Chapter 1
Introduction to Acute, Chronic, and Episodic Pain

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Abstract Pain places an enormous burden on the healthcare system as well as the quality of life of individuals all around the world. With regard to the economic burden alone, it was found that the total annual cost of healthcare due to pain in the United States ranged from $560 to $635 billion. Pain is defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. Appropriate classification of pain is essential for research and clinical documentation, authorization of services, and facilitation of communications between healthcare providers as well as between clinicians and their patients. It is also important for determination of the appropriate therapeutic plan. Pain can be characterized as acute, chronic, or episodic based on its duration, and as nociceptive, neuropathic, and nociplastic based on its pathologic mechanism. We discuss current treatments such as pharmacological treatments, non-pharmacological treatments, interventional treatments, and surgical treatments, as well as limitations of these treatments. We highlight the cause of the United States Opioid Crisis and chronic pain during the COVID-19 Pandemic. COVID-19 can produce post-viral chronic pain syndromes in patients identified as "long-haulers." A particular hallmark of the COVID-19 infection is the robust, widespread inflammatory response triggered, which could play a role in the development of new pain conditions as well as the exacerbation of existing pain disorders.

Keywords Acute pain · Chronic pain · COVID-19-related pain · Definition of pain · Episodic pain · Neuropathic pain · Nociceptive pain · Nociplastic pain · Non-pharmacological treatments · Pharmacological treatments

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1.1 The Concept and Classification of Pain

Pain places an enormous burden on the healthcare system as well as the quality of life of individuals all around the world. With regard to the economic burden alone, Gaskin et al. found that the total annual cost of healthcare due to pain in the United States ranged from $560 to $635 billion, which exceeded the combined costs for cardiovascular, neoplastic, digestive, respiratory, and endocrinologic disorders (Gaskin and Richard 2022). This is largely due to the high incidence of chronic pain in the population at large. In fact, pain is one of the main reasons why patients seek medical care, with osteoarthritis and back pain being the top two painful conditions noted in a 2013 epidemiologic study by St. Sauver et al. (2013). The high prevalence of chronic pain carries further downstream ramifications, including increased risk of cardiovascular disease, gastrointestinal and hemostatic changes, diminished sleep quality, as well as higher rates of anxiety, depression, substance abuse, and disability. In fact, back pain, musculoskeletal disorders, and neck pain alone constitute three of the four leading causes of years lost to disability (Murray et al. 2013).

Recognition of the socioeconomic burden of pain has led to concerted efforts to effectively manage it. An integral part of effective management of pain is the ability to identify and properly classify the pain, which can then help guide the development of an appropriate therapeutic strategy. Thus, this chapter will serve as an introduction to pain and the appropriate classification of common painful states.

1.1.1 Defining Pain

In 1979, the International Association for the Study of Pain (IASP) proposed the definition of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP Subcommittee on Taxonomy 1979, p. 249). Since then, it has been widely adopted into practice and used by clinicians, researchers, and healthcare organizations. Despite further revisions to the IASP's publications on the taxonomy of pain in 1986, 1994, and 2011, this definition has remained unchanged. In recent years, many have advocated for an updated definition, which has been met with varying degrees of support and criticism. Therefore, in 2018, the IASP convened a 14-member panel of experts to evaluate the current definition and assess whether it should be preserved or altered. In 2020, Raja et al. published "The Revised IASP Definition of Pain: Concepts, Challenges, and Compromises" recommending the definition be changed to "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al. 2020, p. 1977).

This updated definition emphasizes the advances in our understanding of pain over the past four decades. Research into poorly understood chronic widespread pain disease states, such as fibromyalgia and headaches, has demonstrated the

possibility for pain to exist without tissue damage but instead due to altered function of pain-related sensory pathways in the peripheral and central nervous systems (PNS and CNS), causing increased sensitivity (Fitzcharles et al. 2021). In fact, microneurography studies in patients with fibromyalgia have shown that peripheral C-nociceptors in these patients exhibit hyperexcitability, spontaneous activity, and sensitization to mechanical stimuli (Serra et al. 2014). Cerebrospinal fluid (CSF) analyses in fibromyalgia patients have also demonstrated elevated levels of substance P and glutamate, two neurotransmitters known to have excitatory effects on pain receptors (nociceptors) and pathways (Becker and Schweinhardt 2012). This leads to an over-activation of *N*-methyl-*D*-aspartate (NMDA) receptors in specific spinal cord dorsal horn neurons that promote pain transmission (Littlejohn and Guymer 2020).

This definition as "an unpleasant sensory and emotional experience" acknowledges both the physical and emotional components of pain. Further investigations into the brain's pain-processing pathways have revealed two main ascending pathways – the medial and lateral pain pathways. The lateral pathways transmit the information that is most commonly associated with our understanding of pain. It involves the somatosensory cortex and processes the sensory information related to pain from the periphery, such as pain intensity, location, and character, through activation of C- and Aδ-fibers. The medial pathway involves the anterior cingulate and anterior insular cortex and is responsible for the unpleasant emotional component of pain through activation of C-fibers. A meta-analysis by Beissner el al. demonstrated that the medial pathway is involved in cognitive, emotional, somatosensory, and sympathetic autonomic processing (Beissner et al. 2013). Functional imaging studies have further supported these findings and confirmed that the structures of the medial pathways are responsible for the negative emotions associated with acute and chronic pain (Bushnell et al. 2013; De Ridder et al. 2021; Schreckenberger et al. 2005). These findings have in turn led to research on how our therapies, such as dorsal column neuromodulation, can help tamper the emotional suffering associated with painful states (De Ridder and Vanneste 2016).

1.1.2 Classification

Appropriate classification of pain is essential for research and clinical documentation, authorization of services, and to facilitate communication between healthcare providers, as well as between clinicians and their patients. As previously mentioned, it is also important for determination of the appropriate therapeutic plan. For example, nociceptive, axial low back pain may be treated with non-steroidal anti-inflammatory medications and physical therapy, while painful diabetic neuropathy would be better suited to treatment with an anticonvulsant or neuromodulation. Nevertheless, classification systems can vary significantly across different sources and can be arranged based on duration, etiology, affected anatomical system,

location, frequency, and intensity. This can produce confusion among clinicians and complicate documentation.

Given this disparity, the IASP published a classification system in 1986 in an attempt to standardize the classification of chronic pain. The second edition was published in 1994 with subsequent updates made to certain sections in 2011 and 2012. This classification system has since been implemented by the World Health Organization (WHO) through the *International Statistical Classification of Diseases and Related Health Problems (ICD)-11* that came into effect in January 2022 (World Health Organization (WHO 2022)) (Table 1.1). For the purposes of this chapter, pain will be classified per IASP guidelines as acute, chronic, or episodic based on its duration, and as nociceptive, neuropathic, or nociplastic based on its pathologic mechanism.

1.1.3 Acute Pain

Acute pain is defined as pain lasting less than 3 months, according to the new *ICD-11* coding recommendations. It tends to be sudden in onset and results from damage or injury to tissues, causing activation of nociceptive transducers. As such, the pain typically resolves after tissue damage is repaired and nociceptive input ceases. Acute pain serves an evolutionary purpose: it informs behavior in order to avoid harm and significant tissue damage. When the body perceives a painful nociceptive input (i.e., heat, cold, mechanical force, or chemical stimulation), biological mechanisms arise that retract from the environment, protect from further injury, and promote healing (Baliki and Apkarian 2015). In fact, disease processes in which individuals lack peripheral nociceptive afferents result in unrecognized infections and injuries and shortened life spans (Dubin and Patapoutian 2010).

Common examples of acute pain include postoperative pain and pain following a fracture. In these cases, direct tissue trauma leads to the release of potent inflammatory mediators. These mediators activate functionally distinct nociceptors in tissues, which then relay the information through electrical signals to higher brain processing centers. These mediators can also result in adaptive processes such as induction of hyperalgesia and allodynia of the surrounding region through decreased activation threshold of C-fibers and Aδ-fibers in an effort to avoid further harm to the area (Dubin and Patapoutian 2010).

1.1.4 Chronic Pain

Chronic pain, on the other hand, persists for at least 3 months beyond the expected disease course and healing time following the acute pathologic process. However, it does not always arise from an acute injury or pathological process. Often it has an insidious onset without an identifiable trigger, as in the case of arthritic pain and

Table 1.1 IASP *ICD-11* chronic pain classification

IASP ICD-11 chronic pain classification (possible table to include?)
- Chronic primary pain
° Chronic widespread pain
☐ Fibromyalgia
° Complex regional pain syndrome (CRPS)
☐ CRPS, Type 1
☐ CRPS, Type 2
° Chronic primary headache or orofacial pain
☐ Chronic migraine
☐ Chronic tension-type headache
☐ Trigeminal autonomic cephalgias (TACs)
☐ Chronic temporomandibular disorder pains
☐ Chronic burning mouth
☐ Chronic primary orofacial pain
° Chronic primary visceral pain
☐ Chronic primary chest pain syndrome
☐ Chronic primary epigastric pain syndrome
☐ Irritable bowel syndrome
☐ Chronic primary abdominal pain syndrome
☐ Chronic primary bladder pain syndrome
☐ Chronic primary pelvic pain syndrome
° Chronic primary musculoskeletal pain (other than orofacial)
☐ Chronic primary cervical pain
☐ Chronic primary thoracic pain
☐ Chronic primary low back pain
☐ Chronic primary limb pain
- Chronic cancer-related pain
° Chronic cancer pain
☐ Chronic visceral cancer pain
☐ Chronic bone cancer pain
☐ Chronic neuropathic cancer pain
° Chronic post-cancer treatment pain
☐ Chronic post-cancer medicine pain
• Chronic painful chemotherapy-induced polyneuropathy
• Other post-cancer medicine pain
• Post-cancer medicine pain, unspecified
☐ Chronic post-radiotherapy pain
- Chronic postsurgical or posttraumatic pain
° Chronic postsurgical pain
☐ Chronic pain after amputation

fibromyalgia. In contrast to acute pain, chronic pain is maladaptive and serves no biological purpose. Chronic pain is also unlikely to resolve with time and thus requires a different approach to its management.

Over the past few decades, we have transitioned away from the old adage that "pain never killed anyone" and learned to appreciate the immense biological and psychosocial effects that chronic pain has on the body. Pain can take an enormous toll on the body, disrupting nearly every organ system. Much like stress, chronic pain can lead to fatigue; anxiety; depression; irritability; dysphoria; weakness; lightheadedness; increased muscle tension; difficulty with memory, attention, and concentration; reduced appetite and libido; gastrointestinal changes like nausea and decreased gut motility; increased cardiac work due to elevations in heart rate and blood pressure; impaired wound healing; and non-restorative sleep (Chapman and Gavrin 1999; Fitzcharles et al. 2021; Weiner 2001). In fact, chronic pain has such a profound impact on the emotional well-being, function, and quality of life of patients that many have proposed pain as a disease in its own right rather than merely a symptom (Treede et al. 2019). Examples of chronic pain include arthritic pain, neuropathic pain, and fibromyalgia.

1.1.5 Episodic Pain

The precise definition of episodic pain is much debated. The term is often used synonymously with "recurrent pain" and "breakthrough pain." Dating back to 1983, it has been described as the acute flare-up of peripheral tissue pathology as a result of an underlying chronic pathological entity (Crue 1983). It implies recurrent, discrete, and acute episodes, such as those that occur in headaches, gastrointestinal motility disorders, degenerative disk and joint disease, collagen vascular disease, sickle cell disease, and other similar functional disorders. The temporal criteria for episodic pain vary from one disease state to another. For example, episodic migraines are characterized as those occurring on fewer than 15 days per month (Gobel 2022). Episodic cluster headaches and episodic paroxysmal hemicrania, on the other hand, are characterized as lasting from 7 days to 1 year and separated by pain-free remission periods of $\geq$3 months. Treatment of episodic pain can be challenging as painful episodes can be sudden and unpredictable. It often involves a strong emphasis on preventative measures as in the case of prophylactic therapies for migraines and other headaches.

In cancer pain literature, episodic pain describes a different entity: the type of pain known as "breakthrough pain." The European Association for Palliative Care has advocated for the use of the term episodic pain, as it provides a more universal terminology that can more easily be translated to other languages (Mercadante et al. 2002). In the context of cancer pain, episodic pain is described as short periods of higher pain intensity in the presence of otherwise stable, persistent, controlled background pain (Løhre et al. 2016). Episodic pain can be further divided into movement-related (bone pain, neuropathic pain, visceral pain, or somatic soft tissue pain) and

non-movement-related (neuropathic pain, visceral pain, or somatic soft tissue pain) episodic pain. Regardless of the underlying mechanism, there is consensus that episodic pain has no biological basis for benefits. As in the case of chronic pain (and in contrast to acute pain), the painful nociceptive signals in episodic pain do not serve to warn of tissue damage but instead reflect aberrant signals.

1.2 Taxonomy and Common Types of Pain

1.2.1 Nociceptive Pain

The IASP defines nociceptive pain as that which arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors (IASP Subcommittee on Taxonomy 1979). Nociceptive pain can be further divided into visceral pain, affecting the visceral organs, or somatic pain, affecting the skin, muscles, ligaments, tendons, joints, or bones. The characterization of nociceptive pain is highly variable but can be described as dull, aching, and throbbing. Visceral nociceptive pain is usually diffuse and poorly localized, often with associated referral patterns. In contrast, somatic nociceptive pain tends to be more discrete, though it may also be associated with referral patterns.

1.2.2 Nociplastic Pain

Following the IASP's adoption of the term nociceptive pain in 2005, pain came to be characterized as either nociceptive or neuropathic. However, in 2016, the term nociplastic pain was proposed as a third mechanistic descriptor. Kosek et al. offered this term to describe "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" (Kosek et al. 2016, p. 1383). Since then, it has grown significantly in popularity within the pain medicine community and was subsequently adopted into the IASP's terminology (Raja et al. 2020).

In a recent publication series in *The Lancet*, Fitzcharles et al. and Cohen et al. expanded further on the pathophysiologic mechanism of nociplastic pain, describing it as a maladaptive, abnormal processing of nociceptive input or diminished inhibitory pathway activity that can arise de novo, be triggered by a painful stimulus, originate in the central or peripheral nervous systems, or be psychologically driven (Cohen et al. 2021; Fitzcharles et al. 2021). Integral to the diagnosis of nociplastic pain, however, is the absence of known tissue damage or discrete pathology.

Interestingly, based on these criteria, complex regional pain syndrome (CRPS) Type I would be classified as nociplastic pain, while CRPS Type II would fall under

the category of neuropathic pain, given the presence of known nerve injury. Other examples of nociplastic pain include fibromyalgia, irritable bowel syndrome, bladder pain syndrome, and some tension-type headaches. Nociplastic pain is best managed with anticonvulsants, analgesic antidepressants, behavioral interventions, exercise, or a combination thereof.

Examples of somatic nociceptive pain include osteoarthritis, bursitis, and muscle tears. Examples of visceral nociceptive pain include angina and pain associated with pancreatitis. Both types of pain can be managed with analgesic antidepressants, non-steroidal anti-inflammatory drugs, opioids, image-guided injections, neuromodulation, exercise, or a combination thereof depending on the underlying pathology and the body parts involved.

1.2.3 Neuropathic Pain

Neuropathic pain is defined, according to IASP, as that which is caused by a lesion or disease of the somatosensory nervous system (IASP Subcommittee on Taxonomy 1979). It can be further divided into central or peripheral neuropathic pain based on where in the somatosensory nervous system the lesion or disease lies. It is typically characterized as burning, shooting, or like pins and needles, often with associated paresthesia, allodynia, or hyperalgesia. In many cases, there may also be associated numbness or itching. Neuropathic pain typically arises spontaneously and without provocation, although it is often exacerbated by touch, heat, and cold. Based on these criteria, several screening tools, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Neuropathic Pain Questionnaire (NPQ), Douleur Neuropathique en 4 questionnaire (DN4), painDETECT, and ID-Pain, have been developed to help identify patients with neuropathic pain and have demonstrated up to 80% sensitivity and specificity (Bennett et al. 2007).

Examples of neuropathic pain include painful diabetic neuropathy, postherpetic neuralgia, and complex regional pain syndrome Type II. Treatment of neuropathic pain can be a challenge but typically starts with identification of cause and ruling out reversible causes. Therapeutic options include anticonvulsants, analgesic antidepressants, opioids, image-guided injections, neuromodulation, behavioral interventions, or a combination thereof. The most robust data support pharmacologic therapies, of which antidepressants (particularly tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors) and anticonvulsants (gabapentin and pregabalin) are considered first-line therapies (Gilron et al. 2015).

Importantly, pain exists on a continuum and patients' pain cannot always be classified into any one discrete category. Many disease states comprise elements of all three types of pain described above.

1.3 Current Treatments and Limitations

Current available mechanism-based pain therapies will be discussed in more detail in later chapters of this book. The following section, however, will serve as a brief introduction to available therapeutic options. Treatments can be divided into pharmacologic, non-pharmacologic, interventional, and surgical therapies. Pain management is highly complex, and no single therapeutic approach can be used to manage all types of pain. The U.S. Department of Health and Human Services (HHS) published the *Pain Management Best Practices Inter-agency Task Force Report* in 2019 to provide clinicians with recommendations on the management of acute and chronic pain encompassing these various therapies (U.S. Department of Health and Human Services 2019).

1.3.1 Pharmacologic Treatments

Pharmacologic therapies encompass several commonly used classes of medications known to have analgesic properties. These include anti-inflammatory non-steroidal drugs, corticosteroids, anticonvulsants, analgesic antidepressants, topical agents, antispasmodics, muscle relaxants, and opioids. Prior to prescribing one of these medications, it is important to discuss associated side effects with the patient. Often, the associated sedating effects of these medications can be helpful in patients whose sleep has been affected by chronic pain. The patient's age and medical comorbidities should always be taken into consideration when selecting among these drug classes.

1.3.2 Non-pharmacologic Treatments

Non-pharmacologic therapies include ice, heat, cognitive-behavioral therapy (CBT), biofeedback, physical therapy, occupational therapy, traction, therapeutic ultrasound, acupuncture, chiropractic manipulation, massage, yoga, tai chi, and transcutaneous electrical nerve stimulation (TENS). These treatment modalities have been found to be efficacious when used in combination with other therapies and can be of particular utility in nociplastic pain conditions. A 2017 Cochrane Review article by Geneen et al. studied the effects of various exercise programs on diverse pain conditions and showed favorable effects in pain reduction, improvement in physical function, and quality of life despite small sample sizes (Geneen et al. 2017). In additional studies, comprehensive, interdisciplinary pain rehabilitation programs have been shown to significantly improve function in patients with chronic pain while resulting in significant reductions in medical costs (Kurklinsky et al. 2016; Sletten et al. 2015).

1.3.3 Interventional Treatments

Interventional therapies include image-guided injections, radiofrequency denervation, chemical neurolysis, cryoneuroablation, neuromodulation, minimally invasive lumbar decompression, implantation of intrathecal drug delivery systems, regenerative and biologic therapies, and various percutaneous interventions (basivertebral nerve ablation, vertebral augmentation, and interspinous process spacer device placement). Patients are best suited for interventional procedures when their symptoms follow a neuroanatomical distribution, particularly if there are concordant imaging findings.

Neuromodulation is a treatment modality that has gained a lot of traction in recent years. It involves the application of electrical stimulation to peripheral nerves, spinal cord dorsal columns, dorsal root ganglia, motor cortex, or specific deep brain regions, which can be applied through a variety of waveforms, frequencies, and feedback control mechanisms, such as high-frequency, burst, and closed-loop stimulation. With regard to spinal cord stimulation, most of the randomized controlled trials studying these therapies have been used for neuropathic pain or CRPS, so their application to other pain states remains to be seen. Overall, there is good evidence showing superiority of neuromodulation over conventional medical management for the treatment of failed back surgery syndrome, CRPS, and painful diabetic neuropathy, and these studies have been largely industry-sponsored (Knotkova et al. 2021).

1.3.4 Surgical Treatments

Surgical therapies are typically reserved for patients who have failed conservative therapies, who have significant symptoms limiting function, or who have lesions causing specific tissue damage. Options for surgical therapies vary widely depending on the etiology of the pain but can include decompression or fusion in the case of spine pathologies, replacement in the setting of advanced osteoarthritis, or resection in the setting of malignancies.

Regardless of the therapy selected, however, there are general guidelines that should be followed in caring for patients suffering from chronic pain. In most cases, therapies are directed toward managing and attenuating symptoms rather than curing the disease. This often involves a thoughtful discussion between the clinician and the patient and setting realistic, attainable expectations. It is important to cultivate a strong clinician–patient relationship in order to promote patient's engagement and treatment compliance. It is also beneficial to promote an internal locus of control and remind patients of the things they can do for themselves as well through selection of healthy lifestyle habits.

In general, it is imperative to develop an individualized, patient-centered approach, typically through a multimodal, multidisciplinary approach (Cohen et al.

2021). This often begins with a thorough history and physical examination, and, when indicated, imaging studies in order to properly characterize the pain and thus select the appropriate therapeutic options. Careful consideration of the circumstances unique to each patient, such as age, comorbidities, and psychosocial issues such as financial limitations or barriers to care, is essential to this approach. Regardless of the treatment option selected, treatment should always focus on improving quality of life and restoring function.

1.4 Special Issues in Pain Management

1.4.1 The United States Opioid Crisis

Few things have impacted the field of pain management as severely as the United States opioid epidemic and several pivotal events have led to the rise of the nationwide health crisis. Following the release of Percocet and Vicodin to the market in the 1970–1980s, the pharmaceutical industry began pushing for opioids as safe, effective medications for the management of pain. The push from the industry was further supported by publications such as the 1980 *New England Journal of Medicine* letter "Addiction Rare in Patients Treated with Narcotics" and the 1986 *Pain* study "Chronic Use of Opioid Analgesics in Non-Malignant Pain: Report of 38 Cases" (Porter and Jick 1980; Portenoy and Foley 1986). In 1996, OxyContin was released and further marketed through campaigns claiming it was less addictive than its immediate-release counterparts. Supposedly the slow, sustained release formulation posed a lower risk for obtaining a "high" and thus had a very low risk of iatrogenic addiction (Lyden and Binswanger 2019). However, there were little data to support this claim.

The combination of these events caused substantial increases in opioid prescriptions, reaching a record 259 million in 2012 (Paulozzi et al. 2014). This was paralleled by an alarming rise in overdose deaths from prescription opioids, which nearly tripled from 1999 to 2015. In fact, in 2016, the Centers for Disease Control and Prevention (CDC) reported approximately 89 deaths per day and a total of 32,445 deaths in 2016 due to prescription opioid overdoses (Marshall et al. 2019). In recognition of the nationwide problem, in 2016 the CDC published the *CDC Guideline for Prescribing Opioids for Chronic Pain-United States, 2016* to provide guidance for primary care clinicians who were prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care (Dowell et al. 2016). In 2017, the U.S. Department of Health and Human Services (HHS) declared a public health emergency and proposed a five-point strategy to combat the crisis. This focused on: (1) better data on the epidemic by strengthening public health surveillance, (2) better pain management, (3) improving access to treatment, prevention, and recovery services, (4) increasing the availability of overdose-reversing drugs, and (5) supporting cutting-edge research on pain and addiction (Price 2017).

Despite these efforts, opioid misuse continues to be an enormous problem in the United States. Opioid overdose deaths have continued to rise, reaching 93,331 in 2020, which is the highest number to date (Ahmad et al. 2022). On February 10, 2022, the CDC published an update to their 2016 guidelines for opioid prescriptions (Dowell et al. 2022). These recommendations no longer include specific dosage ceilings and abandon the previous three-day prescription limitations for acute pain. However, they continue to emphasize the importance of judicious opioid prescription and support the use of individualized clinical judgment in medical decision-making. The United States opioid epidemic remains a complex issue with devastating consequences that requires a concerted effort by pharmaceutical companies, government agencies, healthcare organizations, and clinicians of all medical specialties. As suggested by the HHS, it is imperative to prioritize additional research on pain and development of safe strategies to address chronic pain.

1.4.2 Chronic Pain and the COVID-19 Pandemic

The COVID-19 pandemic impacted the lives of people all around the world in many ways. It has caused significant and at times even life-threatening illness. Estimates from the United States at the peak of the epidemic placed the overall percentage of patients with laboratory-confirmed COVID-19 suffering from severe disease at 14% and those with fatal illness at 5% (Stokes et al. 2020). According to the current CDC data, there have been 78,855,000 total reported cases of COVID-19 and 947,882 deaths due to COVID-19 in the United States to date (CDC 2020). The data from around the world are even more staggering. The pandemic has also been a substantial psychosocial stressor for individuals through the associated isolation, economic hardships, and fear of illness.

In the healthcare community, the impact of the pandemic has been felt across all medical subspecialties, including in the field of pain management. At the height of the pandemic, with federal restrictions implemented to try to decrease transmission, many pain clinics were forced to suspend elective procedures, which include essentially all interventional pain therapies. The suspension of these procedures limited access to care for chronic pain patients who needed these interventions to return to function, subsequently driving up rates of medication prescriptions, including opioids, for pain management. With the closure of many facilities came limited access to gyms, pools, and physical therapy centers, which further decreased activity and thus function in these patients. The situation of chronic pain patients was further exacerbated by decreased social interactions and an inability to leave the house, leading to escalating anxiety and depression levels that drove increases in pain. Overall, these secondary effects of the pandemic resulted in higher rates of chronic pain, which led to a greater burden on pain management physicians once clinics, many of which had become short-staffed, were able to reopen. In response, medical societies have published recommendations for pain interventionalists on how to safely and responsibly reinitiate pain-related care with an emphasis on

understanding the value of interventional pain therapies to avoid additional harm to chronic pain patients (Deer et al. 2020).

The COVID-19 pandemic has undoubtedly caused an increase in chronic pain rates worldwide. Several mechanisms for the rise in numbers have been proposed, including exacerbation of pre-existing pain due to infection-induced inflammation by the virus, emergence of new post-viral chronic pain syndromes, and development of new pain as a result of increased risk factors related to the secondary effects of the pandemic (increased anxiety and depression, inactivity, poor sleep, and decreased socialization) in non-infected patients (Clauw et al. 2020). Of particular interest in recent research is the possibility that COVID-19 can produce post-viral chronic pain syndromes in patients identified as "long-haulers," characterized by having prolonged (often >12 weeks) symptoms following the initial infection. A large 2020 study by Bowles et al. on 1409 patients admitted to home health care following COVID-19 infection reported that the most common symptoms included daily or constant pain (42%), confusion (47%), anxiety (50%), and dyspnea with any exertion (84%) (Bowles et al. 2021). Risk factors for the development of chronic pain and fatigue identified in this study include: pre-existing comorbidities, history of chronic pain or previous pain experience, history of mental health problems, disadvantaged socioeconomic status, social isolation, and ICU-related specific factors (prolonged stay, ventilation, proning, sepsis, immobility, neuromuscular block). Among the reported painful conditions seen in post-viral COVID-19 syndromes are persistent generalized pain, joint pain/arthralgias, chest pain, and low back pain (Korompoki et al. 2021). These new chronic pain conditions have been observed in patients who experienced severe disease as well as those with even mild to moderate illness and can often be poorly localized making the treatment more challenging (Korompoki et al. 2021).

Post-infection pain syndromes lasting over 12 months have been reported in the past following microbial infections with *Coxiella burnetii* (Q fever), Epstein-Barr virus (mononucleosis), and *Borrelia burgdorferi* (Lyme disease). Thus, it is reasonable to hypothesize that the SARS-CoV-2 virus has similar capabilities. A particular hallmark of the COVID-19 infection is the robust, widespread inflammatory response triggered, which could play a role in the development of new pain conditions as well as the exacerbation of existing pain pathologies. This widespread inflammatory response has also been postulated to be the result of the organ-specific damage that may preferentially occur in individuals with fragile stress response systems (Clauw et al. 2020). Further research is needed to better understand the inflammation-driven pathophysiology behind this post-viral pain syndrome, in order to guide mitigation strategies to curtail further consequences of this pandemic.

1.5 Concluding Remarks

In summary, pain places an enormous burden on the society and healthcare system. According to IASP, pain is defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. Appropriate classification of pain is essential for research, treatments, and communications between healthcare providers and patients. Pain is characterized as acute, chronic, or episodic based on its duration, or as nociceptic, neuropathic, and nociplastic based on its pathologic mechanism. We highlight the cause of the United States Opioid Crisis and chronic pain during the COVID-19 Pandemic. COVID-19 can produce post-viral chronic pain syndromes in patients identified as "long-haulers." Notably, inflammation could be a major driver of this chronic disorder.

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