column was the connection between the brain and other organs. Galen's work demonstrated one of the earliest pathways that suggest pain required an organ to receive information from the outside world, a connecting passageway, and an organizing center to transform outside sensory information to perception.

During the Renaissance, philosopher Rene Descartes would describe a detailed somatosensory pathway. In his 1662 manuscript, *Treatise of Man*, Descartes builds on Galen's theories, describing the existence of nerves in the human body that convey both sensory and motor information. Descartes proposed the existence of gates between the brain and nerves, from which arouse the idea of mechanism; this theory compares the human body to a machine and describes pain as a consequence of damage to said hypothetical machine. Descartes' work showed that pain was an internal process organized by the human brain, rather than an external presence that entered the body, as was historically believed. In many ways, Descartes initiated the proposition of a human physiological process of pain.

In the years that followed these early anatomical studies, several important theories, which will be discussed in the next section of this chapter, would expand on these anatomical findings and be pivotal in constructing our modern-day knowledge of the pain pathway.

The Early Pain Theories

The current working definition of pain, as defined by the International Association for the Study of Pain, is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage." The IASP's definition further describes pain as an integrative experience with both biological and psychosocial components. While there have been numerous theories proposed to explain pain, this chapter will focus on the most prevalent and influential theories of the past.

The Specificity Theory (1811)

The specificity theory was one of the first modern pain theories to suggest a separate anatomical neural pathway for pain perception. Maximilian von Frey postulated that the human body had five sensations (touch, heat, cold, pleasure, and pain), each with their own dedicated receptors and pathways to the brain. He theorized that noxious stimuli activated their own specialized receptors and were relayed by individualized pain fibers. Adding to the specificity theory, Charles Bell later suggested the idea of specialized spinal nerve roots with different functions. He hypothesized that the ventral nerve roots were responsible for motor and sensory activity in the dorsal nerve roots.

From the specificity theory stems some of our modern ideas of the pain pathway – the ideas of specialized pain nociceptors, specialized nerves that carry varying pain signals (i.e., alpha-delta and C-nociceptive fibers), and a specialized spinothalamic tract in the spinal cord dedicated to nociception.

Pattern Theory (1894)

The Pattern theory, proposed by Alfred Goldscheider in 1894, suggests that the perception of pain is not the product of just one stimulation site transmitting to the brain, as proposed by the specificity theory, but rather an aggregate of multiple stimulation sites. It also postulates that the frequency of stimulation is responsible for variance in the intensity of pain. Goldscheider theorized that if a pain stimuli was applied repeatedly in higher frequency (temporal summation), it would appear more intense to the individual. Similarly, he suggested that pain could be spread over a large area and that such stimuli applied to a greater body area would convey a more intense pain (spatial summation).

Gate Control Theory of Pain (1965)

In 1965, Ronald Melzack and Charles Patrick would propose the gate control theory, which answered some of the limitations of its predecessor theories and ultimately revolutionized the field of pain medicine. The research behind the gate control theory of pain is rooted in the notion that pain signals are transmitted from the peripheral nervous system via small afferent pain fibers (alpha-delta and c fibers) to the dorsal horn of the spinal cord, which eventually leads to the brain. Along this pathway lie hypothetical "gates" that can be closed by varying mechanisms in order to inhibit the propagation of pain signals.

The gate control theory outlines two inhibitory pathways. First, it describes the ability of large nerve fibers (alpha-beta fibers), which carry non-noxious information and are located in the substantia gelatinosa of the spinal cord, to inhibit smaller afferent nerve fibers carrying nociceptive information. This proposed mechanism explains the theory behind the practice of rubbing or caressing a painful area of the body in order to alleviate pain. This idea is also the fundamental foundation behind the concepts of neuromodulation and transcutaneous electrical nerve stimulation (TENS).

The second inhibitory pathway is a descending inhibitory mechanism from the brain centered in the reticular formation. The theory states that heightened activity of this descending efferent pathway from the reticular system leads to an increased likelihood of gate closure and the subsequent inhibition of pain. This explains the theory behind hypnosis

and why patients many times ignore the presence of painful stimuli while hypnotized.

Summarized, the overall perception of pain was said to be a balance between the two inhibitory mechanisms and the activity of the small noxious fibers. The gate control theory was important in showing the role of both the central and peripheral nervous systems in the perception of pain and was the first to explain the ability for non-noxious stimuli to modulate and change one's pain perception. As stated, it would also serve as the foundation of neuromodulation, a technique commonly used today for pain management.

Sensitization Models

Although the previous models laid the foundation for the neural pathway of pain, they failed to explain why pain could persist after the removal of the original stimuli, as demonstrated in chronic pain syndromes. The idea of sensitization (which includes both peripheral and central sensitization) would provide an answer to this phenomenon.

The term peripheral sensitization refers to the situation in which a nerve has increased excitability and therefore increased signal transmission. Peripheral sensitization can be applied to the pain pathway as commonly demonstrated following tissue injury, when inflammatory messengers including prostaglandins, cytokines, leukotrienes, and bradykinin are released. These inflammatory messengers cause changes in the voltage-gated sodium channels of neurons, which produce reduced activation potential and increased excitability. Subsequently, peripheral pain receptors are "sensitized" to have a lower threshold for firing, which results in increased response to noxious stimuli and can even result in a response to non-noxious stimuli.

Central sensitization is the idea that persistent pain transmission over time from the peripheral nervous system can cause the pain pathways in the spinal cord and brain to make new, stronger synapses (known as use-dependent plasticity). These new synapses cause a modulated pain transmission containing prolonged responses, or windup. Furthermore, the central sensitization model theorizes that increased activity from brain areas implicated in pain have the ability to modulate pain perception. Central sensitization can be used to explain hyperalgesia, allodynia, and spontaneous pain. There have been more detailed models proposed to explain its mechanism; the details behind these, however, are not the focus of this chapter.

Biopsychosocial Model

Although these historical theories appropriately suggested a biomedical mechanism to pain, the biopsychosocial model, which was proposed in 1977 by Engel, was the first to suggest that psychosocial factors can affect pain perception and maintenance of pain. This refuted the then-traditional view that pain was merely a sensation. Similarly, the Institute of Medicine in 2011 stated its belief that "pain arises in the nervous system, but represents a complex and evolving interplay of biological, behavioral, environmental, and social factors...."

There is not one singularly accepted scientific explanation behind psychology's role in the pain pathway, but many theories rest on the foundation that psychological factors may sensitize both peripheral and central nerve pathways, causing a heightened sensitivity to pain which ultimately affects the cognitive processing of the pain stimulus in the brain. The biopsychosocial model illustrates that pain is the product of a biomedical pathway (activation and transmission of noxious stimuli) and an integration of psychosocial influences, such as beliefs, cognition, mental state, and society.

This model can be used to explain why chronic pain patients often develop negative coping mechanisms (e.g., catastrophizing perceived helplessness and low self-efficacy), which ultimately influence pain severity and prolong a patient's symptoms. Similarly, depression has been found to be highly associated with chronic pain, with a prevalence rate between 30 and 54% and often serving as a prognostic indicator for greater disability. The biopsychosocial model draws further support from evidence that patients with chronic pain often benefit from cognitive- and behavioral-based interventions. Ultimately, the biopsychosocial model helped to evolve pain treatment approaches to more holistic ones, encompassing treatments for both the body and the mind.

Overview of the Current Pain Pathway

When considered in aggregate, these early pain theories provide substantial evidence in illustrating pain as a biological process with a dedicated pathway in the nervous system. This section will bring together these theories to outline the current scientific thinking of nociception and its mechanism, which is an important consideration in understanding the various treatment modalities of today. Future chapters will also provide more detailed information on the various components of the pain pathway.

The pain pathway starts with dedicated receptors and nociceptors, which respond to local tissue damage including mechanical (pressure and pinch), heat, and chemical. If an original stimulus exceeds the activation threshold, nociceptors convert the original stimulus into an electrical signal that is transmitted to the central nervous system for processing. When activated, these nociceptors produce a cascade of inflammatory mediators, which only further activate and sensitize them (a process known as peripheral sensitization).

Examples of these mediators include prostaglandins, bradykinin, and histamine.

From here, the transduced electrical signal is carried via A-delta (Aδ) and C fibers, which serve as the primary afferent nerve fibers in the pain pathway. Thinly myelinated Aδ fibers are responsible for sharp and stinging pain sensations, whereas C fibers typically convey duller pain. These fibers carry signal to the spinal cord where they eventually terminate in the dorsal horn and synapse with second-order neurons. The signal then travels up to the brain along the spinothalamic and spinoreticular tracts, which are located in the anterolateral white matter of the spinal cord. Once in the brain, the signal is processed by the thalamus and projected to the somatosensory cortices, insula, anterior cingulate cortex, and prefrontal cortex, all of which are important for pain perception. The lateral system is thought to be responsible for analyzing pain location, duration, intensity, and quality, whereas the medial system is thought to be responsible for perception.

Throughout the pathway lie mechanisms that can inhibit the propagation of pain signal. Information about non-noxious stimuli are carried by alpha-beta fibers and travel adjacent to the alpha-delta and C fibers; as postulated by the gate control theory, these non-noxious fibers may inhibit the fibers of nociception if activated simultaneously. Furthermore, the signal can be modulated by a variety of spinal mechanisms, which include endogenous opioids and cannabinoid systems, as well as inhibitory aminos such as GABA and nitric oxide. Lastly, the signal can be inhibited by descending pathways from the brain. These descending pathways are mediated by noradrenaline and serotonin; the two parts of the brain most important in the descending inhibition pathway are the periaqueductal gray and the nuclei raphe magnus.

Permanent lesions or persistent damage to different parts of the pain pathway can lead to central and peripheral sensitization. The modulation of the pathway via sensitization can also lead to many different types of pain, including chronic pain states and hyperalgesia.

Types of Pain

To better understand the treatment of pain as a disease state, one should first understand the various types of pain we know to exist today. With continued and increasingly advanced research within the field of pain medicine, physicians have developed more standardized methods in classifying the many different types of pain; one way to identify pain type is to analyze its characteristics of duration, anatomic source, and etiology. In 2002, the SCI Pain Task Force of the International Association of the Study of Pain developed a taxonomy to subdivide the various pain states, which is now one of the most common methods used to classify pain. This classification system uses a physiological/etiological approach, stratifying pains by the physiological mechanism behind each type based on etiology. In this method of pain classification, three types of pain can be identified. The first two types, known as nociceptive and neuropathic, carry distinguishing characteristics, while the third type (mixed) combines characteristics of both nociceptive and neuropathic pain.

Nociceptive Pain

Nociceptive pain describes pain that typically arises from the injury of somatic structures such as the skin, muscles, tendons, ligaments, bones, and joints. Nociceptive pain is the consequence of the transduction of noxious stimuli by A-delta and C fibers, as previously described in this chapter. Nociceptive pain can be further subdivided into somatic pain and visceral pain.

A. Somatic pain is pain associated with peripheral tissue damage sensed by cutaneous nociceptors. Specialized nociceptors sense somatic pain in response to various harmful stimuli, most notably thermal (hot vs. cold), chemical (such as those produced by cuts and the inflammatory mediators produced by damaged tissues), and mechanical (e.g., stretching and pinching). Somatic pain can be thought of as a protective mechanism; it allows the body to localize tissue damage and withdraw itself from the source.
B. While somatic pain is typically associated with external stimuli, visceral pain draws on information from internal organs (more specifically and most typically, the mucosal lining of hollow organs). In further contrast, somatic pain withdraws the body from potential harm, where visceral pain is the inner organs' defense mechanism to signal danger given their inability to elicit motor activity and move away from the pain signal. For example, the mucosal lining of the GI tract contains receptors with the ability to detect harmful changes such as dangerously high/low pH levels or the overstretching of the organ, which in turn produce symptoms of nausea and bowel distention and lead to defecation, vomiting, etc. Simplistically, visceral pain can be viewed as an attempt to maintain an internal homeostasis of the body.

   Visceral pain is the product of vagal and spinal visceral afferent neurons. In contrast to somatic pain, there are no dedicated centers in the central nervous system specifically concerned with the transmission of visceral pain signals. This broadly explains why patients with visceral pain often have difficulty localizing the exact location of their pain. Furthermore, visceral pain can be felt in loca-

tions distant from the source of the stimulation, which is termed referred pain. The exact mechanism of referred pain is not known. One hypothesis suggests that sensory afferents supply multiple locations and that the stimulation of one location activates its other branches which in turn obscures the exact localization of the original stimulus.

Neuropathic Pain

Neuropathic pain is pain caused by damage of either the peripheral or central nervous system. The International Association of the Study of Pain formally defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system." Central neuropathic pain is sourced from lesions within the spinal cord or brain. Some common disease states implicated in central neuropathic pain include spinal cord lesions, multiple sclerosis, transverse myelitis, and syringomyelia. In contrast, peripheral neuropathic pain is caused by lesions within the small unmyelinated C fibers and the myelinated A fibers. The peripheral neuropathies can be further subdivided based on distribution. Most peripheral neuropathies generally fall within two categories: peripheral focal/multifocal lesions and peripheral generalized lesions. Some examples of focal and multifocal lesions include entrapment syndromes, post-traumatic neuralgia, postherpetic neuralgia, and diabetic mononeuropathy; generalized lesions include polyneuropathies associated with diabetes mellitus, alcoholism, and HIV.

Research reveals a complex pathophysiology behind the etiology of neuropathic pain. In general, however, it can be stated that the peripheral nervous system responds to the presence of noxious stimuli when, in the absence of such stimuli, it would otherwise remain dormant. With lesion/damage/chronic disease, these nerves are sensitized (as detailed previously) and develop pathological baseline activity that causes neuropathic pain, even in the absence of noxious stimuli.

Acute Versus Chronic Pain

Pain can also be categorized by duration; these designations include acute and chronic pain. Acute pain is normally described as pain that extends for less than 3 days. It is the consequence of a specific disease or injury and is normally self-limited. For example, patients often experience a degree of pain in the days immediately following surgery, but this pain tends to subside thereafter with the passage of a moderate amount of time. Conversely, chronic pain is pain that persists beyond the expected healing period for a specific injury or disease; typically pain greater than 3 months is defined as chronic pain. Chronic pain is hypothesized to be the result of permanent changes within the nervous system (central and peripheral sensitization, as discussed previously), and the associated syndromes of chronic pain are typically the focus of pain management and treatment. Some examples include chronic lower back pain, headache, myofascial pain, and fibromyalgia. These chronic pain syndromes comprise components of both neuropathic and nociceptive pain and are marked by distinguishing biological etiologies.

Treatment: A Multimodal Approach

Today's approach to pain treatment is the result of many decades of research into the effectiveness and efficiencies of treatment methods and reflects the depth of the patient pool currently seeking treatment. It has been estimated that roughly 100 million adults suffer from chronic pain and that chronic pain is responsible for 90 million physician visits, 14% of all prescriptions, and 50 million lost workdays annually. The total healthcare cost associated with pain treatment in the United States is estimated to be $650 billion dollars per year. With such a prevalent burden on both society and medicine, the American Board for Hospital Accreditation has adopted pain as the "fifth vital sign." Similarly, Canada added pain assessment and management to its Achieving Improved Measurement Standards in 2005. Continued increases in the number of patients seeking treatment for pain have led to the formal protocolization of pain assessment and treatment in the inpatient setting.

The task of developing efficacious and cost-effective treatment methods has challenged physicians and scientists for decades. A well-received and widely utilized solution was developed by anesthesiologist John J. Bonica, who pioneered the multidisciplinary approach to pain treatment. As a physician who treated chronic pain in soldiers after World War II, Bonica was one of the first physicians to consult experts from different disciplines (neurology, psychiatry, surgery) in an attempt to find more effective and all-encompassing treatments for his patients. Utilizing this multidisciplinary approach, Dr. Bonica witnessed vast improvements in his patients' pain ratings and led him to open the first multidisciplinary pain clinic in 1950. This multidisciplinary approach to treatment produced greater patient satisfaction and decreased healthcare costs.

Since the landmark events of Dr. Bonica's multidisciplinary approach to treatment, physicians have accepted the multifaceted mechanism involved in the generation, adaptation, and chronicity of pain, as illustrated throughout this chapter. With this acceptance, pain management has evolved into a multimodal approach, and pain treatment now often encompasses a combination of pharmaceutical, surgical, behavioral, and alternative treatments. Utilizing a multidisciplinary approach, the goal of pain management today is not only to reduce a patient's pain symptoms but to improve the individual's overall physical

function, better manage chronic diseases, and improve psychological well-being in relation to a patient's pain in the hopes of creating an improved overall general state.

This section of the chapter serves as an introduction to the current modalities of pain treatment and the diseases they treat. Pain treatment can be simplified into two broad categories: pharmacological and nonpharmacological strategies. Future chapters will be dedicated to more detailed descriptions and analyses of each of the modalities.

Pharmacological Treatments

Pharmacological treatment is one of the oldest methods of pain treatment that is still widely used today. Specific pharmacological algorithms, which will be discussed in a future chapter, have been proposed to aid practitioners in treating pain. When implementing pharmacological strategies, it is important to consider the type of pain that is being treated, whether it be nociceptive, neuropathic, or mixed; specific classes of medication treat different types of pain with varying efficacies. Furthermore, a multimodal approach to pharmacological treatment is considered most beneficial for patients. The aim of a multimodal approach is to use medications that act on different receptors and/or parts of the pain pathway to create synergistic effects and consequently stronger pain relief. Some of the most commonly utilized pharmacological treatments include nonsteroidal anti-inflammatory drugs (NSAIDS), antidepressants, anticonvulsant medications, and opioids.

Nonsteroidal Anti-inflammatory Drugs (NSAIDS)

Nonsteroidal anti-inflammatory drugs (NSAIDS) are one of the most popular agents in the treatment of multiple pain states, most notably inflammatory pain. NSAIDS provide pain relief via anti-inflammatory mechanisms by inhibiting prostaglandins-producing enzymes, which are present in both the central and peripheral parts of the pain pathway. Prostaglandins are produced by the COX class of enzymes, with COX-1 and COX-2 being the most pertinent isoforms to the pain pathway [62]. Although NSAIDS inhibit both COX-1 and Cox-2, it has been suggested that most of its analgesic properties arise from its COX-2 inhibition. Nonselective COX agents inhibit both COX-1 and Cox-2 isoforms; some examples of nonselective inhibitors include aspirin, paracetamol, ibuprofen, and naproxen. Selective COX inhibitors, or those that only inhibit COX-2, were later designed to prevent the common side effects associated with nonselective agents (most notably GI intolerance and renal injury). Examples of selective COX inhibitors include celecoxib, meloxicam, and rofecoxib. It is important to note that NSAIDS, although frequently used in the treatment of neuropathic pain, have been shown to have little utility in the treatment of nociceptive pain. NSAIDS have been found most effective in treating diseases with an inflammatory mechanism such as osteoarthritis and rheumatoid arthritis.

Antidepressants

Antidepressants, although originally intended for the treatment of psychiatric illnesses, have also been found effective in pain treatment. Antidepressant medications work by inhibiting the reuptake of certain neurotransmitters, most notably serotonin and norepinephrine, causing a buildup that potentiates inhibitory pain pathways in the spinal cord.

The three classes of antidepressants most commonly utilized in pain management are tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Tricyclic antidepressants were the first class to be used in pain medicine and work by blocking the reuptake of serotonin and noradrenaline. TCAs have been found beneficial in the treatment of neuropathic pain, fibromyalgia, and headaches. However, notable side effects of TCAs include cardiac arrhythmia and hypertension.

Selective serotonin reuptake inhibitors, unlike tricyclic antidepressants, only inhibit the reuptake of serotonin and were developed in an attempt to avoid the side effects of TCAs. There has also been increased research on newer SNRI drugs, which inhibit the reuptake of serotonin and noradrenaline, showing their helpfulness in treatment of neuropathic pain and fibromyalgia.

Anticonvulsant Medications

Anticonvulsant medications have been effective in the field of chronic pain management since their inception in the 1960s due to their neuromodulating properties. Anticonvulsants assert their activity by enhancing the inhibitory pathway of the gamma-aminobutyric acid (GABA) pathway; gabapentin and pregabalin are the most researched and most commonly utilized anticonvulsants in the field of pain management. These drugs have become clinically favored as adjunct agents in the treatment of chronic neuropathic pain, particularly in postherpetic neuralgia and diabetic neuropathy. Carbamazepine, also in this class of drugs, is considered a mainstay in the treatment of chronic neuropathic pain associated with trigeminal neuralgia. The popularity of anticonvulsants has risen over time because of their wide safety margin. The most common side effect of anticonvulsants is dose-dependent sedation.

Opioids

Opioids are one of the oldest, most potent, and most popular drug classes used in pain management and treatment. Opiates is the term used to encompass naturally occurring derivatives of opium such as morphine and codeine; opioids is a broader term used to describe any drug that produces morphine-like

actions, whether they be naturally occurring (opiates) or artificially synthesized (as with fentanyl, heroin, and methadone). The effectiveness of these drugs in treating pain, particularly acute pain within the first 6 weeks of an acute pain trigger, is undisputed, but there is currently no proven data to show efficacy beyond the acute pain period. In addition, adverse effects have been a significant source of scrutiny in the medical field; due to the current rise in opioid misuse, addiction, and overprescribing, there has been a sway in the pendulum of pain treatment to minimize the use of opioids at this time.

Opioids exert their desired effects via G-coupled protein receptors, which are subclassified as mu, kappa, and delta receptors. Simplistically, opioid receptors inhibit adenylyl cyclase, which subsequently inhibit cyclic AMP (cAMP) and the release of certain neurotransmitters implicit in pain production and perception. Opioids for chronic pain treatment are usually prepared in either oral or transdermal forms.

Although many would accept their role in the management of acute pain, opioids have been highly scrutinized in the context of chronic pain management, predominantly due to their adverse side effects and potentially abusive qualities. The primary side effects of opioids are reported to be constipation, nausea, and sedation. More serious side effects, such as hypogonadism, amenorrhea in women, and impairment in neuropsychological function, have also been associated with chronic opioid use. Furthermore, opioids have been shown to have addictive properties, and the concepts of drug addiction, tolerance, and dependence must be addressed with patients when administered for prolonged use in the treatment of chronic pain.

Interventional Techniques

Although pharmacological and noninvasive techniques are typically the first and primary line of defense in the treatment of chronic pain, it has been estimated that approximately 10% of patients cannot be adequately treated with these methods. In these select patients, the role of interventional techniques has been explored to find potential solutions in the treatment and management of their pain. Interventional techniques are usually utilized when a patient's pain arises from a spinal etiology, such as discogenic or sacroiliac joint pain. Interventional techniques have been used to both help alleviate pain, as well as to locate and diagnose the source of a patient's pain. Common interventional techniques include injection therapy, intrathecal drug delivery, and discography.

Injection Therapy

Injection therapy encompasses a wide array of injection types used in the treatment of chronic pain and were first reported to be utilized in 1901. With the development of modern techniques, injection therapy has become an accepted tool in treating pain patients.

Peripheral injection therapies include trigger point and intra-articular joint injections. Trigger point injections involve dry needling into tender muscle points, which attempts to elicit a twitch in the targeted muscle and subsequently alleviate any painful preexisting muscle contractures. The dry needling can also be supplemented with concomitant injections of local anesthetics, though this has not been scientifically proven effective. Anecdotally, physicians have witnessed the benefits of trigger point injections in the treatment of myofascial pain, while intra-articular joint injections have been utilized in the treatment of chronic joint pain. These injections are performed with corticosteroids, which are aimed at reducing inflammation in the joint.

Central injection therapies include intrathecal therapy, epidural injections, and radiofrequency ablation. In the United States, epidural steroid injections are the most common intervention form of this type utilized in pain treatment. Epidural steroid injections achieve their pain-alleviating properties by reducing inflammation of nerve roots and their surrounding environment and have been shown to be useful in the treatment of radiculopathies caused by disc pathology such as disc herniation. Traditionally, epidural steroid injections had been administered via the interlaminar approach, where the injection is placed in the space between two laminae. Other approaches, such as caudal and transforaminal, have also become more common with the advancement of technique and the advent of fluoroscopic-guided practices.

Radiofrequency ablation (RFA) is the process by which a generated radio frequency wave is injected via an insulated needle to produce heat energy from the induction of ion oscillation. The heat energy produced subsequently causes the thermal ablation of the surrounding environment. In relation to pain treatment, RFA has been targeted at dorsal root ganglions and nerve plexus in various diseases in an attempt to cause nerve denervation and block pain signal propagation. RFA has been shown helpful in the treatment of trigeminal neuralgia (gasserian ganglion), cluster headaches (sphenopalatine ganglion), and postherpetic neuralgia (percutaneous dorsal root ganglions). The most common use of radiofrequency ablation has been witnessed in the treatment of facet-mediated back pain, given RFAs particular effectiveness in its ability to denervate medial branch nerves.

Neuromodulation

Neuromodulation is one of the newest emerging treatment concepts in the field of pain management. Although largely still considered an evolving treatment, the foundation of neuromodulation originated in the mid-1960s with Melzack and Wall's gate control theory of pain, which states that the transmission of pain depends upon the opening and closing of a "gate" by large and small fibers. Neuromodulation functions