Acute and Chronic Pain Medicine during the COVID-19 Pandemic

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Edited by

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CHAPTER 1

CANCER PAIN

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Introduction to Cancer Pain

Around 20 million cases of cancer were diagnosed in 2020 around the world, with current data revealing that close to 40% of those living in the developed world will be diagnosed in their lifetime. It is predicted that in 2024, more than 28 million patients will be diagnosed with cancer[1] Cancer is a life-changing diagnosis that drastically impacts the patient as well as their loved ones. Among the multitudes of emotional stressors and physical hardships that patients face, cancer pain is one of the most prevalent and distressing symptoms that plague patients' quality of life. As such, it remains one of the most feared consequences of cancer. The International Association for the Study of Pain (IASP) describes pain as an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[2] Pain that is attributed to a patient's cancer diagnosis is defined as cancer pain. In 2022, approximately 45% of patients with cancer reported cancer pain, and 30.6% of patients reported moderate to severe pain.[1,3] Although recent advancements in cancer treatment have helped prolong patient lives, physicians need to optimize cancer pain management to care for the whole person and maximize patients' quality of life.

Cancer Pain Etiology

There are various etiologies of cancer pain. Approximately two-thirds of cancer pain is caused by the primary or metastatic tumor itself, while the remaining one-third is caused by pain syndromes developed as sequelae of various cancer treatments.[4] Cancer pain can be categorized as nociceptive,

neuropathic, or both. Nociceptive pain arises from painful stimuli that activate nociceptors throughout the human body. The activation of these nociceptors leads to firing of electrical signals via neuronal pain pathways. These signals travel to the brain where information is processed for the perception of pain. Nociceptive pain can be due to both somatic and visceral sources. Somatic pain arises from the somatic system, originating from the skin, muscle, bone, and fascia. Pain that is somatic is typically localized to the area of injury, such as a vertebral compression fracture at a specific spinal cord level resulting in pain. In contrast, visceral pain arises from internal structures. It is mediated by the autonomic system and is described as a diffuse type of pain that is less localized than somatic pain. An example of visceral pain is the nagging, intermittent pain due to pancreatic cancer or liver metastases. Lastly, neuropathic pain is due to dysregulation of the normal pain signaling pathway. Nerve damage and dysfunction result in abnormal stimulation and firing of pain pathways, leading to pain that is often described as burning, tingling, and numbing. A classic example of this is chemotherapy causing neuropathic pain as an unwanted side effect of the medication.

Cancer Pain Treatments

Treatments of the cancer itself may also lead to cancer pain.[5] As an example, various chemotherapy agents can cause infusion-related pain through venous spasms, chemical phlebitis, vesicant extravasation, and flare reactions. Cytotoxic agents, EGFR inhibitors, and tyrosine kinase inhibitors have been associated with severe mucositis. Myalgias, arthralgias, and dermatitis are also common pain syndromes experienced by patients taking certain chemotherapy medications such as paclitaxel and EGFR inhibitors. In addition, patients taking recombinant granulocyte colony-stimulating factors such as filgrastim often experience severe bone pain and ostealgia.

Radiation therapy is another treatment modality that often results in cancer pain. Radiation beams can cause mucosal inflammation as well as tissue necrosis at the target site of therapy, leading to long-term pain post-treatment.

Lastly, acute pain post-operatively from surgeries, when not adequately controlled, may evolve into chronic cancer pain. Around 30-50% of patients after oncological surgeries such as thoracotomies, rectal surgeries, and mastectomies develop chronic cancer pain post-operatively.[6]

Assessment of Pain

Pain is subjective and can be greatly influenced by past experiences and future expectations. When considering a patient's overall pain, in addition to reviewing relevant imaging and performing a thorough physical examination, it is important to delve into his/her history to evaluate the different factors which may be contributing to the symptoms.

In cancer pain management, in addition to the above, it is important to consider the impact of the underlying diagnoses and psychological stressors. Barriers may be present that might present challenges to accurately assessing a patient's pain. There may be misconceptions of how patients feel or express pain, cultural differences, and concerns of patients and families about addiction to pain medications. Some patients may feel reluctant to admit the severity of their pain as it may signify cancer progression. Many cancer patients are often also geriatric and/or frail. Cognitive impairment and physiologic barriers, such as sensory losses, may be present and should be considered when assessing pain symptoms. If possible, behavioral observation or obtaining additional information from friends and family members can be helpful.

WHO 3-Step Ladder

The World Health Organization's (WHO) Three-Step Ladder, created in 1988, has been used worldwide for treating cancer pain.[7,8] Before this guideline was put forth, many cancer patients were undertreated for their pain due to the fear and stigma of opioid pain medications. Although this strategy is controversial, it has served as a great foundation to help guide physicians with cancer pain management throughout the years. The three-step ladder was structured to help physicians escalate pharmacological treatment of cancer pain based on the severity of pain. Step-one of the ladders is indicated for patients who report "mild" pain, where the recommended treatments are non-opioid pain medications such as NSAIDs and Tylenol. If pain remains poorly-controlled, it is then considered "moderate" pain, and the treatment is escalated to step-two which consists of weak opioid analgesics, with or without non-opioid adjuvants. Weak opioids include codeine, tramadol, and hydrocodone; adjuvants include serotonin-specific reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, anticonvulsants, topical anesthetics, cannabinoids, and corticosteroids. Step-three of the

ladder involves the addition of a strong opioid, such as morphine, hydromorphone, and fentanyl for “severe pain.”

Limitations and Revisions to the Three-step Ladder: Inclusion of a Fourth-step

There has been much debate about the limitations of this model. Some have expressed concerns about step-two of the ladder. Although weak opioids are typically less potent than strong opioids, their effects can be variable depending on a patient’s genetic makeup. For example, the same dose of codeine, a weak opioid, can have different analgesic effects based on one's cytochrome CYP2D6 genetic polymorphism. In addition, some weak opioids such as tramadol also act on non-opioid receptors, giving rise to unwanted drug-to-drug interactions and complications such as serotonin syndrome. Studies in recent years have also highlighted weak opioids as major contributors to the opioid epidemic as well as opioid use disorder. Codeine-related deaths have increased eightfold over the last 30 years in England, with recent data showing that codeine and oxycodone are the two opioids most likely to lead to opioid use disorder.[8] This can be mostly attributed to how weak opioids are contained in compound analgesic preparations causing it to be more difficult to effectively titrate the dosage for each patient. As a result, patients may often receive more opioids than needed which increases their risk of addiction and dependence.

Critics have also called this Three-Step Ladder one-dimensional as the guideline did not include procedural interventions and non-pharmacological methods of treating pain. With modern technology and advancements in pain research, cancer pain management has shifted towards a more individualized and multimodal approach. As such, the ladder has been revised several times since its creation, most notably with the addition of a fourth-step to the guideline which integrates non-pharmacological interventional procedures. These procedures include neuraxial therapy such as spinal and epidural blocks, sympathetic plexus blockade, spinal cord stimulation with implantable devices, neurolytic agents, and peripheral nerve blocks. The revisions also made the ladder bi-directional, as physicians were encouraged to start at whichever step necessary on the ladder instead of a step-wise, bottom up approach. This is because studies have shown evidence that interventional nerve blocks may be more effective in treating cancer pain if considered earlier or in combination with pharmacological treatments. Regardless, current literature has shown that 20% - 100% of patients with cancer pain who follow the WHO guidelines

have greater than 50% relief of their pain symptoms. The revised WHO 3-step ladder has continued to serve as a strong basis for cancer pain management and have helped many cancer patients get the treatment they need for their pain. It is important to note that this analgesic ladder has only been validated for cancer-related pain, and should not be generalized for use in patients experiencing chronic non-malignant pain.

The Effect of the Opioid Epidemic on Cancer Pain

Opioids have remained a cornerstone in the management of cancer pain. Although opioids have been proven to be greatly effective, its accessibility has been greatly challenged due to the opioid epidemic. Production and supply of opioids in hospitals and pharmacies have declined within recent years in efforts to reduce opioid-related deaths from opioid use disorder. Physicians now face many challenges when prescribing opioids to patients with cancer as they must navigate effectively addressing a patient's cancer pain while being cognizant of the risk of opioid dependence and misuse.

The COVID-19 Pandemic's Effect on Patients with Cancer Pain

The COVID-19 pandemic added further challenges to cancer pain management. The impact of this viral pandemic on cancer care highlights that the lack of disaster preparation ultimately puts cancer patients at risk of worsening clinical results. For some, the delay in timely diagnosis led to decreases in quality of life and exacerbations of pain, leading to long-term psychosocial impacts on mental health. During the pandemic, the Center for Disease Control and Prevention (CDC) established guidelines to reduce viral transmission and people all around the country were advised to stay at home.[9] Certain high-risk populations, including the elderly and immunocompromised, were especially recommended to limit their exposure to the virus. This ultimately led to a number of interruptions and delays in healthcare, including cancer screenings, biopsies, surgical interventions/procedures, and temporary pauses in clinical trials.[9] The overall impact on mortality and morbidity as a result of these delays are not entirely known due to insufficient high-quality data.

The National Cancer Institute projects an additional 10,000 deaths secondary to breast and colorectal cancer over the next decade as a result of lapse in preventive screening and treatment.[9] Prior to the pandemic, the U.S. had seen a continuous decline in cancer mortality for the past 25 years.

However, the American Cancer Society predicts an increase of about 3% in cancer related deaths when analyzing data from 2019-2020. Similarly, according to Canadian meta-analysis, delay in treatment by as little as four weeks was associated with a statistically significant increase in mortality.[10,11] Delay was defined as "the time to diagnosis until the initial treatment or the end of one treatment to the beginning of the next." The seven most common cancers globally include: head and neck, breast, lung, bladder, colon, and rectum cancer. These were chosen using data from the Canadian cancer registry between March 2020 to June 2021.[11] Analysis using a simulated prediction model to assess long term impacts, illustrated a 2% increase in cancer related deaths over the next decade in this region. The projection model identified a decline in the number of surgeries, chemotherapy, radiation treatments, and diagnoses based on pathology reports in comparison to pre-pandemic time period.[11] These findings are similar globally and ultimately may provide guidance for cancer-directed care should another viral pandemic arise.

Barriers to Cancer Pain Treatment

The American College of Surgeons recommended reducing the number of elective surgical procedures in patients during the Covid-19 pandemic. Unfortunately, depending on the type of procedure, this recommendation extended to oncology patients. Urgent to emergent surgical procedures were designated based on the type and staging of specific cancers. In lieu of surgery, guidance for alternative modalities to treatment was recommended.[12] Similarly, in an attempt to reduce overall health care burdens on the United States' existing system, the Center for Medicare and Medicaid services designated screenings and preventive care as a low acuity service.[13] Throughout the Covid-19 pandemic, low acuity services were either postponed or maintained through virtual visits. While virtual visits allowed for some degree of continuity of care, disadvantages to telehealth include lack of in-person physical examination, decreased rapport and connection between patient and physician, no laboratory testing, and potential exclusion of care to those without digital literacy, access to internet resources, and those with limited English proficiency.[14] All of the aforementioned may have led to an increased disease burden in oncologic patients as well as delays in detection in those yet to be diagnosed with cancer.

Another major barrier to oncologic care during the pandemic includes the financial and economic impacts of unemployment and thus insurance loss.

On average, cancer patients spend more money for medical care than those without a cancer diagnosis, especially as costs have risen with the advent of newer targeted cancer pharmacologic treatments.[15] Current literature shows that economic hardship in cancer patients leads to poorer clinical outcomes, reduced quality of life, increased mortality, and increased perceived symptom burden.

One of the most important considerable impacts was the delay in care in patients with active malignancy and COVID-19 infection. The American Society of Clinical Oncology COVID-19 data registry comprised of over 3000 patients, noted that near 50% of patients experienced interruption or termination of treatment.[16] Interruption of treatment was classified as more than 14 days from the initial appointment to the re-scheduled date. These delays were more profound in those with metastatic burden, Latino and Black persons, and those with multiple comorbidities in comparison to Non-Hispanic or Latino patients with a single or no chronic condition.[16] Delays were also longer in those with lower median income. This illustrates how impactful social determinants of health and socioeconomic status affect clinical outcomes, especially in the midst of a pandemic.

Minimizing interruptions in cancer treatment is paramount to survival. Future initiatives that allow for home-based detection and screening, improved telemedicine consultations, and emphasis on digital literacy may help us design a directed approach to cancer care during a global health crisis.

Impact of COVID-19 Pandemic on Chronic Pain Interventions

The pandemic also negatively affected cancer pain management by disrupting access to chronic pain interventions. COVID-19 precautionary measures that placed an emphasis on COVID-19-related medical management shifted priorities away from non-urgent and elective pain interventional procedures, causing delay, interruptions, and missed interventional treatments for patients with cancer pain. One study reported that interventional pain procedures decreased to a mere 13% of pre-pandemic procedural volume.[17] In addition, there was a 17.7% reduction in in-person clinic visits as 75% of chronic pain visits were conducted virtually during the pandemic.[18] This made it more difficult for cancer pain patients to get the interventional care they need, while also making it more

challenging for physicians to perform a thorough physical exam and fully understand the nature and degree of their patient's pain.

During the pandemic, expert panels from American Society of Interventional Pain Physicians, the American Academy of Pain Medicine (AAPM) jointly with the American Society of Regional Anesthesia and Pain Medicine (ASRA), the American Society of Anesthesiologists (ASA), the World Institute of Pain (WIP), American Academy of Physical Medicine and Rehabilitation (AAPMR), and Nord-America Neuromodulation Society (NANS), created recommendations for best practice management of pain patients. In these guidelines, they stated that physicians should triage pain procedures based on elective, urgent, and emergent situations, and to suspend elective cases, consider urgent cases on a case by case basis, and proceed with emergent cases.[19] Pain physicians were left with the difficult task of deciding whether a procedure is essential in order to mitigate the risk of virus spread. As a result, emergent cases such as intrathecal pump refills were frequently still performed during the pandemic, but other pain interventions that affected cancer pain management were often interrupted and postponed.

Psychosocial Implications

The words "pain" and "suffering" are often used interchangeably. For example, definitions of pain include bodily suffering, mental or emotional suffering, or distress. It is understandable how these words are intertwined, particularly when relating them to cancer patients and their experiences. However, there are distinctions. Pain is a physical sensation or signal indicating an event within the body. Suffering is the interpretation of that event and involves thoughts, beliefs, or judgments, and reflects the human experience of pain.[20]

Pain can cause suffering when it is uncontrolled or persists. Uncontrolled pain can lead to physical impacts and major disruptions in a patient's quality of life. Uncontrolled pain has deleterious effects on one's outlook on life, often creating a sense of hopelessness. Chronic pain not only affects quality of life but may predispose one to further complications psychologically and physically.[21]

A serious illness can fundamentally disrupt previously established expectations for the future. Dame Cicely Saunders, the founder of the modern hospice movement, recognized this and applied the term "total pain" as having physical, psychological, social, and spiritual components

interacting upon one another.[22] While clinicians often focus on the physical pain component, the effect of a life-limiting illness on the spiritual, social, and psychological components often gets overlooked.[23] Consequently, treatable suffering may get missed or overmedicated.

During the Covid-19 pandemic, people worldwide experienced high levels of stress due to economic uncertainty and the negative impacts of various mitigation strategies, such as social isolation. This stress level was often increased in cancer patients. With their immunocompromised states, cancer patients had an increased vulnerability for infection and often experienced high morbidity and mortality once infected. Hospitals became sources of high transmission, further escalating stress and anxiety in patients seeking further medical evaluation when experiencing uncontrolled cancer-related symptoms.

For patients newly diagnosed with cancer during the Covid-19 pandemic, it is unsurprising to learn of the high rates of concurrent diagnoses of anxiety and depression. Due to the risks of potential viral exposure, patients often experienced high levels of anxiety when entering healthcare settings to receive infusions, surgery, and radiation therapy. At the same time, social isolation and other virus risk reduction strategies caused many patients to feel isolated, with very limited psychosocial support. At a time when patients needed the most support, family members were often restricted from accompanying them to doctor appointments and sitting with them during chemotherapy treatments. Cancer support groups transitioned from being in-person to virtual. This restriction often prevented patients from feeling as connected with others during their time of need.

In patients with advanced disease who experienced a sudden change in their clinical status, many families were opting to enroll in hospice earlier rather than going to the hospital for further evaluation, where there were often strict isolation protocols against family members visiting. However, even so, there were often disruptions in providing quality end-of-life care faced by many hospice agencies.

Complementary and Alternative Therapies

In addition to the standard approach to managing pain, cancer patients often benefit from complementary and alternative therapies. Some of these include mindfulness-based stress reduction, meditation, and breathing exercises, all of which can all be done anywhere, including at home, while the patient is sitting and receiving infusions, or in a hospital setting. Many

patients also incorporate acupuncture for chronic pain states, including chemotherapy-induced peripheral neuropathy, chronic post-operative pain, and pain from the underlying tumor. There are very few strict contraindications to acupuncture. Patients with an AICD should avoid any electromagnetic stimulation that might be used as part of their acupuncture treatments, and patients who suffer from psychosis and delusions should not undergo acupuncture. While not strictly contraindicated, most practitioners do not recommend acupuncture for patients with clotting disorders, those on anticoagulation, patients with active infection, especially cutaneous, as well as severe neutropenia.[24] Patients may also take various supplements for cancer-related pain or other symptoms. It is important to always perform a thorough medication reconciliation

The number of patients using medical cannabis and cannabidiol (CBD) products have increased as the number of states that have legalized recreational marijuana has increased. However, it is still considered a Schedule 1 substance under the Controlled Substances Act. Patients may opt to substitute marijuana over opioids due to their concerns of opioid epidemic and long-term risks of opioid therapy. It is important to accurately assess their baseline use in a non-judgmental way and educate patients that cannabis has its own inherent risks, and that one option may not necessarily be better or worse than the other.

Conclusion

The Covid-19 pandemic has ultimately led to several negative consequences for patients diagnosed with cancer and suffering from cancer-related pain. Due to multiple unknown variables early in the pandemic, there was often a lack of consistency across hospital systems. Many patients were diagnosed in later stages of their malignancy, when the disease was already metastatic. There were also instances where cancer patients experienced gaps in their treatment regimen due to covid infections and lack of effective treatment at the time. As cancer-related pain was often not deemed to be an emergency, cancer-related procedures and nerve blocks were often delayed, leading to unnecessary suffering and distress.

Through these life-altering experiences of the many individuals that were affected, one hopes that public health responses can be learned and applied for any future occurrences of similar international crises to better protect our most vulnerable cancer patients.

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CHAPTER 2

ADDICTION MEDICINE CONSULT AND FOLLOW-UP FOR CHRONIC PAIN PATIENTS IN THE COVID-19 PANDEMIC

JULIO MEZA MD

Introduction

The COVID-19 pandemic has brought forth unprecedented challenges in healthcare delivery, especially for patients with chronic pain, many of whom also grapple with addiction issues. This chapter delves into the pivotal role of addiction medicine consultation and follow-up within the context of chronic pain patients during the COVID-19 pandemic. By examining the intricate interplay between chronic pain, addiction, and the pandemic's impact on healthcare delivery, this chapter seeks to provide healthcare professionals with a comprehensive framework for delivering effective, patient-centered care, while considering the recent regulatory changes that shape the evolving healthcare landscape and the pharmacokinetics and pharmacodynamics of medications used for chronic pain and opioid use disorder.

The Intersection of Chronic Pain and Addiction Chronic pain, a pervasive condition, has long presented challenges for healthcare providers attempting to balance effective pain relief with the risks of opioid misuse and addiction [1]. The convergence of chronic pain and addiction necessitates a holistic understanding and a multidisciplinary care strategy that addresses both pain management and underlying addiction issues. Recognizing the intersection of these two critical aspects of patient care is essential in providing effective, comprehensive care to those with chronic pain [2]. Chronic pain, a persistent and debilitating condition affecting millions worldwide, can fuel the development of Substance Use Disorder (SUD), while SUD itself can exacerbate pain and hinder recovery [3]. Understanding the mechanisms

and percentages involved in this intersection is crucial in developing effective treatment strategies for both conditions [4].

Definitions:

Chronic pain: Pain that persists for three months or more, even after any injury or underlying medical condition has healed. It can significantly interfere with daily life and activities [1].

Substance use disorder (SUD): A medical condition characterized by compulsive and unhealthy use of a substance, such as a drug or alcohol, despite harmful consequences. It was previously referred to as "addiction" [2].

Mechanisms:

Brain reward system hijacking: SUDs often involve substances that activate the brain's reward system, creating feelings of euphoria and pleasure. Over time, chronic use can rewire the reward system, making it crave the substance and its temporary relief from pain, even when pain levels stabilize [3].

Increased stress and vulnerability: Chronic pain can be a significant stressor, triggering the release of hormones like cortisol and adrenaline. These hormones contribute to anxiety, depression, and sleep disturbances, making individuals more susceptible to SUDs as a coping mechanism [4].

Genetic predisposition: Studies suggest that genetic factors can influence both pain sensitivity and vulnerability to SUDs. Certain genes might make individuals more prone to experiencing pain relief from certain substances, increasing the risk of dependence and potentially SUD [5].

Pain-enhancing effects of SUDs: Paradoxically, SUDs themselves can worsen pain perception. Substance abuse can damage the nervous system, leading to increased pain sensitivity and making pain management more challenging [6].

Epidemiology:

Estimates suggest that 20-40% of individuals with chronic pain misuse prescription opioids, with 8-12% developing an opioid use disorder [7].

The risk of SUD is significantly higher for individuals with chronic pain conditions that are poorly controlled by medication, such as back pain, neuropathic pain, and complex regional pain syndrome [8].

SUDs involving other substances, including alcohol and cocaine, are also more prevalent among individuals with chronic pain, further complicating the treatment landscape [9].

How can we start to explain this relationship?

The biopsychosocial model: This model emphasizes the complex interplay of biological, psychological, and social factors in understanding chronic pain and SUDs. Chronic pain can lead to biological changes in the brain that increase vulnerability to SUDs, while psychological factors like depression and anxiety can fuel both conditions. Social factors such as lack of access to adequate pain management and limited support systems can further contribute to the risk of SUDs [10].

Individualized treatment: Recognizing the unique factors contributing to chronic pain and SUDs in each individual is crucial for successful treatment. A multidisciplinary approach that addresses both pain management and SUD recovery, alongside psychosocial support, is necessary for long-term success [11].

Impact of the COVID-19 Pandemic on Pain Management

The pandemic has brought significant disruptions to healthcare systems globally, significantly affecting the ability to deliver consistent care. Patients with chronic pain, who often depend on regular in-person visits for pain management, have been particularly impacted [12]. The reduction in elective procedures, limited access to in-person appointments, and the overwhelming demand on healthcare resources have magnified the challenges of effectively managing chronic pain [13]. Therefore, innovative solutions are essential to ensure continuous, high-quality care for these patients, especially as the pandemic's duration extends beyond initial expectations [14].

The COVID-19 pandemic significantly impacted chronic pain management around the world, posing numerous challenges and uncovering pre-existing vulnerabilities. Here's a breakdown of the pandemic's impact, encompassing epidemiology, contributing factors, and its effects on morbidity and mortality:

Disruptions in routine pain management: Lockdowns, restricted access to healthcare facilities, and resource reallocation towards COVID-19 cases led to disrupted access to essential pain management services like in-person consultations, physical therapy, and interventional procedures [12].

Exacerbation of existing pain conditions: Stress, anxiety, and social isolation associated with the pandemic exacerbated existing pain symptoms for many individuals. Additionally, reduced physical activity due to lockdowns could worsen pain in some cases [14].

Increased reliance on pain medications: Disruptions in routine care may have led to some individuals relying more heavily on pain medications, potentially increasing the risk of misuse and dependence [14].

Contributing Factors:

Healthcare system overload: The surge in COVID-19 cases overwhelmed healthcare systems, diverting resources and personnel away from chronic pain management services [15].

Fear of contracting COVID-19: Patients with chronic pain were often hesitant to visit healthcare facilities due to fear of exposure to the virus, leading to delays in seeking essential care [16].

Mental health burden: The pandemic's psychological impact, including increased anxiety and depression, can significantly contribute to chronic pain perception and management [17].

Social isolation and lack of support: Social isolation and disruption of support networks, common during lockdowns, can worsen pain severity and hinder emotional coping mechanisms [18].

Morbidity:

Increased pain severity and disability: Disrupted access to pain management services and the psychological impact of the pandemic can lead to worsening pain symptoms and reduced functional capacity [19].

Exacerbation of mental health conditions: Pain and mental health are closely intertwined, and the pandemic's impact on both can have a cumulative effect on overall well-being [20].

Higher risk of adverse health outcomes: Poorly managed chronic pain can increase the risk of other health complications like cardiovascular disease, diabetes, and sleep disorders [21].

Mortality:

Indirect association with increased mortality: While there's no direct link between COVID-19 and chronic pain mortality, poorly managed pain can weaken the immune system and potentially increase susceptibility to severe infections, including COVID-19 [21].

Increased risk of opioid-related deaths: Disruptions in pain management and potential increases in reliance on pain medications during the pandemic may have contributed to a rise in opioid-related deaths in some regions [22].

Moving Forward:

The pandemic highlighted the existing vulnerabilities in chronic pain management systems and the need for improved resilience and adaptability. Moving forward, efforts should focus on:

Strengthening healthcare systems: Investing in telehealth and alternative service delivery models to improve access to chronic pain management during pandemics [23].

Addressing mental health needs: Integrating mental health support into chronic pain management programs to address the psychological burden associated with both conditions [24].

Promoting self-management strategies: Empowering individuals with chronic pain with self-management techniques and resources to cope with pain and maintain well-being during challenging times [25].

The COVID-19 pandemic served as a stark reminder of the complex interplay between chronic pain, mental health, and access to healthcare. Understanding its impact on chronic pain management is crucial for developing more resilient and responsive systems that cater to the needs of individuals living with chronic pain, both during and beyond pandemics [26].

Increased Risk of Substance Misuse During the Pandemic

The psychological toll of the pandemic, characterized by heightened stress, anxiety, and social isolation, has created an environment conducive to the escalation of substance misuse. This risk is particularly pertinent for patients managing chronic pain, as they may already be using opioids or other medications. The convergence of chronic pain, restricted access to medical care, and the emotional strain of the pandemic amplifies the potential for addiction issues to manifest or worsen. Additionally, individuals with a history of addiction may face increased challenges in maintaining their recovery during the pandemic [27], [28].

One particularly concerning trend was the increased risk of substance use disorders (SUDs), especially involving opioids. This rise presented a complex web of epidemiological factors, contributing influences, and concerning consequences for morbidity and mortality [29].

Integrated Approach: Addiction Medicine Consult for Chronic Pain Patients

A pivotal strategy to address the complex needs of chronic pain patients with addiction concerns during the pandemic is the integration of addiction medicine consultation into pain management protocols. This approach ensures that patients receive comprehensive care that considers both their pain and addiction profiles. The addiction medicine consultation should encompass a thorough assessment of the patient's pain condition, ongoing opioid therapy, and a comprehensive evaluation of their addiction risk [30].

Healthcare providers conducting addiction medicine consultations should be skilled in recognizing the signs of opioid misuse, identifying patients at risk of developing opioid use disorder, and creating tailored treatment plans that address the patient's pain while minimizing the potential for addiction [31]. This collaborative approach between pain management and addiction medicine specialists allows for a more nuanced understanding of the patient's overall health and ensures that potential addiction issues are not overlooked [32].

Pharmacokinetics and Pharmacodynamics of Medications for Chronic Pain and Opioid Use Disorder To effectively manage chronic pain and opioid use disorder, healthcare providers must have a comprehensive understanding of the pharmacokinetics and pharmacodynamics of the medications used in treatment [33].

Medications for Chronic Pain Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): NSAIDs are commonly used for mild to moderate chronic pain. They inhibit prostaglandin synthesis, reducing inflammation and pain. Examples include ibuprofen and naproxen. NSAIDs are absorbed in the gastrointestinal tract and undergo hepatic metabolism. They are primarily excreted in the urine [34].

Opioids: Opioids are potent analgesics but carry a risk of addiction. They exert their effects through binding to opioid receptors in the central nervous system. Common opioids include oxycodone, morphine, and hydrocodone. Opioids are metabolized by hepatic enzymes, and their metabolites are excreted in the urine [36].

Antidepressants and Anticonvulsants: Medications such as amitriptyline, duloxetine, and gabapentin are used to manage neuropathic pain. These drugs modulate neurotransmitters involved in pain perception and transmission. They are metabolized in the liver and excreted in the urine [37].

Medications for Opioid Use Disorder

Opioid use disorder (OUD) is a chronic and potentially life-threatening condition characterized by compulsive opioid use despite harmful consequences. Thankfully, medications for opioid use disorder (MOUD) offer a scientifically proven approach to managing the condition and supporting recovery.[38]

Here's a closer look at the three main MOUDs, exploring their mechanisms of action, advantages, and limitations:

Methadone:

Mechanism of Action: Full opioid agonist, binds to the same receptors as opioids but with weaker activation, reducing cravings and withdrawal symptoms.

Advantages:

Highly effective in managing cravings and preventing relapse, particularly for severe OUD.

Offers pain relief and can be long-acting.

Can reduce mortality risk associated with OUD.

Limitations:

Requires daily supervised administration at clinics, increasing dependence on healthcare services.

Potential for diversion and misuse due to opioid agonist properties.

Strict regulations and stigma can limit access.

Can cause side effects like constipation, sweating, and drowsiness.

Requires QT monitoring as can lead to such conduction changes increasing the potential for Torsades de Pointes.[38]

Mortality benefit: Studies show methadone maintenance treatment (MMT) significantly reduces mortality risk associated with OUD. A large US study found MMT participants had a 59% lower risk of dying from an opioid overdose compared to untreated individuals.[39]

Recidivism: Research suggests MMT reduces recidivism, with some studies showing up to a 60% decrease in criminal activity among participants compared to untreated individuals.

Crime: MMT participation is associated with reduced crime rates due to decreased drug-related offenses and improved employment opportunities. One study estimated a 38% reduction in overall crime costs for counties offering MMT[40]

Buprenorphine:

Mechanism of Action: Partial opioid agonist, binds to receptors but with limited activation, preventing full opioid effects and reducing cravings.

Advantages:

Available in various formulations (sublingual tablets, films, implants) for flexible dosing and administration.

Can be prescribed by any physician after the waiver established during DATA 2000 was removed in 2022 after the MAT act took effect

Partial agonist action limits euphoria, reducing overdose risk.

Lower potential for diversion compared to methadone.

Limitations:

Less effective for severe OUD compared to methadone.

Can cause withdrawal if abruptly discontinued.

Not ideal for patients with chronic pain due to limited pain relief capabilities.

Mortality: Buprenorphine maintenance treatment (BMT) has demonstrated efficacy in reducing mortality risk, though not as consistently as MMT. A meta-analysis found BMT participants had a 45% lower risk of opioid overdose death compared to controls.[41]

Recidivism: BMT is also effective in reducing recidivism, with studies showing decreases in criminal activity ranging from 30% to 50% among participants compared to untreated individuals. [

Crime: Similar to MMT, BMT participation is associated with reduced crime rates, particularly drug-related offenses. One study estimated a 35% reduction in crime costs for states with increased BMT access.[42]

Naltrexone:

Mechanism of Action: Opioid antagonist, blocks opioid receptors altogether, preventing any opioid effects and causing withdrawal if opioids are taken.

Advantages:

Blocks opioid effects, preventing cravings and relapse.

Available in injectable and oral forms, offering long-acting or daily options.

Can be used after detoxification and can help maintain sobriety.

No risk of dependence or misuse.

Limitations:

Does not alleviate cravings or withdrawal symptoms.

Requires abstinence from opioids for effectiveness, making initial implementation challenging, depending on the opioid 5-10 days prior initiation

Can trigger severe withdrawal if opioids are used.

Not suitable for patients with opioid dependence due to immediate withdrawal induction.

Mortality: While effective in preventing relapse, naltrexone alone may not significantly reduce mortality risk in the absence of comprehensive support. However, combining naltrexone with psychosocial interventions has shown promise in reducing overdose deaths.

Recidivism: Naltrexone can decrease recidivism, with studies showing up to a 40% reduction in criminal activity among participants compared to untreated individuals.[43]

Crime: The relationship between naltrexone and crime reduction is less clear, but studies suggest it may contribute to overall decreases in drug-related offenses due to its relapse prevention properties.[44]

Effective relapse prevention: By blocking opioid effects, naltrexone serves as a potent deterrent against relapse, aiding in long-term recovery efforts [45]

No withdrawal symptoms during treatment: Unlike agonist medications, Naltrexone doesn't cause withdrawal symptoms during treatment, making it easier for individuals to initiate and maintain therapy.[46]

Safe for patients with co-occurring medical conditions: Naltrexone doesn't significantly interact with other medications or exacerbate pre-existing health conditions, offering a safer option for those with comorbidities.[47]

Limitations:

Requires abstinence from opioids: Naltrexone is only effective if an individual is already opioid-free, as it cannot reverse ongoing opioid effects or alleviate withdrawal symptoms.

Limited impact on cravings: Naltrexone primarily blocks the euphoric effects of opioids, but may not offer significant relief from cravings, potentially requiring additional support mechanisms.

Lower adherence rates: Due to its lack of immediate withdrawal prevention and craving suppression, some individuals may struggle with adherence to Naltrexone therapy.[48] [51]

Characteristic	Methadone	Buprenorphine	Long acting naltrexone
Drug class	Opioid agonist	Partial opioid agonist	Opioid antagonist
Mechanism of action	Binds to opioid receptors and activates them, preventing withdrawal symptoms and reducing cravings	Binds to opioid receptors and partially activates them, preventing withdrawal symptoms and reducing cravings, but with a lower risk of overdose than methadone	Blocks opioid receptors and prevents them from being activated by opioids, reducing cravings and preventing the effects of opioids
Administration	Oral liquid or tablet, taken daily under supervision at a specialized clinic, after COVID-19 pandemic some flexibility was given	Sublingual tablet or film, or buccal film, taken daily or less frequently, can be prescribed by certified physicians and dispensed at pharmacies	Intramuscular injection, given once a month by a health care provider