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https://orcid.org/0000-0002-2417-8095

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Gabija Laubner – Sakalauskienė

The Impact of Elective Detoxification on Quality of Life in Patients with Chronic Pain on Long-Term Prescription Opioids

DOCTORAL DISSERTATION

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The dissertation was prepared between 2021 and 2025 at the Clinic of Anaesthesiology and Intensive Care, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University.

Academic Supervisor – Prof. Dr. Jūratė Šipylaitė (Vilnius University, Medicine and Health Sciences M 000, Medicine – M 001).
Academic Consultant – Prof. Dr. Robertas Badaras (Vilnius University, Medicine and Health Sciences, Medicine – M 001).

This doctoral dissertation will be defended in a public meeting of the Dissertation Defence Panel:

Chairman – Prof. Dr. Janina Tutkuvienė (Vilnius University, Medicine and Health Sciences M 000, Medicine – M 001).

Members:
Prof. Dr. Andrius Macas (Lithuanian University of Health Sciences, Medicine and Health Sciences, Medicine – M 001),
Assoc. Prof. Dr. Eva Strike (Riga Stradins University, Riga, Latvija, Medicine and Health Sciences, Medicine –M 001),
Prof. Dr. Antanas Vaitkus (Lithuanian University of Health Sciences, Medicine and Health Sciences, Medicine – M 001),
Assoc. Prof. Dr. Aleksandras Vilionskis (Vilnius University, Medicine and Health Sciences, Medicine – M 001).

The dissertation shall be defended at a public meeting of the Dissertation Defence Panel at 13.00 on 5th September 2025 in MF Large Auditorium of the Faculty of Medicine.
Address: Čiurlionio st. 21, Room No. 203, Vilnius, Lithuania
Tel. +370 5 239 8700; e-mail: mf@mf.vu.lt

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https://orcid.org/0000-0001-2345-6789

VILNIAUS UNIVERSITETAS

Gabija Laubner – Sakalauskienė

Detoksikacijos įtaka gyvenimo kokybei lėtinį skausmą patiriantiems pacientams, ilgą laiką vartojantiems receptinius opioidus

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Mokslinė vadovė – prof. dr. Jūratė Šipylaitė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).
Mokslinis konsultantas – prof. dr. Robertas Badaras (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001).

Gynimo taryba:

Pirmininkė – prof. dr. Janina Tutkuvienė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina – M 001);
Nariai:
Prof. dr. Andrius Macas (Lietuvos sveikatos mokslų universitetas, medicinos ir sveikatos mokslai, medicina – M 001);
Doc. dr. Eva Strike (Rygos Stradinio universitetas, Latvija, medicinos ir sveikatos mokslai, Medicina – M 001).
Prof. dr. Antanas Vaitkus (Lietuvos sveikatos mokslų universitetas, medicinos ir sveikatos mokslai, Medicina – M 001);
Doc. dr. Aleksandras Vilionskis (Vilniaus universitetas, medicinos ir sveikatos mokslai, Medicina – M 001);

Disertacija ginama viešame Gynimo tarybos posėdyje 2025 m. rugsėjo 5 d. 13,00 val., VU Medicinos fakulteto Didžiojoje (203) auditorijoje, Čiurlionio g. 21, 03101 Vilnius, Lietuva. tel. +370 5 239 8700; el. paštas mf@mf.vu.lt

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ABBREVIATIONS

ACEs - Adverse childhood experiences
CBT - Cognitive-behavioral therapy
CNCP - Chronic noncancer pain
COPD - Chronic obstructive pulmonary disease
CWP - Chronic widespread pain
CTZ - Chemoreceptor trigger zone
DPN - Diabetic peripheral neuropathy
GI - Gastrointestinal
GnRH - Gonadotropin-releasing hormone
HPA - Hypothalamic-pituitary-adrenal axis
MAT - Medication-assisted treatment
MEDs - Morphine-equivalent doses
MORs - Mu-opioid receptors
NAc - Nucleus accumbens
NK - Natural killer
NMDA - N-methyl-D-aspartate
NSAIDs - Nonsteroidal anti-inflammatory drugs
OIBD - Opioid-induced bowel dysfunction
OIH - Opioid-induced hyperalgesia
OME - Oral Morphine Equivalents
OOWS - Objective Opioid Withdrawal Scale
ORT - Opioid Risk Tool
OUD - Opioid use disorder
PAS - Psychoactive substances
PDMP - Prescription Drug Monitoring Program
PTSD - Post-traumatic stress disorder
QoL - Quality of life
SAMHSA - The Substance Abuse and Mental Health Services Administration
SOWS - Subjective Opioid Withdrawal Scale
SUD - Substance use disorder
VAS - Visual Analogue Scale
VTA - Ventral tegmental area

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INTRODUCTION

RESEARCH PROBLEM, RELEVANCE, AND SIGNIFICANCE

In the past two decades, opioids have increasingly been utilized for the management of persistent pain, particularly in cases where conventional therapies have proven insufficient. [1]

The management of chronic pain often involves the use of prescription opioids, which are recognized for their efficacy in acute pain relief and short-term settings. However, the long-term use of these medications has become increasingly controversial due to mounting evidence highlighting their association with adverse effects, including the development of opioid tolerance and dependency. Despite their effectiveness in alleviating pain, chronic opioid therapy is linked to a significant range of challenges, such as escalating doses required to maintain efficacy, the risk of addiction, and broader societal consequences, including economic burdens. Additionally, the prolonged use of opioids is frequently associated with a decline in patients' overall quality of life (QoL), as well as physical, psychological, and social impairments, underscoring the complexity and risks inherent in their use for chronic pain management. These concerns have prompted ongoing debates regarding their role in long-term treatment strategies and the need for alternative approaches that prioritize both efficacy and safety. [1,2]

Chronic non-cancer pain (CNCP) remains a prevalent and debilitating condition affecting up to 22% of adults globally [1], affecting millions worldwide, significantly impairing QoL and functional outcomes. Opioids have shown limited effectiveness in the long-term management of CNCP. While they may provide significant short-term relief, their efficacy diminishes over time, particularly in the context of persistent pain conditions that require prolonged therapy. Evidence from a multicenter, prospective cohort study underscores this limitation, revealing that patients using opioids for CNCP did not experience substantial improvements in key areas such as pain symptoms, physical function, emotional well-being, or social and familial disability over a two-year period [3].

This lack of sustained benefit is often attributed to the development of opioid tolerance, where increased dosages are needed to achieve the same level of analgesia, potentially exacerbating adverse effects without enhancing therapeutic outcomes. Additionally, opioids may contribute to opioid-induced hyperalgesia (OIH), a paradoxical condition in which prolonged opioid use heightens sensitivity to pain, further complicating their utility in chronic pain management [4].

Given these findings, the routine use of opioids for CNCP is increasingly questioned, particularly when weighed against their risks, including dependence, addiction, and the potential for misuse. Consequently, clinical guidelines and pain management strategies are shifting toward multidisciplinary approaches, integrating non-opioid pharmacological treatments and non-pharmacological therapies, such as cognitive-behavioral therapy, physical rehabilitation, and interventional pain procedures, to optimize patient outcomes and mitigate the risks associated with long-term opioid use [5-7].

Despite the widespread utilization of opioids for chronic pain management and increasing awareness of their addictive potential, there remains a significant gap in research exploring the effects of detoxification on quality of life (QoL) and pain management outcomes [8]. Detoxification, defined as the medically supervised withdrawal from opioids, serves as a critical component of treatment for opioid dependence. However, it is frequently met with skepticism within clinical practice due to concerns regarding its impact on pain management, the potential exacerbation of withdrawal-associated discomfort, and the risk of relapse following cessation [8].

One of the key challenges associated with detoxification is the perception that it may leave patients with chronic pain undertreated, particularly when effective alternative pain management strategies are not readily available. Additionally, withdrawal symptoms, including anxiety, agitation, and hyperalgesia, may exacerbate pre-existing pain conditions, creating a barrier to successful detoxification [9]. As a result, patients and healthcare providers often express reluctance to pursue detoxification, fearing a reduction in QoL and increased pain burden.

While limited, some studies suggest that detoxification, when paired with comprehensive care models, can yield positive outcomes. For instance, programs integrating detoxification with behavioral interventions, non-opioid analgesics, and multidisciplinary pain management approaches have demonstrated improvements in patient-reported outcomes, including reductions in opioid dependence and enhancements in physical and emotional well-being [10, 11].

However, there is an increasing focus on exploring whether successful detoxification can lead to measurable improvements in QoL by addressing the adverse effects associated with long-term opioid use. Prolonged opioid therapy is often accompanied by significant negative outcomes, including physical dependence, opioid-induced hyperalgesia, hormonal dysregulation, and cognitive impairment, all of which can diminish overall well-being and functionality [12]. Opioid-induced bowel dysfunction (OIBD) significantly

compromises both the physical and psychological well-being of affected patients. Consequently, detoxification, which facilitates the cessation of opioid use, has the potential to alleviate these burdens and enhance QoL by restoring physiological and psychological homeostasis.

Emerging evidence suggests that successful detoxification may indeed contribute to improved QoL, particularly when it is part of a comprehensive care approach. For example, studies have found that patients who successfully transition off opioids through medically supervised detoxification report benefits such as reduced sedation, improved cognitive clarity, and a restoration of natural pain modulation mechanisms over time [13]. These improvements may also extend to psychosocial dimensions, as individuals experience enhanced emotional stability, increased capacity for social engagement, and reduced stigma associated with opioid dependence [14].

Furthermore, detoxification may allow patients to engage more fully with non-opioid-based therapies for chronic pain management, such as physical rehabilitation, behavioral interventions, and complementary modalities. These strategies, when implemented alongside detoxification, may collectively enhance QoL by fostering long-term functional improvements and empowering patients with self-management tools [15].

Both physicians and patients frequently approach the initiation of prescription opioids with caution, primarily due to concerns about the potential for addiction and the challenges associated with discontinuing these medications once dependence has developed. Physicians' reluctance to initiate opioid therapy also stems from concerns about the difficulty of managing dependence and withdrawal once patients begin using these medications. The process of discontinuing opioids can be complex and is often accompanied by withdrawal symptoms, heightened pain sensitivity, and a risk of relapse, all of which may discourage both patients and healthcare providers from pursuing opioid therapy in the first place [16]. This apprehension is rooted in the complex interplay between the benefits and risks of opioid therapy for chronic pain management, as well as the growing recognition of the opioid epidemic's impact on public health. These concerns are particularly relevant in light of the variability in reported addiction rates among patients with chronic pain, which range from as low as 3-4% to as high as 8-12%, depending on the population studied and the criteria used to define addiction [17, 18].

The lower end of the risk spectrum is often associated with well-controlled studies in which opioids are prescribed to carefully selected patients under stringent monitoring. In contrast, higher rates of addiction are reported in populations with risk factors such as a history of substance use disorders, psychiatric comorbidities, or inadequate pain management plans [16]. This

variability highlights the importance of individualizing treatment decisions and assessing the risks and benefits of opioid therapy on a case-by-case basis.

Addressing these concerns requires a multifaceted approach that emphasizes proper patient selection, education about the risks of opioid therapy, and the implementation of robust monitoring and tapering strategies. Additionally, the integration of alternative pain management modalities, such as cognitive-behavioral therapy, physical therapy, and non-opioid pharmacological treatments, may help mitigate reliance on opioids and reduce the risk of addiction.

The wide range of addiction risk estimates, from 3–4% to 8–12%, underscores the multifaceted nature of addiction, which arises from the interplay of physical, psychological, and genetic factors [17,18]. Addiction is not solely a pharmacological consequence of opioid use but rather a complex disorder influenced by individual vulnerabilities, environmental factors, and the context in which opioids are prescribed and used [13]. These factors create significant variability in the likelihood of addiction development among patients receiving opioids for chronic pain.

Physiological factors, such as the neurochemical changes induced by prolonged opioid use, play a key role in the development of addiction. Chronic exposure to opioids alters the brain's reward pathways, reducing the natural production of endogenous opioids and increasing dependence on exogenous sources to maintain homeostasis. This neuroadaptation is further exacerbated by opioid-induced hyperalgesia, which can increase patients' pain sensitivity and reliance on opioids [9, 19].

Psychological factors, including pre-existing mental health conditions such as anxiety, depression, or post-traumatic stress disorder (PTSD), are also significant contributors to addiction risk. Individuals with such conditions may use opioids not only for pain relief but also as a coping mechanism for psychological distress, thereby increasing their susceptibility to misuse and dependence [20]. Additionally, a history of substance use disorder is a strong predictor of opioid addiction, as it reflects underlying vulnerabilities in reward system regulation.

Genetic factors further complicate the landscape of addiction risk. Research indicates that genetic predispositions can influence opioid metabolism, receptor sensitivity, and individual susceptibility to addiction. Variations in genes such as OPRM1, which encodes the mu-opioid receptor, have been associated with differences in opioid efficacy and addiction risk [21]. These genetic components interact with environmental exposures, including socioeconomic status, access to healthcare, and social support systems, to shape an individual's overall risk profile.

This complexity highlights the necessity of personalized approaches to opioid prescribing and addiction prevention. Comprehensive risk assessments that consider physical, psychological, and genetic factors can aid in identifying patients at higher risk for addiction, enabling the implementation of targeted interventions. Furthermore, ongoing research into the underlying mechanisms of addiction is essential to inform the development of more effective prevention and treatment strategies.

Physical dependence on opioids is a well-documented phenomenon characterized by the occurrence of withdrawal symptoms when the medication is discontinued or the dosage is significantly reduced. Withdrawal symptoms may include nausea, vomiting, diarrhea, muscle aches, anxiety, and insomnia, among others, making the cessation of opioid use both physically and psychologically challenging [9,16]. These symptoms arise due to the body's physiological adaptation to the presence of opioids, resulting in altered neurochemical processes. When opioids are abruptly withdrawn, the body struggles to restore its natural balance, leading to the distressing symptoms of withdrawal.

In addition to physical dependence, tolerance is another significant factor complicating opioid use. Tolerance occurs when repeated exposure to opioids reduces their effectiveness, requiring progressively higher doses to achieve the same level of pain relief or euphoria [13]. This phenomenon is linked to neuroadaptive changes in opioid receptors and downstream signaling pathways, which diminish the drug's analgesic effects over time. The escalating dosages associated with tolerance not only increase the risk of side effects and overdose but also deepen the cycle of dependence [22].

These intertwined phenomena of dependence and tolerance create substantial barriers to ceasing opioid use, particularly for individuals managing chronic pain. For many patients, the fear of experiencing withdrawal symptoms or inadequately controlled pain deters attempts to taper or discontinue opioids [15]. Moreover, the neurobiological changes induced by long-term opioid use may persist even after cessation, potentially leading to cravings and an increased risk of relapse [23].

Addressing these challenges requires a comprehensive, multidisciplinary approach that incorporates gradual tapering schedules, non-opioid pain management strategies, and psychosocial support to mitigate withdrawal symptoms and facilitate recovery.

RESEARCH AIM: This study aims to systematically examine whether the discontinuation of prescription opioid therapy leads to measurable improvements in physical, psychological, and social well-being.

RESEARCH OBJECTIVES:

1. To assess changes in the quality of life of in patients with chronic pain with long-term prescription opioids usage before and after detoxification.
2. To characterize the specific demographic, clinical attributes of patients and to identify the indications, duration, type, and dosage of opioid therapy in patients with chronic pain undergoing long-term prescription opioid treatment.
3. To evaluate the effectiveness of detoxification treatment in terms of pain perception and opioid cessation and duration of detoxification
4. To investigate the relationship between baseline blood vitamin D concentration and detoxification outcomes, examining its potential influence on quality of life and pain perception.

NOVELTY OF THE RESEARCH

While existing research extensively examines the physiological and psychological aspects of opioid detoxification, this study uniquely prioritizes quality of life (QoL) as a central outcome. It provides a holistic perspective by assessing improvements in physical, emotional, and social well-being post-detoxification.

Unlike many studies that focus on withdrawal symptoms or relapse rates, this research investigates changes in pain perception following opioid cessation. By determining whether detoxification leads to pain relief or exacerbation, the study addresses a crucial but underexplored aspect of opioid dependence treatment.

The investigation into the role of baseline vitamin D levels in quality of life and pain perception pre-detoxification is a novel contribution. Existing research on vitamin D primarily focuses on musculoskeletal health and chronic pain, whereas this study explores its potential influence on detoxification success and overall well-being.

While many studies focus on short-term detoxification outcomes, this research aims to assess the long-term impact on patients' QoL. By evaluating whether detoxification translates into sustained improvements in well-being, the study addresses an essential gap in opioid dependence research.

The findings have the potential to inform clinical guidelines for opioid detoxification programs, emphasizing a patient-centered approach that

considers QoL improvements alongside withdrawal management. Additionally, the study may provide evidence for policy changes related to opioid prescribing, detoxification protocols, and adjunctive therapies such as vitamin D supplementation.

This research contributes novel insights by combining clinical, biochemical, and psychosocial perspectives, offering a more comprehensive understanding of the impact of opioid detoxification on patients' overall well-being.

PRACTICAL RELEVANCE OF THE RESEARCH

Prolonged use of prescription opioids frequently leads to the development of tolerance, necessitating progressively higher doses to achieve the same analgesic effect. As tolerance increases, patients are at heightened risk of physical and psychological dependence, further complicating pain management and leading to long-term opioid use. Chronic administration of opioids at supra-therapeutic doses is associated with a broad spectrum of adverse effects, including gastrointestinal disturbances (constipation, nausea), neuropsychiatric complications (depression, cognitive impairment, sleep disturbances), increased risk of trauma, and cardiovascular events such as myocardial infarction. Moreover, prolonged opioid use negatively impacts endocrine and immune system function, contributing to metabolic disturbances, immunosuppression, and overall physiological deterioration. Critically, opioid dependence significantly elevates the risk of overdose, respiratory depression, and cardiac arrest, making it a major public health concern. These adverse effects collectively result in a decline in patients' quality of life and impose substantial economic burdens on healthcare systems due to increased hospitalizations, emergency interventions, and long-term pharmacological treatments.

Detoxification remains a fundamental treatment strategy for patients seeking to discontinue opioid use. The primary objective of detoxification is to facilitate opioid cessation within an optimally short duration while minimizing withdrawal symptoms and mitigating the negative consequences of dependence. Although detoxification is widely implemented in clinical practice, research specifically examining its effectiveness in improving quality of life among individual’s dependent on prescription opioids remains limited. Many studies focus on illicit opioid use, such as heroin or fentanyl, while prescription opioid dependence presents distinct challenges due to its clinical origins, patient demographics, and comorbidities. This study seeks to bridge this gap by evaluating the impact of detoxification on quality of life,

pain perception, and overall well-being in patients who have been prescribed opioids for chronic pain management.

Previous research on opioid detoxification has led to notable advancements in treatment approaches. Notably, the dissertation defended by Dr. T. Jovaiša in 2006, titled "The Effects of N-Methyl-D-Aspartate Receptor Antagonist Ketamine and General Anesthesia on Opioid-Induced Withdrawal" [24, 25] explored pharmacological strategies to alleviate withdrawal symptoms. More recently, Dr. R. Badaras 2016 dissertation, "Rapid Opioid Detoxification Using a Novel Method of Gradual Naltrexone Dose Induction" [26], introduced an alternative approach for opioid discontinuation with a focus on minimizing withdrawal discomfort. However, despite these contributions, research remains scarce on the long-term impact of detoxification on patients' quality of life, pain perception and psychological well-being.

This dissertation extends and builds upon these prior investigations by providing a comprehensive analysis of opioid detoxification outcomes in patients dependent on prescription opioids. A key innovative aspect of this study is its focus on quality-of-life assessment, including psychological, social, and functional domains, rather than solely measuring withdrawal severity or relapse rates. Additionally, this research will explore the role of vitamin D levels in influencing detoxification outcomes, a novel factor that has not been extensively studied in the context of opioid dependence. The findings of this study have the potential to inform clinical practice, optimize detoxification protocols, and contribute to the development of personalized treatment strategies aimed at improving long-term patient outcomes.

POTENTIAL BENEFITS OF THE BIOMEDICAL STUDY (SCIENTIFIC AND PARTICIPANT-RELATED)

1. Validation of Hypotheses on Quality of Life Improvement.

The study aimed to validate the hypothesis that detoxification improves the quality of life for pain patients dependent on prescription opioids. By systematically analyzing changes in participants' physical, emotional, and social well-being, the research sought to establish a link between effective detoxification and enhanced life quality.

2. The Importance of Providing Access to Detoxification.

This is an additional possibility for the patients to start opioid detoxification procedure. By participating in the research, patients can start a complex treatment of opioid use disorder.

Detoxification should be recognized as a fundamental treatment option for individual's dependent on prescription opioids. Opioid medications are widely prescribed for various clinical indications, ranging from acute pain management to the long-term treatment of chronic pain conditions. Due to the pharmacological properties of opioids, the development of tolerance is a biochemically inevitable process, necessitating progressively higher doses to achieve the same analgesic effect. As a result, prolonged opioid use often leads to physical dependence, even in cases where the medication has been used strictly in accordance with medical guidelines.

However, while tolerance and dependence are well-documented consequences of long-term opioid therapy, the critical issue is not their inevitability but rather the need to ensure unhindered access to detoxification as a means of improving quality of life. Many patients remain on opioids due to fear of withdrawal symptoms, concerns about pain recurrence, or uncertainty regarding alternative pain management strategies. Such apprehensions can lead to prolonged opioid use, increasing the risk of adverse effects, dependence, and diminished overall well-being.

This study underscores the necessity of viewing detoxification not as an insurmountable challenge but as a structured therapeutic intervention designed to facilitate opioid cessation while minimizing discomfort and improving patient outcomes. When appropriately managed, detoxification has the potential to restore physical health, psychological stability, and social functioning, ultimately enhancing patients' quality of life. By addressing prevailing misconceptions and identifying barriers associated with opioid discontinuation, this research aims to promote greater confidence in detoxification as a viable and beneficial step toward recovery. Furthermore, the findings will contribute to the development of evidence-based clinical practices that facilitate safer and more effective opioid withdrawal strategies, ensuring that patients receive the necessary support throughout the detoxification process.

1. LITERATURE REVIEW

1.1. Chronic Pain Management with Non-Opioid Medicine and Prescription Opioids

Chronic pain, defined as pain persisting for more than three months, represents a significant clinical challenge due to its profound impact on quality of life, functionality, and overall health [27]. It often leads to considerable distress and impairs daily activities, highlighting the necessity for effective pain management strategies. While chronic pain has been partially recognized in the ICD-10 classification (e.g., G89.1, R52.1), it lacked a comprehensive and systematic representation, limiting epidemiological research and complicating health policy decisions related to resource allocation and access to multimodal pain management.

To address these limitations, the International Association for the Study of Pain [28], in collaboration with the World Health Organization (WHO) [29], developed a refined classification system for chronic pain within ICD-11. This updated framework provides a structured approach to categorizing chronic primary pain (e.g., fibromyalgia, chronic nonspecific low back pain) and chronic secondary pain (e.g., cancer pain, postsurgical pain, neuropathic pain), ensuring improved diagnostic precision and facilitating better integration of pain management into diverse healthcare settings, including primary care and resource-limited environments.

In certain syndromes, chronic pain manifests as the primary or sole clinical complaint, necessitating specialized treatment and management. Conditions such as fibromyalgia and nonspecific low back pain are classified under the broader category of chronic primary pain, recognizing them as distinct disease entities rather than symptoms of an underlying pathology. In contrast, other forms of chronic pain arise secondary to identifiable medical conditions and are categorized into six distinct subgroups: chronic cancer-related pain, chronic neuropathic pain, chronic secondary visceral pain, chronic posttraumatic and postsurgical pain, chronic secondary headache and orofacial pain, and chronic secondary musculoskeletal pain. This classification framework facilitates the differentiation between pain as a symptom of an underlying disease and pain as a disease entity in its own right [28, 29].

The incorporation of these classifications into the 11th edition of the International Classification of Diseases (ICD-11) represents a significant advancement in the diagnostic coding of chronic pain. By providing a more structured and comprehensive approach, this revision is expected to enhance

the recognition of chronic pain as a distinct and significant health condition, thereby improving epidemiological research, clinical decision-making, and health policy formulation. The standardized classification will further support resource allocation and the development of targeted pain management strategies, ensuring more effective treatment for affected individuals.

Historically, chronic pain management has oscillated between pharmacological and non-pharmacological treatment modalities, reflecting the complexity of pain pathophysiology and patient variability. Among pharmacological interventions, opioids have traditionally played a central role in pain management; however, their long-term efficacy and safety remain subjects of ongoing debate [15, 30]. Concerns regarding tolerance, dependence, adverse effects, and the potential for misuse have led to increased scrutiny over their appropriateness in chronic pain treatment. As a result, there is a growing emphasis on multimodal and interdisciplinary pain management strategies, incorporating non-opioid pharmacotherapies, psychological interventions, physical rehabilitation, and integrative therapies to optimize patient outcomes while mitigating the risks associated with long-term opioid use.

1.1.1. Non-Opioid Medicine in Chronic Pain Management

Non-opioid pharmacological agents play a crucial role in the management of chronic pain, offering diverse mechanisms of action that target various underlying pain pathways while avoiding the risks associated with long-term opioid use. These medications include common analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as adjuvant therapies like antidepressants and anticonvulsants, which are particularly effective for neuropathic and mixed pain conditions.

Acetaminophen and NSAIDs, such as ibuprofen and naproxen, are widely used as first-line treatments for mild to moderate chronic pain. These agents primarily act by inhibiting the cyclooxygenase (COX) enzymes, thereby reducing inflammation and peripheral sensitization of nociceptors. Despite their effectiveness, NSAIDs are associated with gastrointestinal, cardiovascular, and renal side effects, particularly when used long-term [31]. Acetaminophen, though generally safer, carries a risk of hepatotoxicity at higher doses [32].

Antidepressants, such as amitriptyline, nortriptyline, and duloxetine, are frequently prescribed for chronic pain, particularly neuropathic pain and fibromyalgia. Tricyclic antidepressants (TCAs) like amitriptyline exert their analgesic effects by inhibiting the reuptake of serotonin and norepinephrine, enhancing endogenous pain modulation pathways. Selective serotonin-

norepinephrine reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine, offer similar benefits but with a more favorable side effect profile [33]. These medications are particularly effective in reducing pain intensity and improving quality of life in conditions such as diabetic neuropathy and chronic musculoskeletal pain.

Anticonvulsants, including gabapentin and pregabalin, are integral to the management of neuropathic pain. These drugs bind to the α2δ subunit of voltage-gated calcium channels, reducing excitatory neurotransmitter release in hyperexcitable neurons [34]. Clinical trials have demonstrated their efficacy in conditions such as postherpetic neuralgia, diabetic neuropathy, and spinal cord injury-related pain. Common side effects include dizziness, sedation, and weight gain, necessitating cautious titration to minimize adverse effects [35].

While non-opioid pharmacological agents are effective in many forms of chronic pain, their benefits are often condition specific. For instance, NSAIDs may be more effective in inflammatory conditions such as osteoarthritis, while anticonvulsants and antidepressants are better suited for neuropathic pain [33]. However, non-opioid therapies are not without limitations; their efficacy may be insufficient for severe pain syndromes, and their side effect profiles require careful consideration in vulnerable populations such as the elderly or those with comorbidities. These medications often serve as first-line treatments due to their relatively favorable safety profiles and efficacy in specific pain syndromes, such as neuropathic pain.

1.1.2. Prescription Opioids: Efficacy and Safety in Chronic Pain

Prescription opioids, such as morphine, oxycodone, and fentanyl, are potent analgesics widely prescribed for the management of moderate to severe pain that does not respond to non-opioid therapies. These medications act primarily on the mu-opioid receptors in the central nervous system, altering the perception of pain and producing analgesia [13]. Opioids have demonstrated significant efficacy in managing acute pain and cancer-related pain, where their benefits often outweigh associated risks [36, 37]. However, the use of opioids for chronic non-cancer pain (CNCP) remains highly debated within the medical community. While some studies suggest opioids may provide moderate relief for CNCP in select patients, concerns about the long-term effectiveness and safety of these drugs persist. Potential issues include tolerance, physical dependence, opioid use disorder (OUD), and the risk of overdose [15]. Additionally, evidence suggests that opioids may have limited

efficacy in improving functional outcomes in CNCP patients, raising questions about their overall benefit in this population [38].

Given the risks associated with long-term opioid therapy, clinical guidelines emphasize a cautious and judicious approach to prescribing opioids for CNCP, prioritizing non-pharmacological and non-opioid pharmacological interventions whenever possible [36].

The long-term efficacy of opioids for CNCP remains uncertain, as randomized controlled trials often span only a few months and fail to capture long-term outcomes. For instance, Krebs et al. found no significant difference in pain-related function between opioid and non-opioid treatments in patients with chronic back pain and osteoarthritis over a 12-month period [30]. This finding underscores the potential limitations of opioids in providing sustained relief for CNCP.

1.1.3. Unanswered Questions: Long-Term Benefits and Dosing Strategies

Two critical questions persist in the literature:

1. Is opioid therapy beneficial in the long term? While short-term studies suggest that opioids can improve pain intensity and quality of life, evidence regarding their long-term benefits is sparse. Observational studies and retrospective analyses often indicate diminishing returns with prolonged use, accompanied by risks such as tolerance, dependence, and opioid-induced hyperalgesia [13]. Additionally, long-term opioid therapy is associated with adverse outcomes, including cognitive impairment, hormonal dysregulation, and increased risk of overdose.

2. Does the dose influence the efficacy and safety of long-term opioid therapy? The relationship between opioid dose and clinical outcomes remains complex. Higher doses are often correlated with increased risks of adverse effects, including respiratory depression, sedation, and opioid use disorder [36]. Conversely, insufficient dosing may fail to provide adequate analgesia, leading to functional limitations and poor quality of life. The fundamental principle of pain management-increasing the dose until maximal analgesia is achieved with minimal side effects-is particularly challenging in chronic pain due to interpatient variability in opioid responsiveness and tolerance.

1.1.4. Recommendations for Dosing Strategies

Experts advocate for cautious and individualized dosing in chronic pain management. Initial dose titration should occur over weeks, starting with the lowest effective dose and monitoring for efficacy and side effects. Subsequent dose increases should be introduced only after careful consideration of risks and benefits, particularly for patients with comorbidities or a history of substance use disorder. Dowell et al. emphasize the importance of regular reassessment, tapering unnecessary opioid use, and integrating multimodal approaches to optimize outcomes [36].

The management of chronic pain requires a nuanced approach that balances the benefits and risks of pharmacological therapies. Non-opioid medications play a vital role in many cases, particularly for neuropathic and mild to moderate pain. While opioids may provide relief for select patients with severe pain, their long-term utility is limited by concerns about efficacy, safety, and the development of tolerance and dependence. Addressing unanswered questions through well-designed longitudinal studies is crucial to inform evidence-based guidelines and optimize treatment strategies for chronic pain.

1.2. Evaluating Changes in Quality of Life in Patients with Chronic Pain with Prescription Opioid usage Before and After Detoxification

The neurobiological mechanisms underlying tolerance and addiction to psychoactive substances are highly intricate, involving dysregulated reward pathways, maladaptive neuroplasticity, stress system activation, and impaired executive control. Understanding these processes is critical for developing targeted treatments, such as pharmacological interventions that restore neurochemical balance or behavioral therapies that strengthen executive control.

1.2.1. Neurobiological Mechanisms of Psychoactive Substance Addiction Development

The development of addiction to psychoactive substances (PAS) is rooted in complex neurobiological mechanisms involving the interplay of brain reward, stress, and executive control systems. These processes are primarily driven by the dysregulation of neurotransmitter systems, neuroplasticity, and altered brain circuitry, which collectively reinforce compulsive substance use behaviors [36].

At the core of addiction is the dysregulation of the brain's reward system, predominantly mediated by the mesolimbic dopamine pathway. Psychoactive substances overstimulate dopaminergic neurons in the ventral tegmental area (VTA), leading to excessive dopamine release in the nucleus accumbens, a key region associated with reward and pleasure [39]. This overstimulation creates a heightened sense of euphoria, reinforcing substance-seeking behavior. Over time, repeated substance use diminishes the brain's natural reward responses, requiring increasing amounts of the substance to achieve the same effect, a phenomenon known as tolerance [23].

Chronic substance use induces significant neuroplastic changes in the brain, particularly in the synaptic connections within the prefrontal cortex, amygdala, and striatum. These changes alter the brain's ability to regulate reward and motivation, enhancing the salience of substance-related cues while diminishing the value of natural rewards [40]. This maladaptive learning process strengthens substance-seeking behaviors and contributes to the persistence of addiction, even in the face of adverse consequences.

The hypothalamic-pituitary-adrenal (HPA) axis and extended amygdala play a critical role in the transition from recreational use to addiction. Psychoactive substances activate the stress response system, initially providing temporary relief from negative emotional states. However, chronic use leads to dysregulation of the stress system, resulting in heightened sensitivity to stress and negative emotions during withdrawal [40]. This perpetuates a cycle of substance use to avoid or alleviate withdrawal-induced discomfort, known as negative reinforcement.

Addiction also involves the impairment of executive control functions, primarily mediated by the prefrontal cortex. Chronic substance use disrupts decision-making, impulse control, and the ability to assess long-term consequences. This diminished executive control, combined with heightened reward sensitivity and stress dysregulation, creates a neural environment that favors compulsive substance use [40, 41].

Genetic predisposition and epigenetic modifications further influence addiction vulnerability. Variations in genes related to dopamine signaling, stress regulation, and synaptic plasticity have been associated with increased susceptibility to addiction [42]. Additionally, epigenetic changes induced by chronic substance use can alter gene expression, reinforcing addictive behaviors and complicating recovery efforts.

1.2.2. Opioid Tolerance

Chronic prescription opioid use is associated with the development of tolerance, a physiological process where the body becomes less responsive to a drug over time. Tolerance occurs because repeated exposure to opioids leads to adaptations in the nervous system, such as downregulation or desensitization of opioid receptors [13]. This process is largely attributed to neuroadaptive changes within the central nervous system, particularly at the level of opioid receptors. Continuous exposure to opioids leads to the downregulation, desensitization, or internalization of mu-opioid receptors (MORs), the primary targets of these drugs, resulting in a diminished pharmacological response [59]. The development of tolerance involves complex intracellular signaling pathways, including the activation of protein kinase C and beta-arrestin, which modulate receptor activity and contribute to the attenuation of drug efficacy [9]. Consequently, individuals on long-term opioid therapy may require progressively higher doses to achieve the same level of analgesia, increasing the risks of adverse effects and dependence [1].

This dose escalation can exacerbate dependence, a state where the body adapts to the presence of the drug and experiences withdrawal symptoms upon cessation [43]. Dependence, coupled with tolerance, increases the risk of misuse and complicates the management of chronic pain, as higher doses are associated with greater side effects, including respiratory depression and hyperalgesia-heightened sensitivity to pain caused by long-term opioid use [1]. Consequently, this cycle of tolerance, dependence, and escalating doses underscores the challenges of chronic opioid therapy and the need for careful monitoring and alternative pain management strategies.

1.2.3. Opioid-Induced Hyperalgesia

Patients prescribed opioids for pain management may encounter a paradoxical phenomenon known as opioid-induced hyperalgesia (OIH), which complicates the clinical picture of chronic pain. OIH is a condition where prolonged use of opioid medications not only fails to alleviate pain but paradoxically increases pain sensitivity, thereby exacerbating the very symptoms these medications are intended to relieve. This state is marked by a reduction in pain threshold and tolerance, leading to heightened pain perception and, consequently, higher pain scores reported by patients [44-46]. OIH can manifest in both chronic pain patients and those undergoing surgical interventions, particularly when treated with potent opioids such as remifentanil, fentanyl, or morphine [46-47].

The pathophysiology of OIH is multifaceted and involves neuroplastic changes in the central nervous system. Key mechanisms include the activation of pronociceptive pathways, particularly through the upregulation and increased activity of N-methyl-D-aspartate (NMDA) receptors. NMDA receptor activation has been linked to central sensitization, a state in which neurons in the spinal cord and brain become hyperresponsive to sensory input, thereby amplifying pain signals [48]. Additionally, prolonged opioid use can lead to the activation of glial cells, such as microglia and astrocytes, which release proinflammatory cytokines and other mediators that exacerbate nociceptive signaling [49]. Dysregulation of descending inhibitory pathways and increased oxidative stress further contribute to the hyperalgesic state [50].

The clinical implications of OIH are profound, as it not only undermines the primary therapeutic goal of opioids-pain relief-but also complicates the management of chronic pain. Patients with OIH may report worsening pain despite escalating doses of opioids, leading to a self-perpetuating cycle of dose escalation and further hyperalgesia [47]. This cycle not only increases the risk of adverse effects such as sedation, respiratory depression, and opioid use disorder but also places a significant burden on healthcare resources

Given the implications of OIH, clinicians are urged to adopt multimodal pain management strategies that minimize opioid reliance. These may include non-opioid analgesics, adjuvant therapies, and integrative approaches such as cognitive-behavioral therapy and physical rehabilitation. Furthermore, tapering or rotating opioids, as well as exploring emerging pharmacological interventions targeting the mechanisms of OIH, may offer potential pathways to mitigate its impact [46, 47]. Early identification and intervention are crucial to breaking the cycle of OIH, improving pain outcomes, and enhancing the overall quality of life for patients.

Emerging research into pharmacological agents that target the underlying mechanisms of OIH holds promise for improving outcomes in this patient population. For example, NMDA receptor antagonists such as ketamine have demonstrated efficacy in reducing hyperalgesia by modulating excitatory signaling [51]. Similarly, drugs that inhibit glial cell activation or block pronociceptive mediators are being explored as potential adjuncts to opioid therapy [48]. These advancements underscore the importance of a comprehensive and personalized approach to managing chronic pain in the context of opioid therapy.

1.2.4. Short-Term Somatic Effects of Long-term Prescription Opioid Usage

Prescription opioids, widely utilized for managing chronic pain, exert their analgesic effects primarily through their action on the central nervous system (CNS) by binding to opioid receptors. However, even in the short term, their use can result in several adverse somatic effects, some of which may necessitate medical intervention.

1.2.4.1. Gastrointestinal Effects

Opioid medications, widely used for managing both acute and chronic pain, are frequently associated with a range of gastrointestinal side effects collectively referred to as opioid-induced bowel dysfunction (OIBD). These adverse effects, which include nausea, vomiting, and constipation, significantly impact patients' quality of life and may complicate long-term pain management strategies.

The primary mechanism underlying OIBD is the interaction of opioids with mu-opioid receptors in the gastrointestinal tract. Opioids inhibit the release of acetylcholine and other neurotransmitters within the enteric nervous system, leading to reduced peristaltic activity and prolonged transit time in the intestines [52]. This reduction in motility results in constipation, the most prevalent and clinically significant symptom of OIBD.

Additionally, opioids increase the tone of the intestinal smooth muscles, including the sphincters, further impeding normal GI motility [53]. These effects are compounded by the reduced secretion of intestinal fluids and impaired coordination of reflexes necessary for defecation.

Clinical Manifestations and Implications:

1. Nausea and Vomiting**:** The stimulation of opioid receptors in the chemoreceptor trigger zone (CTZ) of the brainstem leads to nausea and vomiting, particularly during the initiation of opioid therapy or with dose escalation. These symptoms are distressing and may lead to decreased adherence to prescribed opioid regimens [54].
2. Constipation: Constipation is the hallmark symptom of OIBD and occurs in approximately 40–95% of patients on long-term opioid therapy [52, 53]. It is characterized by infrequent bowel movements, straining, hard stools, and a sensation of incomplete evacuation. Constipation not only impairs physical well-being but also contributes to psychological distress, further exacerbating the overall disease burden.
3. Abdominal Discomfort: Patients may experience bloating, cramping, and abdominal pain because of slowed gastrointestinal transit and the accumulation of gas and fecal matter [53].
4. Malabsorption and Nutritional Deficits: Prolonged constipation can impair nutrient absorption, leading to secondary nutritional deficiencies. These deficits are particularly concerning in elderly or debilitated patients, where adequate nutrition is critical to recovery and overall health [52-54].

OIBD is a major contributor to reduced quality of life in patients requiring opioid therapy. Chronic constipation imposes a substantial physical and psychological burden, often resulting in diminished daily functioning, reduced social engagement, and increased healthcare utilization [55]. In severe cases, untreated OIBD may lead to complications such as fecal impaction, rectal prolapse, or bowel perforation. Effective management of OIBD is essential to improving patient outcomes and minimizing the adverse effects of opioid therapy [55]. Strategies include:

1. Laxatives**:** First-line treatments include stimulant laxatives (e.g., senna) and osmotic agents (e.g., polyethylene glycol), which help counteract reduced motility and facilitate bowel movements.
2. Prokinetic Agents**:** Medications such as prucalopride, a serotonin receptor agonist, may improve GI motility and alleviate symptoms.
3. Peripherally Acting Mu-Opioid Receptor Antagonists: Drugs like naloxegol and methylnaltrexone selectively block opioid receptors in the GI tract without affecting analgesia, providing targeted relief from OIBD.

4. Lifestyle Modifications**:** Increased dietary fiber intake, adequate hydration, and physical activity are recommended to support gastrointestinal health.
5. Opioid Rotation or Tapering: Transitioning to opioids with lower constipating potential or reducing the opioid dose may also alleviate symptoms in select patients.

Gastrointestinal effects, particularly constipation, represent a significant challenge in the management of chronic pain with opioids. Recognizing and addressing these adverse effects is crucial to maintaining patient adherence, optimizing therapeutic outcomes, and enhancing overall quality of life. Further research is needed to develop more targeted therapies that mitigate these effects without compromising analgesic efficacy.

1.2.4.2. Neurological Effects

Acute administration of prescription opioids is associated with various neurological effects, including drowsiness, dizziness, and cognitive impairments. These effects are mediated by the action of opioids on the central nervous system, particularly through their interaction with μ-opioid receptors, which modulate pain perception but also influence alertness and cognitive function [39].

Drowsiness and sedation are among the most reported adverse effects and can significantly impair an individual's ability to stay alert, react swiftly, and maintain focus. Similarly, dizziness, often linked to opioid-induced hypotension or vestibular dysfunction, can compromise physical stability and increase the risk of falls or injuries [7].

Cognitive impairments, including slowed information processing and reduced executive functioning, have been observed even at therapeutic doses, highlighting the potential dangers of acute opioid use in situations requiring high levels of attention and decision-making [7].

These symptoms present risks for individuals engaged in activities requiring sustained alertness, such as driving or operating heavy machinery. Studies have demonstrated that opioid-induced impairments can significantly affect psychomotor performance, increasing the likelihood of accidents and injuries in such contexts [56, 57]. Given these risks, guidelines often emphasize the need for caution and advise against engaging in potentially hazardous activities during periods of opioid use, particularly shortly after initiation or dose escalation [58].

1.2.4.3. Respiratory Depression

Respiratory depression represents one of the most severe and potentially life-threatening adverse effects associated with the acute use of prescription opioids. This condition arises due to the suppression of brainstem respiratory centers, particularly through the activation of μ-opioid receptors. These receptors modulate not only pain but also neural circuits involved in respiratory control, leading to a reduction in both the respiratory rate and tidal volume [59]. The resultant hypoventilation may cause hypercapnia (elevated carbon dioxide levels in the blood) and hypoxemia (reduced oxygen levels), posing significant risks to patient safety.

The risk of respiratory depression increases with higher opioid doses, as greater μ-opioid receptor activation exerts a more profound inhibitory effect on respiratory centers [60]. This risk is further exacerbated when opioids are combined with other central nervous system (CNS) depressants, such as benzodiazepines, alcohol, or sedative-hypnotics, which also contribute to respiratory suppression through distinct but synergistic mechanisms [61]. Polypharmacy involving opioids and CNS depressants is particularly concerning, as it markedly increases the likelihood of overdose and fatal respiratory arrest, even at doses that might be considered therapeutic if taken individually [62].

Clinicians prescribing opioids must be acutely aware of this risk, particularly when managing patients with pre-existing respiratory conditions such as chronic obstructive pulmonary disease (COPD) or sleep apnea, where the baseline vulnerability to hypoventilation is already heightened [63]. Patient education on the dangers of combining opioids with alcohol or sedatives, close monitoring during opioid initiation or dose escalation, and the availability of naloxone-a rapid opioid antagonist-are critical measures to mitigate the risk of respiratory depression [58].

1.2.4.4. Cardiovascular Effects

Prescription opioid use has notable effects on the cardiovascular system, with hypotension and bradycardia being commonly observed short-term outcomes. These effects primarily arise from opioid-induced vasodilation and a reduction in sympathetic nervous system tone [64]. Opioids exert their influence by activating μ-opioid receptors, which can inhibit the release of norepinephrine and diminish adrenergic signaling. This mechanism leads to decreased vascular resistance and reduced heart rate [65].

Hypotension, characterized by abnormally low blood pressure, can pose a significant risk in individuals with underlying cardiovascular conditions, such as ischemic heart disease or heart failure, where adequate perfusion is critical for organ function. Similarly, opioid-induced bradycardia-a slower than normal heart rate-may exacerbate issues in patients predisposed to arrhythmias or conduction abnormalities, increasing the likelihood of adverse cardiovascular events [66].

Furthermore, these effects are particularly concerning in elderly patients and those with coexisting conditions such as diabetes or chronic kidney disease, where autonomic regulation may already be impaired. Clinical vigilance is warranted in these populations, as the cardiovascular effects of opioids may lead to syncope, falls, or even life-threatening hemodynamic instability [7].

1.2.4.5. Dermatological Reactions

Prescription opioid use is frequently associated with dermatological reactions, with pruritus (itching) and urticaria (hives) being the most reported. These reactions result primarily from opioid-induced histamine release from mast cells, a process independent of the immunoglobulin E (IgE)-mediated allergic pathway typically involved in hypersensitivity reactions [67]. Histamine release occurs predominantly with natural and semi-synthetic opioids, such as morphine and codeine, and tends to be dose dependent [68].

Pruritus, characterized by an intense and uncomfortable itching sensation, is a well-recognized adverse effect of opioid therapy. It is thought to be mediated through the activation of μ-opioid receptors in peripheral sensory nerves and the central nervous system [69]. In some cases, this can escalate to urticaria, presenting as raised, red, and itchy welts on the skin. While these reactions are generally not life-threatening, they can significantly impact a patient's comfort and adherence to opioid therapy, particularly during long-term use. Management strategies for opioid-induced pruritus and urticaria typically involve the use of antihistamines to counteract histamine-mediated symptoms. First-generation antihistamines, such as diphenhydramine, are often effective but may cause sedation as a side effect [70].

Alternatively, switching to synthetic opioids with lower histamine-releasing potential, such as fentanyl or hydromorphone, may mitigate these symptoms [69]. In severe cases, adjuvant therapies such as μ-opioid receptor antagonists (e.g., naloxone or naltrexone) have been explored to address opioid-induced pruritus without compromising analgesic efficacy [71].

1.2.5. Long-Term Effects Somatic Effects of Long-term Prescription Opioid Usage

Prolonged use of prescription opioids introduces a different spectrum of adverse effects that can significantly impact patients' overall health and necessitate comprehensive management strategies.

1.2.5.1. Endocrine Dysregulation

Long-term use of prescription opioids is increasingly recognized as a significant risk factor for endocrine dysregulation, particularly through its effects on the hypothalamic-pituitary-adrenal (HPA) axis. Chronic opioid therapy suppresses the hypothalamic release of gonadotropin-releasing hormone (GnRH), leading to a cascade of hormonal imbalances commonly referred to as opioid-induced endocrinopathy [72]. In men, this dysregulation often manifests as hypogonadism, characterized by reduced testosterone levels. Clinical consequences include diminished libido, erectile dysfunction, infertility, muscle wasting, and an increased risk of osteoporosis due to decreased bone mineral density [7, 73].

In women, opioid-induced endocrinopathy can result in menstrual irregularities, such as amenorrhea or oligomenorrhea, due to disrupted ovulatory cycles [74]. Chronic suppression of gonadotropins and estradiol also predisposes women to reduced bone density, heightening the risk of osteopenia and osteoporosis over time. These effects are particularly concerning in premenopausal women, where long-term consequences of reduced estrogen can have lifelong implications on skeletal health [75].

Additionally, alterations in the HPA axis can impair adrenal function, resulting in inadequate cortisol production, which is essential for stress response, metabolism, and immune regulation [76]. Patients with opioid-induced adrenal insufficiency may experience symptoms such as fatigue, weight loss, hypotension, and increased vulnerability to infections.

Given these significant risks, it is imperative for clinicians to monitor endocrine function in patients on long-term opioid therapy. Regular assessment of gonadal and adrenal hormones, combined with early

intervention strategies such as hormone replacement therapy, can mitigate some of these adverse effects.

1.2.5.2. Immune Suppression

Chronic prescription opioid use is linked to immunosuppressive effects, which pose significant risks by increasing susceptibility to infections. The immunomodulatory effects of opioids are primarily mediated through their interaction with opioid receptors expressed on immune cells, including macrophages, lymphocytes, and natural killer (NK) cells [77]. Activation of these receptors alters the functional activity of immune cells, leading to impaired host defenses and dysregulated immune responses.

A critical aspect of opioid-induced immune suppression is the reduction in NK cell activity. NK cells are pivotal in the early defense against viral infections and tumor surveillance. Studies indicate that long-term opioid exposure diminishes NK cell cytotoxicity, potentially increasing the risk of opportunistic infections and malignancies [77]. This effect is particularly concerning in populations already at risk for immune compromise, such as individuals with chronic illnesses or those undergoing invasive procedures.

Additionally, opioids modulate cytokine production, skewing the immune response toward an anti-inflammatory phenotype. This is characterized by decreased levels of pro-inflammatory cytokines, such as interleukin-2 (IL-2) and interferon-gamma (IFN-γ), and increased production of anti-inflammatory cytokines, including interleukin-10 (IL-10) [78]. While this may provide some benefit in reducing inflammation, it simultaneously compromises the immune system's ability to mount an effective response against pathogens.

Clinical implications of opioid-induced immunosuppression include a heightened risk of bacterial infections, such as pneumonia and septicemia, as well as reactivation of latent viral infections, including herpes simplex virus and Epstein-Barr virus [79]. Infections in opioid-treated patients often present with increased severity and poorer outcomes, particularly in those receiving high-dose or long-term therapy.

Recognizing these immunosuppressive effects is critical for clinicians managing chronic pain with opioids. Strategies to mitigate these risks include the judicious use of opioids, prioritizing non-opioid analgesics when feasible, and considering prophylactic measures such as vaccinations and infection monitoring in high-risk populations [80].

1.2.5.3. Musculoskeletal Effects

The chronic use of prescription opioids is associated with significant adverse effects on the musculoskeletal system, which contribute to increased morbidity in long-term users. These effects primarily arise from the combined impact of opioid-induced sedation, reduced physical activity, and direct physiological influences on muscle and bone health.

Muscle Wasting and Weakness: Prolonged opioid use often leads to reduced physical activity and immobilization, as patients may become less engaged in normal daily activities or exercise due to sedation, fatigue, or pain-related inactivity [81]. Over time, this decreased activity can result in muscle atrophy and weakness, particularly in weight-bearing muscles. Additionally, opioids may directly impair muscle protein synthesis and increase proteolysis, compounding muscle wasting [82].

Bone Mineral Density and Fracture Risk: Opioids also adversely affect bone health by reducing bone mineral density (BMD). This effect is mediated by both indirect and direct mechanisms. Indirectly, chronic opioid use can suppress the hypothalamic-pituitary-gonadal (HPG) axis, leading to hypogonadism. Lower levels of sex hormones, particularly testosterone in men and estrogen in women, are critical contributors to reduced BMD and the development of osteoporosis [83]. Directly, opioids may influence bone metabolism by altering the activity of osteoblasts and osteoclasts, thereby disrupting the balance between bone formation and resorption [83]. The clinical implications of reduced BMD are significant, as long-term opioid users face a substantially higher risk of fractures, especially in the hip, spine, and wrist. These fractures are associated with increased morbidity, prolonged recovery, and, in some cases, mortality [84].

Myoclonus and Neuromuscular Symptoms: A less common but notable musculoskeletal side effect of chronic opioid use is myoclonus, which manifests as involuntary, sudden muscle jerks. Opioid-induced myoclonus is thought to result from alterations in the central nervous system, particularly within the spinal cord and brainstem, due to excessive opioid receptor activation [85]. While the exact mechanism is unclear, it is believed that an imbalance in inhibitory and excitatory neurotransmission contributes to the development of this condition. Myoclonus can be distressing and, in severe cases, interfere with activities of daily living.

To mitigate these musculoskeletal effects, clinicians should implement strategies such as encouraging physical activity, resistance training, and weight-bearing exercises to counteract muscle wasting and maintain bone density. Routine monitoring of BMD using dual-energy X-ray absorptiometry

(DEXA) scans is recommended for long-term opioid users, especially those with additional risk factors for osteoporosis [36]. Hormone replacement therapy may be considered for patients with confirmed hypogonadism to mitigate bone loss.

1.2.5.4. Cardiovascular Complications

Long-term use of prescription opioids has been linked to significant cardiovascular complications, including an elevated risk of arrhythmias and other forms of cardiovascular dysfunction. These adverse effects are believed to arise from disruptions in autonomic regulation and possible changes in myocardial electrophysiology. Specifically, chronic opioid therapy has been associated with a prolonged QT interval, which can predispose patients to life-threatening arrhythmias such as torsades de pointes [7].

A large cohort study conducted among Medicare beneficiaries with arthritis demonstrated that opioid use was associated with a 77% increased risk of cardiovascular events compared to NSAIDs and selective cyclooxygenase-2 (COX-2) inhibitors. After six months of therapy, this risk was notably higher for certain opioids, such as codeine, which showed a 62% increased likelihood of adverse events relative to hydrocodone users [86]. Another study found that long-term opioid use was linked to higher incidences of myocardial infarction and cardiovascular revascularization procedures compared to the general population, underlining the cumulative cardiovascular risks over time [87].

Furthermore, opioids' depressive effects on respiratory centers can cause hypoxemia, which, over time, may contribute to pulmonary hypertension and right heart strain [88]. Chronic opioid use has also been associated with reductions in heart rate variability, indicating disrupted autonomic regulation. This can predispose patients to arrhythmias and impair their cardiovascular response to stress [89].

The link between opioids and increased cardiovascular risk may also stem from indirect effects. For example, opioid-induced endocrine dysregulation, such as decreased testosterone and increased prolactin levels, can lead to metabolic syndrome, insulin resistance, and hyperlipidemia, which are independent risk factors for cardiovascular disease [90].

1.2.5.5. Chronic Respiratory Issues

Long-term prescription opioid use is significantly associated with chronic respiratory issues, primarily due to the depressant effects of opioids on the

central respiratory centers. These effects manifest as respiratory depression, sleep-disordered breathing, and in some cases, exacerbation of pre-existing respiratory conditions [7].

Opioids exert their effects by binding to μ-opioid receptors in the brainstem, particularly in areas such as the pre-Bötzinger complex, which plays a critical role in respiratory rhythm generation. This binding suppresses the respiratory drive by reducing the sensitivity of chemoreceptors to carbon dioxide and oxygen levels, leading to hypoventilation [88]. Chronic use can result in tolerance to analgesic effects without a parallel tolerance to respiratory depression, thereby increasing the risk of respiratory complications [89].

Chronic opioid use has been strongly linked to sleep-disordered breathing, including both obstructive and central sleep apnea. Central sleep apnea (CSA) is particularly prevalent in patients on long-term opioid therapy, with studies reporting a prevalence as high as 30% to 50% in this population [91]. CSA in opioid users is characterized by disrupted respiratory patterns, such as ataxic breathing, and episodes of apnea or hypopnea, which are more severe with higher opioid doses [88]. This condition can lead to chronic hypoxemia, hypercapnia, and, over time, pulmonary hypertension and right heart strain.

Patients with pre-existing respiratory disorders, such as chronic obstructive pulmonary disease (COPD) or asthma, are particularly vulnerable to the respiratory depressant effects of opioids. In these patients, the decreased respiratory drive caused by opioids can exacerbate baseline hypoxemia and hypercapnia, increasing the risk of acute respiratory failure [92]. Furthermore, hypoventilation due to chronic opioid use can worsen ventilation-perfusion mismatch, a hallmark of conditions like COPD.

The adverse respiratory effects of opioids appear to follow a dose-dependent pattern. Studies have demonstrated that higher doses of opioids, particularly when exceeding a morphine-equivalent dose of 200 mg per day, significantly increase the risk of respiratory depression and apnea [89, 92]. This highlights the importance of careful dose management and patient monitoring in long-term opioid therapy.

Given the high prevalence of respiratory issues in patients receiving long-term opioids, clinicians must exercise caution when prescribing these medications, particularly to individuals with known respiratory comorbidities. Regular monitoring for signs of hypoxemia, hypercapnia, and sleep-disordered breathing is essential. Polysomnography should be considered for patients exhibiting symptoms such as excessive daytime sleepiness, snoring,

or observed apneic episodes. Furthermore, alternative pain management strategies, such as non-opioid analgesics or multimodal pain management, should be prioritized to minimize the respiratory risks associated with opioids.

1.2.5.6. Substance Use Disorder and Withdrawal

Substance use disorder (SUD) is currently classified as a chronic and relapsing medical condition, underpinned by complex interactions between biological, psychological, and environmental factors [93]. Addiction to psychoactive substances (PAS), including opioids, is marked by compulsive drug-seeking behavior, loss of control over substance use, and the emergence of negative emotional states-such as dysphoria, anxiety, and irritability-when access to PAS is restricted [40]. These emotional disturbances are central features of withdrawal syndrome; a significant driver of continued substance use despite harmful consequences [41].

Long-term prescription opioid use is commonly associated with physical dependence, a state wherein the body adapts to the presence of the drug, and its abrupt discontinuation triggers withdrawal symptoms. These symptoms, often referred to as "somatic withdrawal symptoms," are a result of physiological adaptations in neural and neurochemical systems due to prolonged opioid exposure. Dependency and withdrawal contribute significantly to the challenges of opioid tapering and detoxification, posing barriers to safe and effective discontinuation.

Opioids exert their effects primarily by binding to μ-opioid receptors in the central and peripheral nervous systems, resulting in analgesia, sedation, and euphoria. Chronic use leads to neuroadaptations, including receptor desensitization and downregulation, as well as alterations in intracellular signaling pathways. These changes increase the body's tolerance to opioids, necessitating higher doses to achieve the same effect and creating physical dependence [23].

When opioids are abruptly discontinued, the sudden removal of their inhibitory effects on neurotransmitter release leads to a hyperactivation of noradrenergic neurons in the locus coeruleus. This hyperactivity is associated with the manifestation of withdrawal symptoms, including muscle aches, abdominal cramping, nausea, diarrhea, piloerection, and diaphoresis [9].

Withdrawal from opioids typically follows a well-defined timeline. Acute withdrawal symptoms, such as tachycardia, mydriasis, and intense cravings, often begin within hours of the last dose and peak at 24 to 72 hours. These symptoms are followed by a prolonged withdrawal phase, characterized

by dysphoria, fatigue, and sleep disturbances, which can persist for weeks or months [94]. The severity of withdrawal is influenced by the opioid used, the dose, the duration of use, and individual patient factors, including underlying mental health conditions.

These withdrawal symptoms create a significant psychological and physical barrier to opioid tapering, leading many patients to resume opioid use to alleviate discomfort. This phenomenon, often referred to as the "withdrawal-relapse cycle," perpetuates dependency and complicates efforts to discontinue opioid therapy [39].

The fear of withdrawal symptoms remains a critical barrier for opioid-dependent individuals seeking to discontinue their use. This fear is often reinforced by prior failed attempts to quit and the severity of withdrawal symptoms, which can include both physical (e.g., nausea, muscle pain, sweating) and psychological (e.g., depression, agitation) distress [23, 95]. Such experiences highlight the need for comprehensive approaches to treatment, integrating pharmacological interventions, such as medication-assisted treatment (MAT), with psychosocial support [96].

One of the critical challenges in managing dependency and withdrawal is distinguishing physical dependence from opioid use disorder (OUD). While physical dependence is a predictable physiological response to chronic opioid use, OUD is characterized by compulsive drug-seeking behavior despite negative consequences [97]. However, the overlap between dependence and behavioral addiction can blur these distinctions in clinical practice.

Opioid tapering is a cornerstone of managing physical dependence but must be approached cautiously to avoid triggering severe withdrawal symptoms. Gradual dose reductions, often by 5-10% of the total daily dose every 2-4 weeks, are recommended to minimize withdrawal symptoms. In some cases, adjunctive medications such as clonidine, gabapentin, or lofexidine can be used to alleviate withdrawal-related symptoms [98]. For patients with severe dependency, transitioning to medication-assisted treatment (MAT) using methadone or buprenorphine may be necessary to facilitate a safer taper and prevent relapse. The psychological distress associated with withdrawal symptoms further complicates opioid tapering. Anxiety, depression, and fear of pain recurrence are common psychological barriers that deter patients from attempting tapering [99].

Managed withdrawal treatment, or detoxification, is a critical initial step before transitioning to further treatment for opioid dependence or discontinuing long-term maintenance therapy with opioids. Detoxification prepares the patient for subsequent phases of rehabilitation by alleviating acute withdrawal symptoms and stabilizing physiological functions. Globally, various methods of opioid detoxification are employed, but two principal approaches dominate: abstinence-based treatment programs and opioid agonist substitution therapy.

The abstinence-based approach aims for complete cessation of opioid use. This method typically involves the abrupt discontinuation of opioids, supplemented with symptomatic and supportive care to manage withdrawal symptoms. Medications such as benzodiazepines, clonidine, carbamazepine, antidepressants, and/or neuroleptics are frequently used to address the physical and psychological discomfort associated with withdrawal [9]. While effective in some cases, this approach often poses challenges due to the severity of withdrawal symptoms and the high risk of relapse during the acute withdrawal phase [98].

The opioid agonist substitution approach, on the other hand, uses long- or short-acting opioids, such as methadone or buprenorphine, in gradually tapering doses to ease the transition off opioids. This approach mitigates withdrawal symptoms more effectively and reduces cravings, improving the patient's comfort and increasing the likelihood of successful detoxification. Methadone, a long-acting full opioid agonist, has been extensively studied for its role in detoxification programs and is particularly beneficial for patients with severe dependence or prior unsuccessful detox attempts [100]. Buprenorphine, a partial opioid agonist, is similarly effective and offers the additional safety benefit of a ceiling effect on respiratory depression, making it a preferred choice in some clinical settings [101].

In both approaches, symptomatic treatment plays a crucial role. Clonidine, for example, reduces withdrawal symptoms by dampening the hyperactivity of the sympathetic nervous system. Similarly, benzodiazepines help manage anxiety and agitation, while antidepressants address mood disturbances commonly associated with withdrawal [9].

Importantly, patients who understand the neurobiological underpinnings of addiction are better positioned to view their condition as a medical disorder rather than a moral failing. This perspective not only reduces stigma but also enhances engagement in evidence-based treatments [102]. Studies suggest that education on the role of the central nervous system in addiction fosters a more constructive patient-provider dialogue, empowering patients to actively participate in their recovery journey [23].

The integration of neuroscience into public and clinical education has also been shown to improve outcomes. By framing addiction as a condition that alters brain circuitry-specifically within the reward and stress systems-patients can better contextualize their cravings and withdrawal symptoms, reducing shame and self-blame [103, 104], effective in designing intervention strategies that address both the biological roots and the psychosocial dimensions of SUD.

1.2.6. Opioid Detoxification

Detoxification represents a critical step in addressing prescription opioid dependence. Its primary aim is to facilitate the safe and effective cessation of opioid use while minimizing withdrawal symptoms and improving patient outcomes [105]. Despite its importance, research focused on the detoxification of individuals dependent on prescription opioids remains limited, particularly concerning its impact on long-term quality of life. Detoxification from prescription opioids is increasingly recognized as a critical intervention for improving health outcomes and overall quality of life in patients with chronic pain. Beyond physical health concerns, prolonged opioid use also has significant implications for emotional well-being, social functioning, and quality of life, underscoring the importance of effective detoxification strategies [105]. However, the detoxification process is inherently complex and requires a holistic approach that integrates medical, psychological, and social interventions [16].

The primary challenge in detoxification lies in managing withdrawal symptoms, which can be severe and include both physical (e.g., pain, nausea, sweating) and psychological (e.g., anxiety, depression, cravings) components. Failure to adequately address these symptoms often leads to relapse, highlighting the importance of comprehensive support during and after detoxification. Evidence suggests that incorporating multimodal pain management alternatives, such as non-opioid analgesics, physical therapy, and interventional techniques, can help alleviate withdrawal-related pain and improve patient adherence to treatment protocols [39]. Moreover, psychological interventions, including cognitive-behavioral therapy (CBT) and motivational interviewing, play a vital role in addressing the emotional aspects of dependency and building resilience against relapse [106].

Detoxification from prescription opioids allows for the reversal of many somatic complications associated with chronic opioid use. For instance, opioid-induced suppression of the hypothalamic-pituitary-adrenal axis can lead to hormonal dysregulation, fatigue, and immune suppression [107]. Successful detoxification often results in the restoration of these physiological systems, contributing to improved energy levels, immune function, and overall physical health.

Chronic opioid use has been linked to emotional dysregulation, including increased rates of anxiety, depression, and mood instability [108]. Detoxification provides an opportunity to address these issues, as patients may experience a reduction in the psychological burdens imposed by opioid dependence. Importantly, detoxification programs that incorporate psychological support, such as cognitive-behavioral therapy (CBT), can further enhance emotional well-being by equipping patients with strategies to manage pain and emotional stress without reliance on opioids [109].

The social repercussions of opioid dependence are profound, often manifesting as strained relationships, isolation, and occupational challenges. Detoxification can facilitate reintegration into social and professional life by alleviating the stigma and functional impairments associated with opioid use disorder (OUD). Patients who successfully complete detoxification often report improved social relationships, increased participation in community activities, and enhanced capacity to fulfill familial and occupational responsibilities [110].

The interplay between physical and emotional dysfunction can create a vicious cycle: reduced physical capabilities often exacerbate psychological stress, while emotional strain further undermines motivation and capacity for physical activity. Detoxification from opioids allows patients to break free from this cycle. As their neurochemical balance stabilizes and physical side effects subside, patients often report significant improvements in energy levels, pain tolerance, and emotional stability [111]. Detoxification from prescription opioids contributes to a marked improvement in quality of life. The resolution of opioid-related side effects, combined with enhanced emotional stability and social reintegration, empowers patients to regain a sense of autonomy and purpose. Quality of life improvements are particularly notable in comprehensive, multidisciplinary detoxification programs that address the physical, emotional, and social dimensions of recovery [112]. Longitudinal studies have also demonstrated that patients who successfully discontinue opioids report sustained improvements in life satisfaction and functional status compared to those who remain on long-term opioid therapy [111]. The integration of medical, psychological, and social support within detoxification

programs maximizes the likelihood of positive outcomes and underscores the importance of a holistic approach to recovery.

1.2.7. Breaking the Cycle of Opioid Dependency

Breaking the cycle of prescription opioid dependency is a multifaceted challenge that requires addressing both the neurobiological and behavioral dimensions of addiction. Detoxification plays a pivotal role in this process by stabilizing brain chemistry, reducing withdrawal symptoms, and minimizing the risk of transitioning to illicit opioid use [4]. Moreover, it creates a pathway for safe opioid tapering and provides patients with the tools and support needed for long-term recovery. As the opioid crisis continues to pose significant public health challenges, expanding access to evidence-based detoxification programs is essential for improving patient outcomes and reducing the societal burden of opioid dependency [113].

Patients prescribed opioids for legitimate medical purposes may unintentionally develop physical and psychological dependence due to the neuroadaptive changes opioids induce in the brain [39]. The interaction of noradrenaline and dopamine systems plays a key role in this dependency, creating a reinforcing cycle of misuse and craving. Detoxification serves as a crucial intervention to disrupt this cycle, reduce the risk of transitioning to illicit opioid use, and establish a pathway for safer, medically supervised opioid tapering. Prolonged opioid use alters the brain's reward, stress, and pain pathways, primarily through its effects on the dopaminergic and noradrenergic systems. Opioids stimulate the release of dopamine in the mesolimbic reward system, creating feelings of euphoria and reinforcement that can lead to misuse and dependency [23]. Simultaneously, opioids suppress noradrenaline activity, which contributes to their sedative and analgesic effects. Over time, the brain compensates for these changes by upregulating noradrenaline production and downregulating endogenous dopamine activity, resulting in tolerance, physical dependence, and withdrawal symptoms upon cessation [9].

This neurobiological basis of dependency underscores the challenges of discontinuing opioids without medical intervention. Withdrawal symptoms, driven by dysregulated noradrenaline release and diminished dopamine signaling, can include anxiety, insomnia, hyperalgesia, and severe dysphoria, creating significant barriers to cessation [9]. Detoxification provides a structured approach to managing these symptoms, breaking the neurochemical cycle of dependency, and initiating recovery. Detoxification provides a critical opportunity for addressing the behavioral and psychological dimensions of opioid misuse. Integrating counseling, cognitive-behavioral therapy (CBT),

and motivational interviewing into detoxification programs enhances patients' ability to cope with cravings and develop healthier strategies for managing pain and emotional distress [39].

One of the most pressing risks associated with opioid dependency is the transition to illicit opioid use, such as heroin or synthetic opioids like fentanyl [113]. Studies have shown that patients unable to access or afford prescription opioids often turn to illicit sources, increasing their risk of overdose and exposure to adulterated substances [114]. Detoxification programs, particularly those integrated into broader harm reduction strategies, can significantly reduce this risk by providing patients with structured support, access to medication-assisted treatment (MAT), and a pathway to long-term recovery.

Detoxification also establishes a foundation for the safe tapering of opioids under medical supervision. For patients with chronic pain, abrupt discontinuation of opioids is neither feasible nor advisable, as it may exacerbate pain and withdrawal symptoms. Detoxification provides a structured process for gradually reducing opioid doses while implementing alternative pain management strategies, such as physical therapy, non-opioid analgesics, and psychological interventions [15].

Detoxification programs often serve as a gateway to interdisciplinary care, connecting patients with resources for long-term pain management and recovery. This holistic approach not only addresses the underlying causes of opioid use but also empowers patients to regain control over their health and quality of life [111].

Multimodal pain management integrates multiple therapeutic modalities to target various aspects of the pain experience. Following detoxification, healthcare providers can incorporate non-opioid pharmacologic treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs) and antidepressants, to address underlying pain mechanisms. NSAIDs reduce inflammation and nociceptive pain, while certain antidepressants, such as serotonin-norepinephrine reuptake inhibitors (SNRIs), are particularly effective for neuropathic pain [115]. These options allow for tailored treatments that address specific pain etiologies without the risks of opioid dependency.

In addition to pharmacologic options, physical therapy plays a vital role in multimodal pain management. Guided physical activity can improve strength, flexibility, and mobility, thereby reduce musculoskeletal pain and improve overall functionality. Physical therapy also empowers patients to take an active role in their recovery, fostering a sense of control over their condition.

Detoxification also allows healthcare providers to integrate non-pharmacologic interventions into a patient's pain management plan. Non-pharmacologic methods have demonstrated efficacy in providing sustained pain relief and improving quality of life with fewer adverse effects compared to opioid therapy [115]. Key strategies include:

- Mindfulness-Based Stress Reduction (MBSR): Mindfulness and meditation practices can help patients develop greater awareness and acceptance of their pain, reducing emotional distress and improving coping mechanisms. These practices have been particularly beneficial for patients with chronic conditions such as fibromyalgia and low back pain.
- Acupuncture: As a traditional therapy, acupuncture has shown promise in alleviating pain by stimulating endorphin release and modulating pain pathways in the central nervous system.
- Exercise Therapy: Regular, low-impact exercises such as yoga, swimming, or walking are effective in reducing chronic pain and enhancing physical and mental health. Exercise also addresses deconditioning and improves functional outcomes for patients transitioning off opioids.

These strategies provide several advantages over opioid-based pain management. First, they address pain at its source, often targeting the underlying pathology rather than masking symptoms. Second, they reduce the risk of adverse effects commonly associated with opioids, such as sedation, constipation, and dependency. Finally, these approaches encourage patient engagement and self-management, fostering a sense of empowerment and autonomy.

1.2.8. Quality of Life

Chronic pain is a pervasive and debilitating condition that significantly affects patients' overall well-being and daily functioning. Opioids are commonly prescribed for chronic pain management, yet their long-term use is associated with a range of physiological and psychological complications. While opioids can provide pain relief, their impact on quality of life (QoL) remains controversial. The risks of dependence, tolerance, opioid-induced hyperalgesia, and cognitive impairments raise concerns about their long-term efficacy and safety. Despite the widespread utilization of opioids for chronic pain management and increasing awareness of their addictive potential, there

remains a significant gap in research exploring the effects of detoxification on QoL and pain management outcomes [8].

Opioid therapy has been traditionally regarded as an effective strategy for alleviating chronic pain, with a significant proportion of patients and clinicians believing that opioids improve pain relief and QoL [116]. According to a national survey, 92% of opioid users reported some degree of pain relief, and 57% claimed their QoL improved due to opioid use [116]. However, contrary to these perceptions, scientific literature suggests that long-term opioid therapy does not consistently enhance overall QoL and may, in fact, lead to a decline in functionality and psychological well-being [8].

Prolonged opioid therapy is associated with adverse effects, including physical dependence, opioid-induced hyperalgesia, hormonal dysregulation, and cognitive impairment [116]. These factors contribute to a paradoxical worsening of pain perception and a decline in daily life activities. As a result, the long-term balance between benefits and risks of opioid therapy remains a subject of debate.

Detoxification, defined as the medically supervised withdrawal from opioids, serves as a critical component of treatment for opioid dependence. However, it is frequently met with skepticism within clinical practice due to concerns regarding its impact on pain management, the potential exacerbation of withdrawal-associated discomfort, and the risk of relapse following cessation [8].

One of the key challenges associated with detoxification is the perception that it may leave patients with chronic pain undertreated, particularly when effective alternative pain management strategies are not readily available [116]. Additionally, withdrawal symptoms, including anxiety, agitation, and hyperalgesia, may exacerbate pre-existing pain conditions, creating a barrier to successful detoxification [9]. As a result, patients and healthcare providers often express reluctance to pursue detoxification, fearing a reduction in QoL and increased pain burden.

While limited, some studies suggest that detoxification, when paired with comprehensive care models, can yield positive outcomes. For instance, programs integrating detoxification with behavioral interventions, non-opioid analgesics, and multidisciplinary pain management approaches have demonstrated improvements in patient-reported outcomes, including reductions in opioid dependence and enhancements in physical and emotional well-being [10, 116]. Moreover, long-term outcomes appear more favorable when detoxification is followed by maintenance therapies such as buprenorphine or naltrexone, which can help mitigate relapse risk and support sustained recovery [11].

Furthermore, there is increasing interest in exploring whether successful detoxification can lead to measurable improvements in QoL by addressing the adverse effects associated with long-term opioid use. Prolonged opioid therapy is often accompanied by significant negative outcomes, including physical dependence, opioid-induced hyperalgesia, hormonal dysregulation, and cognitive impairment, all of which can diminish overall well-being and functionality [12]. Consequently, detoxification, which facilitates the cessation of opioid use, has the potential to alleviate these burdens and enhance QoL by restoring physiological and psychological homeostasis. Studies have found that patients who successfully transition off opioids through medically supervised detoxification report benefits such as reduced sedation, improved cognitive clarity, and a restoration of natural pain modulation mechanisms over time [10, 13, 116]. These improvements may also extend to psychosocial dimensions, as individuals experience enhanced emotional stability, increased capacity for social engagement, and reduced stigma associated with opioid dependence.

An essential component of improving QoL for chronic pain patients undergoing detoxification is access to effective, non-opioid-based pain management strategies [15]. Multimodal approaches, including physical rehabilitation, behavioral therapies, and complementary modalities such as acupuncture and mindfulness, have shown promise in managing pain while minimizing reliance on opioids [116]. When implemented alongside detoxification, these strategies may collectively enhance QoL by fostering long-term functional improvements and empowering patients with self-management tools.

There is a significant gap in the literature specifically investigating the impact of detoxification on quality of life (QoL) in patients who have been on long-term opioid therapy. While many studies focus on the effects of opioid therapy itself on QoL-often using tools like SF-36 questionnaire-research directly assessing QoL outcomes before and after detoxification is limited. Most existing studies on detoxification focus on aspects such as withdrawal symptoms, relapse rates, and medication-assisted treatments (e.g., methadone, buprenorphine, or naltrexone) rather than specifically measuring QoL changes post-detoxification.

Recent studies have investigated the impact of detoxification on the quality of life (QoL) of patients undergoing long-term opioid therapy. A study published in the Journal of Opioid Management found that significant pain reduction, QoL improvement, and opioid usage cessation were observed after opioid detoxification in most patients with chronic pain, suggesting that such treatment can be safely administered and is appropriate [117]. Another study

published in Frontiers in Psychiatry examined the effects of long-term detoxification using opium tincture. The results indicated that all areas of craving, anxiety, and depression significantly decreased, while QoL and sleep significantly increased at the end of the study [118].

These findings suggest that detoxification treatments, when managed appropriately, can potentially improve QoL by reducing dependence on opioids and minimizing their negative health impacts. However, these studies are relatively scarce, and further research is needed to explore longitudinal changes in QoL following opioid detoxification; differences in QoL outcomes between detoxification with and without medication-assisted treatment; the role of psychosocial and behavioral interventions in QoL improvements post-detoxification.

This lack of focused research represents an opportunity for further studies to provide more robust evidence on the impact of detoxification on QoL, using validated instruments like SF-36 questionnaire.

1.3. Identifying Characteristics of Patients with Chronic Pain under Long-Term Prescription Opioids Use

Tolerance and addiction to prescription opioids represent significant challenges in pain management and public health, necessitating a thorough understanding of the characteristics that differentiate these conditions. Tolerance is defined as a physiological state wherein patients require progressively higher doses of a drug to achieve the same therapeutic effect due to neuroadaptations in the central nervous system (CNS) [119]. In contrast, addiction is characterized by compulsive drug-seeking behavior and use despite adverse consequences, encompassing both physiological and psychological dimensions [97]. Although these states may coexist, they are distinct phenomena with unique patient profiles.

Patients who develop tolerance to opioids often present with chronic pain conditions requiring long-term opioid therapy. They may exhibit the need for increasing doses of medication to maintain analgesia, while still adhering to prescribed regimens and demonstrating no evidence of misuse [120]. Tolerance is typically associated with the natural progression of opioid use and is not inherently indicative of addiction. These patients often experience diminished efficacy of opioids over time, leading clinicians to consider adjunct therapies or alternative approaches to pain management [58].

Conversely, patients with addiction exhibit a range of behavioral, psychological, and physiological indicators that extend beyond the realm of tolerance. These characteristics include the inability to control opioid use,

cravings, preoccupation with obtaining opioids, and continued use despite harm to personal, occupational, or social functioning. Physical signs may include withdrawal symptoms when opioids are reduced or discontinued, as well as the use of non-prescribed opioids or other substances.

Psychosocial factors, such as a history of substance use disorders, mental health comorbidities (e.g., depression, anxiety, or post-traumatic stress disorder), and social instability, are strongly associated with addiction [121]. Additionally, certain risk factors, including younger age, genetic predisposition, and a history of trauma, have been identified as predictors of opioid addiction [119].

1.3.1. The Role of Substance Use Disorder History in Opioid Misuse and Addiction

A history of substance use disorders (SUDs) is widely recognized as one of the most significant predictors of opioid misuse and addiction. Individuals with previous dependence on substances such as alcohol, benzodiazepines, or illicit drugs are particularly vulnerable to transitioning from therapeutic opioid use to problematic use [121]. This vulnerability arises from the shared neurobiological mechanisms of addiction and the reinforcing effects of opioids on the brain's reward pathways [119].

The brain's reward system, particularly the mesolimbic dopamine pathway, plays a central role in the development of addiction. Opioids, like other addictive substances, act on this pathway by increasing dopamine release in the nucleus accumbens, resulting in feelings of euphoria and reinforcement of drug-taking behavior [23]. For individuals with a history of substance use disorders, the neural adaptations that underlie addiction may already be primed, leading to an amplified response to opioids. This heightened sensitivity can accelerate the progression from prescribed use to misuse and addiction [121].

Alcohol use disorder (AUD) has been specifically associated with an increased risk of opioid addiction. Studies have demonstrated that individuals with AUD are more likely to receive prescriptions for opioids and to use them at higher doses than those without AUD [122]. This dual use of alcohol and opioids is particularly concerning due to the synergistic depressant effects on the central nervous system, increasing the risk of respiratory depression and overdose.

Similarly, individuals with benzodiazepine use disorder are at elevated risk of opioid misuse. Benzodiazepines and opioids are frequently co-prescribed despite guidelines discouraging their concurrent use due to the

significant risk of adverse outcomes, including sedation, respiratory depression, and death [123]. The combined use of these substances is often seen in individuals with polysubstance use disorders, further compounding their risk of opioid addiction.

The link between illicit drug use and opioid misuse is also well-documented. Individuals with a history of using drugs such as cocaine, methamphetamine, or heroin often exhibit a pattern of impulsivity and risk-taking behavior that predisposes them to opioid misuse [124]. Moreover, the transition from prescribed opioids to heroin has been extensively studied, with findings suggesting that prior dependence on other substances significantly increases the likelihood of heroin initiation once prescription opioids are no longer accessible [125].

These patterns underscore the importance of screening for a history of substance use disorders when prescribing opioids for pain management. Tools such as the Opioid Risk Tool (ORT) and the Prescription Drug Monitoring Program (PDMP) can aid clinicians in identifying high-risk patients [126]. Integrating this information into clinical practice allows for tailored interventions, such as the use of non-opioid analgesics, close monitoring of opioid use, and early referral to addiction specialists when needed.

1.3.2. Mental Health Comorbidities and Their Role in Opioid Addiction

Mental health comorbidities, including depression, anxiety, and post-traumatic stress disorder (PTSD), are strongly associated with opioid addiction. These conditions not only increase the likelihood of opioid misuse but also exacerbate its progression through maladaptive coping mechanisms. Patients suffering from psychological distress may use opioids as a means of self-medication, seeking temporary relief from emotional pain. This dynamic creates a reinforcing cycle that heightens vulnerability to opioid dependence and addiction [119].

Depression, one of the most common mental health disorders associated with opioid addiction, has been shown to increase both the likelihood of opioid prescription and dosage escalation. Patients with depression may experience heightened pain sensitivity due to shared neurobiological pathways between pain and mood disorders, leading clinicians to prescribe opioids more frequently or at higher doses [127]. Furthermore, the overlap between chronic pain and depression creates a complex clinical presentation in which patients may receive long-term opioid therapy without adequate attention to their mental health, increasing the risk of misuse and addiction.

Anxiety disorders, including generalized anxiety disorder and panic disorder, are similarly implicated in opioid misuse. Individuals with anxiety may misuse opioids to alleviate symptoms such as restlessness, tension, and fear. This behavior reflects a maladaptive attempt to regulate emotional states, which can lead to dependence over time. Studies have shown that patients with anxiety are more likely to receive opioids for pain management, even when non-opioid alternatives are available [128].

PTSD represents a particularly high-risk condition for opioid misuse, especially among populations with significant trauma exposure, such as military veterans. Patients with PTSD often experience chronic emotional dysregulation, intrusive memories, hyperarousal, and co-occurring chronic pain, all of which increase their vulnerability to opioid misuse [129]. Veterans with PTSD, for example, are significantly more likely to be prescribed opioids for pain management compared to those without PTSD. Moreover, they are more likely to exhibit high-risk opioid use behaviors, including dose escalation, concurrent use of sedatives, and early refills, which elevate the risk of developing opioid use disorder (OUD) [124].

The association between mental health comorbidities and opioid addiction underscores the importance of integrated care approaches. Screening for depression, anxiety, and PTSD in patients receiving opioid therapy is critical for identifying those at heightened risk of misuse. Additionally, addressing mental health conditions through evidence-based treatments, such as cognitive-behavioral therapy (CBT), trauma-focused therapy, or pharmacotherapy, can reduce reliance on opioids and improve long-term outcomes. Collaborative care models that integrate pain management and mental health support are particularly effective in mitigating risks and promoting holistic recovery [130].

1.3.3. Social instability

Social instability significantly exacerbates the risk of opioid addiction, as it creates conditions that heighten stress and reduce resilience to substance misuse. Key factors such as unemployment, homelessness, and the absence of social support networks contribute to this vulnerability. Unemployment, for example, is associated with reduced access to healthcare, including mental health services, and an increased likelihood of psychological distress, both of which can lead individuals to self-medicate with opioids [114]. Similarly, homelessness is linked to chronic stress, exposure to trauma, and barriers to healthcare, all of which foster a heightened risk of opioid misuse and addiction [131].

The lack of a stable social support network further amplifies this risk, as social isolation often reduces individuals' ability to cope with stress and increases susceptibility to substance use as a maladaptive coping mechanism [132]. Financial insecurity, a common thread in socially unstable environments, can drive individuals to seek opioids as an accessible and short-term relief from chronic stress and psychological discomfort, reinforcing patterns of misuse and dependency [133]. These compounded vulnerabilities illustrate the critical need for holistic interventions addressing both the social determinants of health and the psychological dimensions of opioid addiction.

1.3.4. Younger age

Is a well-documented risk factor for opioid addiction, attributed to both behavioral and neurobiological factors. Adolescents and young adults, particularly those aged 18-25, exhibit higher rates of impulsivity and risk-taking behaviors, which are influenced by developmental processes in the prefrontal cortex-a brain region responsible for decision-making, impulse control, and risk assessment [134]. These developmental characteristics increase the likelihood of experimenting with substances, including opioids, and can contribute to patterns of misuse and addiction [135].

In addition to behavioral tendencies, younger individuals are more susceptible to the neurobiological effects of opioids due to the ongoing maturation of the brain during adolescence and early adulthood. Critical periods of brain development involve heightened plasticity, particularly in the mesolimbic reward pathway, which plays a key role in reinforcing the pleasurable effects of opioids. Exposure to opioids during this time can disrupt normal neurochemical processes, leading to stronger conditioning of drug-seeking behaviors and an increased risk of addiction [136]. Furthermore, early exposure to opioids has been shown to alter the dopaminergic system, potentially priming the brain for long-term vulnerabilities to substance use disorders [137].

The social context of younger age groups also amplifies risk. Peer influence and social pressures are particularly pronounced during adolescence and young adulthood, further driving experimentation and substance use. Additionally, younger individuals may face limited awareness of the risks associated with opioid use or lack access to preventive education and healthcare services, which can hinder early intervention efforts [138]. These intersecting behavioral, neurobiological, and social vulnerabilities underscore the need for targeted prevention strategies aimed at reducing opioid exposure and misuse among younger populations.

1.3.5. Genetic factors

Research indicates that genetic predispositions can influence opioid metabolism, receptor sensitivity, and individual susceptibility to addiction. Variations in genes such as OPRM1, which encodes the mu-opioid receptor, have been associated with differences in opioid efficacy and addiction risk [21]. This study explores the genetic variants associated with the risk of developing opioid use disorder (OUD) following opioid exposure. Twenty-three participants, previously prescribed opioid-based painkillers for minor surgical treatments, were divided into two groups: 12 persistent opioid users (cases) and 11 nonpersistent opioid users (controls). Saliva samples were collected and subjected to DNA sequencing to identify genetic variations. Genome-wide association studies (GWAS) revealed 13 significant variants associated with OUD, including two previously known missense variants: rs6265 (p. Val66Met in BNDF isoform a) and rs1799971 (p. Asn40Asp in OPRM1). Expanding the analysis to include variants unique to persistent users identified 11 new variants. Co-occurrence analysis of genes harboring multiple variants identified eight additional genes, including LRFN3, ZMIZ1, RYR3, and OR1L6, which showed three or more variants in persistent users but not in controls. Further functional enrichment and protein-protein interaction (PPI) network analyses revealed that the identified variants are linked to pathways involved in calcium signaling, circadian entrainment, morphine addiction, alcoholism, and opioid signaling, all of which are closely associated with OUD and addiction. These findings highlight the genetic complexity of OUD and its potential relationship to multiple interacting pathways [21]. These genetic components interact with environmental exposures, including socioeconomic status, access to healthcare, and social support systems, to shape an individual's overall risk profile.

Genetic factors are increasingly recognized as critical contributors to an individual's susceptibility to opioid addiction. Research in the field of pharmacogenomics has identified several genetic variations that influence the metabolism, efficacy, and potential for addiction associated with opioid use. These genetic differences can affect opioid receptors, enzymes involved in opioid metabolism, and neurotransmitter systems that mediate reward and addiction pathways, thereby shaping an individual's risk of developing opioid use disorder (OUD) [139, 140]. The exact dose and duration of opioid use that consistently led to addiction remain uncertain; nevertheless, the likelihood of opioid addiction significantly differs among individuals, with genetic susceptibility contributing to at least 35 to 40% of the overall risk [140].

A key genetic factor in opioid addiction susceptibility lies in variations within the OPRM1 gene, which encodes the mu-opioid receptor, the primary target of most opioids. The most studied polymorphism, A118G (rs1799971), results in a substitution of asparagine to aspartic acid at position 40 of the receptor. This variation has been associated with altered binding affinity for opioids and differences in the analgesic and euphoric effects of these drugs [141]. Individuals carrying the G allele have been found to require higher doses of opioids for effective pain management, potentially increasing their risk of misuse and addiction [142].

Genetic variations in enzymes responsible for opioid metabolism also play a pivotal role. For example, polymorphisms in the CYP2D6 gene, which encodes an enzyme involved in the metabolism of codeine to morphine, can significantly influence opioid efficacy and toxicity. Individuals with poor CYP2D6 metabolism may experience inadequate analgesia, leading to higher opioid doses, while ultra-rapid metabolizers may face increased risks of toxicity and adverse effects, both of which can heighten the potential for misuse and dependency [143].

Additionally, genetic variants in the COMT (catechol-O-methyltransferase) gene, which influences dopamine metabolism in the brain, have been linked to differences in pain perception, opioid efficacy, and addiction vulnerability. For instance, the Val158Met polymorphism in COMT affects enzymatic activity and dopamine levels in the prefrontal cortex, modulating the brain's reward system and impacting an individual's response to opioids [144].

Moreover, genes involved in the dopaminergic and serotonergic systems, such as DRD2 (dopamine receptor D2) and 5-HTTLPR (serotonin transporter-linked polymorphic region), have been associated with opioid addiction risk. Variations in these genes can influence the rewarding effects of opioids and the likelihood of compulsive drug-seeking behavior [145].

Understanding the genetic factors underlying opioid addiction is vital for tailoring personalized approaches to pain management and addiction prevention. Pharmacogenomic testing could enable clinicians to predict an individual's response to opioids, optimize dosing strategies, and identify those at higher risk for addiction. This approach may reduce the prevalence of opioid misuse by ensuring that pain management strategies are both effective and safe. Understanding these genetic factors can help in developing personalized approaches to pain management and addiction treatment [146].

1.3.6. A History of Trauma

Trauma, including physical, emotional, or sexual abuse, is a well-established risk factor for opioid addiction. Adverse childhood experiences (ACEs), which encompass various forms of abuse, neglect, and household dysfunction, are particularly predictive of later substance use disorders, including opioid addiction. Exposure to ACEs disrupts the normal development of the hypothalamic-pituitary-adrenal (HPA) axis, a central component of the body's stress regulation system, leading to dysregulated stress responses and heightened vulnerability to mental health disorders, such as anxiety, depression, and post-traumatic stress disorder (PTSD), which are frequently co-occurring conditions with opioid misuse [147, 148].

Individuals with high ACE scores are significantly more likely to misuse opioids and develop addiction, particularly when managing chronic pain or other medical conditions requiring opioid treatment. This connection arises from the compounding effects of trauma on both psychological and physical health. For instance, childhood trauma is associated with an increased sensitivity to pain and a reduced capacity to cope with it, which may predispose individuals to seek opioids not only for physical relief but also as a maladaptive coping mechanism for emotional distress [149, 150]. The reinforcing effects of opioids on the brain's reward system may further entrench substance use behaviors among trauma survivors, as opioids provide temporary relief from both psychological pain and dysregulated stress responses [151].

Moreover, individuals with a history of trauma often encounter barriers to accessing effective mental health care, leaving their underlying psychological and emotional needs unaddressed. In such cases, opioids may become a self-managed solution to alleviate emotional suffering, increasing the risk of misuse and dependence. Trauma-informed care, which acknowledges and addresses the impact of ACEs, is therefore essential in preventing and treating opioid addiction. Integrating trauma-focused interventions within pain management and addiction treatment settings can help address the root causes of opioid misuse and improve long-term outcomes [96].

Addressing these psychosocial and individual risk factors requires a comprehensive and interdisciplinary approach. Screening for mental health conditions, trauma history, and social determinants of health in clinical settings can help identify patients at risk of opioid addiction. Interventions such as integrated mental health care, trauma-informed therapy, and social

support services can mitigate risk and improve outcomes for vulnerable populations.

2.1. 1.4. Determining the Effectiveness of Detoxification Treatment

1.4.1. The Importance of Opioid Detoxification in Treating Prescription Opioid-Induced Addiction

Opioid detoxification plays a crucial role in the treatment of addiction caused by prescription opioids. This form of addiction presents unique challenges due to the often unintentional nature of dependency, the medical context of opioid use, and the stigma that can hinder seeking treatment. Detoxification is a vital first step in addressing both the physical dependence and psychological aspects of addiction, facilitating recovery and reintegration into a substance-free lifestyle [2, 106,117]

Detoxification is essential in managing the withdrawal symptoms associated with prescription opioid dependence. These symptoms, including muscle pain, anxiety, restlessness, and gastrointestinal distress, can range from mild to severe and are often overwhelming without medical intervention [23]. Detoxification is critical in breaking the cycle of misuse by addressing the physiological dependence while maintaining a focus on the patient's initial pain condition [152]. This approach ensures that the underlying medical needs are considered, and alternative pain management strategies are implemented.

Patients with prescription opioid addiction are at heightened risk of overdose, especially during periods of unsupervised attempts to discontinue use. Tolerance levels drop quickly during abstinence, increasing the likelihood of overdose if the patient relapses and resumes prior dosage levels. Medically supervised detoxification reduces this risk by providing a structured environment and access to overdose prevention tools, such as naloxone [40].

Detoxification serves as a gateway to long-term treatment, enabling patients to transition into maintenance therapies and psychosocial interventions. For prescription opioid addiction, these programs often include a combination of MAT, counseling, and behavioral therapies to address the psychological and emotional dimensions of addiction [96]. Detoxification provides an essential starting point by stabilizing the patient and fostering readiness for ongoing care.

Prescription opioid addiction is frequently associated with stigma, as patients may feel shame or guilt about their condition due to its medical origins. Detoxification within a compassionate and nonjudgmental clinical setting helps to reduce stigma and empower patients to view their condition

as a treatable medical issue. This perspective encourages treatment adherence and promotes better long-term outcomes [40, 41].

1.4.2. Effectiveness of treatment

The Substance Abuse and Mental Health Services Administration (SAMHSA) in the United States outlines a comprehensive, phased approach to the treatment of opioid addiction, emphasizing the importance of addressing both the immediate and long-term needs of individuals undergoing treatment. This approach consists of six distinct phases: acute treatment, rehabilitative care, maintenance therapy, medication management, optional tapering of medication doses, and long-term care [96].

1. Acute Treatment Phase: This phase focuses on managing the immediate effects of opioid withdrawal and stabilizing the patient. Psychological support is critical during this phase to help individuals cope with the discomfort and stress of withdrawal. The primary goal of the acute phase in the treatment of opioid addiction is to cease opioid use while simultaneously addressing the myriads of medical, social, legal, familial, and other issues associated with addiction. This phase is critical in establishing the foundation for long-term recovery, as it begins to reduce the multifaceted burden of addiction on both the individual and their broader environment. Detoxification is widely recognized as the initial, yet indispensable, step in the acute phase. It serves as a gateway to comprehensive treatment, without which further therapeutic interventions are not feasible or effective [96].

Opioid detoxification must be readily accessible to individuals who express the desire to discontinue opioid use and commit to sobriety. The process aims to manage the physical symptoms of withdrawal in a safe and controlled environment, reducing the immediate risks associated with abrupt cessation of opioids, such as severe withdrawal symptoms or medical complications [16]. Medically supervised detoxification often involves the use of evidence-based pharmacological interventions, such as methadone, buprenorphine, or clonidine, to alleviate withdrawal symptoms and enhance patient comfort [153]. Beyond medical management, detoxification provides an opportunity to engage patients in behavioral and psychosocial interventions that address the broader dimensions of addiction.

However, detoxification alone is insufficient to achieve sustained recovery. Research indicates that individuals who undergo detoxification without transitioning to long-term maintenance therapy or rehabilitation are at a significantly higher risk of relapse, often within days or weeks of completing

detoxification [154]. Therefore, ensuring that detoxification is seamlessly integrated into a broader continuum of care, including rehabilitation, maintenance, and long-term follow-up, is essential for optimizing treatment outcomes.

2. Rehabilitative Phase: Once stabilization is achieved, the focus shifts to addressing the underlying causes of addiction and developing coping strategies. This phase typically includes behavioral therapies, such as cognitive-behavioral therapy or contingency management, alongside medication-assisted treatment. These interventions aim to improve mental health, reduce relapse risk, and build the skills needed for long-term recovery [39].
3. Maintenance Phase: During this phase, individuals continue medication-assisted treatment with a stable dosage of opioids like methadone or buprenorphine. The primary goal is to suppress cravings and prevent relapse while enabling the individual to lead a stable, productive life. Maintenance therapy is often supplemented with counseling and psychosocial support to address ongoing challenges [155].
4. Medication Management Phase: This phase focuses on ensuring the safe and effective use of medications, monitoring for adverse effects, and addressing any changes in the patient's health or circumstances. Regular follow-ups with healthcare providers help to assess progress and make necessary adjustments to the treatment plan [96].
5. Medication Tapering Phase (Optional): For individuals who wish to discontinue opioid medications, a gradual tapering process is undertaken under medical supervision. This process aims to minimize withdrawal symptoms and ensure a smooth transition, though it is not a mandatory component of treatment. Decisions regarding tapering are typically made collaboratively between the patient and the healthcare provider [155].
6. Long-Term Care Phase: The final phase involves sustained support to prevent relapse and maintain recovery over the long term. This phase includes ongoing counseling, participation in peer support groups, and access to healthcare services for comorbid conditions. Long-term care aims to address the chronic nature of addiction and support individuals in achieving stable, fulfilling lives [39].

1.4.3. Evaluation of Effectiveness of Detoxification

The effectiveness of prescription opioid detoxification extends beyond the management of acute withdrawal symptoms and encompasses a broader range of outcomes, including successful opioid cessation, changes in pain perception, and long-term recovery metrics. These outcomes are critical in understanding the impact of detoxification on patients' overall health and quality of life.

1.4.3.1. Successful Opioid Cessation

A primary goal of detoxification is achieving and maintaining abstinence from opioids. Successful cessation can also be evaluated over different time frames, with short-term abstinence indicating the immediate effectiveness of detoxification and long-term abstinence reflecting the integration of detoxification within a continuum of care. Research has demonstrated that detoxification alone, without follow-up treatment, has limited success in sustaining opioid cessation due to high relapse rates [154]. However, when integrated into a comprehensive treatment plan, including medication-assisted treatment and behavioral therapy, detoxification can act as a critical first step in breaking the cycle of dependence [39]. The proportion of patients achieving opioid cessation at various follow-up intervals (e.g., 30 days, 6 months, or 1-year post-detoxification) serves as a key metric in evaluating its success.

1.4.3.2. Changes in Pain Perception

An often overlooked but critical dimension in evaluating detoxification is its impact on pain perception. Many patients with opioid use disorder (OUD) initially begin opioid therapy for chronic pain, and their continued dependence is often driven by a fear of unmanageable pain without opioids [156]. Detoxification provides an opportunity to assess how patients' pain perception evolves once opioid use is discontinued. Successful detoxification can reduce OIH over time, leading to more accurate pain perception and improved functioning. Evaluating changes in pain intensity, tolerance, and the use of alternative pain management strategies (e.g., physical therapy, mindfulness-based approaches, or non-opioid medications) provides valuable insight into the effectiveness of detoxification in addressing both dependency and pain.

Standardized tools such as the *Visual Analogue Scale (VAS), Brief Pain Inventory (BPI)* or the *Numeric Pain Rating Scale (NPRS)* can be used to track changes in pain perception before, during, and after detoxification [157]. A

reduction in pain scores or an increased ability to manage pain without opioids is indicative of successful treatment.

Effective detoxification is often determined by the extent to which patients can achieve abstinence while maintaining or improving their quality of life, including the management of chronic pain. Programs that combine detoxification with evidence-based pain management strategies, such as cognitive-behavioral therapy for pain, acupuncture, or mindfulness-based stress reduction, report higher rates of success in both opioid cessation and pain outcomes [156].

1.4.3.3. Sustainability of Outcomes

The long-term sustainability of opioid cessation and changes in pain perception can be assessed by tracking relapse rates, ongoing pain levels, and quality of life metrics over time. Studies have shown that patients who experience significant improvements in pain perception and functioning are less likely to relapse, as pain-related triggers for opioid use are diminished [158]. Therefore, evaluating these interconnected outcomes provides a holistic understanding of detoxification's impact.

Evaluating the effectiveness of prescription opioid detoxification is a multifaceted process that requires consideration of clinical, psychological, and social outcomes. While detoxification serves as an initial step in the continuum of addiction treatment, its success is not solely determined by the cessation of opioid use but also by the extent to which it facilitates sustained recovery and addresses the broader consequences of opioid dependency.

1.4.3.4. Withdrawal Symptoms

The primary clinical measure of detoxification effectiveness is the successful management of withdrawal symptoms, which are often a significant barrier to discontinuing opioid use. Effective detoxification minimizes withdrawal-related discomfort and ensures medical safety throughout the process. This can be evaluated using validated scales such as the *Clinical Opiate Withdrawal Scale (COWS)*, which assesses the severity of withdrawal symptoms, or the *Subjective Opiate Withdrawal Scale (SOWS)* for self-reported symptoms [159]. Reduction in withdrawal severity indicates that the detoxification protocol, including pharmacological support such as methadone, buprenorphine, or clonidine, is effective [26, 154]

1.4.3.5. Short-Term Abstinence

Defined as the ability to refrain from opioid use during and immediately after detoxification, is another key measure. Biological markers, such as urine drug screens, are commonly used to verify opioid abstinence. However, achieving abstinence during detoxification does not necessarily predict long-term recovery, underscoring the need to assess outcomes beyond the acute phase [16].

1.4.3.6. Transition to Long-Term Treatment

The success of detoxification is also contingent on its role as a bridge to ongoing addiction treatment. Detoxification alone is insufficient for sustained recovery, as individuals who do not transition to maintenance therapy or rehabilitation programs face high relapse rates, often exceeding 90% within weeks or months [160]. Thus, an important metric of effectiveness is the proportion of patients who enroll in and adhere to subsequent treatment modalities, such as medication-assisted treatment or residential rehabilitation.

1.4.3.7. Psychosocial Outcomes

The effectiveness of detoxification can also be evaluated in terms of psychosocial improvements. Metrics such as reductions in craving intensity, improvements in mental health, and enhanced quality of life provide a broader perspective on the patient's progress. Tools such as the *Addiction Severity Index (ASI)* and the *World Health Organization Quality of Life (WHOQOL)*, *SF-36 Quality of Life* questionnaire are commonly used to assess these dimensions [161-163]. Enhanced psychosocial stability, including improved relationships, housing stability, and employment, are also indicative of a successful detoxification process.

1.4.3.8. Reduction in Relapse Rates

A key long-term indicator of detoxification effectiveness is its impact on relapse rates. While detoxification is not curative, its success is reflected in its ability to set the stage for sustained recovery. A lower incidence of relapse in patients who have undergone detoxification as part of a comprehensive treatment plan suggests effective integration of detoxification within the continuum of care [164].

1.4.3.9. Patient-Centered Metrics

Evaluating patient satisfaction and perceived efficacy of detoxification is increasingly recognized as an essential component of effectiveness. Patient-reported outcomes (PROs), such as satisfaction with care, perceived ease of withdrawal, and overall treatment experience, provide valuable insights into the subjective aspects of detoxification and its acceptability [165].

1.4.3.10. Cost-Effectiveness of Detoxification

Such a protocols can be an important metric for evaluation. Programs that achieve high rates of successful withdrawal management, transition to further care, and relapse prevention while minimizing costs can be deemed more effective. Economic analyses that include healthcare utilization, criminal justice involvement, and productivity loss are essential for understanding the broader impact of detoxification [166].

The effectiveness of prescription opioid detoxification extends beyond the immediate cessation of drug use. A comprehensive evaluation must incorporate clinical, psychosocial, and long-term outcomes, as well as patient-centered and economic metrics. These multidimensional evaluations underscore the importance of integrating detoxification within a broader framework of care that includes maintenance therapy, psychosocial interventions, and long-term support.

1.4.4. The Significance of Subjective and Objective Opioid Withdrawal Scales (SOWS and OOWS) for Quantitative Assessment of Opioid Withdrawal Severity

The use of subjective and objective opioid withdrawal scales plays a pivotal role in the quantitative assessment of opioid withdrawal expression. These scales provide structured frameworks for evaluating the multidimensional nature of withdrawal symptoms, encompassing both self-reported experiences and clinician-observed signs.

Subjective scales, such as the Subjective Opioid Withdrawal Scale (SOWS), rely on the patient's self-assessment of withdrawal symptoms, including anxiety, irritability, and physical discomfort [159]. These scales capture the personal experience of withdrawal, which is essential for understanding the psychological and emotional dimensions of the condition. They are particularly useful in identifying subtle symptoms that may not be

readily apparent during clinical examination, thereby enabling a more comprehensive evaluation of the withdrawal process.

Objective scales, such as the Clinical Opioid Withdrawal Scale (COWS), focus on measurable physiological and behavioral manifestations of withdrawal, including heart rate, pupil dilation, and tremors [167]. These scales offer a standardized approach for clinicians to evaluate the severity of withdrawal symptoms, ensuring consistency and reliability across assessments. By quantifying observable indicators, objective scales facilitate the monitoring of withdrawal progression and the evaluation of treatment efficacy.

The integration of both subjective and objective measures provides a holistic understanding of opioid withdrawal. This dual approach enhances the accuracy of severity assessments and supports personalized treatment planning. For instance, combining patient-reported data with clinician-observed metrics can improve the identification of patients at risk of severe withdrawal or those requiring intensified intervention [155].

Moreover, the quantitative data generated by these scales are invaluable in clinical research, enabling comparisons across studies and the evaluation of new therapeutic interventions. They also play a critical role in monitoring the effectiveness of pharmacological treatments, in alleviating withdrawal symptoms [168].

1.5. Assessing the Influence of Vitamin D Concentration on Detoxification Outcomes and Quality of Life

1.5.1. Physical functioning, immunomodulation, neuroprotection.

In recent years, there has been a growing interest in the potential role of vitamin D in pain management due to its multifaceted physiological functions. Vitamin D, a fat-soluble vitamin, plays a pivotal role in regulating numerous biological processes that extend beyond its traditional involvement in calcium homeostasis and bone health. Among its critical functions, vitamin D modulates immune responses, reduces inflammation, suppresses tumor growth, exhibits antioxidant properties, and provides neuroprotective effects [169, 170].

Immune modulation by vitamin D involves enhancing the activity of regulatory T cells and suppressing the proliferation of pro-inflammatory cytokines, thereby contributing to an anti-inflammatory environment [171]. This effect is particularly significant in chronic pain conditions characterized by low-grade systemic inflammation, such as fibromyalgia, rheumatoid

arthritis, and chronic low back pain [172]. Additionally, vitamin D has been shown to reduce oxidative stress by upregulating the expression of antioxidant enzymes, which may help mitigate oxidative damage in tissues and contribute to pain relief [173].

Furthermore, neuroprotection provided by vitamin D has been implicated in the regulation of nociceptive pathways. Evidence suggests that vitamin D influences the production of neurotrophic factors, such as nerve growth factor, which are essential for maintaining neuronal health and function [174]. This mechanism could have implications for conditions involving neuropathic pain, where neuronal damage and dysfunction are prevalent.

Low baseline levels of vitamin D have been consistently linked to diminished physical functioning, increased pain sensitivity, and heightened fatigue, all of which significantly contribute to a reduced quality of life, particularly in individuals with chronic pain. Vitamin D deficiency has emerged as a prevalent concern in chronic pain populations, with evidence suggesting a bidirectional relationship between low vitamin D levels and chronic pain pathophysiology [175, 176].

Physical functioning is often impaired in individuals with suboptimal vitamin D levels due to its critical role in musculoskeletal health. Vitamin D enhances calcium absorption and facilitates proper muscle function, which are essential for maintaining physical strength and mobility. Deficiency in vitamin D has been associated with muscle weakness, reduced physical performance, and an increased risk of falls, particularly in older adults [177, 178]. This loss of physical capacity is further exacerbated in chronic pain conditions, where musculoskeletal dysfunction is a common comorbidity.

Increased pain sensitivity, or hyperalgesia, has also been observed in individuals with low vitamin D levels. This may be explained by vitamin D's role in modulating inflammatory pathways and its neuroprotective effects on nociceptive processes. Vitamin D has been shown to reduce the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are known to sensitize nociceptors and amplify pain signaling [179]. In conditions such as fibromyalgia, osteoarthritis, and chronic back pain, vitamin D deficiency has been correlated with heightened pain perception, suggesting its potential contribution to central and peripheral sensitization mechanisms [180].

Fatigue, another debilitating symptom commonly reported in chronic pain patients, is also associated with vitamin D deficiency. This fatigue may stem from a combination of musculoskeletal weakness, increased inflammatory burden, and impaired mitochondrial energy production, as

vitamin D plays a role in regulating cellular energy metabolism [181]. Chronic fatigue syndrome and other related conditions have shown an overlap with vitamin D deficiency, further underscoring its impact on overall energy levels and quality of life.

1.5.2. Vitamin D Concentration Impact on Pain severity

Patients with chronic pain frequently exhibit insufficient or deficient levels of vitamin D, with evidence pointing to a significant relationship between lower vitamin D concentrations and increased pain severity. This association has been observed across various chronic pain conditions, suggesting that vitamin D deficiency may be both a marker and a modifiable factor in the management of chronic pain. Several studies have suggested a significant link between vitamin D levels and the occurrence of both acute and chronic pain, with evidence pointing to the potential benefits of vitamin D supplementation in pain management [182-187]. Research highlights the role of vitamin D in modulating pain pathways, inflammation, and nerve function, which may explain these associations.

A randomized double-blind placebo-controlled study investigated the effects of high-dose vitamin D supplementation in patients with musculoskeletal pain. The study demonstrated that adding high-dose vitamin D to conventional analgesic regimens led to significant reductions in pain intensity and improved functional outcomes [182]. These findings suggest that vitamin D supplementation may enhance the efficacy of standard pain management protocols in individuals with musculoskeletal pain.

Further evidence comes from a randomized placebo-controlled trial, which evaluated the effects of vitamin D supplementation in patients with fibromyalgia syndrome. The study revealed that patients who received vitamin D experienced substantial improvements in pain symptoms compared to those in the placebo group [183]. This supports the hypothesis that vitamin D deficiency may contribute to central sensitization and chronic pain conditions such as fibromyalgia.

In the context of diabetic peripheral neuropathy (DPN), study explored the association between reduced vitamin D levels and the severity of pain symptoms [184]. The study found that lower vitamin D levels were correlated with increased pain intensity and greater nerve dysfunction in patients with painful DPN. These findings suggest that vitamin D deficiency may exacerbate neuropathic pain through its effects on neuronal health and inflammatory processes.

Research demonstrated that peritraumatic vitamin D levels could predict chronic pain severity following major thermal burn injuries [185]. The study revealed that lower vitamin D levels not only contributed to greater pain severity but also played a role in racial disparities in pain outcomes, emphasizing the potential for targeted interventions to address these disparities. This study highlights vitamin D's relevance in trauma-related chronic pain and suggests that its supplementation could improve long-term pain outcomes in specific populations.

The relationship between vitamin D and chronic widespread pain (CWP) was further explored in a cross-sectional study of a white middle-aged British population [186]. The findings indicated that individuals with lower vitamin D levels were significantly more likely to report CWP compared to those with sufficient levels. These results suggest that vitamin D deficiency may exacerbate pain perception and that maintaining adequate vitamin D levels could potentially reduce the prevalence or severity of CWP.

Moreover, a systematic review and meta-analysis consolidated evidence from multiple studies, demonstrating a consistent association between low vitamin D concentrations and heightened pain [187]. The analysis further supported the hypothesis that vitamin D plays a role in modulating pain pathways, particularly through its anti-inflammatory and neuroprotective properties. Despite its role in modulating mechanical pain sensitivity, vitamin D appears to have a less direct association with the subjective experience of spontaneous chronic pain as reported by patients. This distinction may be explained by the multifactorial nature of chronic pain syndromes, where psychological, behavioral, and environmental factors interact with physiological processes to shape the perception of pain. For instance, while low vitamin D levels may amplify responses to external stimuli, they might not significantly influence the intrinsic pain pathways responsible for spontaneous pain episodes, which are often driven by central nervous system dysregulation. Importantly, the review highlighted that vitamin D supplementation may improve pain outcomes in deficient individuals, though further research is required to determine optimal dosing and treatment regimens.

1.5.3. Vitamin D Concentration Impact on QoL

Deficient vitamin D levels have been linked to poorer health-related quality of life (HRQoL), potentially due to the compound effects of heightened central sensitivity and an augmented pain response to mechanical stimulation. Central sensitization, a process involving the amplification of pain signals within the

central nervous system, is often implicated in chronic pain conditions such as fibromyalgia and neuropathic pain. Vitamin D deficiency may exacerbate this phenomenon through its role in modulating neuroinflammation and nociceptive processing. Research has shown that vitamin D influences the expression of pro-inflammatory cytokines and contributes to the regulation of neurotrophic factors that maintain neuronal health and function, thereby impacting pain sensitivity and HRQoL [183, 184].

Moreover, studies suggest that vitamin D deficiency's impact on HRQoL extends beyond pain perception to include fatigue, mood disturbances, and physical dysfunction, all of which can indirectly exacerbate the experience of chronic pain. For example, individuals with low vitamin D levels frequently report increased levels of fatigue and depressive symptoms, which are themselves associated with diminished pain tolerance and worsened HRQoL [185, 186]. Furthermore, the musculoskeletal weakness associated with vitamin D deficiency can impair physical activity, contributing to a cycle of deconditioning, reduced functionality, and increased pain perception [177].

These combined effects-reduced physical functioning, heightened pain sensitivity, and persistent fatigue-result in a significantly diminished quality of life for chronic pain patients with low vitamin D levels. Studies have consistently demonstrated that addressing vitamin D deficiency through supplementation can improve physical performance, reduce pain severity, and alleviate fatigue, thereby enhancing overall well-being and functionality [188].

1.5.4. Vitamin D Concentration Impact on Opioid Consumption and Tolerance

There is growing evidence to suggest that reduced levels of 25-hydroxyvitamin D (25-OHD), a biomarker of vitamin D status, are associated with increased prescription opioid consumption, indicating a potential link between vitamin D deficiency and opioid tolerance [189]. This relationship has significant implications for the management of chronic pain, as opioid tolerance often leads to the requirement for escalating doses of opioids, which increases the risks of dependency, adverse effects, and overdose [190].

Vitamin D plays a critical role in the modulation of pain perception through its effects on both the peripheral and central nervous systems. Low levels of 25-OHD have been associated with heightened sensitivity to pain and impaired pain inhibitory mechanisms, which may drive higher analgesic requirements in individuals with vitamin D deficiency [175]. Moreover, vitamin D is thought to interact with opioid receptors and influence endogenous opioid signaling pathways. Experimental studies have

demonstrated that vitamin D deficiency may impair the regulation of these pathways, potentially reduce the efficacy of exogenous opioids and contribute to opioid tolerance [182].

Study found that patients with chronic pain and low vitamin D levels were more likely to require higher doses of opioid medications compared to those with adequate vitamin D levels [190]. Similarly, supplementation of vitamin D has been associated with reductions in opioid consumption and improvements in pain management outcomes. A randomized controlled trial showed that high-dose vitamin D supplementation, when added to standard analgesic regimens, significantly reduced pain intensity and opioid requirements in patients with musculoskeletal pain [182].

Additionally, vitamin D deficiency is associated with pro-inflammatory states, which may exacerbate pain and opioid tolerance. Chronic inflammation, characterized by elevated levels of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), has been implicated in the development of opioid tolerance through its effects on nociceptive pathways and opioid receptor desensitization [191-193]. By modulating inflammatory responses, vitamin D may help to mitigate these processes and enhance the efficacy of opioid therapy.

The potential role of vitamin D deficiency in exacerbating opioid tolerance highlights the importance of assessing and addressing vitamin D levels in patients receiving long-term opioid therapy. Identifying and correcting vitamin D deficiency could represent a low-cost, non-invasive strategy to optimize pain management, reduce opioid consumption, and potentially delay the onset of opioid tolerance.

Despite the associations between vitamin D deficiency and increased pain sensitivity, the precise physiological relationship between vitamin D status and pain genesis remains poorly understood and continues to be a topic of scientific investigation [186]. Vitamin D is believed to modulate pain through various mechanisms, including its anti-inflammatory, neuroprotective, and musculoskeletal effects.

However, the complexity of pain pathophysiology and the multifactorial nature of chronic pain conditions have made it challenging to establish a definitive causal link. These inconsistencies highlight the need for more rigorous, well-designed clinical trials to clarify the relationship between vitamin D supplementation, pain outcomes, and QoL. Future research should focus on identifying specific patient subgroups most likely to benefit from supplementation, optimizing dosing strategies, and elucidating the physiological mechanisms by which vitamin D influences pain perception and inflammatory processes.

2. PARTICIPANTS AND METHODOLOGY

2.1. Participants and Their Selection

This prospective study was conducted over a four-year period, from 2019 to 2023, and involved the recruitment of a cohort of 45 patients undergoing prescription opioid detoxification at the Toxicology Centre of Republican Vilnius University Hospital in Lithuania. All 45 patients who were enrolled successfully completed the study, ensuring a robust dataset for analysis. The study protocol received formal approval from the Vilnius Regional Committee on Biomedical Research Ethics (license no. 2019/10-1153-644, issued on October 8, 2019), in accordance with Lithuanian and international ethical guidelines for biomedical research. Prior to inclusion in the study, all participants provided written informed consent after being fully briefed about the study's objectives, procedures, and potential risks.

Referrals to the Toxicology Centre were initiated by a network of healthcare providers, including primary care physicians and secondary care facilities such as the National Centre for Cancer and pain management clinics. These institutions identified patients using prescription opioids and assessed their suitability for participation in opioid detoxification programs. These institutions played a critical role in identifying eligible participants, conducting preliminary assessments, and facilitating their enrollment in the research program.

The informed consent process adhered to rigorous ethical standards to ensure the protection of participants' rights and privacy. Participants were provided with a detailed Participant Information Sheet and an Informed Consent Form in Lithuanian language, both of which outlined the study's objectives, procedures, and confidentiality measures. Each participant was given the opportunity to ask questions and seek clarifications before providing consent. Specific permission was obtained to access and utilize medical records, ensuring compliance with ethical standards. To protect participant privacy, all collected data were anonymized, with identifying information removed to prevent traceability. These measures upheld ethical guidelines for biomedical research, ensuring transparency and safeguarding participant rights.

2.1.1. Inclusion Criteria

1. Documented Opioid Tolerance and Dependence: Participants with a verified history of opioid tolerance, characterized by a diminished

analgesic response requiring progressively higher doses to achieve equivalent pain relief, and dependence on prescription opioids.
2. Admission for Elective Detoxification: Participants admitted to the Toxicology Centre specifically for elective detoxification from prescription opioids.

2.1.2. Exclusion Criteria

1. Acute Opioid Poisoning: Patients presenting with signs of acute opioid poisoning at the time of assessment.
2. Addiction to Illicit Opioids: Patients diagnosed with addiction to illicit opioids rather than prescription medications.
3. Polysubstance Addiction: Patients diagnosed with addiction to multiple psychoactive substances beyond opioids.

These criteria were designed to ensure that the study population consisted exclusively of individuals with prescription opioid dependence, enabling a targeted evaluation of detoxification outcomes. Exclusion of patients with acute opioid poisoning or polysubstance addiction minimized potential confounding variables and ensured the homogeneity of the cohort.

2.1.3. Cohort Characteristics and Suitability for Detoxification

Following referral, participants underwent a comprehensive medical and psychosocial evaluation at the Toxicology Centre to confirm their eligibility. This assessment included a detailed review of their medical history, current opioid use patterns, and readiness for elective detoxification. The final cohort of 45 patients represented a diverse demographic group, including variations in age, gender, and clinical backgrounds, enhancing the generalizability of the study findings to broader populations of patients undergoing prescription opioid detoxification.

By adhering to stringent recruitment, consent, and selection procedures, the study ensured that all participants were suitable for the intervention, ethically protected, and appropriately informed, thereby contributing to the validity and reliability of the research outcomes.

The patient cohort consisted of individuals prescribed opioids primarily for managing various pain conditions, including headaches, cancer-related pain, back pain, rheumatoid arthritis, gastrointestinal pathology, chronic muscle pain, and arthrosis of the humerus. Notably, all cancer patients included in the study were in the remission phase and not undergoing active cancer treatment at the time of data collection.

2.2. Data Collection and Clinical Assessment

Upon admission to the Toxicology Centre, comprehensive clinical and demographic information was systematically gathered for all participants. This process aimed to capture a detailed profile of each patient to facilitate subsequent analysis and interpretation of the study findings. The collected data included the patient's age, gender, the duration of their chronic pain, the primary pain location or underlying diagnosis, and their patterns of opioid consumption. Additionally, the length of time each patient had been using opioids was recorded to assess the chronicity of opioid use and its potential impact on dependence and treatment outcomes.

To accurately determine the opioid dosage at admission, a multi-faceted approach was employed. Patients were asked to provide a self-reported account of their current opioid regimen, including the specific medications used, dosages, and frequency of administration. This self-reported information was then cross-referenced with data from their medical records to ensure accuracy and reliability. By corroborating self-reports with documented prescriptions, potential discrepancies were minimized, thereby enhancing the validity of the dosage data.

To standardized analysis and comparison, the recorded opioid dosages were converted into oral morphine equivalents (OME). This conversion allowed for the normalization of opioid potency across different medications, facilitating uniformity in the measurement of opioid use among participants. The use of OME as a standard unit is widely recognized in clinical research as it enables a more precise evaluation of the total opioid burden and supports comparisons across studies involving diverse opioid formulations.

The following categories of data were systematically gathered, documented, and subsequently analyzed to achieve the study objectives:

1. Demographic Indicators

Demographic data were collected to characterize the study population and assess potential relationships between patient demographics and treatment outcomes. These data included the patient’s age, gender, height, weight, and body mass index (BMI). This information provided a understanding of the participants' backgrounds and their potential influence on opioid use and detoxification success.

2. Somatic Pathology

The presence of somatic medical conditions was recorded to assess comorbidities that might influence treatment responses and study outcomes. Documented conditions included any chronic or acute illnesses reported during the initial clinical assessment. This data provided insight into the overall health status of participants and allowed for a nuanced analysis of how comorbidities might interact with opioid use and detoxification.

3. Prescription Opioid Use Characteristics

Detailed information about opioid use was gathered to evaluate the patterns and chronicity of opioid consumption. Data included the specific opioids used, their dosages (standardized into oral morphine equivalents, OMEs), the duration of opioid use, and the primary intended purpose of opioid consumption, such as pain management or other indications. Additionally, participants were asked about any previous detoxification treatments, including the frequency and outcomes of these interventions.

4. Quality of Life Assessment

Quality of life (QoL) among study participants was evaluated using the Short Form-36 Version 2 (SF-36v2™) questionnaire, which had been translated into the Lithuanian language to ensure cultural and linguistic appropriateness. The assessment was conducted at three distinct time points to capture changes in QoL throughout the detoxification process and post-treatment period. These time points included: (1) prior to the initiation of detoxification (baseline), (2) on the day of discharge from the Toxicology Centre (post-detoxification), and (3) at least six months after discharge during a follow-up telephone interview. This longitudinal approach provided insights into both short-term and longer-term QoL outcomes following prescription opioid detoxification.

The SF-36v2™ questionnaire is a validated, multidimensional instrument designed to measure health-related QoL across a broad range of populations and conditions. It consists of 36 items that are grouped into eight domains or scales: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health perceptions. Each domain is scored on a scale ranging from 0 to 100, where higher scores indicate better functioning or fewer limitations within that specific aspect of QoL.

To derive an overall QoL score, the scores from the eight individual scales were averaged, providing a comprehensive measure of the participants

perceived health status. This composite score enabled a holistic evaluation of QoL, reflecting both physical and mental health dimensions. By utilizing the SF-36v2™, the study ensured the application of a robust and internationally recognized tool for measuring QoL, thereby enhancing the reliability and comparability of the findings.

The use of a standardized assessment tool like the SF-36v2™ allowed for the quantification of changes in QoL over time and provided valuable data for evaluating the impact of detoxification interventions. The inclusion of a follow-up period of at least six months also ensured that longer-term effects of detoxification on participants' quality of life were adequately captured, offering a broader perspective on the efficacy and sustainability of the intervention.

5. Pain Intensity Assessment

Patient pain intensity was assessed using the Visual Analogue Scale (VAS), a widely recognized and validated tool for measuring subjective pain levels. The VAS used in this study ranged from 0 to 10, with 0 representing "no pain" and 10 indicating "the worst pain imaginable." This unidimensional scale provided a simple yet effective method for quantifying pain intensity, allowing for direct comparison of pain levels at different time points.

VAS Score	Pain Description
0	No pain
1 – 3	Mild pain
4 – 6	Moderate pain
7 – 9	Severe pain
10	Worst pain imaginable

Pain intensity was evaluated at two specific time points to assess the immediate impact of the detoxification procedure on participants perceived pain levels. The first measurement was taken on the day [of the detoxification process (baseline), and the second was conducted on the day of discharge, following the completion of the detoxification procedure. By comparing VAS scores at these two time points, the study aimed to evaluate changes in pain intensity during the detoxification period and to identify potential improvements in pain management because of the intervention.

The decision to measure pain only at these two critical junctures was informed by the study's focus on the short-term outcomes of detoxification. This approach provided insight into how the detoxification process influenced acute pain levels, offering a valuable perspective on the interplay between

opioid withdrawal, detoxification interventions, and pain perception. The use of the VAS allowed for standardized and easily interpretable data collection, ensuring the reliability and consistency of pain intensity measurements across all participants.

6. Measurement of Serum 25-Hydroxyvitamin D Levels

Serum levels of 25-hydroxyvitamin D (25-OHD), a widely recognized biomarker for assessing vitamin D status, were measured in all participants prior to the initiation of the detoxification process. Blood samples were collected in an ambulatory setting under standardized conditions to ensure consistency and reliability in the measurement of 25-OHD levels. The serum 25-OHD concentration was determined using validated laboratory methods, such as immunoassay or liquid chromatography-tandem mass spectrometry (LC-MS/MS), which are considered gold standards for vitamin D analysis.

For this study, participants were classified into two categories based on their baseline serum 25-OHD levels. Individuals with serum 25-OHD concentrations below 75 nmol/L (30 ng/mL) were classified as having vitamin D deficiency, in line with international guidelines that associate such levels with suboptimal bone and metabolic health. Conversely, participants with serum 25-OHD levels of 75 nmol/L or higher were categorized as having sufficient vitamin D levels, indicating an adequate vitamin D status.

This classification provided a clear framework for evaluating the potential relationship between vitamin D status and the outcomes of the detoxification process. By assessing baseline 25-OHD levels prior to the initiation of detoxification, the study aimed to investigate whether vitamin D deficiency might influence withdrawal symptoms, treatment efficacy, or overall patient recovery. Furthermore, the stratification of participants into deficient and sufficient vitamin D groups facilitated a comparative analysis, enabling the identification of any significant differences in clinical outcomes associated with variations in vitamin D status.

The use of serum 25-OHD as a biomarker ensured the accuracy and reliability of vitamin D status assessment, while the pre-detoxification measurement timing allowed for the establishment of a clear baseline unaffected by the detoxification process. This methodological rigor enhanced the validity of the findings and their potential implications for clinical practice.

2.3. Prescription Opioid Detoxification Protocol

The detoxification protocol utilized in this study was designed with reference to our earlier work [26] and approved on 2nd April 2019 in Republic Vilnius University hospital [Appendix 2] which employed a structured pharmacological approach involving benzodiazepines and α2-adrenergic agonists to manage withdrawal symptoms during opioid abstinence. In this protocol, benzodiazepines, specifically diazepam, and the α2-adrenergic agonist clonidine were administered to mitigate the physiological and psychological manifestations of opioid withdrawal. The dosage and frequency of these medications were adjusted in response to the severity of withdrawal symptoms, which were continuously assessed using the Objective Opioid Withdrawal Scale (OOWS) and the Subjective Opioid Withdrawal Scale (SOWS)**.** These validated tools provided a systematic framework for evaluating withdrawal severity and tailoring interventions to the individual needs of each patient.

During detoxification, the administration of opioid medications was entirely discontinued, and patients were closely monitored for the emergence of withdrawal symptoms. A key component of the protocol was the timely and carefully titrated pharmacological intervention aimed at alleviating withdrawal symptoms early in their presentation. This approach was intended to minimize patient discomfort while supporting the successful progression of the detoxification process.

In addition to diazepam and clonidine, the protocol incorporated a multidisciplinary pharmacological strategy that included medications targeting specific symptoms of withdrawal. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen**,** diclofenac**,** and ketorolac were utilized for their analgesic and anti-inflammatory properties to address musculoskeletal pain and general discomfort associated with withdrawal. Antipsychotic medications, including haloperidol and quetiapine, were employed to manage agitation, anxiety, and insomnia that commonly occur during opioid withdrawal. Anticonvulsants such as gabapentin were administered for their efficacy in reducing neuropathic pain and modulating hyperexcitability in the nervous system. Tetracyclic antidepressants like mirtazapine were included to address mood disturbances and insomnia, further enhancing the protocol's ability to manage the multifaceted nature of withdrawal symptoms.

Each medication was titrated to the individual needs of the patient, with dosing adjustments guided by the severity and progression of withdrawal symptoms. This personalized approach ensured that the treatment was both effective and tolerable for the patients undergoing detoxification. Continuous

monitoring throughout the detoxification process allowed for the early identification and prompt management of withdrawal symptoms, ensuring patient safety and comfort during this critical period.

Unlike the referenced original protocol, which included the administration of naltrexone for opioid antagonist induction, naltrexone was not used in this study**.** The decision to omit naltrexone was based on the specific objectives of this study, which focused on evaluating detoxification outcomes without the additional stress responses associated with opioid antagonist induction, as observed in previous research.

This tailored detoxification protocol reflects a comprehensive and evidence-based approach to managing opioid withdrawal, drawing on prior research while incorporating individualized patient care and multidisciplinary pharmacological strategies. The adjustments made to the protocol, including the exclusion of naltrexone, were intended to optimize treatment outcomes and minimize patient distress during the detoxification process.

2.4. Pre-Detoxification Assessment of the Relationship Between baseline Vitamin D Levels, Quality of Life (QoL), and Pain Perception

For the purposes of this specific analysis, data collection and analysis were focused exclusively on pre-detoxification measures. Specifically, QoL, as assessed using the SF-36v2™ questionnaire, and VAS pain scores recorded prior to the detoxification process were analyzed in relation to baseline serum 25-hydroxyvitamin D (25-OHD) levels. Participants were stratified into two distinct groups based on their baseline vitamin D status: one group with deficient serum 25-OHD levels (<75 nmol/L) and another with sufficient levels (≥75 nmol/L).

This targeted approach was designed to evaluate the relationship between pre-detoxification QoL, subjective pain perception, and vitamin D status. By focusing exclusively on pre-detoxification data, the study aimed to explore whether vitamin D deficiency might contribute to poorer QoL or heightened pain perception prior to undergoing detoxification. This analysis sought to generate clinically relevant insights into the potential role of vitamin D status as a modifiable factor influencing patient well-being in the context of opioid dependence.

On the first day of detoxification, participants with deficient serum 25-OHD levels received vitamin D supplementation, administered as a single dose of 50,000 IU of cholecalciferol. The selection of this specific dosing regimen and formulation-an oral solution-was based on the recommendations provided by the Lithuanian College of Family Physicians Guidelines [194] for

the management of vitamin D deficiency. This approach ensured adherence to evidence-based clinical practices while addressing the identified deficiency in a timely manner during the detoxification process.

To support long-term vitamin D repletion, all participants were advised to continue supplementation and follow-up care under the supervision of their family physician upon discharge. This recommendation was provided to both those with initially deficient and sufficient serum 25-OHD levels, acknowledging the potential benefits of maintaining optimal vitamin D levels for overall health.

It is noteworthy that serum 25-OHD levels were not re-measured after inpatient detoxification, as the primary focus of this sub-study was to examine the influence of baseline 25-OHD levels on pre-detoxification QoL and pain perception. While the broader study incorporated post-detoxification outcomes, this analysis intentionally concentrated on the interplay between initial vitamin D status and patient-reported outcomes before the initiation of detoxification interventions. This methodological choice was made to isolate the potential impact of baseline vitamin D deficiency on subjective measures of health and well-being in individuals undergoing opioid detoxification.

2.5. Features of Detoxification Treatment

The detoxification treatment administered during hospitalization was comprehensively analyzed to assess its clinical characteristics, efficacy, and outcomes. Data collection focused on multiple aspects of the treatment protocol, providing a detailed overview of the interventions utilized and their effects on participants.

Key data points included the medications administered during the detoxification process, along with their respective dosages. These medications were selected based on clinical guidelines and tailored to individual patient needs to manage withdrawal symptoms and support the detoxification process effectively. The selection of pharmacological interventions aimed to minimize discomfort, address opioid withdrawal symptoms, and prevent complications.

The management of withdrawal symptoms was a critical component of the treatment analysis. This involved monitoring the type, frequency, and severity of withdrawal symptoms experienced by participants throughout the detoxification process. Documentation of withdrawal severity provided valuable insights into the physiological and psychological challenges associated with opioid detoxification and the effectiveness of the treatment in alleviating these symptoms.

Additional treatment features included the duration of hospitalization, which was recorded for each participant to assess the time required for completing the detoxification process and achieving clinical stabilization. The length of stay was considered a key indicator of treatment efficiency, balancing the need for adequate care with the goal of minimizing hospital resource utilization.

The severity of withdrawal manifestations was systematically evaluated using validated clinical SOWS and OOWS scales and through direct observation by healthcare providers. This enabled the study to quantify the withdrawal experience and to identify potential correlations between withdrawal severity, treatment regimens, and patient outcomes.

Finally, overall treatment outcomes were documented to evaluate the success of the detoxification intervention. These outcomes included measures such as the resolution of withdrawal symptoms, participant readiness for discharge, and the achievement of a drug-free state upon completion of hospitalization.

2.6. Data Documentation and Statistical Analysis

All collected data were meticulously documented and managed to ensure precision, accuracy, and reproducibility throughout the research process. The data were systematically entered into a Microsoft Office Excel spreadsheet, which served as the primary repository for storage and initial data organization. Subsequently, statistical analyses were conducted using IBM SPSS Statistics 23.0 software, ensuring a comprehensive and rigorous evaluation of the dataset. Descriptive statistics were employed to summarize demographic and clinical characteristics, including measures of central tendency and variability, while inferential statistical methods were applied where applicable to assess relationships between variables and treatment outcomes. This structured and methodical approach to data management and analysis ensured the robustness, reliability, and relevance of the findings within the field of biomedical science.

Data analysis incorporated a dual-software strategy, utilizing both MS Excel for preliminary data handling and SPSS for advanced statistical processing. Continuous variables were summarized as means with accompanying standard deviations, providing a clear representation of data variability, while categorical variables were expressed as percentages to facilitate comparisons. For group comparisons, the independent samples t-test was used to evaluate differences in mean values, with statistical significance defined at the conventional threshold of $p < 0.05$.

To investigate the relationships among serum 25-hydroxyvitamin D (25-OHD) levels, Visual Analog Scale (VAS) pain scores, and Quality of Life (QoL) scores prior to opioid detoxification, a linear regression analysis was performed using ordinary least squares (OLS) estimation. Within this model, 25-OHD levels were log-transformed to correct for skewness and ensure linearity, while VAS pain scores were reversed and log-transformed to improve distributional properties and interpretability. The QoL score served as the dependent variable, capturing the subjective well-being of participants. Statistical significance was evaluated at the 0.05 level, with t-statistics and corresponding p-values used to determine the individual contribution of each predictor variable to the model. This analytical framework provided robust insights into the interplay between biochemical, clinical, and quality-of-life parameters.

Additionally, an independent samples t-test was conducted to examine differences between two participant groups: those with sufficient 25-OHD levels ($\geq$ 75 nmol/L) and those with deficient levels ($<$ 75 nmol/L). This test, performed under the assumption of unequal variances, assessed mean differences across critical variables, including VAS pain scores prior to intervention (reversed and log-transformed) and QoL scores as derived from the SF-36v2™ questionnaire. The results of the t-test were reported with mean differences, standard errors, and p-values to establish the statistical significance of observed differences at the 0.05 threshold.

The application of data transformations, including logarithmic adjustments, was carefully implemented to normalize skewed distributions and enhance the interpretability of regression and group comparison results. This thoughtful and rigorous approach ensured the statistical validity of the findings and their meaningful contribution to understanding the complex interrelationships among vitamin D status, pain perception, and quality of life in the context of opioid detoxification.

2.7. Duration of Participant Involvement in the Biomedical Study

Participant involvement in the study was carefully structured to ensure a thorough evaluation of the detoxification program's efficacy and long-term impact. Data were collected prospectively, with the duration of each participant's involvement extending from the initiation of the opioid detoxification process to a follow-up period of at least six months post-completion of inpatient treatment. This extended timeline allowed for the assessment of both immediate outcomes, such as the success of the detoxification process, and longer-term outcomes, including sustained

changes in pain perception, quality of life, and overall health status. By incorporating a longitudinal design, the study provided a robust framework for evaluating the effectiveness and durability of the treatment interventions.

3. RESULTS

3.1. Patient's characteristics

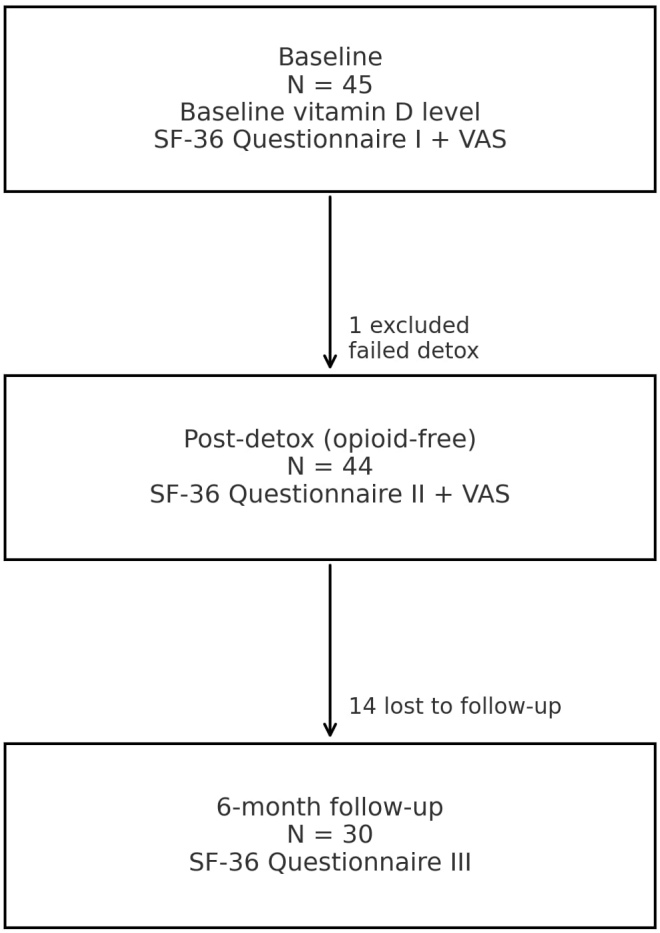
The analysis was conducted on a cohort of 45 patients, of which 44 successfully completed the detoxification process, meaning they achieved the cessation of prescription opioid use. This represents a high success rate of 97.8%, demonstrating the effectiveness of the intervention in helping patients discontinue opioid use.

Among the cohort, 28 participants were women, constituting 62.22% of the group, indicating a slight predominance of female patients. The average age of the participants was 53.62 years, with a standard deviation of ±12.70 years, representing a middle-aged population. Participants reported a history of prescribed opioid use lasting an average of 60.51 months (±67.81 months), reflecting substantial variability in duration. The detoxification process itself lasted an average of 9.2 days (±3.2 days), demonstrating the feasibility of achieving opioid withdrawal in a relatively short period. [Table 1].

Table 1. Patient Characteristics

Average age of the participants (years±SD) (n=45)	53.62±12.7
Avarage duration of opioid usage (months±SD) (n=45)	60.51 ± 67.81
Average detoxification duration (days±SD) (n=45)	9.2± 3.2

Chart 1. Study Flow: Patient Progression in Detoxifications and SF-36 QoL, VAS and Vitamin D Assessment



3.2. Indication for Long-Term Prescription Opioid Use

The patient cohort consisted of individuals prescribed opioids primarily for managing various pain conditions, including headaches, cancer-related pain, back pain, rheumatoid arthritis, gastrointestinal pathology, chronic muscle pain, and arthrosis of the humerus. The primary indications for opioid use were headaches and cancer-related pain, each accounting for 14 cases out of 45. Notably, all cancer patients included in the study were in the remission phase and not undergoing active cancer treatment at the time of data collection Back pain was the next most frequent reason, cited by 10 patients. Other, less common conditions included rheumatoid arthritis (2 cases), gastrointestinal

pathology (2 cases), and single instances of post-burn sequelae, chronic muscle pain, and humerus arthrosis. These findings underscore the diversity of pain-related conditions for which opioids were prescribed in this cohort [Table 2] [Figure 1].

Table 2. Reason for Prescription Opioid Use

Reason for opioid use (n=45)	
Oncological (remission phase)	14 (31.1 %)
Neurological	14 (31.11 %)
Musculoskeletal	10 (22.2 %)
Rheumatoidal	2 (4.44 %)
Gastrointestinal	2 (4.44 %)
Other	3 (6.67 %)

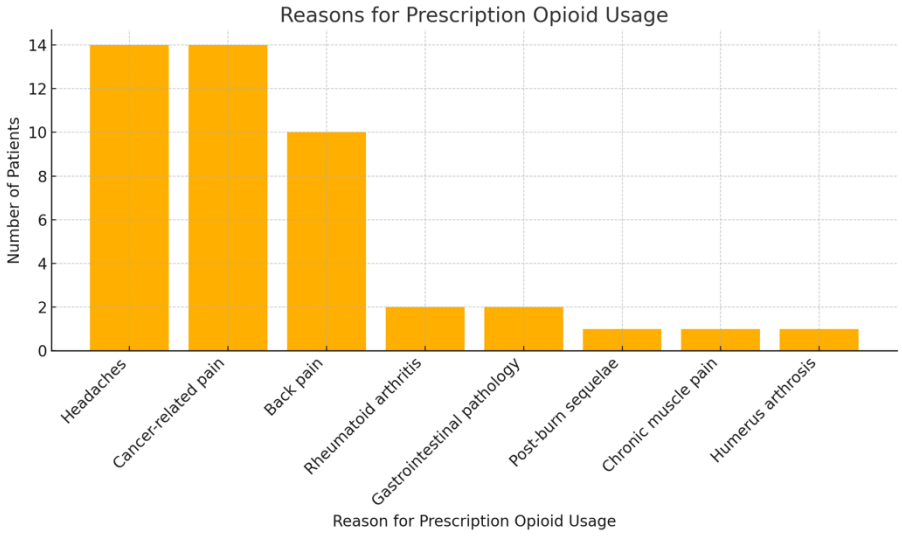


Figure 1. Reason for Prescription Opioid Use

3.3. Prescription Opioid Type

The prescription patterns revealed a wide range of opioids used by the participants. Tramadol was the most frequently prescribed opioid, reported in 13 patients, followed by codeine and morphine, each prescribed to 9 patients. Fentanyl, in its transdermal form, was prescribed to four patients, while pethidine was prescribed to two. Methadone and oxycodone were each prescribed to one patient. Several patients used multiple opioids concurrently, illustrating the complexity of their treatment regimens. Specifically, two patients were prescribed both morphine and fentanyl, two received fentanyl and tramadol, one patient was prescribed morphine and tramadol, and one patient concurrently used codeine, morphine, and tramadol. [Table 3] [Figure 2].

Table 3. Medications

Opioid analgesics (used alone and in combinations) (n=45) (n, %)	
Tramadol	13 (28.9 %)
Codeine	9 (20 %)
Morphine	9 (20 %)
Fentanyl	4 (8.9 %)
Pethidine	2 (4.4 %)
Methadone	1 (2.2 %)
Oxycodone	1 (2.2 %)
Combined Opioid Usage (n, %)	
Morphine and Fentanyl	2 (4.5 %)
Fentanyl and Tramadol	2 (4.5 %)
Morphine and Tramadol	1 (2.3 %)
Codeine, Morphine, and Tramadol	1 (2.3 %)

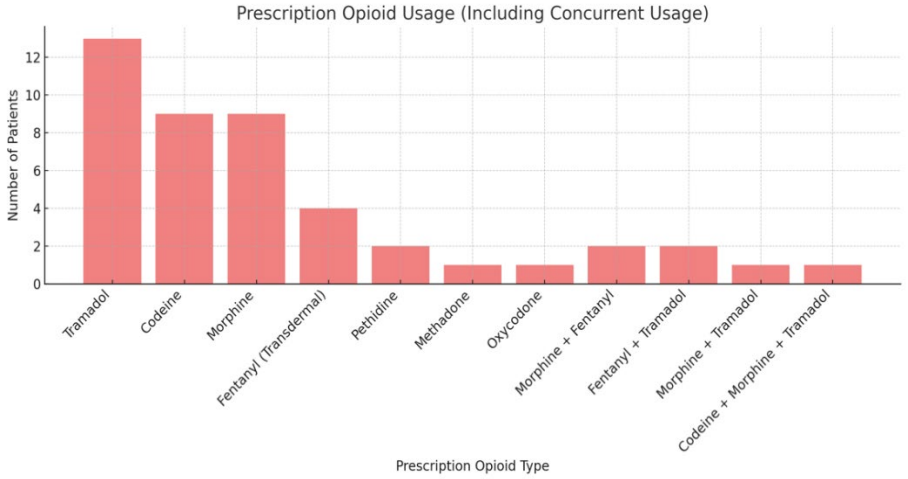


Figure 2. Medications

3.4. Prescription Opioid Dose

The prescribed dose of opioids averaged 139.8 ± 153.9 mg per day in oral morphine equivalent doses (MEDs). For single opioids, the MEDs ranged from 20.54 mg (±22.71) for Codeine to 450 mg for Oxycodone. For combined opioid therapies, the MEDs varied, with highest being 315 mg (±75) for the combination of Morphine and Fentanyl [Table 4].

Table 4. The mean and standard deviation (SD) of morphine equivalent doses (MED) for each prescribed opioid

Average initial morphine equivalent dose before treatment (mg/d±SD) (n=45)	139.8 ± 153.9
Single opioid	
Tramadol (n=13)	85±71.68
Codeine (n=9)	20.54±22.71
Morphine (n=9)	200±211.82
Fentanyl (n=4)	323.12±151.67
Pethidine (n=2)	100±0
Methadone (n=1)	70.5
Oxycodone (n=1)	450
Combined opioids	
Morphine and Fentanyl (n=2)	315±75
Fentanyl and Tramadol (n=2)	213.75±116.25
Morphine and Tramadol (n=1)	90
Codeine, Morphine, and Tramadol (n=1)	41.6

3.5. Prescription Opioid Dose by Pain Category

The analysis of prescription opioid use for different pain conditions revealed distinct patterns in opioid selection and dosage. The following observations were made [Table 5]:

Neurological Pain: the most prescribed opioids were codeine and tramadol. Morphine-equivalent doses ranged from 1.3 mg to 240 mg. Tramadol was used at higher doses (up to 240 mg MED), whereas codeine was prescribed at lower doses.

Musculoskeletal Pain: Opioids used included tramadol, fentanyl, morphine, and oxycodone. Morphine-equivalent doses ranged from 15 mg to 720 mg. The highest dose was observed with morphine (720 mg MED), while fentanyl and oxycodone were also used at substantial doses.

Oncological Pain: The most diverse opioid selection was noted, including morphine, fentanyl, methadone, and combinations of opioids. Morphine-equivalent doses varied widely from 30 mg to 550 mg. Fentanyl and morphine were frequently combined for high-dose regimens.

Gastrointestinal Pain: The only opioid prescribed was pethidine, with a consistent 100 mg MED dose.

Rheumatological Pain: Morphine was the only opioid prescribed, at a 240 mg MED dose.

Other Pain Categories: For burn-related pain, tramadol was used at 40 mg MED. For trauma-related pain, tramadol was prescribed at 40 mg MED. For undetermined lower spine pathology, a combination of codeine, morphine, and tramadol was prescribed at 41.6 mg MED.

This analysis highlights that tramadol and codeine were preferred for neurological pain, morphine and fentanyl dominated oncological and musculoskeletal pain, and pethidine was restricted to gastrointestinal pain. High doses were primarily seen in oncological and musculoskeletal cases, suggesting greater opioid requirements in these conditions.

Table 5. Prescription Opioid Use by Pain Category

No.	**Prescription Opioid type**	**Pain Reason**	**Equivalent morphine dose (MED) mg/d**
1	codeine	neurological	3.2
2	tramadol	neurological	200.0
3	tramadol	others (burns)	40.0
4	codeine	neurological	60.0
5	morphine	oncological	40.0
6	tramadol	musculoskeletal	80.0
7	codeine	neurological	57.0

No.	Prescription Opioid type	Pain Reason	Equivalent morphine dose (MED) mg/d
8	tramadol	neurological	240.0
9	fentanyl	oncological	270.0
10	fentanyl	musculoskeletal	270.0
11	codeine	neurological	9.6
12	tramadol	neurological	40.0
13	methadone	oncological	70.5
14	codeine	neurological	1.3
15	morphine	musculoskeletal	200.0
16	tramadol	musculoskeletal	20.0
17	fentanyl	oncological	550.0
18	morphine, fentanyl	oncological	390.0
19	tramadol	others (humerus trauma)	40.0
20	codeine	neurological	24.0
21	fentanyl	oncological	202.5
22	tramadol	musculoskeletal	30.0
23	morphine	rheumatological	240.0
24	tramadol	musculoskeletal	160.0
25	pethidine	gastrointestinal	100.0
26	tramadol	musculoskeletal	15.0
27	morphine	oncological	150.0
28	tramadol	neurological	120.0
29	pethidine	gastrointestinal	100.0
30	morphine	musculoskeletal	720.0
31	morphine	oncological	30.0
32	fentanyl, tramadol	oncological	330.0
33	morphine	oncological	30.0
34	morphine	oncological	150.0
35	morphine	rheumatological	240.0
36	oxycodone	musculoskeletal	450.0
37	morphine, tramadol	oncological	90.0
38	codeine	neurological	16.0
39	codeine	neurological	8.0
40	tramadol	musculoskeletal	20.0
41	codeine	neurological	4.8
42	tramadol	neurological	100.0
43	fentanyl, tramadol	oncological	97.5
44	codeine, morphine, tramadol	others (pain in lower spine, pathology undiagnosed)	41.6
45	morphine, fentanyl	oncological	240.0

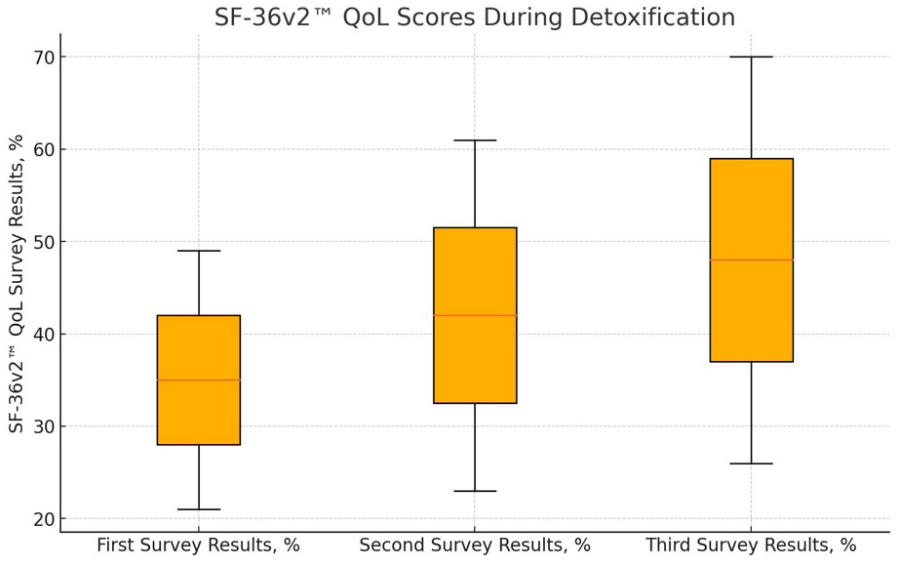
3.6. Quality of Life Assessment

Full follow-up was obtained for 30 patients, with the remaining 15 patients either declining to complete the third SF-36v2TM form or being uncontactable. Statistical analysis revealed a significant improvement in QoL scores across all three time points. The mean QoL scores were as follows: first—before detoxification, 35 ± 14%; second—on the day of discharge, 42 ± 19% ($p = 0.004$ compared to predetox); and third—at least six months after detoxification (follow-up call), 48 ± 22% ($p < 0.001$ compared to predetox; $p = 0.025$ compared to discharge) [Table 6] [Figure 3]. These results indicate a continuous improvement in QoL from predetoxification to post-detoxification, demonstrating the beneficial impact of opioid detoxification on patients' overall wellbeing.

Table 6. SF-36v2™ Questionnaire Results Across Three Stages (%)

Patient No.	I Questionnaire	II Questionnaire	III Questionnaire
1	20	23	13
2	56		
3	68	69	66
4	43	81	86
5	39	52	
6	15	18	27
7	21	24	
8	32		
9	37	29	39
10	13	35	
11	53	74	
12	49	59	
13	22	24	20
14	42	51	60
15	12	10	12
16	20	33	33
17	35	28	38
18	26	10	
19	53	63	82
20	12		
21	21		
22	46	48	47
23	44	61	43
24	27	26	22
25	44	46	38

Patient No.	I Questionnaire	II Questionnaire	III Questionnaire
26	32	41	89
27	28	31	24
28	25	25	34
29	45	49	43
30	21	22	39
31	53	59	62
32	35	45	49
33	55	52	65
34	34	32	40
35	50	55	87
36	28	30	63
37	49	42	
38	41	68	82
39	42	78	49
40	34		
41	33	53	
42	14	30	49
43	40		
44	20	26	58
45	39	33	



Figures 3. Results of SF-36v2™ QoL questionnaires during detoxification (n=30). There is a statistically significant difference between the estimates of the first and second questionnaires ($p = 0.004$) and between the first and third questionnaires ($p < 0.001$) and between the second and third questionnaires ($p = 0.025$).

3.7. Pain Scores Before and After Detoxification

The Visual Analog Scale (VAS) pain scores were measured for 44 patients before and after undergoing opioid detoxification. The mean VAS scores were 6.68±2.0 points before detoxification and 2.17±1.93 points after detoxification ($p < 0.001$). This average reduction of 4.51± 1.83 points underscores a substantial decrease in pain levels following the detoxification process [Table 7], [Table 8], [Figure 4].

Table 7. Results of VAS pain score before and after detoxification (n=44).

Pain level (n=44)	
VAS before detoxification (points±SD)	6.68±2
VAS after detoxification (points±SD)	2.17±1.93

Table 8. VAS pain score for each disease before and after detoxification (n=44)

VAS for each disease before and after detoxification (n=44) (points±SD)		
Oncological disease (n=14)	5.9±2.59	1.60±1.88
Neurological disease (n=14)	6.07±1.55	1.78±1.63
Musculoskeletal disease (n=10)	7.7±2.13	2.6±2.46
Rheumathoidal disease (n=2)	6.75±1.06	2.5±0
Gastrointestinal (n=2)	8.5±0.71	2.25±2.48
Other (n=2)	8.5±0.71	4.75±1.77

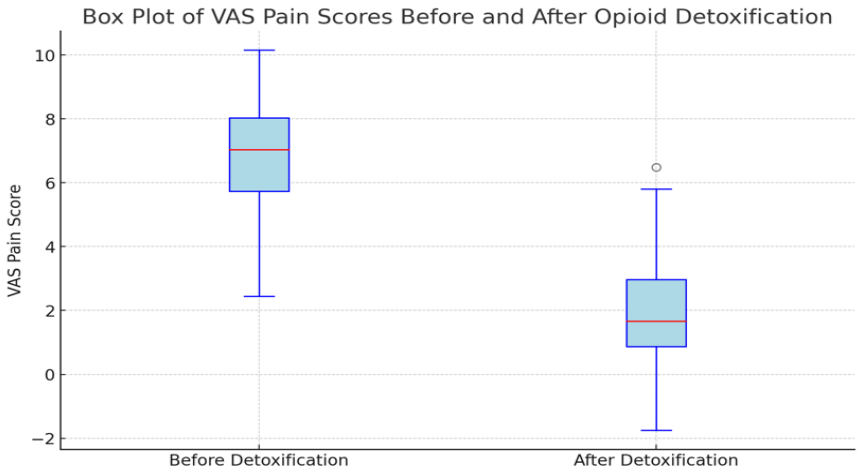


Figure 4. Results of VAS pain score before and after detoxification (n=44).

3.8. Prescription Opioid Cessation

Among the 45 patients, 44 (97.8 %) successfully ceased opioid use following the detoxification program. This high success rate underscores the effectiveness of the detoxification process in eliminating opioid dependence in patients with chronic pain [Figure 5].

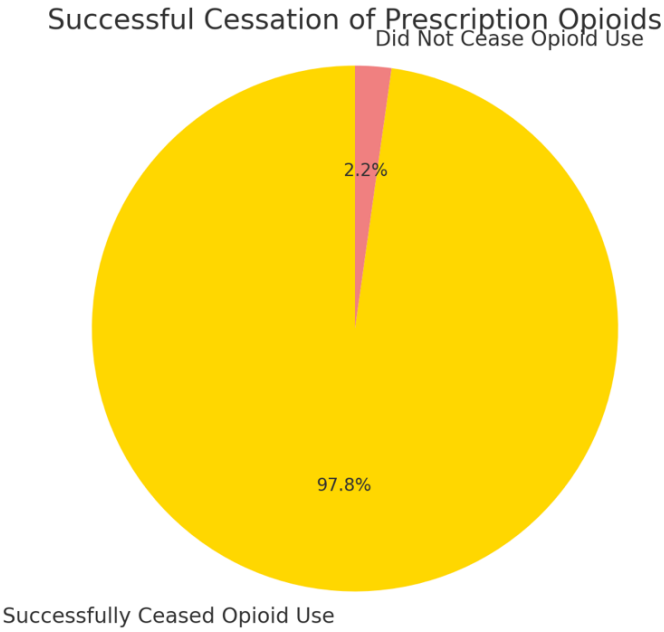


Figure 5. Outcome of Opioid Detoxification

3.9. Average Baseline 25-hydroxyvitamin D (25-OHD) Levels by Pain Reason

The mean serum 25-OHD concentration across the study cohort was 58.3 ± 35.2 nmol/L. Among participants, those with serum 25-OHD levels ≥75 nmol/L (n = 16) had a mean concentration of 98.39 ± 28.04 nmol/L, whereas individuals with levels <75 nmol/L (n = 29) exhibited a mean concentration of 38.26 ± 17.22 nmol/L (see Table 2). Notably, 64.4% of the cohort fell into the deficient category, defined by serum 25-OHD levels below the 75 nmol/L threshold. Figure 1 illustrates the average 25-Hydroxyvitamin D (25-OHD) levels (nmol/L) across different pain-related conditions [Figure 6].

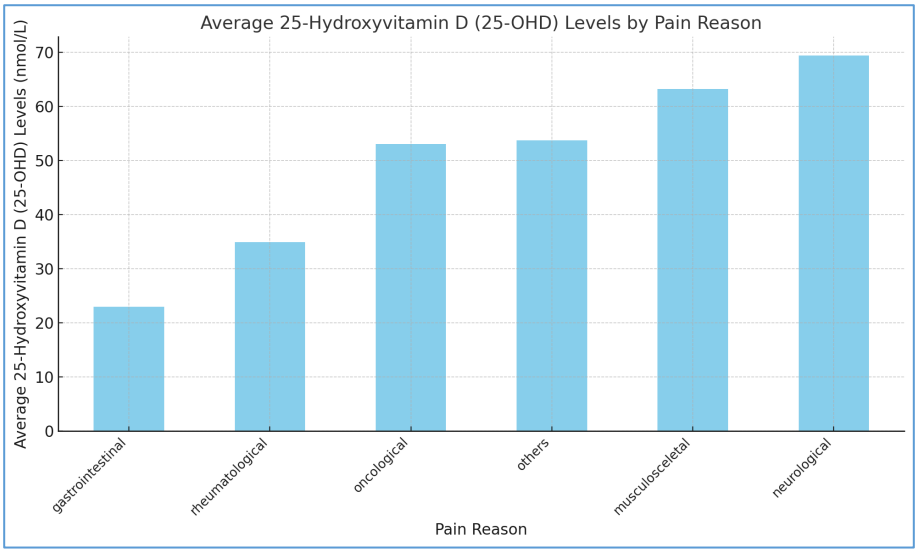


Figure 6. Average 25-hydroxyvitamin D (25-OHD) levels by pain reason.

3.10. Association of baseline 25-OHD Levels, Pain Scores, and Quality of Life: Regression Findings

A linear regression analysis was conducted to evaluate the relationship between 25-OHD levels (log-transformed), VAS pain scores before opioid detoxification (reversed and log-transformed), and QoL scores. The model fit measures indicated a low correlation coefficient (R = 0.123) and an R-squared value (R^2) of 0.0150, suggesting that only 1.5% of the variance in QoL SF-36v2™ Questionnaire scores can be explained by the predictors in the model.

The intercept was statistically significant (β = 35.32, SE = 13.37, t = 2.642, p = 0.012), indicating that the baseline QoL score was significantly different from zero when the predictor variables were at their reference values.

However, the coefficients for 25-OHD levels (β = -1.79, SE = 7.88, t = -0.227, p = 0.821) and VAS pain scores (β = 2.73, SE = 3.42, t = 0.796, p = 0.430) were not statistically significant, suggesting no meaningful relationships between these variables and QoL scores.

3.11. Association Between Baseline Serum 25-OHD Levels and QoL SF-36v2™ Questionnaires

The independent samples t-test results indicated no statistically significant differences in QoL between participants with sufficient and deficient 25-OHD levels. Specifically, no significant differences were observed in SF-36v2™ questionnaire responses related to QoL (t (43) = 0.110, p = 0.913). The mean difference was 0.472 (SE = 4.286), with the sufficient vitamin D group scoring a mean of 35.44 (SD = 14.198) and the deficient group a mean of 34.97 (SD = 13.524). These findings suggest that vitamin D sufficiency did not significantly impact QoL scores in this sample [Figure 7].

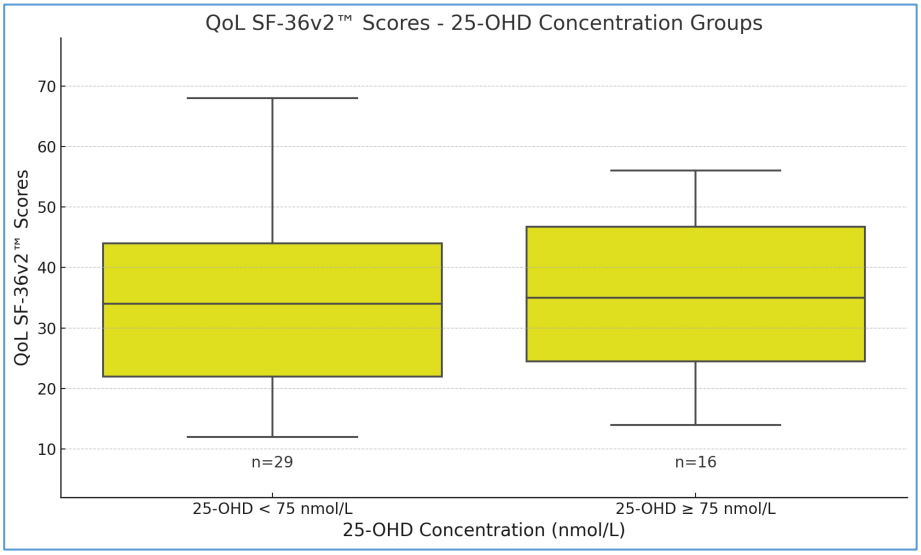


Figure 7. The association between 25-hydroxyvitamin D (25-OHD) levels and quality of life (QoL) as measured by the SF-36v2™ Questionnaire score

3.12. Association Between Serum 25OHD Levels and VAS Pain Scores

An independent samples t-test was conducted to evaluate differences in VAS pain scores between two groups based on serum 25-OHD levels (≥ 75 nmol/L vs. < 75 nmol/L). Participants with serum 25-OHD levels ≥ 75 nmol/L (n = 16) had a mean VAS pain score of 6.06 ± 2.32, while those with levels < 75

nmol/L (n = 29) had a mean score of 6.86 ± 2.10. (Table 2). The normalized scores for the groups were 1.22 ± 0.571 and 0.950 ± 0.632, respectively.

The t-test results indicated no statistically significant difference in VAS pain scores between the two groups (t (43) = 1.415, p = 0.164), with a mean difference of 0.269 (SE = 0.190). This suggests that, although the group with sufficient vitamin D levels had a marginally higher mean VAS score (M = 1.22, SD = 0.571) compared to the deficient group (M = 0.950, SD = 0.632), this difference was not statistically significant, indicating no substantial effect of vitamin D levels on pain scores in this cohort [Figure 8].

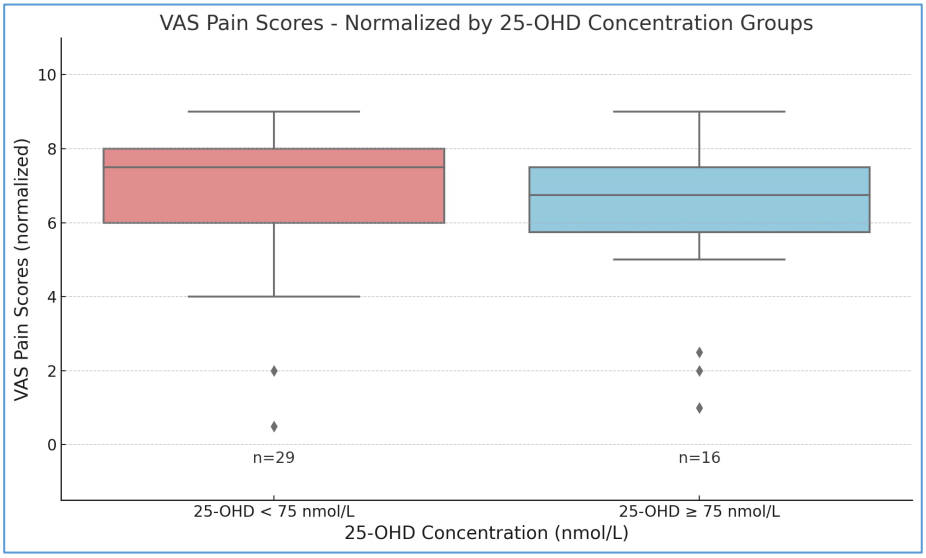


Figure 8. The association between baseline 25-hydroxyvitamin D (25-OHD) levels and pain intensity

3.13. Impact of 25-OHD Cut-Off Level at 50 nmol/L

An additional analysis was performed using a 25-OHD cut-off level of 50 nmol/L to explore potential differences in normalized VAS pain scores (Reflect Ln) between groups. Independent samples t-test analysis revealed no statistically significant differences in normalized VAS pain scores between patients with 25-OHD levels below and above the 50 nmol/L threshold (t(43) = -0.930, p = 0.357).

Although the primary hypothesis of the study focused on a 25-OHD cut-off of 75 nmol/L, this supplementary analysis suggests that lowering the threshold to 50 nmol/L does not yield significant differences in this specific outcome. This finding may indicate that the impact of 25-OHD levels on

normalized VAS pain scores does not differ substantially between these groups at the lower threshold.

3.14. The Baseline Vitamin D concentration in respect to characteristic of patient, drug used and dosage

A comprehensive table [Table 9] has been prepared to summarize key characteristics of the study participants. This table includes data on the reasons for pain, types of opioids prescribed, baseline serum vitamin D concentrations (25-OHD), and morphine equivalent doses (MED). The summary provides a clear overview of the primary variables under investigation, offering insights into the relationships between pain etiologies, opioid usage patterns, vitamin D status, and opioid dose equivalencies across the study cohort.

Table 9. Data on the reasons for pain, types of opioids prescribed, baseline serum vitamin D concentrations (25-OHD), and morphine equivalent doses (MED).

NNo.	**Prescription Opioid type**	**Pain Reason**	**Vitamin D nmol/l**	**Equivalent morphine dose (MED) mg/d**
1	codeine	neurological	105.6	3.2
2	tramadol	neurological	76.0	200.0
3	tramadol	others (burns)	35.8	40.0
4	codeine	neurological	186.0	60.0
5	morphine	oncological	41.8	40.0
6	tramadol	musculoskeletal	74.5	80.0
7	codeine	neurological	69.1	57.0
8	tramadol	neurological	70.0	240.0
9	fentanyl	oncological	36.0	270.0
10	fentanyl	musculoskeletal	32.0	270.0
11	codeine	neurological	39.26	9.6
12	tramadol	neurological	75.0	40.0
13	methadone	oncological	14.6	70.5
14	codeine	neurological	27.0	1.3
15	morphine	musculoskeletal	61.8	200.0
16	tramadol	musculoskeletal	35.0	20.0
17	fentanyl	oncological	75.0	550.0
18	morphine, fentanyl	oncological	78.0	390.0
19	tramadol	others (humerus trauma)	39.47	40.0

NNo.	Prescription Opioid type	Pain Reason	Vitamin D nmol/l	Equivalent morphine dose (MED) mg/d
20	codeine	neurological	30.9	24.0
21	fentanyl	oncological	27.1	202.5
22	tramadol	musculoskeletal	88.0	30.0
23	morphine	rheumatological	19.78	240.0
24	tramadol	musculoskeletal	103.0	160.0
25	pethidine	gastrointestinal	19.5	100.0
26	tramadol	musculoskeletal	79.0	15.0
27	morphine	oncological	34.0	150.0
28	tramadol	neurological	11.9	120.0
29	pethidine	gastrointestinal	26.5	100.0
30	morphine	musculoskeletal	72.0	720.0
31	morphine	oncological	114.5	30.0
32	fentanyl, tramadol	oncological	94.0	330.0
33	morphine	oncological	114.5	30.0
34	morphine	oncological	29.9	150.0
35	morphine	rheumatological	50.0	240.0
36	oxycodone	musculoskeletal	33.9	450.0
37	morphine, tramadol	oncological	29.8	90.0
38	codeine	neurological	95.0	16.0
39	codeine	neurological	37.89	8.0
40	tramadol	musculoskeletal	53.0	20.0
41	codeine	neurological	42.0	4.8
42	tramadol	neurological	106.2	100.0
43	fentanyl, tramadol	oncological	13.4	97.5
44	codeine, morphine, tramadol	others (pain in lower spine, pathology undiagnosed)	86.0	41.6
45	morphine, fentanyl	oncological	39.8	240.0

3.15. Medication Use During Detoxification

Key data points included the medications administered during the detoxification process, along with their respective dosages. The selection of

pharmacological interventions aimed to minimize discomfort, address opioid withdrawal symptoms, and prevent complications.

The primary medications used to support opioid withdrawal were diazepam, a long-acting benzodiazepine, and clonidine, an alpha-2 adrenergic agonist. Administration of these agents was guided by daily clinical assessments using two standardized tools: the Subjective Opioid Withdrawal Scale (SOWS) and the Objective Opioid Withdrawal Scale (OOWS). This dual-scale approach enabled clinicians to tailor treatment to both patient-reported symptoms and observable physiological signs of withdrawal.

Across the study cohort ($N = 44$), total diazepam doses ranged from 70 mg to 680 mg, with a SD of approximately 156.7 mg. This wide range reflects the significant interindividual variability in withdrawal severity and the corresponding need for symptom-driven titration of benzodiazepine therapy.

Clonidine doses were ranging from 0 mg to 3.3 mg, with a SD of 0.92 mg. Several patients received no clonidine, suggesting that this medication was used selectively, likely in response to elevated autonomic symptoms such as hypertension, tachycardia, or sweating—hallmarks captured more accurately by OOWS scoring.

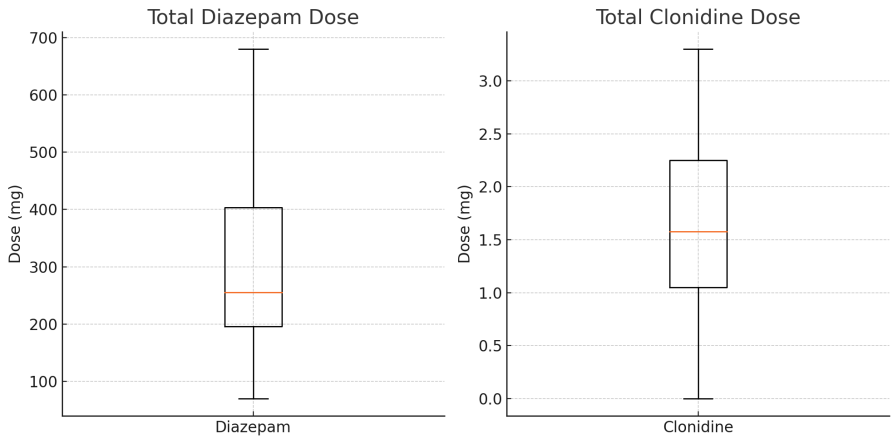


Figure 9. Distribution of Total Medication Doses., reflecting its more conservative use.

4. DISCUSSION OF RESULTS

4.1. Patient Characteristics

4.1.1. Prescription Opioid Cessation

The patient cohort analyzed in this study demonstrated a high success rate in achieving opioid cessation, with 44 out of 45 participants (97.78%) successfully completing the detoxification process.

The high success rate of opioid cessation among the study participants further supports the effectiveness of the detoxification protocol. This outcome is particularly significant given the substantial challenges associated with opioid tolerance and withdrawal. The structured detoxification protocol, which included the use of benzodiazepines, α2 agonists, nonsteroidal anti-inflammatory drugs, antipsychotics, anticonvulsants, and antidepressants, was crucial in managing withdrawal symptoms and facilitating successful opioid cessation. Previous studies have highlighted the importance of comprehensive support during detoxification to address both the physical and psychological aspects of dependency [8].

This remarkable success rate underscores the effectiveness of the intervention employed, suggesting that with appropriate support, even individuals with prolonged histories of opioid use can discontinue these medications. The nearly universal success also highlights the feasibility and applicability of structured detoxification programs in real-world clinical settings.

4.1.2 Age and Sex of Participants

The demographic composition of the cohort revealed a slight predominance of female participants, with women constituting 62.22% of the study population. This aligns with broader epidemiological trends showing that women are often disproportionately affected by chronic pain conditions, leading to higher rates of opioid prescriptions compared to men. The average age of the cohort, 53.62 years (±12.70), indicates a middle-aged population, a group that frequently requires long-term pain management. This demographic profile suggests that middle-aged women may represent a key target group for interventions aimed at addressing opioid dependency.

4.1.3. Avarage of Duration of Prescription Opioid Use

The participants' history of prescribed opioid use, averaging 60.51 months (±67.81), reflects the chronic nature of their pain conditions and the prolonged exposure to opioids. The substantial variability in the duration of opioid use highlights the diverse trajectories of opioid therapy, ranging from relatively short-term use to several years of dependency. This variability may also point to differences in prescribing practices, patient adherence, or pain severity across the cohort, all of which merit further investigation.

4.1.4. Opioid Detoxification Duration

Notably, the detoxification process itself was completed within an average of 9.2 days (±3.2), suggesting that opioid withdrawal can be managed effectively within a relatively short timeframe. This finding emphasizes the practicality of implementing structured detoxification programs in both inpatient and outpatient settings. The short duration also indicates that many patients may tolerate the process well, potentially increasing the willingness of individuals to seek help for opioid dependence.

4.2. Indications for Prescription Opioid Use

The analysis of indications for prescription opioid use revealed a diverse range of pain-related conditions within the patient cohort, reflecting the broad application of opioids in managing acute and chronic pain. Headaches and cancer-related pain were the most frequent indications, each accounting for 14 cases out of 45 patients.

For patients with headaches, all were diagnosed with primary migraines and had been transitioned to opioid therapy only after other standard treatment options failed to provide sufficient relief. This highlights the refractory nature of their migraines, necessitating escalation to opioids as a last resort. However, the use of opioids for managing migraines remains controversial due to the risk of dependency and the potential for opioid-induced hyperalgesia, which may exacerbate pain in some cases. This finding underscores the need for alternative approaches and innovative treatments for patients with refractory migraines to avoid reliance on opioids.

Among the 14 patients prescribed opioids for cancer-related pain, all were in remission and not undergoing active cancer treatment. Despite being in remission, these patients continued to experience significant pain, suggesting not only the development of opioid tolerance over time

but also the potential for substance use disorder (SUD) and addiction. Additionally, the presence of pain in this group raises concerns about opioid-induced hyperalgesia, a condition where prolonged opioid use paradoxically increases pain sensitivity. This phenomenon may further complicate pain management in cancer survivors, highlighting the critical need for reassessment of opioid therapy in this population to balance pain relief with the risks of continued opioid use.

Back pain was the third most common indication, reported by 10 patients. As a prevalent cause of chronic pain, back pain frequently leads to long-term opioid prescriptions, especially in cases where non-opioid treatments fail to provide adequate relief. However, this finding also raises concerns about the appropriateness of extended opioid therapy for non-malignant pain conditions, given the potential for dependency and other adverse effects.

Other indications for opioid use included rheumatoid arthritis (2 cases), gastrointestinal pathology (2 cases), and single instances of post-burn sequelae, chronic muscle pain, and humerus arthrosis. While these conditions were less common, they illustrate the variety of clinical scenarios in which opioids are prescribed, often for patients with complex or refractory pain syndromes.

These findings highlight several critical issues in opioid prescribing. The transition to opioids for refractory migraines and the persistent pain among cancer survivors in remission point to the challenges in managing chronic and complex pain conditions without relying heavily on opioids. Moreover, the potential for SUD, addiction, and opioid-induced hyperalgesia in these populations underscores the urgent need for alternative pain management strategies and stricter monitoring of opioid use.

4.3. Prescription Opioid Type

The analysis of prescription patterns revealed significant diversity in the types of opioids utilized by the study participants, reflecting the complexity of pain management strategies. Tramadol was the most used opioid, reported in 13 patients, followed by codeine and morphine, each prescribed to nine patients. Fentanyl in its transdermal form was prescribed to four patients, while pethidine was prescribed to two. Methadone and oxycodone were each prescribed to one patient. Additionally, several patients used multiple opioids concurrently, illustrating the intricacy of their treatment regimens.

Regarding codeine, it was observed that its use was akin to self-medication, as this opioid is non-prescribed in Lithuania and is often the first-

choice switch from nonsteroidal anti-inflammatory drugs (NSAIDs). This pattern highlights the accessibility of codeine in the country, which may contribute to its widespread use for mild to moderate pain. According to World Health Organization (WHO) guidelines, mild to moderate pain can often be managed without opioid analgesics or with weak opioids such as codeine. However, the ease of access to codeine without medical oversight raises concerns about improper use, dependency risks, and suboptimal pain management.

Tramadol, reported in 13 cases, was the most frequently prescribed opioid. Unlike codeine, tramadol is classified by the WHO as a potent analgesic rather than a weak opioid, due to its dual mechanism of action, which includes both opioid receptor activation and inhibition of norepinephrine and serotonin reuptake. Its frequent use in this cohort underscores its popularity in managing moderate to severe pain, particularly as a step-up therapy after NSAIDs. However, the reliance on tramadol as a first-line option in some cases raises questions about adherence to pain management guidelines, which advocate for a more judicious and stepwise approach to opioid use.

The use of morphine, prescribed to nine patients, reflects its role as a cornerstone for managing severe pain. Morphine's prevalence in this cohort highlights its continued importance in chronic pain management, particularly for patients with more advanced or refractory pain conditions. Similarly, fentanyl was prescribed to four patients in its transdermal form, illustrating its use in cases requiring potent, sustained analgesia, especially in opioid-tolerant patients. Pethidine, though prescribed to only two patients, is notable for its limited role in modern clinical practice due to its short half-life and potential for neurotoxic effects, which make it a less favorable option for chronic pain management.

Methadone and oxycodone, prescribed to one patient each, represent specialized therapeutic options tailored to individual needs. Methadone's unique pharmacokinetic profile makes it particularly suitable for neuropathic pain or in patients requiring long-acting opioids with additional receptor activity. Oxycodone, favored for its potency and tolerability, may be used selectively for severe pain in patients unresponsive to other opioids.

The concurrent use of multiple opioids in some patients further emphasizes the complexity of opioid prescribing in this cohort. Combinations such as morphine and fentanyl (two patients), fentanyl and tramadol (two patients), and codeine, morphine, and tramadol (one patient) reflect efforts to address multifaceted pain presentations through pharmacologic synergy. However, such polypharmacy increases the risk of adverse effects, drug

interactions, and challenges in managing withdrawal or dose adjustments, necessitating cautious monitoring.

The findings highlight diverse prescribing practices shaped by patient-specific factors and local healthcare policies, such as the availability of non-prescribed codeine. The widespread use of tramadol and codeine raises critical concerns about adherence to evidence-based guidelines and the potential for inappropriate use. These patterns underscore the urgent need to refine prescribing practices, promote the use of non-opioid alternatives where appropriate, and enhance patient education on the risks and limitations of opioid therapy.

4.4. Prescription Opioid Dose

The analysis of prescribed opioid doses, expressed in oral morphine equivalent doses (MEDs), revealed substantial variability across different opioid types and combinations. The average daily MED for the cohort was 139.8 ± 153.9 mg, reflecting significant heterogeneity in dosing practices and the individualized nature of opioid therapy. Such variability is indicative of differences in pain severity, patient tolerance, and the potency of prescribed opioids.

For single opioids, MEDs ranged widely, from 20.54 mg (±22.71) for Codeine to 450 mg for Oxycodone. Codeine, which had the lowest average MED, is a weaker opioid often used for mild to moderate pain. However, its use as a self-medicated option in Lithuania raises concerns about suboptimal pain management and the lack of medical oversight in its administration. Tramadol, with an average MED of 85 mg (±71.68), was the most frequently prescribed single opioid. Despite being considered a less potent opioid than morphine or fentanyl, its MED variability indicates differing approaches to dosing, influenced by patient-specific factors and the dual mechanism of action of the drug.

Morphine, prescribed to nine patients, had an average MED of 200 mg (±211.82), illustrating its role as a primary option for managing severe pain. The high standard deviation suggests a wide range of dosing requirements, possibly reflecting varying degrees of opioid tolerance among patients. Similarly, fentanyl, prescribed in its transdermal form to four patients, had an average MED of 323.12 mg (±151.67), highlighting its use in managing severe, refractory pain, especially in patients with established opioid tolerance. The high doses of fentanyl emphasize its potency and the challenges of managing pain in patients requiring such strong analgesics.

For patients prescribed combined opioid therapies, the average MEDs were notably high. The highest doses were observed in patients receiving a combination of Morphine and Fentanyl, with an average MED of 315 mg (±75). Other combinations, such as Fentanyl and Tramadol (213.75 mg ± 116.25), and Morphine and Tramadol (90 mg), further illustrate the complexity of multimodal opioid regimens. These combinations may be employed to leverage the different pharmacological mechanisms of the opioids, achieving synergistic analgesia while potentially minimizing dose-related adverse effects of individual drugs. However, such regimens also present challenges in terms of dose titration and the risk of opioid-induced hyperalgesia or dependency.

The wide range of doses observed across the cohort underscores the individualized nature of opioid therapy. High-dose opioids, such as those involving Oxycodone (450 mg MED) or Fentanyl, raise concerns about safety, including the risks of overdose, tolerance, and opioid-induced side effects. On the other hand, the relatively low doses of Codeine and Tramadol in some patients may reflect efforts to manage pain with less potent opioids when appropriate, though their efficacy in treating moderate to severe pain can be limited.

4.5. Prescription Opioid Use by Pain Category

The findings of this study demonstrate distinct prescribing patterns for opioids based on the type of pain condition. Neurological pain was primarily managed with codeine and tramadol, reflecting a preference for lower-potency opioids in this category. The observed dose variations within this group may indicate differences in individual patient responses or severity of pain.

Musculoskeletal pain exhibited a broader range of opioid prescriptions, including tramadol, fentanyl, morphine, and oxycodone. The wide range of morphine-equivalent doses (15 mg to 720 mg) suggests a high degree of variability in treatment approaches, potentially due to differences in the chronicity and severity of musculoskeletal conditions.

Oncological pain had the most diverse opioid selection, with frequent use of morphine and fentanyl, either individually or in combination. The high doses observed in this category (up to 550 mg MED) align with established pain management strategies for cancer-related pain, where stronger opioids are often required to provide adequate analgesia.

Pethidine was exclusively used for gastrointestinal pain, possibly due to its historical use in treating acute abdominal pain despite concerns regarding its long-term efficacy and safety. Similarly, rheumatological pain was managed solely with morphine, indicating a reliance on strong opioids for severe cases.

Other pain categories, including burns and trauma, were predominantly treated with tramadol, suggesting a preference for moderate-strength opioids in these conditions. The prescription of a mixed regimen for undetermined lower spine pathology (codeine, morphine, and tramadol) highlights the complexity of managing ambiguous or chronic pain conditions.

Overall, the data indicate a structured approach to opioid prescribing, with stronger opioids being reserved for oncological and severe musculoskeletal pain, while milder opioids were used for neurological and moderate pain conditions. Future research should explore the long-term efficacy and risk profiles of these prescribing patterns to optimize pain management strategies.

4.6. Quality of Life Assessment

The assessment of quality of life (QoL) using the SF-36v2™ revealed a significant and sustained improvement in QoL scores across three time points: before detoxification, at discharge, and at least six months post-detoxification. Among the cohort, full follow-up data were available for 30 patients, while 15 were lost to follow-up or declined to complete the third QoL assessment. Despite this limitation, the results provide compelling evidence for the positive impact of opioid detoxification on patients' overall well-being.

The mean QoL score before detoxification was 35 ± 14%, reflecting the significant physical, emotional, and social burden associated with prolonged opioid use. This baseline score is consistent with previous findings that chronic opioid use, particularly in the context of pain management, is associated with diminished QoL due to a combination of factors such as physical dependency, opioid-related side effects, and the underlying chronic pain conditions.

At discharge, the mean QoL score increased to 42 ± 19%, representing a statistically significant improvement ($p = 0.004$) compared to predetoxification levels. This immediate post-detoxification improvement suggests that the cessation of opioids, combined with structured medical and psychological support during detoxification, may alleviate some of the negative effects associated with opioid use, such as withdrawal symptoms, sedation, and emotional instability. Additionally, the physical and psychological benefits of detoxification likely contributed to this initial improvement in QoL.

The most substantial improvement in QoL was observed at least six months after detoxification, with a mean score of 48 ± 22%. This score was significantly higher compared to both predetoxification levels ($p < 0.001$) and discharge scores ($p = 0.025$). The continued improvement over time indicates that the benefits of detoxification extend beyond the immediate post-treatment period, as patients likely adapt to a drug-free lifestyle, regain physical and mental stability, and possibly engage in alternative pain management strategies. The long-term improvement in QoL also highlights the potential for enhanced social functioning, reduced dependency, and improved psychological well-being after detoxification.

The observed improvement in QoL scores across the three assessment points demonstrates the beneficial impact of opioid detoxification. Before detoxification, patients had significantly lower QoL scores, reflecting the detrimental effects of long-term opioid use on their physical and emotional well-being [7, 8]. The increase in QoL scores on the day of discharge and six months post-detoxification suggests that the benefits of detoxification are not only immediate but also sustained over time. This aligns with findings from previous research, which indicate that reducing opioid dependence can lead to better overall health outcomes and improved patient satisfaction [208].

These findings underscore the value of opioid detoxification not only in reducing dependency but also in improving patients' overall quality of life. The continuous increase in QoL scores suggests that detoxification is a critical step toward recovery and reintegration into a healthier and more fulfilling lifestyle. However, the study's inability to obtain full follow-up data for all patients represents a limitation, as those who were lost to follow-up might have had different outcomes.

Future research should explore factors that contribute to long-term improvements in QoL, including the role of post-detoxification support, pain management strategies, and social reintegration programs. Additionally, further studies are warranted to identify barriers to follow-up and ensure that patients maintain and build upon the gains achieved during detoxification. These findings highlight the importance of a holistic approach to managing chronic pain and opioid dependency, prioritizing not just physical health but also emotional and social well-being.

4.7. Pain Scores Before and After Detoxification

The Visual Analog Scale (VAS) pain scores revealed a significant reduction in pain levels among patients following opioid detoxification. The mean VAS scores decreased from 6.68 ± 2.0 points before detoxification to 2.17 ± 1.93 points after detoxification ($p < 0.001$). This average reduction of 4.51 ± 1.83 points highlights a substantial improvement in pain management and patient comfort, challenging the assumption that opioid discontinuation necessarily leads to worsened pain.

When examining pain scores by disease category, significant reductions were observed across all conditions, further underscoring the effectiveness of detoxification in improving pain perception:

- Oncological disease (n=14): The mean VAS score decreased from 5.9 ± 2.59 to 1.60 ± 1.88. These findings are particularly notable given the complexity of managing pain in cancer survivors. The reduction may reflect a mitigation of opioid-induced hyperalgesia, a condition in which prolonged opioid use paradoxically exacerbates pain sensitivity.
- Neurological disease (n=14): The mean VAS score dropped from 6.07 ± 1.55 to 1.78 ± 1.63. This significant improvement suggests that detoxification and alternative pain management strategies may offer effective relief for chronic neurological pain, which is often difficult to treat.
- Musculoskeletal disease (n=10): The VAS score showed a substantial reduction from 7.7 ± 2.13 to 2.6 ± 2.46. These results emphasize the potential of non-opioid therapies to manage pain in musculoskeletal conditions, which are a leading cause of chronic opioid use.
- Rheumatoid disease (n=2): Pain scores decreased from 6.75 ± 1.06 to 2.5 ± 0. Although based on a small sample size, this result is promising and suggests that alternative approaches to pain management could benefit patients with inflammatory joint diseases.

- Gastrointestinal disease (n=2): The VAS score dropped from 8.5 ± 0.71 to 2.25 ± 2.48, representing a dramatic improvement in this subgroup. Patients with gastrointestinal conditions may experience unique challenges in pain management, making this reduction particularly noteworthy.
- Other conditions (n=2): This group exhibited a reduction from 8.5 ± 0.71 to 4.75 ± 1.77. While the decrease was less pronounced compared to other categories, it still indicates meaningful pain relief. The higher post-detoxification score may reflect underlying complexities in these cases, such as mixed pain syndromes or inadequate alternative pain management strategies.

A significant reduction in pain levels, as measured by the VAS, was observed following detoxification. This finding is particularly noteworthy given the common concern that withdrawal from opioids might exacerbate pain symptoms [45]. The average reduction of 4.51 points on the VAS scale highlights the effectiveness of the detoxification process in managing pain, contradicting the notion that opioid cessation invariably leads to worsened pain outcomes. The observed reductions in VAS scores across all conditions strongly suggest that opioid detoxification not only addresses dependency but also alleviates pain, potentially through the resolution of opioid-induced hyperalgesia, where long-term opioid use paradoxically increases pain sensitivity. These results challenge traditional paradigms that equate opioid use with effective pain management and highlight the need for re-evaluating chronic pain treatment strategies. By eliminating the opioids from the system, patients may experience a normalization of their pain thresholds, contributing to the observed pain relief [195].

Additionally, the substantial improvements across diverse conditions underscore the importance of individualized, multimodal pain management approaches during and after detoxification. These strategies may include non-opioid pharmacological treatments, physical therapy, psychological support, and lifestyle modifications.

4.8. Vitamin D Levels and Pain Conditions

The analysis of serum 25-hydroxyvitamin D (25-OHD) levels revealed a notable prevalence of deficiency among the study cohort, with 64.4% of participants exhibiting serum levels below the recommended threshold of 75 nmol/L. The mean serum 25-OHD concentration for the cohort was 58.3 ± 35.2 nmol/L, highlighting a significant variation in vitamin D status. Participants with sufficient levels (≥75 nmol/L) demonstrated a mean

concentration of 98.39 ± 28.04 nmol/L, while those in the deficient category (<75 nmol/L) had a substantially lower mean concentration of 38.26 ± 17.22 nmol/L. The findings indicate variation in average serum 25-OHD levels across different pain etiologies:

- Gastrointestinal pain: This group exhibited the lowest average 25-OHD levels, suggesting that gastrointestinal pathology may contribute to impaired vitamin D absorption or metabolism. Such deficiencies may exacerbate pain or negatively impact overall health, given the known role of vitamin D in musculoskeletal and immune function.
- Rheumatological conditions: Participants in this group had slightly higher vitamin D levels compared to those with gastrointestinal pain, though still insufficient on average. Vitamin D deficiency has been implicated in the pathogenesis and progression of rheumatological diseases, suggesting that addressing deficiency could improve outcomes.
- Oncological conditions: Participants with cancer-related pain demonstrated intermediate 25-OHD levels. While these levels were higher than those observed in gastrointestinal or rheumatological conditions, many individuals in this group remained below the sufficiency threshold. Suboptimal vitamin D levels may contribute to chronic pain in cancer survivors, as well as to their overall reduced quality of life.
- Neurological and musculoskeletal conditions: These groups had the highest average serum 25-OHD levels, nearing or surpassing the threshold for sufficiency. Higher vitamin D levels in these patients may reflect better nutritional or supplemental intake; however, even within these groups, variability was observed, with some patients still falling into the deficient range.

Vitamin D deficiency and insufficiency are widespread public health issues. Research suggests that around 40% of adults in the United States have suboptimal serum vitamin D levels. In Europe, the prevalence of deficiency varies by region, with estimates ranging from 13% to 60%. [196-198]. Low vitamin D levels are also common in Lithuania, with studies indicating that as many as 70% of adults have insufficient vitamin D levels [199]. The results of this study align with these patterns, showing that 64.4% of participants had 25-OHD levels below the normal range.

The overall high prevalence of vitamin D deficiency in the cohort underscores its potential role in chronic pain conditions. Vitamin D is known to play a critical role in modulating inflammation, muscle strength, and bone health, all of which are relevant to the pathophysiology of pain. Deficiency may exacerbate pain symptoms, delay recovery, and contribute to poorer quality of life.

These findings suggest that addressing vitamin D deficiency through supplementation or lifestyle interventions could be a valuable adjunct in the management of chronic pain. Further research is warranted to explore the causal relationship between vitamin D levels and pain severity, as well as to determine the efficacy of vitamin D repletion in improving pain outcomes and overall health in these populations.

4.9. Association Between Baseline Serum 25-OHD Levels and Quality of Life (QoL)

The analysis of the relationship between serum 25-hydroxyvitamin D (25-OHD) levels and quality of life (QoL), as assessed by the SF-36v2™ questionnaire, revealed no statistically significant differences between participants with sufficient and deficient 25-OHD levels. The independent samples t-test results ($t(43) = 0.110$, $p = 0.913$) demonstrated that mean QoL scores for the sufficient vitamin D group (35.44 ± 14.198) and the deficient group (34.97 ± 13.524) were nearly identical, with a mean difference of only 0.472 (SE = 4.286). These findings suggest that serum vitamin D status did not have a measurable impact on QoL outcomes within this cohort.

This lack of association challenges the expectation that vitamin D sufficiency may enhance QoL, as vitamin D is known to influence physical health, mood, and inflammation, all of which could potentially affect overall well-being. Several explanations may account for this finding:

1. Complexity of QoL Determinants: QoL, as assessed by the SF-36v2™, encompasses multiple domains, including physical, emotional, and social functioning. These dimensions are influenced by a variety of factors beyond vitamin D status, such as pain severity, psychological health, socioeconomic conditions, and comorbidities. It is possible that these other factors outweighed any potential impact of vitamin D on QoL in this sample.
2. Sample Characteristics: The cohort was comprised of individuals undergoing opioid detoxification, a process that itself may significantly impact QoL due to physical withdrawal symptoms, psychological challenges, and adjustments to new pain management strategies. These

influences might have masked any subtle effects of vitamin D sufficiency on QoL.

3. Vitamin D Thresholds: The threshold used to define sufficiency (≥75 nmol/L) may not be sensitive enough to capture nuanced relationships between vitamin D levels and QoL. Alternatively, the effects of vitamin D on QoL may only manifest at substantially higher levels than those achieved by the sufficient group in this study.
4. Cross-Sectional Design: This analysis was cross-sectional in nature, examining vitamin D levels and QoL at specific time points. Longitudinal studies may be necessary to better understand whether changes in vitamin D levels over time correlate with QoL improvements.

Studies examining the impact of vitamin D on quality of life (QoL) in individuals with chronic pain have produced mixed results. Some research suggests that supplementation may enhance physical and psychological well-being [200, 201], while other findings indicate minimal effects, emphasizing that baseline vitamin D levels alone may not significantly influence QoL without accounting for factors like overall health and pain severity [202]. Additionally, evidence points to only a modest effect of routine supplementation on QoL, with any benefits primarily observed in short-term clinical studies [203]. Furthermore, existing research indicates that improvements in QoL from vitamin D supplementation may require long-term, sustained intervention, which may not be practical or detectable within a short detoxification period [203]. Consequently, this study may not fully reflect the potential long-term effects of vitamin D on QoL, which might be more apparent in studies with extended follow-up and thorough vitamin D monitoring.

Our study did not identify a statistically significant relationship between baseline 25-OHD levels and QoL scores, consistent with research indicating that QoL outcomes in chronic pain patients are influenced by multiple factors beyond vitamin D alone [202]. The lack of a clear association in this cohort may suggest that aspects related to opioid tolerance and dependence and detoxification-such as withdrawal symptoms, emotional stress, and social support-have a greater impact on QoL during this phase.

While the results of this study suggest no significant impact of vitamin D sufficiency on QoL in this sample, it is important to interpret these findings cautiously. Future research could benefit from larger sample sizes, more sensitive assessments of vitamin D levels (e.g., subdividing sufficient levels into high-normal and low-normal categories), and a broader examination of confounding factors that may influence the relationship between vitamin D and QoL. Additionally, interventional studies exploring the effects of vitamin D supplementation on QoL in populations with chronic pain or undergoing detoxification may provide further insights into this complex relationship.

4.10. Association Between Baseline Serum 25-OHD Levels and VAS Pain Scores

The relationship between serum 25-hydroxyvitamin D (25-OHD) levels and pain intensity, as measured by the Visual Analog Scale (VAS), was assessed using an independent samples t-test. The findings revealed no statistically significant difference in VAS pain scores between participants with sufficient vitamin D levels (≥ 75 nmol/L) and those with deficient levels (< 75 nmol/L) ($t(43) = 1.415$, $p = 0.164$). Participants with sufficient 25-OHD levels ($n = 16$) had a mean VAS pain score of 6.06 ± 2.32, while those with deficient levels ($n = 29$) had a mean score of 6.86 ± 2.10. The normalized scores for the groups were 1.22 ± 0.571 and 0.950 ± 0.632, respectively, with a mean difference of 0.269 (SE = 0.190).

Although the group with sufficient 25-OHD levels exhibited a slightly lower mean VAS pain score than the deficient group, this difference was not statistically significant. These findings suggest that vitamin D status, as defined by serum 25-OHD levels, did not have a substantial impact on perceived pain intensity in this cohort.

Several factors may explain the lack of a significant association between 25-OHD levels and VAS pain scores:

1. Complex Pain Mechanisms: Pain is a multifactorial phenomenon influenced by physiological, psychological, and social factors. While vitamin D has been implicated in pain modulation through its anti-inflammatory properties and role in neuromuscular function, its effects may be overshadowed by other determinants of pain, such as the underlying pathology, psychological distress, and prior opioid use.
2. Threshold Effects: The threshold of 75 nmol/L used to define vitamin D sufficiency may not adequately capture the nuances of its relationship with pain. Higher levels of vitamin D may be required to observe

clinically significant changes in pain perception, or the benefits may only be apparent in specific subgroups of patients with chronic pain.

3. Sample Characteristics: The cohort consisted of individuals undergoing opioid detoxification, a process that can influence pain perception through mechanisms such as opioid withdrawal and changes in central pain processing. These confounding factors may have attenuated any potential relationship between vitamin D levels and pain intensity.
4. Small Sample Size: The relatively small sample size, particularly in the sufficient vitamin D group (n = 16), may have limited the statistical power to detect subtle differences in VAS pain scores between groups.

These results align with previous studies that have produced mixed findings regarding the role of vitamin D in pain management. While some research suggests that vitamin D supplementation may reduce pain in certain populations, others have failed to establish a clear relationship between serum 25-OHD levels and pain intensity.

Although improving VAS scores through vitamin D supplementation could be beneficial for individuals with chronic pain and healthcare providers [204-206], our study did not find a significant association between baseline vitamin D levels and pain scores. While it is plausible that vitamin D supplementation during detoxification might impact pain perception, the lack of significant differences in pain outcomes, coupled with the absence of post-detoxification vitamin D measurements, limits our ability to draw firm conclusions. This limitation is due to the gradual metabolism of vitamin D [207] and the relatively short detoxification period, during which fluctuations in 25-OHD levels were unlikely to produce meaningful long-term effects.

Future research should aim to explore the relationship between vitamin D and pain more comprehensively. Larger, more diverse cohorts, as well as longitudinal studies examining the effects of vitamin D supplementation on pain outcomes, are needed to clarify its potential role in pain management. Additionally, investigating the interactions between vitamin D levels, pain mechanisms, and other contributing factors, such as inflammation and psychological health, could provide deeper insights into this complex association.

4.11. Impact of 25-OHD Cut-Off Level at 50 nmol/L

A supplementary analysis was conducted to assess whether using a lower 25-hydroxyvitamin D (25-OHD) cut-off level of 50 nmol/L would reveal differences in normalized VAS pain scores (Reflect Ln) between groups. The independent samples t-test showed no statistically significant differences in

normalized VAS pain scores between patients with 25-OHD levels below and above this threshold ($t(43) = -0.930$, $p = 0.357$). This lack of statistical significance indicates that the cut-off adjustment did not alter the observed relationship between 25-OHD levels and VAS pain scores.

The primary hypothesis of the study focused on the commonly used cut-off of 75 nmol/L to define vitamin D sufficiency. However, this additional analysis suggests that even when the threshold is lowered to 50 nmol/L, no significant differences in pain outcomes are detected. This result may have several implications:

1. Robustness of the Findings**:** The consistency of results across both cut-offs (75 nmol/L and 50 nmol/L) suggests that the relationship between serum 25-OHD levels and VAS pain scores is relatively stable and not sensitive to minor variations in the sufficiency threshold. This reinforces the finding that serum 25-OHD levels do not appear to have a substantial impact on pain perception in this cohort.
2. Threshold Suitability: The lack of significant differences at the 50 nmol/L threshold raises questions about the appropriateness of using fixed cut-offs to evaluate the association between vitamin D and pain. It is possible that pain-related benefits of vitamin D are only observed at levels substantially higher than 75 nmol/L or that individual variability in vitamin D sensitivity plays a role.
3. Role of Confounding Factors**:** The results may also reflect the influence of other factors, such as the underlying pain condition, duration of opioid use, or withdrawal effects, which may overshadow any potential contributions of vitamin D levels to pain modulation.
4. Potential Non-Linear Effects: Vitamin D may have a non-linear relationship with pain outcomes, where its effects are not appreciable within certain ranges of serum levels. Future studies using broader vitamin D ranges and advanced statistical methods may help clarify whether there are thresholds beyond which its impact on pain becomes significant.

Overall, the supplementary analysis supports the conclusion that serum 25-OHD levels, whether assessed at the 75 nmol/L or 50 nmol/L threshold, do not significantly influence normalized VAS pain scores in this sample. This finding highlights the need for further research to better understand the role of vitamin D in pain management, particularly through studies with larger cohorts, prospective designs, and comprehensive assessments of confounding variables. Exploring potential synergistic effects of vitamin D

supplementation with other pain management strategies may also provide valuable insights into its clinical utility.

4.12. Medication Use During Detoxification

This study highlights the importance of individualized, symptom-guided pharmacological support during opioid detoxification. Diazepam and clonidine were the primary medications used, with dosing adjusted based on daily assessments using both the Subjective Opioid Withdrawal Scale (SOWS) and the Objective Opioid Withdrawal Scale (OOWS). This dual-scale approach allowed clinicians to address both patient-reported discomfort and observable physiological symptoms.

Diazepam was widely used, with total doses ranging from 70 mg to 680 mg (SD = 156.7 mg). This broad range reflects significant variability in withdrawal severity and the need for tailored benzodiazepine dosing. Clonidine was used with doses from 0 mg to 3.3 mg (SD = 0.92 mg), typically in response to elevated autonomic symptoms identified through OOWS.

This study reinforces the value of tailored detoxification protocols that integrate standardized assessment tools with clinician expertise. The findings also raise important considerations for developing best-practice guidelines, particularly regarding dose ceilings, monitoring strategies, and the optimal balance between comfort and safety during opioid withdrawal.

LIMITATIONS

While the results of this study are promising, several limitations must be acknowledged. The sample size was relatively small, and the study was conducted at a single center, which may limit the generalizability of the findings. Additionally, the follow-up period was limited to six months, and longer-term outcomes were not assessed. Furthermore, the study did not assess whether there was an improvement in VAS pain scores or the necessity for opioids among patients beyond the initial 6-month detoxification period. It is important to note that VAS pain scores measurements were not conducted after this 6-month period, as they could be confounded by additional variables, including the use of other NSAID medications.

The absence of post-detoxification serum 25-OHD measurements limits the ability to evaluate changes in vitamin D levels and their potential impact on pain outcomes throughout the detoxification process. Although the VAS is inherently subjective, it remains a widely accepted and validated tool for assessing pain intensity, making its use in this study appropriate despite its limitations. Moreover, inconsistencies in the definitions of vitamin D deficiency and sufficiency across clinical guidelines present challenges in interpreting 25-OHD levels, emphasizing the need for standardized criteria in future research.

These findings highlight the need for further research to refine our understanding of these associations and to develop more effective pain management strategies in this population.

CONCLUSIONS

Objectives:

1. To assess changes in the quality of life of in patients with chronic pain with long-term prescription opioids usage before and after detoxification.

This study presents compelling evidence that elective opioid detoxification in patients with chronic pain who have developed tolerance due to long-term prescription opioid use can result in substantial enhancements in overall quality of life (QoL). The significant improvements in QoL post-detoxification indicate that, despite the challenges associated with opioid withdrawal, successful detoxification can yield substantial positive outcomes [30, 208]. By discontinuing opioid therapy in a controlled manner, patients may experience reductions in opioid-induced side effects, improved physical and cognitive functioning, and greater emotional well-being. Furthermore, opioid detoxification may facilitate the restoration of endogenous pain modulation mechanisms, potentially leading to more sustainable pain management strategies. These findings underscore the importance of evaluating alternative approaches to chronic pain treatment that prioritize long-term patient outcomes over continued opioid dependence.

2. To characterize the specific demographic, clinical attributes of patients and to identify the indications, duration, type, and dosage of opioid therapy in patients with chronic pain undergoing long-term prescription opioid treatment.

The findings highlight a predominance of middle-aged women, aligning with broader epidemiological trends in chronic pain prevalence and opioid prescribing patterns. The average duration of opioid use exceeded five years, underscoring the chronic nature of pain conditions and prolonged opioid exposure. Indications for opioid therapy were diverse, with headaches, cancer-related pain, and back pain being the most common. Notably, opioids were frequently prescribed for refractory migraines and persistent pain in cancer survivors, raising concerns about dependency, opioid-induced hyperalgesia, and the appropriateness of long-term opioid therapy for non-malignant pain conditions.

Prescription patterns revealed tramadol as the most frequently used opioid, followed by codeine and morphine. The widespread use of non-prescribed codeine highlights potential gaps in pain management strategies and regulatory oversight. The variability in opioid dosing, with a high mean oral morphine equivalent dose (MED), reflects individualized prescribing practices but also raises concerns about safety, dependency, and adherence to clinical guidelines.

These findings underscore the need for improved opioid prescribing practices, enhanced monitoring, and the promotion of non-opioid alternatives where appropriate. Addressing the risks associated with long-term opioid use requires a more structured approach to pain management, integrating multidisciplinary strategies to optimize treatment efficacy while minimizing harm.

3. To evaluate the effectiveness of detoxification treatment in terms of pain perception and opioid cessation and duration of detoxification

This study provides strong evidence that elective opioid detoxification can lead to significant reductions in pain levels for patients with chronic pain who have developed tolerance to long-term prescription opioid use. The mean decrease of 4.51 points on the VAS scale underscores the effectiveness of the detoxification process in pain management, challenging the assumption that discontinuing opioids inevitably results in worsening pain outcomes. The remarkably high success rate of opioid cessation (97.78%) among participants underscores the effectiveness of the structured detoxification protocol, which incorporated multimodal pharmacological support to manage withdrawal symptoms. These findings challenge the conventional assumption that chronic pain necessitates continued opioid therapy, suggesting that alternative, non-opioid pain management strategies may be both effective and preferable in many cases.

The detoxification process was completed within an average of 9.2 days (±3.2), indicating that opioid withdrawal can be effectively managed within a relatively short timeframe. This finding supports the feasibility of structured detoxification programs in both inpatient and outpatient settings. The brief duration suggests that many patients tolerate the process well, which may encourage greater willingness to seek treatment for opioid dependence.

Despite the well-documented challenges associated with opioid withdrawal, including symptom severity, psychological dependence, and the risk of relapse, this study demonstrates that with appropriate medical supervision and a comprehensive, patient-centered approach, detoxification is

a viable and beneficial option. The success of this intervention highlights the need for broader implementation of structured detoxification programs, which could significantly improve long-term health outcomes for patients tolerant to prescription opioids.

However, it is essential to distinguish this population from patients requiring opioids for palliative care or advanced illnesses where long-term opioid use remains clinically necessary. Future research should focus on optimizing detoxification protocols, identifying factors that predict successful opioid cessation, and exploring non-opioid interventions that enhance post-detoxification pain management and quality of life. Expanding access to evidence-based detoxification strategies will enable healthcare systems to better support chronic pain patients in achieving sustainable pain relief while mitigating the risks associated with prolonged opioid therapy.

4. To investigate the relationship between baseline blood vitamin D concentration and detoxification outcomes, examining its potential influence on quality of life and pain perception.

Although baseline vitamin D levels were hypothesized to influence pain perception and quality of life (QoL) in patients with chronic pain undergoing long-term opioid therapy, this study did not establish a statistically significant correlation between baseline 25-OHD levels, pain scores, and QoL. However, a numerical trend suggesting lower pain scores among individuals with higher 25-OHD levels indicates a potential association that warrants further investigation. While opioid cessation appears to be the primary factor affecting pain perception and QoL in this cohort, the potential role of vitamin D optimization in pain management should not be overlooked.

Although prior studies have suggested an association between low 25-OHD levels and the occurrence of both acute and chronic pain [190-193], the present study did not identify a statistically significant relationship between serum 25-OHD levels and pain scores. This finding contrasts with earlier research indicating that vitamin D supplementation may contribute to pain reduction, including improvements in VAS scores and decreased opioid consumption among palliative cancer patients [189, 204-206]. The lack of significant results in this study underscores the complexity of the relationship between vitamin D and pain perception [182, 183, 186].

3. These findings suggest that opioid cessation, rather than baseline vitamin D levels, may be the primary factor influencing QoL and pain perception during detoxification. The results highlight the multifaceted nature of QoL and pain experiences in individuals undergoing detoxification, suggesting that factors beyond baseline vitamin D levels may have a more substantial impact. Further investigation is needed to explore additional biological, psychological, and social determinants of pain and QoL, with an emphasis on larger cohorts to enhance the understanding of vitamin D's role in these domains. Moreover, studies should seek to identify factors that modulate pain perception and determine whether adjunctive therapies, such as vitamin D supplementation, may provide benefits for specific subgroups. Despite these uncertainties, the current findings support opioid detoxification as an effective approach for achieving significant pain relief in opioid-dependent individuals, irrespective of baseline vitamin D status.

PRACTICAL CLINICAL RECOMMENDATIONS

1. Consider Elective Opioid Detoxification for Patients with Chronic Pain under Long-term Opioid Use

The study demonstrates that structured opioid detoxification can lead to significant improvements in quality of life (QoL) and pain perception in patients with long-term opioid use. Physicians should assess patients for opioid tolerance, opioid-induced hyperalgesia, and diminished analgesic efficacy and consider medically supervised detoxification where appropriate. Given that the process was successfully completed in an average of 9.2 days, detoxification appears to be a feasible intervention for patients who meet the criteria for opioid cessation.

2. Prioritize Non-Opioid Pain Management Strategies

The findings underscore the necessity of multimodal pain management approaches as alternatives to long-term opioid therapy. Given that pain levels decreased significantly post-detoxification, physicians should emphasize non-opioid analgesics, interventional pain procedures, physical therapy, and psychological interventions. Implementing personalized, multidisciplinary treatment plans can facilitate long-term pain relief while minimizing opioid dependence.

3. Strengthen Opioid Prescribing Practices and Monitoring

The study revealed that many patients were on opioid therapy for over five years, often for conditions where long-term use is not supported by current clinical guidelines. The predominance of tramadol, codeine, and morphine use, along with the widespread self-administration of non-prescribed codeine, highlights the need for more stringent opioid stewardship policies. Physicians should reassess opioid therapy periodically to determine ongoing necessity; avoid prolonged opioid prescriptions for conditions where alternative treatments exist; adhere to clinical guidelines to ensure safer prescribing practices and minimize dependency risks.

4. Improve Access to Structured Detoxification Programs

The study supports the feasibility and effectiveness of structured opioid detoxification protocols, demonstrating a 97.78% opioid cessation rate among participants. These findings emphasize the need for broader implementation of inpatient and outpatient detoxification programs. Healthcare systems should expand access to detoxification services and integrate them into routine chronic pain management strategies.

5. Enhance Patient Education and Shared Decision-Making

Given the widespread concern among patients that opioid discontinuation may lead to worsening pain, physicians should engage in comprehensive patient counseling to address misconceptions. The study demonstrates that opioid cessation often leads to improved pain control rather than exacerbation. Effective communication should include clear education on the benefits of opioid detoxification; discussion of alternative pain management strategies; reassurance that withdrawal symptoms can be managed effectively in a structured setting.

6. Address the Issue of Non-Prescribed Opioid Use

The frequent use of non-prescribed codeine observed in the study suggests gaps in regulatory oversight and pain management accessibility. Physicians should remain vigilant for signs of self-medication and implement measures to improve patient access to regulated pain management options; enhance screening for opioid misuse in chronic pain populations and to ensure that patients receive evidence-based, supervised pain treatment strategies rather than relying on unregulated opioid sources.

7. Re-Evaluate the Role of Vitamin D in Pain Management

While baseline vitamin D levels were not significantly correlated with pain scores or QoL outcomes, a minor trend suggested that higher 25-OHD concentrations might be associated with lower pain levels. Although this study does not provide definitive support for routine vitamin D supplementation in chronic pain management, further research is warranted. Physicians may consider screening for vitamin D deficiency in select populations where deficiency is suspected, particularly in patients with osteomalacia, osteoporosis, or known risk factors for low 25-OHD levels.

8. Differentiate Between Chronic Pain Management and Palliative Care

While opioid detoxification appears beneficial for non-malignant chronic pain patients, it is imperative to differentiate this population from palliative and end-of-life care patients, for whom long-term opioid therapy remains clinically justified. Physicians should apply individualized treatment approaches to ensure that opioid therapy is continued when appropriate while avoiding unnecessary prolonged opioid use in patients who may benefit from alternative pain management strategies.

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SANTRAUKA

DETOKSIKACIJOS ĮTAKA GYVENIMO KOKYBEI LĖTINĮ SKAUSMĄ PATIRIANTIEMS PACIENTAMS, ILGĄ LAIKĄ VARTOJANTIEMS RECEPTINIUS OPIOIDUS

1. ĮVADAS

Tyrimo problema, aktualumas ir reikšmė

Per pastaruosius du dešimtmečius opioidai vis dažniau taikomi lėtinio skausmo valdymui, ypač tais atvejais, kai įprastiniai gydymo metodai pasirodo esantys nepakankamai veiksmingi [1]. Lėtinio skausmo gydymas neretai apima receptinių opioidų vartojimą - šie vaistai pripažįstami veiksmingomis trumpalaikio ir ūminio skausmo malšinimo priemonėmis. Vis dėlto ilgalaikis jų vartojimas tampa vis labiau prieštaringas, atsižvelgiant į augančią mokslinių duomenų apimtį, rodančią sąsajas su nepageidaujamais reiškiniais, įskaitant opioidų tolerancijos ir priklausomybės išsivystymą. Nepaisant veiksmingumo mažinant skausmą, ilgalaikė opioidų terapija siejama su reikšmingais iššūkiais: būtinybe nuolat didinti dozes siekiant išlaikyti terapinį poveikį, priklausomybės rizika bei platesnėmis socialinėmis pasekmėmis, įskaitant didėjančią ekonominę naštą. Be to, ilgalaikis opioidų vartojimas dažnai koreliuoja su bendros pacientų gyvenimo kokybės blogėjimu bei fiziniais, psichologiniais ir socialiniais sutrikimais, pabrėžiančiais šios terapijos kompleksiškumą ir su ja susijusias rizikas lėtinio skausmo gydyme. Šie nuogąstavimai paskatino nuolatines diskusijas dėl opioidų vaidmens ilgalaikėse gydymo strategijose ir būtinybės ieškoti alternatyvių metodų, kurie užtikrintų tiek veiksmingumą, tiek saugumą [1,2].

Lėtinis neonkologinis skausmas išlieka plačiai paplitusi ir sekinanti būklė, paveikianti iki 22 % suaugusiųjų visame pasaulyje [1] ir reikšmingai trikdanti milijonų žmonių gyvenimo kokybę bei funkcinius gebėjimus. Opioidai, nors ir gali suteikti trumpalaikį palengvėjimą, ilgalaikiam lėtinio neonkologinio skausmo valdymui yra laikomi riboto veiksmingumo. Nors opioidai gali suteikti reikšmingą trumpalaikį palengvėjimą, jų veiksmingumas ilgainiui mažėja, ypač esant nuolatiniam skausmui, kai reikalingas ilgalaikis gydymas. Daugiacentrio perspektyviojo kohortinio tyrimo duomenys pabrėžia šį apribojimą - pacientai, vartoję opioidus lėtinio neonkologinio skausmo gydymui, per dvejus metus nepatyrė reikšmingo pagerėjimo tokiose srityse kaip skausmas, fizinė funkcija, emocinė būsena ar socialinis bei šeimos gyvenimas[3].

Šio ilgalaikio poveikio nebuvimas dažnai siejamas su opioidų tolerancijos išsivystymu - kai norint pasiekti tą patį analgezinį poveikį reikia vis didesnių dozių, o tai gali sustiprinti nepageidaujamus reiškinius, negerinant gydymo rezultatų. Be to, opioidai gali lemti opioidų sukeltą hiperalgeziją (OIH) - paradoksalią būklę, kai ilgalaikis opioidų vartojimas padidina jautrumą skausmui, dar labiau apsunkindamas jų taikymą lėtinio skausmo valdyme [4].

Atsižvelgiant į šiuos duomenis, įprastinis opioidų vartojimas lėtiniam neonkologiniam skausmui gydyti vis dažniau kelia abejonių, ypač vertinant rizikas, tokias kaip priklausomybės vystymasis, piktnaudžiavimas ir galimas netinkamas vartojimas. Dėl to klinikinės gairės ir skausmo valdymo strategijos vis labiau krypsta į daugiadisciplininius metodus, apjungiančius neopioidines farmakologines priemones ir nefarmakologinius gydymo būdus, tokius kaip kognityvinė elgesio terapija, fizinė reabilitacija ir intervencinės skausmo valdymo procedūros. Toks požiūris padeda siekti geresnių pacientų gydymo rezultatų ir mažinti su ilgalaikiu opioidų vartojimu susijusias rizikas [5-7].

Nepaisant plačiai paplitusio opioidų vartojimo lėtinio skausmo valdymui ir augančio sąmoningumo dėl jų priklausomybę sukeliančio pobūdžio, vis dar išlieka reikšminga mokslinių tyrimų spraga, susijusi su detoksikacijos poveikio gyvenimo kokybei ir skausmo valdymui vertinimu [8]. Detoksikacija, apibrėžiama kaip mediciniškai prižiūrimas opioidų vartojimo nutraukimas, yra svarbi priklausomybės nuo opioidų gydymo dalis. Vis dėlto klinikinėje praktikoje į ją dažnai žiūrima skeptiškai dėl nuogąstavimų, susijusių su galimu neigiamu poveikiu skausmo valdymui, galimu abstinencijos simptomų sustiprėjimu bei atkryčio rizika po opioidų nutraukimo [8].

Viena pagrindinių su detoksikacija susijusių problemų yra nuostata, kad ji gali lemti nepakankamą lėtinį skausmą patiriančių pacientų gydymą, ypač tais atvejais, kai veiksmingos alternatyvios skausmo valdymo strategijos nėra lengvai prieinamos. Be to, abstinencijos simptomai, tokie kaip nerimas, sujaudinimas ir hiperalgezija, gali sustiprinti jau esamas skausmo būkles, taip sudarydami kliūtį sėkmingai detoksikacijai [9]. Dėl šios priežasties pacientai ir sveikatos priežiūros specialistai neretai vengia imtis detoksikacijos, baimindamiesi gyvenimo kokybės pablogėjimo ir padidėjusios skausmo naštos.

Nors tyrimų šia tema nedaug, kai kurie duomenys rodo, jog detoksikacija, derinama su kompleksinėmis priežiūros programomis, gali lemti teigiamus rezultatus. Pavyzdžiui, programos, kuriose detoksikacija derinama su elgesio intervencijomis, neopioidiniais analgetikais ir

daugiadisciplinių skausmo valdymu, parodė teigiamus pacientų savijautos rodiklius - sumažėjo priklausomybė nuo opioidų, pagerėjo fizinė bei emocinė būklė [10].

Vis daugiau dėmesio skiriama klausimui, ar sėkminga detoksikacija gali lemti apčiuopiamą gyvenimo kokybės pagerėjimą, sušvelninant ilgalaikio opioidų vartojimo sukeliamus nepageidaujamus padarinius. Ilgalaikė opioidų terapija dažnai siejama su reikšmingais neigiamais poveikiais, tokiais kaip fizinė priklausomybė, opioidų sukelta hiperalgezija, hormonų pusiausvyros sutrikimai ir kognityviniai sutrikimai - visa tai blogina bendrą savijautą ir funkcinį pajėgumą [12]. Opioidų sukeliamas žarnyno funkcijos sutrikimas reikšmingai pablogina tiek fizinę, tiek psichologinę paveiktų pacientų savijautą. Todėl detoksikacija, padedanti nutraukti opioidų vartojimą, gali palengvinti šiuos negalavimus ir pagerinti gyvenimo kokybę, atkuriant fiziologinę ir psichologinę homeostazę.

Atsirandantys moksliniai duomenys rodo, kad sėkminga detoksikacija iš tiesų gali prisidėti prie gyvenimo kokybės gerėjimo, ypač kai ji yra kompleksinės priežiūros dalis. Tyrimai atskleidžia, jog pacientai, kuriems pavyko nutraukti opioidų vartojimą taikant mediciniškai prižiūrimą detoksikaciją, dažnai patiria tokią naudą kaip sumažėjęs mieguistumas, pagerėjusios kognityvinės funkcijos bei palaipsniui atsikuriantys natūralūs skausmo reguliavimo mechanizmai [13]. Pagerėjimai apima ir psichosocialinius aspektus - pacientai dažnai jaučia emocinį stabilumą, sustiprėjusį gebėjimą įsitraukti į socialinį gyvenimą bei sumažėjusį stigmatizavimą, susijusį su priklausomybe nuo opioidų [14].

Be to, detoksikacija gali sudaryti galimybes pacientams aktyviau įsitraukti į neopioidines lėtinio skausmo valdymo terapijas, tokias kaip fizinė reabilitacija, elgesio intervencijos ir papildomi gydymo metodai. Šios strategijos, taikomos kartu su detoksikacija, gali prisidėti prie gyvenimo kokybės gerėjimo, skatindamos ilgalaikį funkcinį atsistatymą ir suteikdamos pacientams savarankiško skausmo valdymo įgūdžių [15].

Tiek gydytojai, tiek pacientai dažnai atsargiai vertina receptinių opioidų vartojimo pradžią, pirmiausia dėl susirūpinimo priklausomybės rizika ir sunkumais, susijusiais su šių vaistų nutraukimu išsivysčius priklausomybei. Gydytojų nenoras pradėti opioidų terapiją taip pat kyla iš susirūpinimo dėl sudėtingo priklausomybės ir abstinencijos simptomų valdymo, kai pacientai jau pradeda vartoti šiuos vaistus. Opioidų vartojimo nutraukimo procesas dažnai būna sudėtingas - jį lydi abstinencijos simptomai, padidėjęs skausmo jautrumas ir atkryčio rizika, o tai gali atgrasyti tiek pacientus, tiek sveikatos priežiūros specialistus nuo sprendimo apskritai taikyti gydymą opioidais[16]. Šis atsargumas kyla iš balansavimo tarp opioidų terapijos naudos ir rizikų

lėtinio skausmo gydyme bei vis didesnio suvokimo apie opioidų krizės poveikį visuomenės sveikatai. Šie nuogąstavimai tampa ypač aktualūs atsižvelgiant į didelę priklausomybės paplitimo variaciją tarp lėtinį skausmą patiriančių pacientų - priklausomybės rodikliai, priklausomai nuo tirtos populiacijos ir taikomų diagnostinių kriterijų, svyruoja nuo 3-4% iki net 8-12%.

Mažesni priklausomybės rizikos rodikliai dažniausiai nustatomi gerai kontroliuojamuose tyrimuose, kuriuose opioidai skiriami kruopščiai atrinktiems pacientams, taikant griežtą stebėseną. Priešingai, didesnis priklausomybės paplitimas fiksuojamas tarp pacientų, turinčių rizikos veiksnių, tokių kaip buvusios priklausomybės nuo psichoaktyviųjų medžiagų, psichikos sutrikimai ar nepakankamai veiksmingas skausmo valdymo planas [16]. Šis rodiklių svyravimas pabrėžia individualizuoto gydymo svarbą bei būtinybę kiekvienu atveju atskirai įvertinti opioidų terapijos naudą ir riziką.

Šių iššūkių sprendimas reikalauja kompleksinio požiūrio, kuriame svarbus vaidmuo tenka atsakingai pacientų atrankai, nuosekliam informavimui apie galimas opioidų terapijos rizikas bei aiškiai apibrėžtoms stebėsenos ir palaipsnio dozės mažinimo strategijoms. Taip pat itin svarbu integruoti alternatyvius skausmo valdymo metodus - kognityvinę elgesio terapiją, fizinę reabilitaciją bei neopioidinius medikamentus. Tokia daugiadisciplinė prieiga gali padėti sumažinti priklausomybės nuo opioidų riziką ir užtikrinti tvaresnius bei saugesnius gydymo rezultatus.

Platus priklausomybės rizikos diapazonas - nuo 3-4% iki 8-12% - pabrėžia priklausomybės daugialypį pobūdį, kylantį iš sudėtingos fizinių, psichologinių ir genetinių veiksnių sąveikos [17,18]. Priklausomybė nėra vien tik farmakologinė opioidų vartojimo pasekmė - tai sudėtingas sutrikimas, kurį lemia individualūs pažeidžiamumo veiksniai, aplinkos įtaka ir kontekstas, kuriame opioidai yra skiriami ir vartojami [13]. Šie veiksniai lemia didelę priklausomybės išsivystymo rizikos variaciją tarp pacientų, gydomų opioidais dėl lėtinio skausmo.

Fiziologiniai veiksniai, tokie kaip ilgalaikio opioidų vartojimo sukelti neurocheminiai pokyčiai, yra esminiai priklausomybės formavimosi grandyje. Nuolatinis opioidų poveikis iškraipo smegenų atlygio sistemų veiklą - slopinama natūrali endogeninių opioidų gamyba, o organizmas vis labiau ima priklausyti nuo išorinių medžiagų, siekiant palaikyti vidinę pusiausvyrą. Šią neuroadaptaciją dar labiau sustiprina opioidų sukelta hiperalgezija, didinanti skausmo jautrumą ir skatinanti tolesnį vaistų vartojimą [9, 19].

Psichologiniai veiksniai, įskaitant iš anksto egzistuojančius psichikos sveikatos sutrikimus, tokius kaip nerimas, depresija ar potrauminio streso sutrikimas (PTSS), taip pat reikšmingai prisideda prie priklausomybės rizikos.

Asmenys, turintys šių sutrikimų, opioidus gali vartoti ne tik fizinio skausmo malšinimui, bet ir kaip priemonę psichologiniam diskomfortui įveikti, taip padidindami polinkį į netinkamą vartojimą ir priklausomybę [20]. Be to, anamnezėje buvęs psichoaktyviųjų medžiagų vartojimas yra reikšmingas opioidinės priklausomybės rizikos rodiklis, nes jis atspindi gilesnius smegenų atlygio sistemos reguliacijos pažeidimus.

Genetiniai veiksniai dar labiau komplikuoja priklausomybės rizikos supratimą. Tyrimai rodo, kad genetiniai polinkiai gali turėti įtakos opioidų metabolizmui, receptorių jautrumui bei individualiam polinkiui į priklausomybę. Pavyzdžiui, OPRM1 geno, koduojančio miu-opioidų receptorių, variacijos siejamos su skirtingu opioidų veiksmingumu ir priklausomybės rizika [21]. Šie genetiniai veiksniai sąveikauja su aplinkos poveikiais, tokiais kaip socioekonominė padėtis, prieiga prie sveikatos priežiūros ir socialinės paramos paslaugų, kartu formuodami bendrą asmens priklausomybės rizikos profilį.

Šis sudėtingas veiksnių tarpusavio ryšys išryškina būtinybę taikyti individualizuotus opioidų skyrimo bei priklausomybės prevencijos metodus. Išsamus rizikos vertinimas, apimantis fizinius, psichologinius ir genetinius aspektus, leidžia identifikuoti didesnės priklausomybės rizikos pacientus ir taikyti tikslingas, pritaikytas intervencijas. Be to, nuoseklūs priklausomybės mechanizmų tyrimai yra itin svarbūs siekiant pagrįsti ir tobulinti veiksmingesnes prevencijos bei gydymo strategijas.

Fizinė priklausomybė nuo opioidų yra gerai dokumentuotas reiškinys, pasireiškiantis abstinencijos simptomais, kai vaisto vartojimas nutraukiamas arba jo dozė reikšmingai sumažinama. Abstinencijos simptomai gali apimti pykinimą, vėmimą, viduriavimą, raumenų skausmus, nerimą, nemigą ir kitus negalavimus, todėl opioidų vartojimo nutraukimas tampa fiziškai ir psichologiškai sudėtingu procesu [9,16]. Šie simptomai kyla dėl organizmo fiziologinės adaptacijos prie nuolatinio opioidų poveikio, kuris sukelia neurocheminių procesų pokyčius. Staiga nutraukus opioidų vartojimą, organizmas patiria sunkumų atstatant natūralią pusiausvyrą, todėl pasireiškia varginantys abstinencijos reiškiniai.

Be fizinės priklausomybės, opioidų vartojimą reikšmingai apsunkina ir tolerancija. Tolerancija išsivysto tuomet, kai pasikartojantis opioidų poveikis mažina jų veiksmingumą, todėl siekiant tokio paties skausmo malšinimo ar euforijos lygio reikia vis didesnių dozių [13]. Šis reiškinys susijęs su neuroadaptaciniais pokyčiais opioidų receptoriuose ir jų signalinėse grandinėse, dėl kurių analgezinis vaisto poveikis laikui bėgant silpnėja. Didėjančios dozės, reikalingos dėl išsivysčiusios tolerancijos, ne tik padidina

šalutinio poveikio ir perdozavimo riziką, bet ir dar labiau įtvirtina priklausomybės ciklą [22].

Šie tarpusavyje susiję reiškiniai - priklausomybė ir tolerancija - sudaro reikšmingas kliūtis nutraukti opioidų vartojimą, ypač asmenims patiriantiems lėtinį skausmą. Daugeliui pacientų baimė patirti abstinencijos simptomus arba nepakankamą skausmo kontrolę atgraso nuo bandymų mažinti dozes ar visiškai nutraukti vartojimą [15]. Be to, ilgalaikio opioidų vartojimo sukelti neurobiologiniai pokyčiai gali išlikti net ir nutraukus vaistą, o tai gali lemti potraukį opioidams bei padidėjusią atkryčio riziką [23].

Šių iššūkių sprendimas reikalauja visapusiško, daugiadalykio požiūrio, apimančio laipsnišką dozių mažinimą, alternatyvias - ne opioidines - skausmo valdymo strategijas bei psichosocialinę pagalbą, siekiant sušvelninti abstinencijos simptomus ir palengvinti sveikimo procesą.

Tyrimo tikslas: Patvirtinti arba paneigti hipotezę, kad detoksikacija pagerina priklausomų nuo receptinių opioidų pacientų gyvenimo kokybę.

Tyrimo uždaviniai:

1. įvertinti priklausomų nuo receptinių opioidų pacientų gyvenimo kokybės pokyčius prieš ir po detoksikacijos
2. nustatyti priklausomų nuo receptinių opioidų pacientų ypatumus
3. nustatyti priklausomų nuo receptinių opioidų pacientų detoksikacinio gydymo efektyvumą
4. priklausomų nuo receptinių opioidų pacientų vitamino D koncentracijos kraujyje įtaka detoksikacijai ir gyvenimo kokybei

Tyrimo naujumas

Nors esami tyrimai išsamiai nagrinėja fiziologinius ir psichologinius opioidų detoksikacijos aspektus, šiame tyrime išskirtinis dėmesys skiriamas gyvenimo kokybei kaip pagrindiniam rezultatui. Siekiant pateikti holistinę perspektyvą, vertinami fizinės, emocinės ir socialinės gerovės pokyčiai po detoksikacijos. Nors daugelis tyrimų apsiriboja trumpalaikiais detoksikacijos rezultatais, šiame tyrime siekiama įvertinti ilgalaikį poveikį pacientų gyvenimo kokybei. Analizuojant, ar detoksikacija lemia ilgalaikį gerovės pagerėjimą, sprendžiama esminė spraga opioidų priklausomybės tyrimų srityje.

Skirtingai nei daugelis tyrimų, kurie daugiausia dėmesio skiria nutraukimo simptomams ar atkryčio dažniui, šiame tyrime analizuojami skausmo suvokimo pokyčiai nutraukus opioidų vartojimą. Nustatant, ar detoksikacija lemia skausmo palengvėjimą ar paaštrėjimą, sprendžiamas

svarbus, tačiau nepakankamai ištirtas opioidų priklausomybės gydymo aspektas.

Tyrimas, nagrinėjantis pradinių vitamino D koncentracijų vaidmenį gyvenimo kokybei ir skausmo suvokimui prieš detoksikaciją, yra naujas indėlis į mokslinius tyrimus. Esami darbai apie vitaminą D daugiausia orientuoti į raumenų ir kaulų sistemos sveikatą bei lėtinį skausmą, tuo tarpu šiame tyrime siekiama atskleisti galimą vitamino D įtaką detoksikacijos sėkmei ir bendrai savijautai. Tyrimo rezultatai gali prisidėti prie klinikinių gairių, skirtų opioidų detoksikacijos programoms, tobulinimo, pabrėžiant paciento gerove grįstą požiūrį, kuriame gyvenimo kokybės gerinimas vertinamas lygiagrečiai su nutraukimo simptomų valdymu. Be to, šis tyrimas gali pateikti įrodymų, kurie padėtų keisti su opioidų skyrimu, detoksikacijos tvarka ir papildomomis priemonėmis, pavyzdžiui, vitamino D vartojimu, susijusią praktiką.

Tyrimo praktinė reikšmė

Ilgalaikis receptinių opioidų vartojimas dažnai lemia tolerancijos išsivystymą, todėl norint pasiekti tą patį analgezinį poveikį, reikia vis didesnių vaisto dozių. Didėjant tolerancijai, didėja ir fizinės bei psichologinės priklausomybės rizika, o tai dar labiau apsunkina skausmo valdymą ir skatina ilgalaikį opioidų vartojimą. Lėtinis didesnių nei terapinių opioidų dozių vartojimas siejamas su plačiu nepageidaujamų reiškinių spektru: virškinamojo trakto sutrikimais (vidurių užkietėjimu, pykinimu), neuropsichiatrinėmis komplikacijomis (depresija, pažinimo funkcijų sutrikimu, miego problemomis), padidėjusia traumų rizika bei širdies ir kraujagyslių įvykiais, tokiais kaip miokardo infarktas [7].

Be to, ilgalaikis opioidų vartojimas neigiamai veikia endokrininės ir imuninės sistemos veiklą, prisideda prie medžiagų apykaitos sutrikimų, imunosupresijos ir bendro fiziologinės būklės blogėjimo. Ypač svarbu tai, kad priklausomybė nuo opioidų reikšmingai padidina perdozavimo, kvėpavimo slopinimo ir širdies sustojimo riziką, todėl ši problema tampa svarbiu visuomenės sveikatos iššūkiu. Visi šie neigiami padariniai lemia pacientų gyvenimo kokybės blogėjimą ir sukelia didelę ekonominę naštą sveikatos apsaugos sistemai dėl dažnesnių hospitalizacijų, skubių intervencijų ir ilgalaikio medikamentinio gydymo poreikio [7].

Detoksikacija išlieka pagrindine gydymo strategija pacientams, siekiantiems nutraukti opioidų vartojimą. Pagrindinis detoksikacijos tikslas - sudaryti sąlygas atsisakyti opioidų per optimaliai trumpą laiką, kartu kuo labiau sumažinant nutraukimo simptomus ir sušvelninant priklausomybės neigiamas pasekmes. Nors detoksikacija plačiai taikoma klinikinėje

praktikoje, tyrimų, kurie nagrinėtų jos veiksmingumą gerinant receptiniams opioidams priklausomų asmenų gyvenimo kokybę, vis dar trūksta. Daugelis mokslinių darbų koncentruojasi į neteisėtą opioidų vartojimą, tokį kaip heroinas ar fentanilis, tuo tarpu priklausomybė nuo receptinių opioidų pasižymi specifiniais iššūkiais, susijusiais su jos klinikine kilme, pacientų demografiniais ypatumais ir gretutinėmis ligomis. Šis tyrimas siekia užpildyti šią spragą, vertindamas detoksikacijos poveikį gyvenimo kokybei, skausmo suvokimui ir bendrai savijautai pacientų, kuriems opioidai buvo skirti lėtinio skausmo gydymui, grupėje.

Ankstesni opioidų detoksikacijos tyrimai padėjo reikšmingai pažengti gydymo metodų srityje. Ypač paminėtina dr. T. Jovaišos 2006 m. apginta disertacija „N-metil-D-aspartato receptorių antagonisto ketamino ir bendrosios anestezijos įtaka sukeltai opioidinei abstinencijai“ [24, 25], kurioje buvo nagrinėtos farmakologinės strategijos nutraukimo simptomams mažinti. Vėliau, 2016 m., dr. R. Badaras disertacijoje „Greitosios opioidinės detoksikacijos eiga taikant naują palaipsniui didėjančių naltreksono dozių indukcijos metodą“ [26] pristatė alternatyvų opioidų nutraukimo būdą, orientuotą į nutraukimo diskomforto ir streso mažinimą. Vis dėlto, nepaisant šių indėlių, vis dar stokojama tyrimų, vertinančių detoksikacijos ilgalaikį poveikį pacientų gyvenimo kokybei, skausmo suvokimui ir psichologinei savijautai.

Ši disertacija tęsia ir plėtoja ankstesnius tyrimus, pateikdama išsamią detoksikacijos rezultatų analizę pacientų, priklausomų nuo receptinių opioidų, grupėje. Inovatyvus šio tyrimo aspektas - dėmesio sutelkimas į gyvenimo kokybės vertinimą, apimantį psichologinius, socialinius ir funkcinės būklės aspektus, užuot apsiribojus vien nutraukimo simptomų sunkumo ar atkryčio dažnio matavimu. Be to, šiame tyrime bus nagrinėjamas vitamino D lygmens vaidmuo detoksikacijos rezultatams - tai naujas, dar menkai ištirtas veiksnys opioidų priklausomybės kontekste. Tikimasi, kad tyrimo rezultatai prisidės prie klinikinės praktikos tobulinimo, detoksikacijos protokolų optimizavimo ir individualizuotų gydymo strategijų, orientuotų į ilgalaikės pacientų būklės gerinimą, kūrimo.

Potenciali tyrimo nauda

1. Hipotezės dėl gyvenimo kokybės pagerėjimo patvirtinimas

Tyrimo tikslas yra patvirtinti arba paneigti hipotezę, jog detoksikacija pagerina pacientų, patiriančių lėtinį skausmą ir vartojančių receptinius opioidus gyvenimo kokybę. Sistemingai analizuojant fizinės, emocinės ir socialinės gerovės pokyčius, siekta nustatyti ryšį tarp sėkmingos detoksikacijos ir gyvenimo kokybės pagerėjimo.

2. Detoksikacijos prieinamumo svarba

Šiame tyrime pacientams suteikiama papildoma galimybė pradėti opioidų detoksikacijos procesą. Dalyvaudami tyrime, jie gali įsitraukti į kompleksinį gydymą, skirtą opioidų vartojimo sutrikimui. Detoksikacija turėtų būti pripažinta kaip esminė gydymo galimybė asmenims, priklausomiems nuo receptinių opioidų. Opioidiniai vaistai plačiai skiriami įvairioms klinikinėms būklėms gydyti - nuo ūmaus skausmo iki lėtinių skausmo sindromų. Dėl specifinių opioidų farmakologinių savybių tolerancijos vystymasis yra biochemiškai neišvengiamas procesas, dėl kurio reikia vis didesnių dozių tam pačiam analgeziniam poveikiui pasiekti. Dėl to ilgalaikis vartojimas dažnai sukelia fizinę priklausomybę net tais atvejais, kai vaistas vartojamas griežtai laikantis gydytojo nurodymų.

Vis dėlto, nors tolerancija ir priklausomybė yra gerai dokumentuoti ilgalaikio opioidų vartojimo padariniai, pagrindinė problema yra ne jų neišvengiamumas, o būtinybė užtikrinti pacientams lengvą prieigą prie detoksikacijos kaip priemonės gyvenimo kokybei gerinti. Daugelis pacientų toliau vartoja opioidus dėl baimės patirti nutraukimo simptomus, dėl nerimo, kad sugrįš skausmas, ar dėl nežinojimo apie alternatyvias skausmo valdymo strategijas. Tokios abejonės gali lemti ilgalaikį opioidų vartojimą, kuris didina nepageidaujamų reiškinių, priklausomybės ir bendros savijautos blogėjimo riziką.

Šis tyrimas pabrėžia būtinybę detoksikaciją vertinti ne kaip sunkiai įveikiamą iššūkį, bet kaip struktūruotą gydymo intervenciją, skirtą saugiam opioidų vartojimo nutraukimui, mažinant diskomfortą ir gerinant gydymo rezultatus. Tinkamai atliekama detoksikacija gali padėti atkurti fizinę sveikatą, psichologinį stabilumą ir socialinį funkcionavimą, galiausiai pagerindama pacientų gyvenimo kokybę. Tyrimas siekia paneigti vyraujančius mitus ir nustatyti kliūtis, trukdančias atsisakyti opioidų, taip skatindamas didesnį pasitikėjimą detoksikacija kaip realia ir naudinga sveikimo kryptimi. Be to, tyrimo rezultatai prisidės prie įrodymais grįstų klinikinių praktikų kūrimo, kurios padės užtikrinti saugesnes ir veiksmingesnes opioidų vartojimo nutraukimo strategijas bei visapusišką pacientų palaikymą detoksikacijos metu.

2. TYRIMO METODIKA

Šis perspektyvusis tyrimas buvo vykdomas ketverius metus – nuo 2019 iki 2023 metų.

Tyrimo vykdymui leidimą suteikė Vilniaus regioninis biomedicininių tyrimų etikos komitetas, vadovaujantis Lietuvos bei tarptautinėmis biomedicininių tyrimų etikos gairėmis. Leidimo Nr. 2019/10-1153-644, išduotas 2019 m. spalio 8 d. [priedas 1].

Tyrimą atliko darbo autorė, padedama Respublikinės Vilniaus universitetinės ligoninės (RVUL) Toksikologijos centro darbuotojų.

2.1. Tiriamieji ir jų atranka

Pacientų nukreipimą į Toksikologijos centrą inicijavo įvairios sveikatos priežiūros įstaigos, įskaitant pirminės asmens sveikatos priežiūros įstaigų gydytojus bei antrinio lygio įstaigas, tokias kaip Nacionalinis vėžio institutas ir skausmo gydymo klinikos. Šios įstaigos identifikavo pacientus, ilgą laiką vartojančius receptinius opioidus, ir vertino jų tinkamumą atlikti detoksikaciją nuo opioidų. Jos atliko svarbų vaidmenį atrenkant tinkamus tyrimo dalyvius, vykdant pirminį vertinimą ir užtikrinant jų įtraukimą į tyrimo programą.

Po siuntimo visi dalyviai buvo nuodugniai įvertinti Toksikologijos centre, siekiant patvirtinti jų tinkamumą detoksikacijai. Vertinimas apėmė išsamią medicininės anamnezės analizę, esamų opioidų vartojimo įpročių įvertinimą bei paciento pasirengimo planinei detoksikacijai nustatymą. Galutinę tiriamųjų grupę sudarė 45 pacientai, pasižymintys įvairiu amžiumi, lytimi ir klinikiniu fonu, kas sustiprina tyrimo rezultatų pritaikomumą platesnėms receptinių opioidų detoksikacijos pacientų populiacijoms.

Laikantis griežtų atrankos, informuoto sutikimo ir įtraukimo procedūrų, buvo užtikrinta, kad visi dalyviai būtų tinkami intervencijai, etiškai apsaugoti ir tinkamai informuoti, o tai prisidėjo prie tyrimo rezultatų patikimumo ir pagrįstumo.

Tiriamąją grupę sudarė pacientai, kuriems opioidai buvo paskirti įvairiems skausmo sindromams gydyti - įskaitant galvos skausmus, onkologinius skausmus, nugaros skausmus, reumatoidinį artritą, virškinamojo trakto patologiją, lėtinį raumenų skausmą bei žasto sąnario artrozę. Pažymėtina, kad visi tyrime dalyvavę onkologiniai pacientai duomenų rinkimo laikotarpiu buvo remisijos stadijoje ir tuo metu nebuvo gydomi aktyviu onkologiniu gydymu.

Įtraukti 45 pacientai, kuriems atlikta planinė detoksikacija nuo receptinių opioidų Respublikinės Vilniaus universitetinės ligoninės Toksikologijos centre. Visi 45 į tyrimą įtraukti pacientai jį sėkmingai baigė, todėl buvo gautas patikimas duomenų rinkinys analizei. Prieš įtraukiant į tyrimą, visi dalyviai pasirašė informuotą asmens sutikimo formą, po to kai jiems išsamiai paaiškinti tyrimo tikslai, eiga ir galimi pavojai.

2.1.1 Įtraukimo kriterijai

1. Patvirtinta tolerancija ir/ar priklausomybė receptiniams opoidams: pacientai, turintys dokumentuotą opioid tolerancijos istoriją, pasireiškiančią sumažėjusiu analgeziniu poveikiu ir poreikiu didinti dozes norint pasiekti tą patį skausmo malšinimo lygį, taip pat priklausomybę nuo receptinių opioidų.
2. Planinė detoksikacija: pacientai, hospitalizuoti į RVUL Toksikologijos centrą planinei detoksikacijai nuo receptinių opioidų.

2.1.2 Atmetimo kriterijai

1. Ūminis apsinuodijimas opioidais: pacientai, kuriems įvertinimo metu nustatyti ūminio apsinuodijimo opioidais požymiai.
2. Priklausomybė nuo nelegalių opioidų: pacientai, kuriems diagnozuota priklausomybė nuo nelegalių opioidų.
3. Priklausomybė nuo keletos psichoaktyvių medžiagų: pacientai, kuriems diagnozuota priklausomybė nuo daugiau nei vienos psichoaktyvios medžiagos, neapsiribojant vien opioidais.

2.2. Duomenų rinkimas ir klinikinis vertinimas

Atvykus į Toksikologijos centrą, sistemingai surinkta visų pacientų išsami klinikinė ir demografinė informacija. Surinkti duomenys apėmė paciento amžių, lytį, lėtinio skausmo trukmę, pagrindinę skausmo lokalizaciją ar diagnozę bei receptinių opioidų vartojimo pobūdį. Taip pat buvo fiksuotas receptinių opioidų vartojimo laikotarpis, siekiant įvertinti vartojimo trukmę ir jo galimą poveikį priklausomybės išsivystymui bei gydymo rezultatams.

Norint tiksliai nustatyti receptinių opioidų dozes buvo taikytas daugiaetapis vertinimo metodas. Pacientai pateikė savarankišką informaciją apie tuo metu vartojamus opioidus, jų pavadinimus, dozes ir vartojimo dažnumą. Šie duomenys buvo palyginti su paciento medicinos dokumentuose esančia informacija, siekiant užtikrinti duomenų tikslumą ir patikimumą. Suderinus paciento nurodytus duomenis su dokumentuotu gydymu, buvo sumažinta galimų neatitikimų rizika. Siekiant užtikrinti analizės standartizavimą ir palyginamumą, visos opioidų dozės buvo konvertuotos į geriamajam morfinui ekvivalentines dozes (MED). Ši konversija leido suvienodinti skirtingų opioidinių vaistų stiprumą ir palengvino bendro opioidų kiekio įvertinimą tarp tyrimo dalyvių. Geriamajam morfinui ekvivalentinė dozė (MED) yra plačiai taikomas matavimo vienetas klinikiniuose tyrimuose,

kadangi jis sudaro prielaidas tiksliau įvertinti bendrą vartojamų opioidų kiekį bei užtikrina rezultatų palyginamumą tarp tyrimų, kuriuose naudojami skirtingi opioidiniai preparatai.

Siekiant įgyvendinti tyrimo tikslus, sistemingai buvo renkami, dokumentuojami ir analizuojami šie duomenys:

2.2.1. Demografiniai rodikliai

Demografiniai duomenys buvo renkami siekiant apibūdinti tiriamąją populiaciją ir įvertinti galimus ryšius tarp pacientų demografinių ypatybių ir gydymo rezultatų. Buvo fiksuojamas pacientų amžius ir lytis. Ši informacija padėjo susidaryti išsamesnį tyrimo dalyvių profilį ir įvertinti galimą demografinių veiksnių įtaką opioidų vartojimui bei detoksikacijos sėkmei.

2.2.2. Somatinė patologija

Somatinių ligų buvimas buvo fiksuojamas siekiant įvertinti gretutines būkles, galinčias turėti įtakos gydymo eigai ir tyrimo rezultatams. Buvo registruojamos visos lėtinės ar ūminės ligos, nustatytos pradinio klinikinio įvertinimo metu. Šie duomenys leido susidaryti bendrą vaizdą apie dalyvių sveikatos būklę ir sudarė prielaidas išsamiai analizei, kaip gretutinės ligos gali sąveikauti su opioidų vartojimu ir detoksikacijos procesu.

2.2.3. Receptinių opioidų vartojimo ypatumai

Išsami informacija apie opioidų vartojimą buvo renkama siekiant įvertinti vartojimo pobūdį ir trukmę. Duomenys apėmė konkrečius vartotus opioidus, jų dozes (standartizuotas į geriamajam morfinui ekvivalentines dozes, OME), vartojimo trukmę, būdą ir pagrindinį vartojimo tikslą. Dalyviai buvo apklausiami dėl ankstesnių detoksikacijos procedūrų, įskaitant jų dažnumą ir rezultatus.

2.2.4. Gyvenimo kokybės vertinimas

Tyrimo dalyvių gyvenimo kokybė buvo vertinama naudojant trumpąją anketos versiją „Short Form-36 Version 2“(SF-36v2™), kuri buvo išversta į lietuvių kalbą, siekiant užtikrinti kultūrinį ir kalbinį tinkamumą. Vertinimas buvo atliktas trijuose skirtinguose laiko taškuose, siekiant fiksuoti gyvenimo kokybės pokyčius detoksikacijos proceso metu ir po gydymo. Vertinimo momentai buvo šie: (1) prieš pradedant detoksikaciją (pradinė būklė), (2) išrašymo iš Toksikologijos centro dieną (po detoksikacijos) ir (3) ne anksčiau

kaip po šešių mėnesių nuo išrašymo, atliekant tęstinį telefoninį pokalbį. Šis išilginis vertinimo modelis leido įvertinti tiek trumpalaikius, tiek ilgalaikius gyvenimo kokybės pokyčius po receptinių opioidų detoksikacijos.

SF-36v2™ – tai patvirtintas, daugiamačio pobūdžio instrumentas, skirtas sveikatos būklei susijusios gyvenimo kokybės vertinimui įvairiose populiacijose ir klinikinėse situacijose. Klausimyną sudaro 36 klausimai, suskirstyti į aštuonis aspektus: fizinis funkcionavimas, fizinės sveikatos nulemti vaidmenų ribojimai, emocinių problemų nulemti vaidmenų ribojimai, energija/nuovargis, emocinė savijauta, socialinis funkcionavimas, skausmas ir bendras sveikatos suvokimas. Kiekvienas aspektas vertinamas skalėje nuo 0 iki 100, kur aukštesnis balas reiškia geresnį funkcionavimą arba mažesnius apribojimus konkrečioje srityje.

Bendras gyvenimo kokybės įvertis buvo apskaičiuotas išvedant aštuonių atskirų skalių vidurkį, kas sudarė išsamų tyrimo dalyvių subjektyvios sveikatos būklės rodiklį. Šis sudėtinis balas leido visapusiškai įvertinti tiek fizinės, tiek psichologinės sveikatos aspektus. Pasirinkus SF-36v2™ klausimyną, tyrime buvo taikytas patikimas ir tarptautiniu mastu pripažintas gyvenimo kokybės vertinimo įrankis, o tai sustiprino gautų rezultatų patikimumą ir tarpusavio palyginamumą.

Naudojant standartizuotą vertinimo priemonę, buvo galima kiekybiškai įvertinti gyvenimo kokybės pokyčius laikui bėgant ir gauti vertingų duomenų apie detoksikacijos poveikį. Įtraukta ne trumpesnė kaip šešių mėnesių stebėsena taip pat leido užfiksuoti ilgalaikį detoksikacijos poveikį pacientų gyvenimo kokybei, suteikiant platesnę perspektyvą apie intervencijos veiksmingumą ir tvarumą.

2.2.5. Skausmo intensyvumo vertinimas

Pacientų skausmo intensyvumas buvo vertinamas naudojant vizualinę analoginę skalę (VAS), plačiai pripažintą ir patikimą priemonę subjektyviam skausmo lygiui įvertinti. Tyrime naudota VAS skalė siekė nuo 0 iki 10, kur 0 reiškė „skausmo nėra “, o 10 – „blogiausias įmanomas skausmas“. Ši vienmatė skalė leido paprastai ir efektyviai kiekybiškai įvertinti skausmo stiprumą ir atlikti tiesioginius skausmo lygio palyginimus skirtingais laikotarpiais.

VAS balas	**Skausmo apibūdinimas**
0	Skausmo nėra
1–3	Lengvas skausmas
4–6	Vidutinio stiprumo skausmas
7–9	Stiprus skausmas
10	Neįsivaizduojamai stiprus skausmas

Skausmo intensyvumas buvo vertintas dviem konkrečiais laikotarpiais, siekiant įvertinti detoksikacijos procedūros tiesioginį poveikį dalyvių patiriamam skausmui. Pirmasis matavimas buvo atliktas pirmą dieną prieš pat detoksikacijos pradžią (pradinė reikšmė), o antrasis - išrašymo dieną, užbaigus detoksikacijos procesą. Lyginant VAS rezultatus šiais dviem laikotarpiais, buvo siekiama įvertinti skausmo intensyvumo pokyčius detoksikacijos metu ir nustatyti galimus skausmo valdymo pagerėjimus dėl taikytos intervencijos.

Sprendimas vertinti skausmą tik šiuose dviejuose esminiuose taškuose atitiko tyrimo tikslą - analizuoti trumpalaikius detoksikacijos rezultatus. Tokiu būdu buvo galima geriau suprasti, kaip detoksikacijos procesas veikia ūminį skausmo suvokimą, atskleidžiant ryšį tarp opioidų nutraukimo, taikytų intervencijų ir paciento patiriamo skausmo. Naudojant VAS buvo užtikrintas standartizuotas ir lengvai interpretuojamas duomenų rinkimas, o tai padidino skausmo matavimų patikimumą ir nuoseklumą tarp visų tyrimo dalyvių.

2.2.6. 25-hidroksivitamino D kiekio kraujyje vertinimas

Prieš detoksikaciją ambulatoriškai visiems dalyviams buvo ištirtas 25-hidroksivitamino D (25-OHD) kiekis kraujo serume, naudojant standartizuotus metodus, tokius kaip imunologiniai tyrimai arba LC-MS/MS. Remiantis pradiniais 25-OHD koncentracijos rodikliais, dalyviai buvo suskirstyti į dvi grupes. Asmenys, kurių vitamino D koncentracija buvo mažesnė nei 75 nmol/l (30 ng/ml), buvo priskirti vitamino D stokos grupei, vadovaujantis tarptautinėmis gairėmis. Dalyviai, kurių 25-OHD koncentracija siekė 75 nmol/l ar daugiau, buvo priskirti pakankamo vitamino D kiekio grupei.

Ši klasifikacija leido tirti galimą sąsają tarp vitamino D būklės, skausmo suvokimo ir gyvenimo kokybės dar prieš detoksikaciją. Tyrimo dieną pacientams, kuriems nustatytas vitamino D trūkumas, buvo skirta vienkartinė 50 000 TV cholekalciferolio dozė (pagal Lietuvos šeimos gydytojų kolegijos rekomendacijas). Visiems dalyviams, nepriklausomai nuo lygio, rekomenduotas tęstinis papildymas pas šeimos gydytoją.

Svarbu pažymėti, kad 25-OHD lygis po hospitalizacijos nebuvo iš naujo matuotas, kadangi šio tyrimo tikslas buvo tirti pradinių vitamino D verčių sąsają su gyvenimo kokybe ir skausmo suvokimu prieš detoksikaciją.

2.3. Receptinių opioidų detoksikacijos protokolas

Šiame tyrime taikytas detoksikacijos protokolas buvo parengtas remiantis ankstesniais mūsų darbais [26] ir oficialiai patvirtintas Respublikinėje Vilniaus universitetinėje ligoninėje 2019 m. balandžio 2 d. [priedas 2]. Protokolas grindžiamas struktūrizuotu farmakologiniu metodu,

kuris apima benzodiazepinų ir α2-adrenerginių agonistų taikymą siekiant suvaldyti abstinencijos simptomus opioidų nutraukimo metu.

Detoksikacijos metu buvo skiriami benzodiazepinai (konkrečiai diazepamas) ir α2-adrerginis agonistas klonidinas, padedantys mažinti fiziologinius bei psichologinius nutraukimo simptomus. Vaistų dozės ir skyrimo dažnis buvo pritaikomi individualiai, atsižvelgiant į abstinencijos simptomų intensyvumą, kuris buvo vertinamas naudojant objektyviąją opioidų nutraukimo skalę (OOWS) ir subjektyviąją opioidų nutraukimo skalę (SOWS). Šie validuoti instrumentai užtikrino sistemingą vertinimą ir leido tiksliai pritaikyti intervencijas kiekvienam pacientui.

Viso detoksikacijos proceso metu opioidiniai preparatai nebuvo skiriami. Pacientai buvo nuolat stebimi dėl abstinencijos simptomų, o pagrindinis protokolo principas buvo savalaikė ir kontroliuojama farmakologinė intervencija, siekiant sumažinti diskomfortą dar ankstyvoje abstinencijos stadijoje ir padėti užtikrinti sklandžią gydymo eigą.

Be diazepamo ir klonidino, detoksikacijos metu buvo taikoma ir platesnė daugiadisciplinė farmakologinė strategija. Skausmui ir uždegimui mažinti buvo skiriami nesteroidiniai vaistai nuo uždegimo (NVNU), tokie kaip ibuprofenas, diklofenakas ir ketorolakas. Nerimui, sujaudinimui ir nemigai valdyti buvo naudojami antipsichotikai - haloperidolis ir kvetiapinas. Neuropatiniam skausmui ir centrinės nervų sistemos hiperaktyvumui mažinti buvo taikomas antiepilepsinis vaistas gabapentinas. Tuo tarpu nuotaikos sutrikimams ir nemigai gydyti buvo skiriamas tetraciklis antidepresantas mirtazapinas.

Kiekvienas vaistas buvo skiriamas atsižvelgiant į individualius paciento poreikius, o dozės buvo koreguojamos pagal simptomų intensyvumą ir eigą. Šis individualizuotas požiūris užtikrino tiek gydymo veiksmingumą, tiek toleravimą. Pacientų būklė buvo nuolat stebima viso detoksikacijos metu, o abstinencijos simptomai vertinami tiek skalėmis (SOWS, OOWS), tiek tiesioginiu sveikatos priežiūros specialistų stebėjimu. Tai leido laiku reaguoti į kylančius simptomus ir užtikrinti pacientų saugumą.

Skirtingai nei pradiniame protokole [26], kuriame buvo numatyta naltreksono - opioidų antagonisto - skyrimas, šiame tyrime naltreksonas nebuvo naudojamas. Šis sprendimas buvo priimtas atsižvelgiant į konkrečius tyrimo tikslus - vertinti detoksikacijos rezultatus be papildomo streso, kurį gali sukelti antagonisto įvedimas, kaip nustatyta ankstesniuose tyrimuose.

2.4. Detoksikacijos gydymo ypatybės

Stacionarinio gydymo metu taikant detoksikacijos protokolą buvo vertinamas jo klinikinis veiksmingumas ir rezultatai. Buvo registruojami paskirti vaistai ir jų dozės, parinkti individualiai pagal paciento būklę bei abstinencijos simptomus. Gydymo tikslas - sumažinti diskomfortą, suvaldyti nutraukimo simptomus ir užkirsti kelią komplikacijoms. Abstinencijos simptomai buvo stebimi ir vertinami naudojant standartizuotas klinikines skales (SOWS ir OOWS), taip pat sveikatos priežiūros specialistų klinikinį vertinimą. Kiekvienam pacientui fiksuota hospitalizacijos trukmė, atspindinti laiką, reikalingą klinikinei būklei stabilizuoti.

Galutiniai gydymo rezultatai apėmė abstinencijos simptomų sumažėjimą, paciento pasirengimą išrašymui ir abstinencijos būklės pasiekimą. Surinkti duomenys leido visapusiškai įvertinti detoksikacijos proceso efektyvumą.

2.5. Statistinė duomenų analizė

Visi surinkti duomenys buvo kruopščiai dokumentuoti ir tvarkomi, siekiant užtikrinti tyrimo tikslumą, patikimumą ir atkuriamumą. Pradžioje duomenys buvo sistemingai suvesti į „Microsoft Excel“ skaičiuoklę, kuri tarnavo kaip pirminė duomenų bazė bei pradinės analizės priemonė. Vėliau išsami statistinė analizė buvo atlikta naudojant „IBM SPSS Statistics 23.0“ programinę įrangą, kuri užtikrino nuoseklų ir metodologiškai pagrįstą duomenų apdorojimo procesą.

Buvo taikytos šios statistinės analizės strategijos. Aprašomoji statistika naudota demografinių ir klinikinių rodiklių apibendrinimui - skaičiuoti vidurkiai, standartiniai nuokrypiai ir dažniai, leidžiantys detaliau apibūdinti tiriamąją imtį. Infrencinė statistika buvo taikoma siekiant nustatyti ryšius tarp kintamųjų bei įvertinti gydymo poveikį. Nuolatiniai kintamieji buvo pateikti kaip vidurkiai su standartiniais nuokrypiais, o kategoriniai - procentinėmis reikšmėmis. Grupėms lyginti buvo naudojamas nepriklausomų imčių t-testas, statistiškai reikšmingais laikant skirtumus, kai $p < 0,05$.

Analizuojant sąsajas tarp pradinio 25-hidroksivitamino D (25-OHD) lygio, skausmo įverčio (pagal VAS) ir gyvenimo kokybės, buvo atlikta linijinė regresinė analizė, taikant mažiausių kvadratų metodą. Kad būtų koreguota reikšmių asimetrija ir užtikrintas analizės linijiškumas, 25-OHD reikšmės buvo logaritmuotos. VAS skausmo balai taip pat buvo logaritmuoti ir invertuoti, siekiant pagerinti jų pasiskirstymą ir analizės interpretaciją.

Priklausomas kintamasis regresijos modelyje buvo bendras gyvenimo kokybės balas, apskaičiuotas pagal SF-36v2™ klausimyno duomenis.

Regresijos modelyje kiekvieno prediktoriaus reikšmingumas buvo vertinamas pagal t-statistiką ir p reikšmes, siekiant nustatyti jų įtaką tiriamųjų subjektyviai vertinamai gyvenimo kokybei.

Papildomai, nepriklausomų imčių t-testas buvo taikytas dviem tiriamųjų grupėms - turintiems pakankamą ir nepakankamą 25-OHD kiekį - palyginti pagal (1) logaritmuotus ir invertuotus VAS skausmo balus, ir (2) gyvenimo kokybės balus, gautus naudojant SF-36v2™ klausimyną.

Analizės metu plačiai taikytos įvairios duomenų transformacijos, ypač logaritminė konversija, siekiant normalizuoti iškreiptus pasiskirstymus ir padidinti statistinės analizės tikslumą bei aiškumą.

2.6. Tiriamųjų dalyvavimo biomedicininiame tyrime trukmė

Tiriamųjų dalyvavimas tyrime buvo kruopščiai suplanuotas, siekiant visapusiškai įvertinti opioidinės detoksikacijos veiksmingumą ir ilgalaikį poveikį. Duomenys buvo renkami perspektyviai, o kiekvieno dalyvio įsitraukimo trukmė apėmė laikotarpį nuo detoksikacijos pradžios iki ne trumpesnio kaip šešių mėnesių stebėjimo po stacionarinio gydymo pabaigos.

Toks išplėstas laiko intervalas leido vertinti tiek trumpalaikius rezultatus, pavyzdžiui, sėkmingą detoksikacijos užbaigimą, tiek ilgalaikius pokyčius - skausmo suvokimo, gyvenimo kokybės ir bendros sveikatos būklės dinamikoje.

3. REZULTATAI

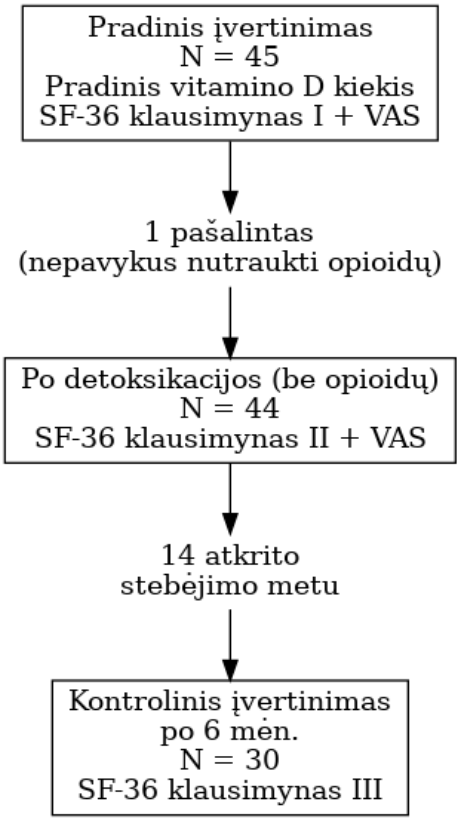
3.1. Tiriamųjų imties charakteristika

Tyrimas buvo atliktas su 45 pacientų imtimi, iš kurių 44 asmenims pavyko sėkmingai užbaigti detoksikacijos procesą, t. y. visiškai nutraukti receptinių opioidų vartojimą. Tai sudaro 97,8 proc. sėkmės rodiklį ir liudija apie taikyto gydymo metodo efektyvumą siekiant nutraukti opioidų vartojimą [1 diagrama].

Tiriamojoje grupėje dominavo moterys - jos sudarė 62,22 proc. visų dalyvių (n = 28), o tai rodo nežymią lytinę disproporciją moterų naudai. Vidutinis tiriamųjų amžius buvo 53,62 metų (±12,70), o tai atitinka vidutinio amžiaus suaugusiųjų populiaciją. Vidutinė receptinių opioidų vartojimo trukmė siekė 60,51 mėnesio (±67,81), atskleidžiant didelį individualios vartojimo trukmės kintamumą. Pats detoksikacijos procesas vidutiniškai truko

9,2 dienos (±3,2), o tai leidžia daryti prielaidą apie galimybę efektyviai nutraukti opioidų vartojimą per palyginti trumpą laikotarpį [1 lentelė].

1 diagrama. Tyrimo eiga: pacientų eiga detoksikacijos metu bei gyvenimo kokybės (SF-36), skausmo (VAS) ir vitamino D vertinimas



1 lentelė. Tiriamųjų demografinė ir klinikinė charakteristika (N = 45)

Kintamasis	Reikšmė
Baigė detoksikaciją, n (%)	44 (97,8 %)
Lytis (moterų skaičius, n (%))	28 (62,22 %)
Vidutinis amžius (metais)	53,62 ± 12,70
Vidutinė receptinių opioidų vartojimo trukmė (mėn.)	60,51 ± 67,81
Vidutinė detoksikacijos trukmė (dienomis)	9,2 ± 3,2

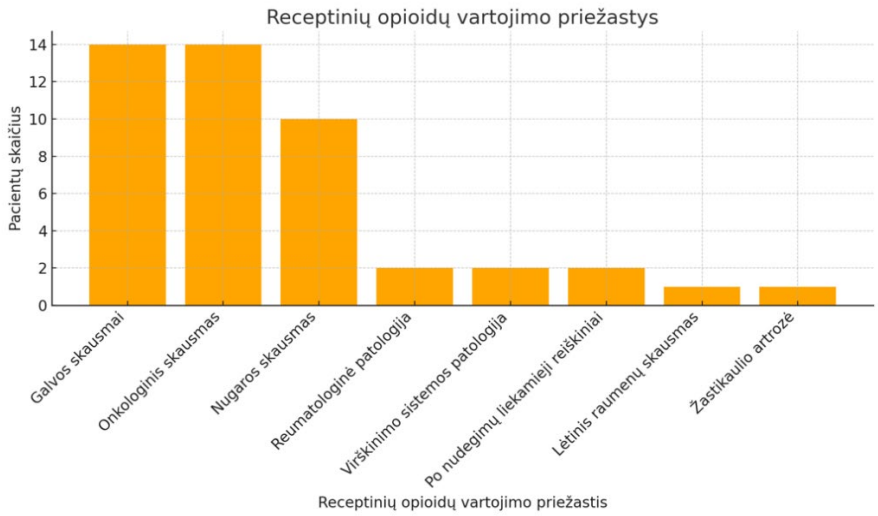
3.2. Ilgalaikio receptinių opioidų vartojimo indikacijos

Tiriamųjų kohorta sudarė asmenys, kuriems opioidai buvo paskirti pirmiausia dėl įvairių skausmo sindromų: galvos skausmų, onkologinio skausmo, nugaros skausmo, reumatoidinio artrito, virškinimo sistemos patologijos, lėtinio raumenų skausmo bei žasto kaulo artrozės. Pagrindinės opioidų paskyrimo indikacijos buvo galvos skausmai ir onkologinis skausmas remisijos fazėje - kiekviena iš šių būklių buvo nustatyta 14 iš 45 pacientų. Svarbu pažymėti, kad visi onkologiniai pacientai tyrimo metu buvo remisijoje ir negavo aktyvaus onkologinio gydymo. Trečia pagal dažnumą indikacija buvo nugaros skausmas, kurį nurodė 10 pacientų.

Rečiau pasitaikę atvejai apėmė reumatoidinį artritą (2 atvejai), virškinimo sistemos patologiją (2 atvejai) ir pavienius atvejus, tokius kaip lėtinis skausmas po nudegimo, lėtinis raumenų skausmas bei žasto sąnario artrozė. Šie rezultatai parodo skausmo sindromų įvairovę, dėl kurios šiai grupei buvo skiriami opioidiniai analgetikai [2 lentelė] [1 pav.].

2 lentelė. Receptinių opioidų vartojimo indikacijos

Indikacija	Pacientų sk. (n)	Procentinė dalis (%)
Onkologinė (remisijos fazė)	14	31,1 %
Neurologinė (galvos skausmai)	14	31,11 %
Raumenų ir skeleto sistema	10	22,2 %
Reumatologinė	2	4,44 %
Virškinimo sistema	2	4,44 %
Kita	3	6,67 %



1 pav. Receptinių opioidų vartojimo indikacijų pasiskirstymas

3.3. Receptinių opioidų rūšys

Receptinių vaistų skyrimo duomenys parodė tiriamųjų grupėje vartotų opioidų įvairovę. Dažniausiai skiriamas opioidas buvo tramadolis – jį vartojo 13 pacientų. Toliau sekė kodeinas ir morfinas – po 9 pacientus kiekvienam. Fentanilis transderminiu pavidalu buvo skirtas keturiems pacientams, o petidinas – dviem. Metadonas ir oksikodonas buvo skirti po vienam pacientui.

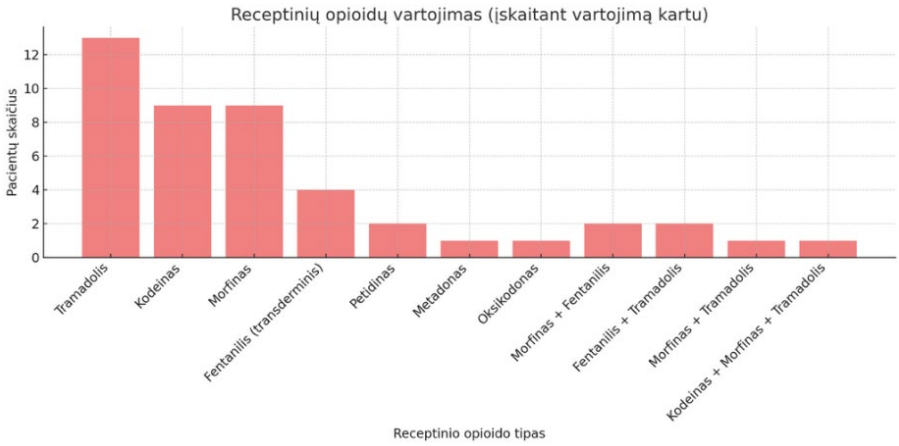
Dalis pacientų vartojo kelis opioidus vienu metu, o tai rodo jų gydymo schemų sudėtingumą. Konkrečiai, dviem pacientams buvo paskirtas ir morfinas, ir fentanilis; dviem – fentanilis ir tramadolis; vienam pacientui – morfinas ir tramadolis; o vienas pacientas vienu metu vartojo kodeiną, morfiną ir tramadolį. [3 lentelė] [2 pav.].

3 lentelė. Receptiniai opioidai (vartoti atskirai arba deriniuose) (n = 45)

Vaistas	n (%)
Tramadolis	13 (28,9 %)
Kodeinas	9 (20 %)
Morfinas	9 (20 %)
Fentanilis	4 (8,9 %)
Petidinas	2 (4,4 %)
Metadonas	1 (2,2 %)
Oksikodonas	1 (2,2 %)

Opioidų vartojimo deriniai

Derinys	n (%)
Morfinas ir fentanilis	2 (4,5 %)
Fentanilis ir tramadolis	2 (4,5 %)
Morfinas ir tramadolis	1 (2,3 %)
Kodeinas, morfinas ir tramadolis	1 (2,3 %)



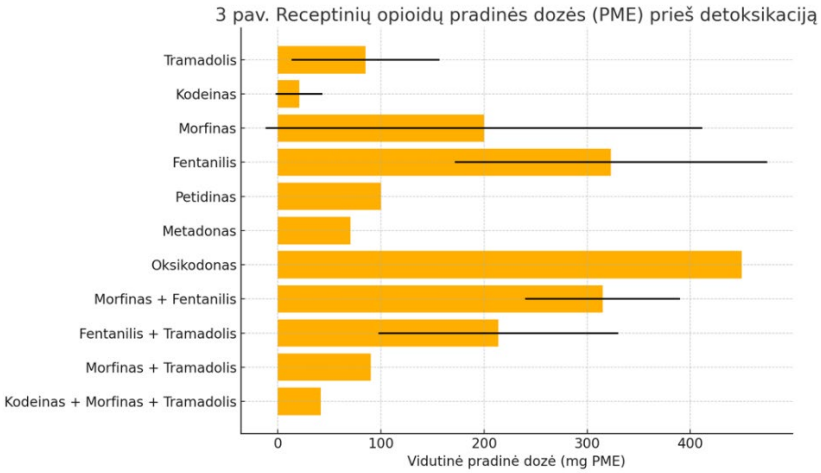
2 pav. Receptiniai opioidai

3.4. Receptinių opioidų dozės

Vidutinė paskirtų opioidų paros dozė, perskaičiuota į geriamojo morfino ekvivalentą (MED), siekė 139,8 ± 153,9 mg. Vartojant pavienius opioidus, MED reikšmės svyravo nuo 20,54 mg (±22,71) kodeinui iki 450 mg oksikodonui. Taikant kombinuotą opioidų terapiją, MED reikšmės taip pat buvo įvairios – didžiausia pasiekta dozė buvo 315 mg (±75), kai buvo vartojamas morfino ir fentanilio derinys [4 lentelė].

4 lentelė. Vidutinės morfino ekvivalento dozės (MED) ir jų standartiniai nuokrypiai (SD) pagal paskirtą opioidą.

Paskirtas opioidas	**Vidutinė dozė (mg/d ± SD)**
Vidutinė pradinė morfino ekvivalento dozė (n = 45)	139,8 ± 153,9
Pavieniai opioidai	
Tramadolis (n = 13)	85 ± 71,68
Kodeinas (n = 9)	20,54 ± 22,71
Morfinas (n = 9)	200 ± 211,82
Fentanilis (n = 4)	323,12 ± 151,67
Petidinas (n = 2)	100 ± 0
Metadonas (n = 1)	70,5
Oksikodonas (n = 1)	450
Kombinuoti opioidai	
Morfinas ir fentanilis (n = 2)	315 ± 75
Fentanilis ir tramadolis (n = 2)	213,75 ± 116,25
Morfinas ir tramadolis (n = 1)	90
Kodeinas, morfinas ir tramadolis (n = 1)	41,6



3 pav. Vidutinės morfino ekvivalento dozės (MED) ir jų standartiniai nuokrypiai (SD) pagal paskirtą opioidą.

3.5. Receptinių opioidų dozės pagal skausmo kategorijas

Receptinių opioidų vartojimo analizė, atsižvelgiant į skirtingas skausmo priežastis, atskleidė aiškias skyrimo ir dozavimo tendencijas. Buvo nustatyti šie dėsningumai [5 lentelė]:

Neurologinis skausmas. Dažniausiai paskirti opioidai buvo kodeinas ir tramadolis. Morfino ekvivalento dozės svyravo nuo 1,3 mg iki 240 mg. Tramadolis dažniausiai buvo vartojamas didesnėmis dozėmis (iki 240 mg MED), tuo tarpu kodeinas - mažesnėmis.

Raumenų ir skeleto sistemos skausmas. Vartoti opioidai: tramadolis, fentanilis, morfinas ir oksikodonas. Morfino ekvivalento dozės svyravo nuo 15 mg iki 720 mg. Didžiausia dozė (720 mg MED) buvo paskirta vartojant morfiną. Taip pat fentanilis ir oksikodonas buvo skiriami didelėmis dozėmis.

Onkologinis skausmas. Pastebėta didžiausia opioidų įvairovė - vartoti morfinas, fentanilis, metadonas bei jų deriniai. Morfino ekvivalento dozės svyravo nuo 30 mg iki 550 mg. Fentanilis ir morfinas dažnai buvo skiriami kartu sudarant aukštų dozių gydymo schemas.

Virškinamojo trakto skausmas. Vienintelis paskirtas opioidas buvo petidinas - nuosekliai vartotas 100 mg MED dozėmis.

Reumatologinis skausmas. Vienintelis paskirtas opioidas buvo morfinas, 240 mg MED dozėmis.

Kitos skausmo kategorijos. Nudegimų sukeltam skausmui gydyti tramadolis buvo skiriamas 40 mg MED dozėmis. Trauminiam skausmui taip pat

paskirtas tramadolis, 40 mg MED. Neaiškios kilmės juosmeninės stuburo dalies patologijai gydyti buvo skirta kombinuota schema - kodeinas, morfinas ir tramadolis, bendroje 41,6 mg MED dozėje.

Ši analizė rodo, kad neurologinio skausmo atvejais dažniausiai buvo skiriami tramadolis ir kodeinas, o onkologiniam bei raumenų ir skeleto sistemos skausmui - dominuoja morfinas ir fentanilis. Petidinas buvo ribojamas tik virškinamojo trakto skausmo atvejais. Didžiausios opioidų dozės stebėtos onkologinio ir raumenų bei skeleto sistemos skausmo gydymo atvejais, kas gali rodyti didesnį analgezinį poreikį šiose klinikinėse situacijose.

5 lentelė. Receptinių opioidų skyrimas pagal skausmo priežastį ir morfino ekvivalento dozę

Nr.	Opioido tipas	Skausmo priežastis	MED (mg/parą)
1	kodeinas	neurologinis	3.2
2	tramadolis	neurologinis	200.0
3	tramadolis	kita (nudegimai)	40.0
4	kodeinas	neurologinis	60.0
5	morfinas	onkologinis	40.0
6	tramadolis	raumenų ir skeleto	80.0
7	kodeinas	neurologinis	57.0
8	tramadolis	neurologinis	240.0
9	fentanilis	onkologinis	270.0
10	fentanilis	raumenų ir skeleto	270.0
11	kodeinas	neurologinis	9.6
12	tramadolis	neurologinis	40.0
13	metadonas	onkologinis	70.5
14	kodeinas	neurologinis	1.3
15	morfinas	raumenų ir skeleto	200.0
16	tramadolis	raumenų ir skeleto	20.0
17	fentanilis	onkologinis	550.0
18	morfinas, fentanilis	onkologinis	390.0
19	tramadolis	kita (žasto trauma)	40.0
20	kodeinas	neurologinis	24.0
21	fentanilis	onkologinis	202.5
22	tramadolis	raumenų ir skeleto	30.0
23	morfinas	reumatologinis	240.0
24	tramadolis	raumenų ir skeleto	160.0
25	petidinas	virškinamojo trakto	100.0
26	tramadolis	raumenų ir skeleto	15.0
27	morfinas	onkologinis	150.0
28	tramadolis	neurologinis	120.0

Nr.	Opioido tipas	Skausmo priežastis	MED (mg/parą)
29	petidinas	virškinamojo trakto	100.0
30	morfinas	raumenų ir skeleto	720.0
31	morfinas	onkologinis	30.0
32	fentanilis, tramadolis	onkologinis	330.0
33	morfinas	onkologinis	30.0
34	morfinas	onkologinis	150.0
35	morfinas	reumatologinis	240.0
36	oksikodonas	raumenų ir skeleto	450.0
37	morfinas, tramadolis	onkologinis	90.0
38	kodeinas	neurologinis	16.0
39	kodeinas	neurologinis	8.0
40	tramadolis	raumenų ir skeleto	20.0
41	kodeinas	neurologinis	4.8
42	tramadolis	neurologinis	100.0
43	fentanilis, tramadolis	onkologinis	97.5
44	kodeinas, morfinas, tramadolis	kita (apatinės nugaros dalies skausmas, patologija nenustatyta)	41.6
45	morfinas, fentanilis	onkologinis	240.0

3.6. Gyvenimo kokybės vertinimas

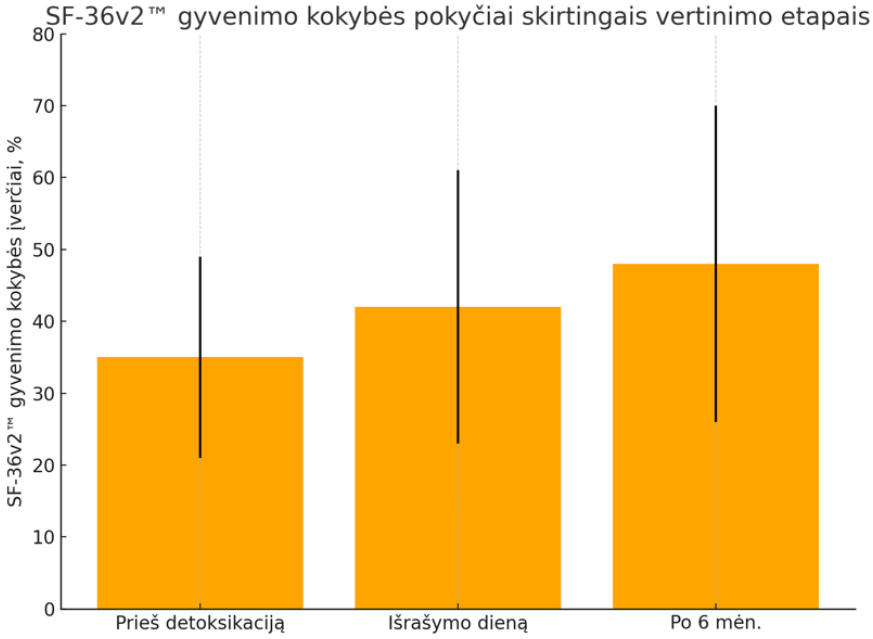
Visi trys vertinimo etapai buvo gauti iš 30 pacientų; likę 15 pacientų atsisakė pildyti trečiąją SF-36v2™ anketą arba su jais nepavyko užmegzti kontakto. Statistinė analizė parodė reikšmingą gyvenimo kokybės rodiklių pagerėjimą visais trimis laiko momentais. Vidutiniai gyvenimo kokybės balai buvo šie: pirmasis - prieš detoksikaciją - 35 ± 14%; antrasis - išrašymo dieną - 42 ± 19% ($p = 0,004$, palyginti su prieš detoksikaciją); trečiasis - praėjus ne mažiau kaip šešiems mėnesiams po detoksikacijos (kontrolinis skambutis) - 48 ± 22% ($p < 0,001$, palyginti su prieš detoksikaciją; $p = 0,025$, palyginti su išrašymo diena) [6 lentelė] [3 pav.].

Šie rezultatai rodo nuoseklų gyvenimo kokybės gerėjimą nuo priešdetoksikacinio laikotarpio iki ilgalaikio stebėjimo po detoksikacijos, patvirtinantį teigiamą opioidų detoksikacijos poveikį pacientų bendrai savijautai.]

6 lentelė. SF-36v2™ gyvenimo kokybės klausimyno rezultatų dinamika trijuose vertinimo etapuose (%)

Paciento Nr.	I klausimynas	II klausimynas	III klausimynas
1	20	23	13
2	56		
3	68	69	66
4	43	81	86
5	39	52	
6	15	18	27
7	21	24	
8	32		
9	37	29	39
10	13	35	
11	53	74	
12	49	59	
13	22	24	20
14	42	51	60
15	12	10	12
16	20	33	33
17	35	28	38
18	26	10	
19	53	63	82
20	12		
21	21		
22	46	48	47
23	44	61	43
24	27	26	22
25	44	46	38
26	32	41	89
27	28	31	24
28	25	25	34
29	45	49	43
30	21	22	39
31	53	59	62
32	35	45	49
33	55	52	65
34	34	32	40
35	50	55	87
36	28	30	63
37	49	42	
38	41	68	82
39	42	78	49

Paciento Nr.	I klausimynas	II klausimynas	III klausimynas
40	34		
41	33	53	
42	14	30	49
43	40		
44	20	26	58
45	39	33	



3 pav. SF-36v2™ gyvenimo kokybės klausimyno rezultatų kitimas detoksikacijos metu (n = 30). Nustatyta statistiškai reikšminga skirtis tarp pirmojo ir antrojo klausimyno įvertinimų (p = 0,004), tarp pirmojo ir trečiojo klausimyno (p < 0,001) bei tarp antrojo ir trečiojo klausimyno (p = 0,025).

3.7. Skausmo įvertinimas prieš detoksikaciją ir po jos

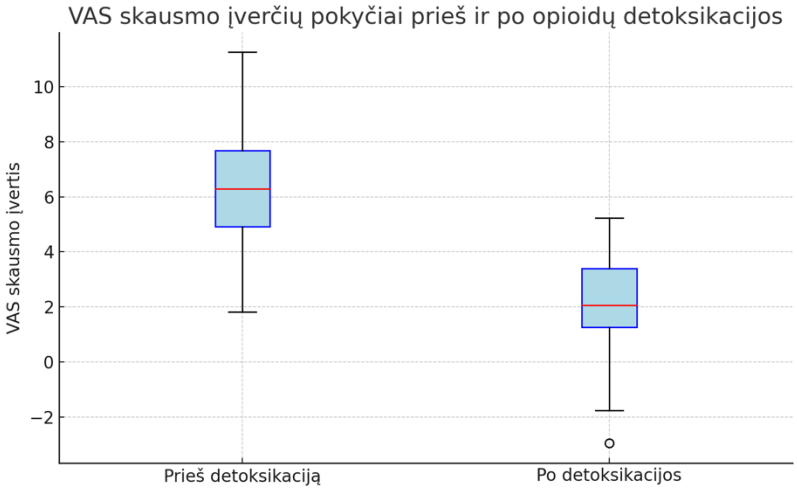
Vizualinės analoginės skalės (VAS) skausmo įverčiai buvo įvertinti 44 pacientams prieš ir po opioidų detoksikacijos. Vidutinis skausmo įvertis prieš detoksikaciją siekė 6,68 ± 2,0 balo, o po detoksikacijos – 2,17 ± 1,93 balo (p < 0,001). Šis vidutinis sumažėjimas – 4,51 ± 1,83 balo – rodo reikšmingą skausmo lygio sumažėjimą po detoksikacijos [7 lentelė], [8 lentelė], [4 pav.].

7 lentelė. Skausmo įverčių pagal VAS rezultatai prieš ir po detoksikacijos (n = 44)

Skausmo lygis (n = 44)	
VAS prieš detoksikaciją (balai ± SD)	6,68 ± 2,00
VAS po detoksikacijos (balai ± SD)	2,17 ± 1,93

8 lentelė. Skausmo įvertinimas pagal VAS kiekvienai ligai prieš ir po detoksikacijos (n = 44)

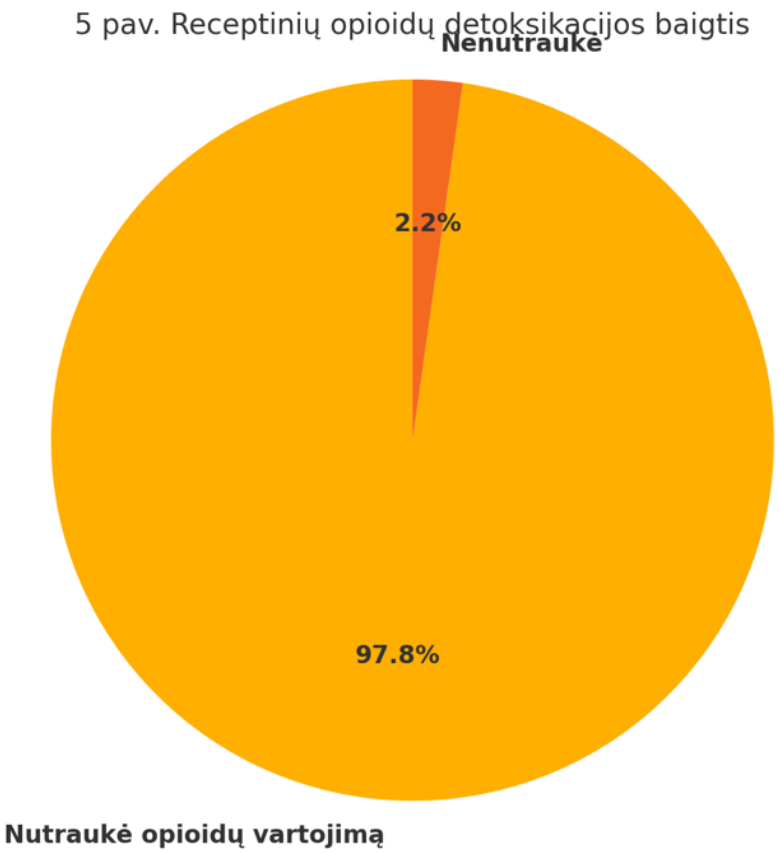
Liga	VAS prieš detoksikaciją (balai ± SD)	VAS po detoksikacijos (balai ± SD)
Onkologinė liga (n = 14)	5,9 ± 2,59	1,60 ± 1,88
Neurologinė liga (n = 14)	6,07 ± 1,55	1,78 ± 1,63
Raumenų ir skeleto liga (n = 10)	7,7 ± 2,13	2,6 ± 2,46
Reumatologinė liga (n = 2)	6,75 ± 1,06	2,5 ± 0
Virškinamojo trakto liga (n = 2)	8,5 ± 0,71	2,25 ± 2,48
Kita (n = 2)	8,5 ± 0,71	4,75 ± 1,77



4 pav. VAS skausmo įvertinimo balai prieš detoksikaciją ir po jos (n = 44)

3.8. Receptinių opioidų vartojimo nutraukimas

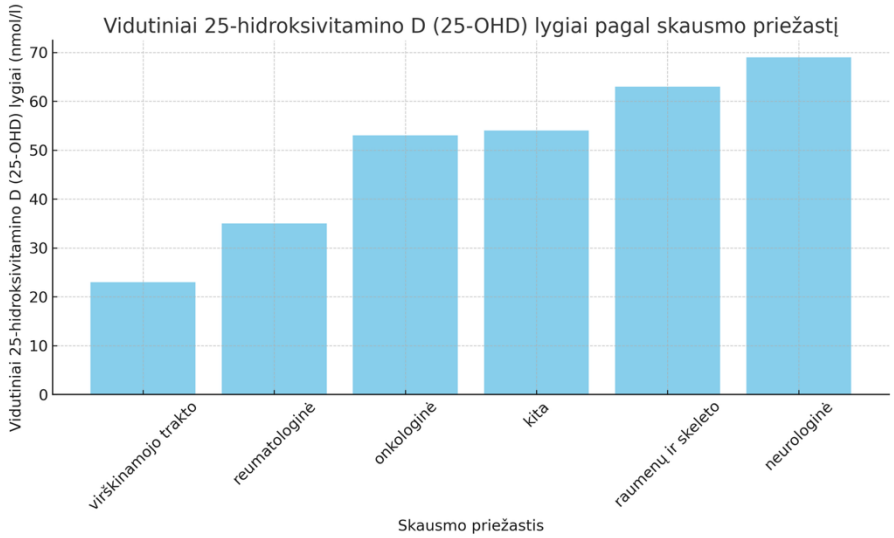
Iš 45 pacientų, net 44 (97,8 %) sėkmingai nutraukė opioidų vartojimą po detoksikacijos programos. Toks aukštas sėkmės rodiklis pabrėžia detoksikacijos proceso veiksmingumą mažinant opioidinę priklausomybę pacientams, kenčiantiems nuo lėtinio skausmo [5 pav.].



5 pav. Receptinių opioidų detoksikacijos rezultatai

3.9. Vidutiniai pradiniai 25-hidroksivitamino D (25-OHD) lygiai pagal skausmo priežastį

Bendras tiriamųjų serumo 25-OHD koncentracijos vidurkis siekė 58,3 ± 35,2 nmol/l. Dalyviai, kurių 25-OHD lygis buvo ≥75 nmol/l (n = 16), turėjo vidutinę koncentraciją – 98,39 ± 28,04 nmol/l, o tų, kurių lygis buvo <75 nmol/l (n = 29), vidutinė koncentracija sudarė 38,26 ± 17,22 nmol/l. Pažymėtina, kad net 64,4 % tiriamųjų pateko į vitamino D stokos kategoriją, apibrėžtą kaip serumo 25-OHD koncentracija mažesnė nei 75 nmol/l. 6 pav. pateikiami vidutiniai 25-hidroksivitamino D (25-OHD) lygiai (nmol/l), suskirstyti pagal skausmo priežastis.



6 pav. Vidutiniai 25-hidroksivitamino D (25-OHD) lygiai pagal skausmo priežastį

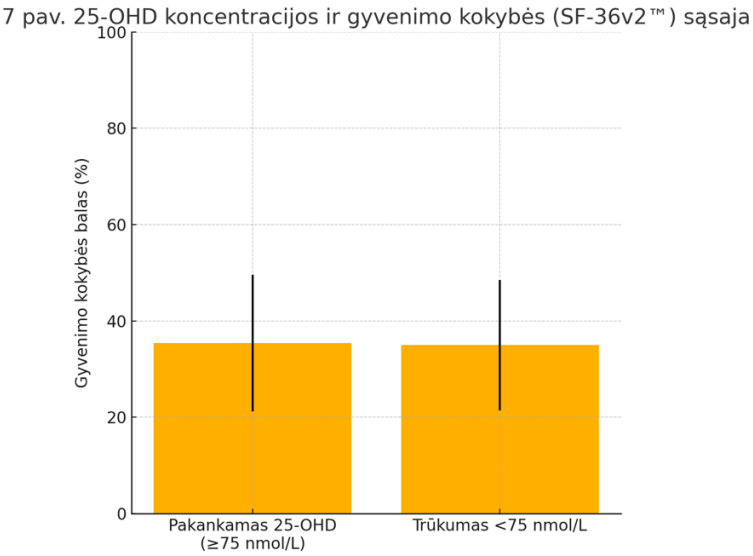
3.10. Pradinių 25-OHD lygių, skausmo intensyvumo ir gyvenimo kokybės sąsajos: regresinės analizės rezultatai

Atlikta linijinės regresijos analizė, siekiant įvertinti ryšį tarp 25-hidroksivitamino D (25-OHD) lygių (logaritmuotų), skausmo įvertinimo pagal VAS prieš opioidų detoksikaciją (inversuoto ir logaritmuoto) bei gyvenimo kokybės balų. Modelio atitikimo rodikliai parodė žemą koreliacijos koeficientą ($R = 0,123$) ir determinacijos koeficientą ($R^2 = 0,0150$), tai reiškia, kad tik 1,5 % gyvenimo kokybės klausimyno SF-36v2™ balų variacijos galima paaiškinti modelyje įtrauktomis nepriklausomomis kintamosiomis.

Modelio laisvasis narys buvo statistiškai reikšmingas ($\beta = 35,32$, $SE = 13,37$, $t = 2,642$, $p = 0,012$), rodantis, kad pradiniai gyvenimo kokybės balai reikšmingai skyrėsi nuo nulio, kai prediktoriai buvo referencinėse reikšmėse. Tačiau tiek 25-OHD lygio ($\beta = -1,79$, $SE = 7,88$, $t = -0,227$, $p = 0,821$), tiek VAS skausmo balų ($\beta = 2,73$, $SE = 3,42$, $t = 0,796$, $p = 0,430$) koeficientai nebuvo statistiškai reikšmingi, o tai leidžia daryti išvadą, kad tarp šių kintamųjų ir gyvenimo kokybės balų nebuvo reikšmingų ryšių.

3.11. Pradinių serumo 25-OHD lygių ir gyvenimo kokybės (SF-36v2™) klausimyno sąsaja

Nepriklausomų imčių t-testo rezultatai parodė, kad gyvenimo kokybės rodikliai statistiškai reikšmingai nesiskyrė tarp dalyvių, turėjusių pakankamą ir nepakankamą 25-OHD koncentraciją kraujyje. Konkrečiai, SF-36v2™ klausimyno atsakymuose, susijusiuose su gyvenimo kokybe, reikšmingų skirtumų nenustatyta (t (43) = 0,110, p = 0,913). Vidutinis skirtumas siekė 0,472 (SE = 4,286): pakankamo vitamino D lygio grupės dalyvių vidurkis buvo 35,44 (SD = 14,198), o nepakankamo - 34,97 (SD = 13,524). Šie rezultatai leidžia daryti išvadą, kad vitamino D pakankamumas neturėjo reikšmingos įtakos gyvenimo kokybės balams šioje imtyje [7 pav.].

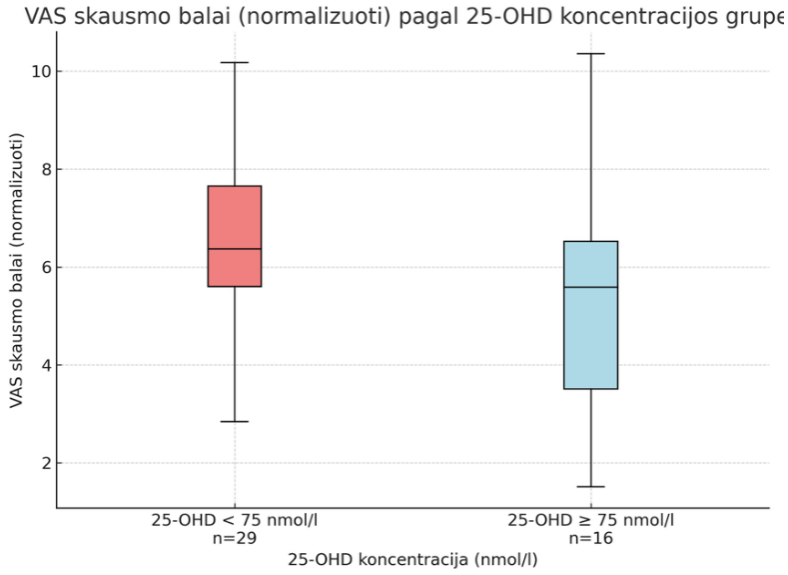


7 pav. 25-hidroksivitamino D (25-OHD) lygių ir gyvenimo kokybės (QoL), įvertintos pagal SF-36v2™ klausimyną, sąsaja

3.12. Pradinių serumo 25-OHD lygių ir skausmo intensyvumo (VAS) sąsaja

Atliktas nepriklausomų imčių t testas, siekiant įvertinti VAS skausmo balų skirtumus tarp dviejų grupių, suskirstytų pagal serumo 25-OHD koncentraciją (≥ 75 nmol/l ir < 75 nmol/l). Dalyviai, kurių 25-OHD lygis buvo ≥ 75 nmol/l (n = 16), turėjo vidutinį VAS skausmo balą - 6,06 ± 2,32, o tie, kurių lygis buvo < 75 nmol/l (n = 29), - 6,86 ± 2,10 (žr. 2 lentelę). Normalizuoti šių grupių balai sudarė atitinkamai 1,22 ± 0,571 ir 0,950 ± 0,632.

T testo rezultatai parodė, kad tarp šių dviejų grupių nebuvo statistiškai reikšmingo VAS skausmo balų skirtumo (t (43) = 1,415, p = 0,164). Vidutinis skirtumas siekė 0,269 (SE = 0,190). Tai rodo, kad nors vitamino D pakankamumo grupėje normalizuotas VAS balas buvo kiek aukštesnis (M = 1,22, SD = 0,571) nei stokos grupėje (M = 0,950, SD = 0,632), šis skirtumas nebuvo statistiškai reikšmingas. Kitaip tariant, vitamino D lygis neturėjo reikšmingos įtakos skausmo intensyvumui šioje imtyje [8 pav.].



8 pav. Pradinių 25-hidroksivitamino D (25-OHD) lygių ir skausmo intensyvumo sąsaja

3.13. Vitamino D (25-OHD) ribinės vertės (50 nmol/l) įtaka

Papildomai atlikta analizė taikant žemesnę 25-OHD ribinę vertę - 50 nmol/l, siekiant įvertinti galimus skirtumus normalizuotuose VAS skausmo baluose (logaritmuoti duomenys). Nepriklausomų imčių t testo rezultatai parodė, kad tarp pacientų, kurių 25-OHD koncentracija buvo žemesnė nei 50 nmol/l, ir tų, kurių koncentracija buvo aukštesnė, normalizuotų VAS balų skirtumai nebuvo statistiškai reikšmingi (t(43) = -0,930, p = 0,357).

Nors pagrindinė šio tyrimo hipotezė rėmėsi 75 nmol/l ribine verte, ši papildoma analizė rodo, kad net ir sumažinus slenkstinę reikšmę iki 50 nmol/l, reikšmingų skirtumų šiuo konkrečiu aspektu nenustatyta. Šis rezultatas gali reikšti, kad 25-OHD koncentracijos įtaka normalizuotiems VAS skausmo balams iš esmės nesiskiria tarp pacientų, atsižvelgiant į šią žemesnę ribą.

3.14. Pradinė vitamino D koncentracija atsižvelgiant į paciento ypatumus, vartojamus vaistus ir jų dozes

Parengta išsami santraukos lentelė [9 lentelė], kurioje pateikiami pagrindiniai tiriamųjų ypatumai. Lentelėje pateikta informacija apie skausmo priežastis, paskirtų opioidų tipus, pradinius serumo vitamino D (25-OHD) lygius bei morfino ekvivalentines dozes (MED). Ši apžvalga suteikia aiškią pagrindinių tiriamų kintamųjų apžvalgą ir leidžia įžvelgti ryšius tarp skausmo etiologijos, opioidų vartojimo pobūdžio, vitamino D būklės bei opioidų dozių ekvivalentų tiriamojoje imtyje.

9 lentelė. Duomenys apie skausmo priežastis, paskirtus opioidų tipus, pradinius serumo vitamino D (25-OHD) lygius ir morfino ekvivalentines dozes (MED)

Nr.	**Paskirto opioido tipas**	**Skausmo priežastis**	**Vitamino D koncentracija (nmol/l)**	**Morfino ekvivalentinė dozė (MED), mg/parą**
1	kodeinas	neurologinė	105.6	3.2
2	tramadolis	neurologinė	76.0	200.0
3	tramadolis	kita (nudegimai)	35.8	40.0
4	kodeinas	neurologinė	186.0	60.0
5	morfinas	onkologinė	41.8	40.0
6	tramadolis	raumenų ir skeleto	74.5	80.0
7	kodeinas	neurologinė	69.1	57.0
8	tramadolis	neurologinė	70.0	240.0
9	fentanilis	onkologinė	36.0	270.0
10	fentanilis	raumenų ir skeleto	32.0	270.0
11	kodeinas	neurologinė	39.26	9.6
12	tramadolis	neurologinė	75.0	40.0
13	metadonas	onkologinė	14.6	70.5
14	kodeinas	neurologinė	27.0	1.3
15	morfinas	raumenų ir skeleto	61.8	200.0
16	tramadolis	raumenų ir skeleto	35.0	20.0
17	fentanilis	onkologinė	75.0	550.0
18	morfinas, fentanilis	onkologinė	78.0	390.0

Nr.	Paskirto opioido tipas	Skausmo priežastis	Vitamino D koncentracija (nmol/l)	Morfino ekvivalentinė dozė (MED), mg/parą
19	tramadolis	kita (žastikaulio trauma)	39.47	40.0
20	kodeinas	neurologinė	30.9	24.0
21	fentanilis	onkologinė	27.1	202.5
22	tramadolis	raumenų ir skeleto	88.0	30.0
23	morfinas	reumatologinė	19.78	240.0
24	tramadolis	raumenų ir skeleto	103.0	160.0
25	petidinas	virškinamojo trakto	19.5	100.0
26	tramadolis	raumenų ir skeleto	79.0	15.0
27	morfinas	onkologinė	34.0	150.0
28	tramadolis	neurologinė	11.9	120.0
29	petidinas	virškinamojo trakto	26.5	100.0
30	morfinas	raumenų ir skeleto	72.0	720.0
31	morfinas	onkologinė	114.5	30.0
32	fentanilis, tramadolis	onkologinė	94.0	330.0
33	morfinas	onkologinė	114.5	30.0
34	morfinas	onkologinė	29.9	150.0
35	morfinas	reumatologinė	50.0	240.0
36	oksikodonas	raumenų ir skeleto	33.9	450.0
37	morfinas, tramadolis	onkologinė	29.8	90.0
38	kodeinas	neurologinė	95.0	16.0
39	kodeinas	neurologinė	37.89	8.0
40	tramadolis	raumenų ir skeleto	53.0	20.0
41	kodeinas	neurologinė	42.0	4.8
42	tramadolis	neurologinė	106.2	100.0
43	fentanilis, tramadolis	onkologinė	13.4	97.5

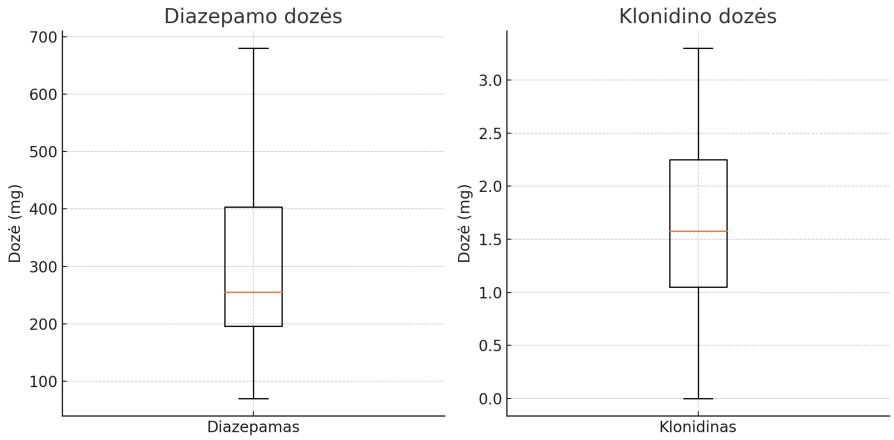
Nr.	Paskirto opioido tipas	Skausmo priežastis	Vitamino D koncentracija (nmol/l)	Morfino ekvivalentinė dozė (MED), mg/parą
44	kodeinas, morfinas, tramadolis	kita (apatinės nugaros dalies skausmas, nenustatyta patologija)	86.0	41.6
45	morfinas, fentanilis	onkologinė	39.8	240.0

3.15. Medikamentų vartojimas detoksikacijos metu

Pagrindiniai vartoti medikamentai buvo diazepamas, ilgai veikiantis benzodiazepinas, ir klonidinas, alfa-2 adrenoreceptorių agonistas. Įvertinta, kokios buvo jų bendros dozės ir kaip jos pasiskirstė tarp pacientų. Vaistai buvo skiriami siekiant palengvinti opioidinės abstinencijos simptomus ir užkirsti kelią galimoms komplikacijoms. Jų skyrimas buvo grindžiamas kasdieniu paciento būklės vertinimu pagal dvi standartizuotas skales: subjektyvią opioidų abstinencijos skalę (SOWS) ir objektyvią opioidų abstinencijos skalę (OOWS). Toks dvigubas vertinimo modelis leido tiksliai pritaikyti gydymą pagal tiek paciento nurodytus simptomus, tiek stebimus fiziologinius požymius.

Tyrime dalyvavusių 45 pacientų tarpe suminė diazepamo dozė viso detoksikacijos laikotarpio metu svyravo nuo 70 mg iki 680 mg, o standartinis nuokrypis sudarė apie 156,7 mg. Šis platus dozavimo spektras atspindi didelius individualius abstinencijos simptomų intensyvumo skirtumus ir būtinybę lanksčiai titruoti gydymą pagal simptomų dinamiką.

Klonidino dozės svyravo nuo 0 mg iki 3,3 mg, o standartinis nuokrypis - 0,92 mg. Dalis pacientų šio vaisto negavo, kas rodo jo selektyvų taikymą - tik esant autonominiams simptomams, tokiems kaip padidėjęs kraujospūdis, prakaitavimas ar tachikardija, kurie objektyviau atsispindi OOWS vertinimuose.



9 pav. Medikamentų dozių pasiskirstymas

4. IŠVADOS

4.1. Planinė opioidinė detoksikacija pacientams, patiriantiems lėtinį skausmą ir išsivysčiusią toleranciją dėl ilgalaikio opioidų vartojimo, lemia reikšmingą bendros gyvenimo kokybės pagerėjimą. Pastebėti statistiškai reikšmingi gyvenimo kokybės rodiklių pokyčiai po detoksikacijos leidžia teigti, kad, nepaisant galimų sunkumų, susijusių su opioidų nutraukimu, sėkminga detoksikacija turi apčiuopiamą teigiamą poveikį pacientų fizinei, psichologinei ir socialinei gerovei.

4.2. Vidutinė opioidų vartojimo trukmė viršijo penkerius metus, atspindėdama lėtinį skausmo pobūdį ir užsitęsusį opioidų vartojimą. Dažniausios vartojimo indikacijos buvo neurologinis, onkologinis ir nugaros skausmas. Ypač neramina opioidų skyrimas esant refrekterioms migrenoms ar onkologiniam skausmui remisijos metu, dėl priklausomybės ir hiperalgezijos rizikos. Dažniausiai skirtas receptinis opioidas buvo tramadolis, po jo - kodeinas ir morfinas. Didelis dozių kintamumas ir aukšta vidutinė MED rodo individualizuotą skyrimą, bet kartu kelia klausimų dėl saugumo ir gydymo gairių laikymosi.

4.3. Planinė opioidinė detoksikacija gali reikšmingai sumažinti skausmo intensyvumą (vidutinis VAS sumažėjimas - 4,51 balo) ir pagerinti jų būklę be nuolatinio opioidų vartojimo. Aukštas detoksikacijos sėkmės rodiklis (97,78 %) ir trumpa trukmė (vidutiniškai 9,2 dienos) patvirtina metodo veiksmingumą bei toleravimą.

4.4. Nors šiame tyrime nenustatyta statistiškai reikšmingos sąsajos tarp pradinės vitamino D (25-OHD) koncentracijos, skausmo intensyvumo ir gyvenimo kokybės, pastebėta tendencija, kad pacientai su aukštesniu 25-OHD kiekiu jautė mažesnį skausmą. Tai leidžia įtarti galimą vitamino D vaidmenį, kurį verta tirti toliau. Visgi pagrindiniu veiksniu, lėmusiu skausmo sumažėjimą ir gyvenimo kokybės pagerėjimą, išlieka opioidų nutraukimas.

5. PRAKTINĖS REKOMENDACIJOS

5.1. Tikslinga apsvarstyti planinės opioidinės detoksikacijos galimybę pacientams, patiriantiems lėtinį skausmą ilgalaikio opioidų vartojimo atvejais.

Opioidinė detoksikacija gali reikšmingai pagerinti gyvenimo kokybę ir skausmo suvokimą pacientams, ilgą laiką vartojusiems opioidus. Gydytojai turėtų įvertinti pacientų toleranciją opioidams, opioidų sukeliamą hiperalgeziją bei sumažėjusį analgezinį veiksmingumą ir, esant tinkamoms aplinkybėms, svarstyti mediciniškai prižiūrimą detoksikacijos procesą. Atsižvelgiant į tai, kad detoksikacija sėkmingai buvo įgyvendinta vidutiniškai per 9,2 dienos, ši intervencija atrodo įgyvendinama pacientams, atitinkantiems kriterijus.

5.2. Prioritetą teikti neopioidinėms skausmo valdymo strategijoms.

Kadangi po detoksikacijos skausmo lygis reikšmingai sumažėjo, gydytojai turėtų teikti pirmenybę neopioidiniams analgetikams, intervencinėms skausmo valdymo procedūroms, kineziterapijai bei psichologinėms intervencijoms. Asmeniškai pritaikyti gydymo planai gali padėti pasiekti ilgalaikį skausmo palengvėjimą kartu sumažinant priklausomybės nuo opioidų riziką.

5.3. Stiprinti opioidų skyrimo praktiką ir stebėseną.

Tyrimas atskleidė, kad daugelis pacientų vartojo opioidus ilgiau nei penkerius metus, dažnai dėl būklių, kurioms ilgalaikis vartojimas nėra pagrįstas šiuo metu galiojančiomis klinikinėmis gairėmis. Tramadolio, kodeino ir morfino vartojimo dominavimas bei plačiai paplitęs nereceptinio kodeino savarankiškas vartojimas pabrėžia griežtesnės opioidų skyrimo kontrolės būtinybę. Gydytojai turėtų periodiškai peržiūrėti opioidų terapiją, siekdami įvertinti jos būtinumą; vengti ilgalaikių opioidų receptų skyrimo, kai

egzistuoja veiksmingos alternatyvos; laikytis klinikinių gairių, kad būtų užtikrintas saugesnis skyrimas ir sumažinta priklausomybės rizika.

5.4. Pagerinti detoksikacijos procedūrų prieinamumą.

Tyrimo rezultatai patvirtina standartizuotų opioidų detoksikacijos protokolų įgyvendinamumą ir veiksmingumą – net 97,78 % dalyvių nutraukė opioidų vartojimą. Sveikatos priežiūros sistemos turėtų didinti detoksikacijos paslaugų prieinamumą ir integruoti jas į įprastines lėtinio skausmo valdymo strategijas.

5.5. Stiprinti pacientų švietimą ir bendro sprendimų priėmimo procesą.

Atsižvelgiant į plačiai paplitusią pacientų baimę, kad nutraukus opioidų vartojimą skausmas gali sustiprėti, gydytojai turėtų aktyviai teikti išsamią konsultaciją, padedančią paneigti klaidingus įsitikinimus. Tyrimas parodė, kad nutraukus opioidų vartojimą dažnai ne padidėja, o sumažėja skausmo intensyvumas. Veiksmingas bendravimas turėtų apimti aiškų švietimą apie opioidų detoksikacijos naudą, alternatyvių skausmo valdymo metodų aptarimą bei patikinimą, kad nutraukimo simptomai gali būti veiksmingai kontroliuojami struktūruotoje aplinkoje.

5.6. Spręsti nereceptinių opioidų vartojimo problemą.

Tyrime dažnai fiksuotas nereceptinio kodeino vartojimas rodo spragas reguliavimo priežiūroje ir ribotą prieigą prie tinkamo skausmo valdymo. Gydytojai turėtų būti budrūs dėl savarankiško gydymosi požymių ir taikyti priemones, kurios: gerintų pacientų prieigą prie reguliuojamų skausmo valdymo galimybių; sustiprintų opioidų vartojimo rizikos vertinimą tarp lėtiniu skausmu sergančių pacientų; užtikrintų, kad gydymas būtų pagrįstas įrodymais ir prižiūrimas specialistų, o ne paremtas nelegaliais ar nekontroliuojamais opioidų šaltiniais.

5.7. Iš naujo įvertinti vitamino D vaidmenį skausmo valdyme.

Nors pradiniai vitamino D kiekiai reikšmingai nekoreliavo su skausmo įverčiais ar gyvenimo kokybės rodikliais, stebėta nedidelė tendencija, jog aukštesnė 25-OH vitamino D koncentracija gali būti susijusi su mažesniu skausmo lygiu. Nors šis tyrimas nepateikia galutinių įrodymų, pagrindžiančių rutininį vitamino D papildų vartojimą lėtinio skausmo valdyme, būtini tolesni

tyrimai. Gydytojai gali apsvarstyti vitamino D trūkumo sekimą tam tikrose pacientų grupėse, ypač jei įtariama hipovitaminozė - pavyzdžiui, sergantiems osteomaliacija, osteoporoze ar turintiems kitų žinomų rizikos veiksnių, susijusių su mažais 25-OHD lygiais.

5.8. Atskirti lėtinio skausmo valdymą nuo paliatyviosios pagalbos.

Nors opioidinė detoksikacija pasirodė naudinga pacientams, patiriantiems lėtinį neonkologinį skausmą, svarbu aiškiai atskirti šią pacientų grupę nuo paliatyviosios bei gyvenimo pabaigos priežiūros pacientų, kuriems ilgalaikė opioidų terapija išlieka kliniškai pagrįsta. Gydytojai turėtų taikyti individualizuotus gydymo sprendimus, užtikrinančius, kad opioidų terapija būtų tęsiama tais atvejais, kai ji būtina, tačiau vengti nepagrįsto ilgalaikio opioidų vartojimo pacientams, kuriems gali būti tinkamesnės alternatyvios skausmo valdymo strategijos.

6. TYRIMO TRŪKUMAI

Nors šio tyrimo rezultatai yra perspektyvūs, būtina atkreipti dėmesį į keletą apribojimų. Pirma, imties dydis buvo palyginti nedidelis, o tyrimas atliktas viename centre, todėl gautų rezultatų pritaikomumas platesnei populiacijai gali būti ribotas. Be to, stebėjimo laikotarpis apsiribojo šešiais mėnesiais - ilgalaikiai rezultatai nebuvo vertinti.

Tyrimas taip pat neanalizavo, ar po pradinio šešių mėnesių detoksikacijos laikotarpio pacientams pagerėjo VAS skausmo įverčiai ar sumažėjo opioidų poreikis. Verta pažymėti, kad VAS skausmo skalės duomenys po šio laikotarpio nebuvo renkami, nes juos galėjo iškreipti papildomi veiksniai, įskaitant kitų NVNU vartojimą.

Pradinės vitamino D (25-OHD) koncentracijos buvo išmatuotos, tačiau po detoksikacijos jos nebuvo vertintos, todėl negalima nustatyti pokyčių vitamino D lygiuose ar jų galimos įtakos skausmo rodikliams viso proceso metu. Nors VAS metodas iš prigimties yra subjektyvus, jis plačiai pripažįstamas ir validuotas skausmo intensyvumo vertinimo įrankis, todėl jo naudojimas šiame tyrime laikytinas tinkamu, nepaisant metodo ribotumų.

Be to, skirtingose klinikinėse gairėse esantys nevienodi vitamino D stokos ir pakankamumo apibrėžimai kelia iššūkių interpretuojant 25-OHD lygius, todėl ateities tyrimuose būtina siekti vieningų vertinimo kriterijų.

Šie tyrimo apribojimai pabrėžia būtinybę tolesniems moksliniams tyrimams, siekiant tiksliau suprasti analizuojamų rodiklių tarpusavio sąsajas ir kurti veiksmingesnes lėtinio skausmo valdymo strategijas šiai pacientų grupei.

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APPENDICES

1. APPROVAL FROM THE VILNIUS REGIONAL COMMITTEE ON BIOMEDICAL RESEARCH ETHICS

VILNIAUS REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS
sui generis darinys prie VILNIAUS UNIVERSITETO

LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2019-10-08 Nr.2019/10-1153-644

Tyrimo pavadinimas:

Priklausomybė receptiniams opioidams: detoksikacija ir išeitys

Protokolo Nr.:	01
Versija:	2.0
Data:	2019 09 12
Informuoto asmens sutikimo forma:	3 2019 09 12
Pagrindinis tyrėjas:	**Gabija Laubner**
Įstaigos pavadinimas: Adresas:	Respublikinė Vilniaus universitetinė ligoninė Šiltnamių g. 29, Vilnius
Leidimas galioja iki:	**2023 12**

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 2019/10), vykusio 2019 m. spalio 8 d. sprendimu.

Pirmininkas prof. dr. (HP) Saulius Vosylius

Viešoji įstaiga
Universiteto g. 3
01513 Vilnius

Duomenys kaupiami ir saugomi
Juridinių asmenų registre
Kodas 211950810

Komiteto duomenys:
M. K. Čiurlionio g. 21, LT-03101 Vilnius
Tel. (8 5) 268 6998, el. p. rbtek@mf.vu.lt

2. OPIOID DETOXIFICATION PROTOCOL USED IN REPUBLIC VILNIUS UNIVERSITY HOSPITAL

PATVIRTINTA
Viešosios įstaigos Respublikinės Vilniaus universitetinės ligoninės direktoriaus
2019 m. balandžio 2 d. įsakymu Nr. V- 64

PLANINĖS STACIONARINĖS DETOKSIKACIJOS NUO OPIOIDŲ (RECEPTINIŲ IR NELEGALIŲ) PROTOKOLAS

1. PASKIRTIS IR TAIKYMO SRITIS

Protokolas yra skirtas aprašyti Toksikologijos centre atliekamą detoksikacijos nuo opioidų (receptinių ir nelegalių) procesą priklausomiems pacientams bei užtikrinti, kad būtų laikomąsi šios proceso atlikimo tvarkos.

2. PROTOKOLO OBJEKTAS

"Greitoji opioidinė detoksikacija" yra metodika, pagreitinanti opioidų vartojimo nutraukimą, vartojant opioidų antagonistus, kartu palengvinanti pacientų būklę ir leidžianti jiems geriau toleruoti detoksikacijos procedūrą. Esant priklausomybei nuo opioidų, kai sumažinama opioido dozė arba nutraukiamas vartojimas, pasireiškia abstinencijos reiškiniai, kurių sunkumas vertinamas pagal subjektyvius ir objektyvius požymius, naudojant subjektyvią opioidinės abstinencijos skalę (SOWS, 2 lentelė) ir objektyvią opioidinės abstinencijos skalę (OOWS, 1 lentelė). Vartojant nelegalius opioidus arba ilgiau nei 3 – 4 savaites vartojant receptinius opioidus terapinėmis dozėmis, nutraukus jų vartojimą, gali pasireikšti abstinencijos klinika: nerimas, nemiga, irzlumas, pablogėjusi atmintis, padidėjęs jautrumas, galvos skausmas, regos haliucinacijos, raumenų, sąnarių ir pilvo skausmai, tremoras, prakaitavimas, pykinimas, viduriavimas. Staigus opioidų nutraukimas po ilgalaikio (> 6 mėnesius trunkančio) vartojimo gali sukelti traukulius ir psichozę.

3. SANTRUMPOS IR SĄVOKOS

Detoksikacija – saugus farmakologinis priklausomybę sukeliančios medžiagos vartojimo nutraukimas, siekiant sumažinti abstinencijos reiškinius.
NVNU – nesteroidiniai vaistai nuo uždegimo.
OOWS – objektyvi opioidinės abstinencijos skalė.
SOWS – subjektyvi opioidinės abstinencijos skalė.
TC – VšĮ Respublikinės Vilniaus universitetinės ligoninės Toksikologijos centras.
TLK-10-AM – Pasaulio sveikatos organizacijos Tarptautinė statistinė ligų ir sveikatos sutrikimų klasifikacija, dešimtasis leidimas, Australijos modifikacija.

4. ATSAKOMYBĖ

4.1. Audito skyriaus vedėjas atsako už Protokolo taikymo priežiūrą.
4.2. TC vadovas atsako už šio protokolo peržiūrą ne rečiau kaip kartą per trejus metus, užtikrinant įrodymais grįstos medicinos reikalavimų laikymąsi ir jo pakeitimų patvirtinimą bei reikalavimų vykdymo kontrolę.
4.3. Ūminių apsinuodijimų ir Toksikologijos reanimacijos ir intensyvios terapijos skyrių vedėjas atsako už šio protokolo vykdymo kontrolę Ūminių apsinuodijimų skyriuje ir Toksikologijos reanimacijos ir intensyvios terapijos skyriuje.
4.4. Konkrečių darbuotojų atsakomybė proceso eigoje nurodyta protokolo veiksmų eigos aprašyme ir "Ūmių apsinuodijimų skyriaus darbo reglamente".

5. PLANINĖS STACIONARINĖS DETOKSIKACIJOS NUO OPIOIDŲ (RECEPTINIŲ IR NELEGALIŲ) VEIKSMŲ APRAŠYMAS

5.1. **Indikacijos**

Remiantis TLK-10-AM diagnozuota priklausomybė nuo opioidų ir motyvuotas paciento sprendimas nutraukti arba sumažinti opioidų vartojimą.

5.2. **Kontraindikacijos**

Negydoma alkoholinė priklausomybė, nepakankama paciento motyvacija nutraukti arba sumažinti opioidų vartojimą, sunki somatinė patologija, apribojanti galimybę atlikti detoksikacijos procedūrą.

5.3. **Planinės stacionarinės detoksikacijos nuo opioidų (receptinių ir nelegalių) eiga:**

5.3.1. **trukmė:** 5 – 7 dienos, receptinių opioidų atveju – iki 10 dienų;

5.3.2. **farmakologinis gydymas:**

5.3.2.1. stabilizacijos arba opiodo nutraukimo fazė: vartojamo opioido nutraukimas arba opioido dozė keičiama į ekvivalentinę morfino dozę (2 priedas). Trukmė 24 – 48 val.;

5.3.2.2. opioidinės abstinencijos simptomatikos korekcija: skiriami centrinio veikimo antihipertenziniai vaistai (klonidinas), benzodiazepinai (diazepamas, lorazepamas), haloperidolis, NVNU ir kristaloidiniai tirpalai iki 1500 ml per parą. Trukmė 48 val. Abstinencija vertinama naudojantis SOWS (2 lentelė) ir OOWS (1 lentelė) skalėmis 3 lentelėje "Abstinencijos sunkumo skalių vertinimo laikas" nurodytu laiku;

5.3.2.3. antagonistų įvedimas: 4 – 5 parą pacientui skiriamas naltreksonas pagal schemą, pradedant indukciją nuo itin mažų 50 µg dozių, jas palaipsniui didinant iki suminės 12,5 mg dozės. Trukmė 12 – 16 valandų. Kiti vaistai, vartojami abstinencijos reiškiniams palengvinti: antidepresantai, antipsichotikai (depresijai, miego, nerimo sutrikimams), β-adrenoblokatoriai (tachikardijai, tremorui), gabapentinas (nerimui, potraukio vartoti numalšinimui). Receptinius opioidus vartojantiems pacientams antagonistų vartoti nereikia.

5.3.3. **psichologinė pagalba**.

5.4. **Gydymas po stacionarinės detoksikacijos**

Priklausomai nuo išlikusių paciento skundų (nemiga, nerimas), ambulatoriniam vartojimui skiriami vaistai (antidepresantai, antipsichotikai). Motyvuotiems ir artimųjų palaikymą turintiems pacientams skiriamas naltreksonas. Rekomenduojamos planinės klinikinio toksikologo ir psichologo konsultacijos, esant galimybei – ilgalaikė reabilitacija terapinėje bendruomenėje.

6. DOKUMENTACIJA

Pacientams, kuriems atliekama planinė stacionarinė detoksikacija nuo opioidų (receptinių ir nelegalių), pildoma visa įprastinė dokumentacija Lietuvos Respublikos įstatymų, Sveikatos apsaugos ministerijos įsakymų ir VšĮ Respublikinės Vilniaus universitetinės ligoninės direktoriaus įsakymų bei vidaus dokumentų numatyta tvarka. Užpildytos OOWS ir SOWS skalės klijuojamos į paciento ligos istoriją pagal ligoninės dokumentacijos tvarkymo tvarką.

7. PRIEDAI

7.1. **1 lentelė**. Objektyvi opioidinės abstinencijos skalė (OOWS).

7.2. **2 lentelė**. Subjektyvi opioidinės abstinencijos skalė (SOWS).

7.3. **3 lentelė**. Abstinencijos sunkumo skalių vertinimo laikas.

7.4. **4 lentelė**. Skirtingų receptinių opioidų dozių morfino ekvivalentai.

Planinės stacionarinės detoksikacijos nuo opioidų (receptinių ir nelegalių) protokolo

1 priedas

OBJEKTYVI OPIOIDINĖS ABSTINENCIJOS SKALĖ (OOWS)

Eil. Nr.	Požymiai	Vertinimas	Balai
1.	Žiovulys	0 – nežiovauja 1 – žiovauja 1 ir daugiau kartų	
2.	Slogavimas	0 – < 3 šnirpštelėjimai 1 – > 3 šnirpštelėjimai	
3.	"Žąsies oda" (vertinti rankas)	0 – nėra 1 – yra	
4.	Prakaitavimas	0 – nėra 1 – yra	
5.	Ašarojimas	0 – nėra 1 – yra	
6.	Rankų tremoras	0 – nėra 1 – yra	
7.	Midriazė	0 – nėra 1 – ≥3 mm skersmens	
8.	Karščio ir šalčio bangos	0– nėra 1 – šiurpulys / susiriečia, kad sušiltų	
9.	Negalėjimas nustygti vietoje	0 – nėra 1 – dažnai kaitalioja pozas	
10.	Vėmimas	0 – nėra 1 – yra	
11.	Raumenų trūkčiojimai	0 – nėra 1 – yra	
12.	Pilvo spazmai	0 – nėra 1 – laikosi už pilvo	
13.	Nerimas	0– nėra 1 – vidutinis arba labai išreikštas	
Bendra balų suma:			

Planinės stacionarinės detoksikacijos nuo opioidų (receptinių ir nelegalių) protokolo

2 priedas

SUBJEKTYVI OPIOIDINĖS ABSTINENCIJOS SKALĖ (SOWS)

Eil. Nr.	Simptomas	Visiškai ne (0 balų)	Truputį (1 balas)	Vidutiniškai (2 balai)	Ganėtinai stipriai (3 balai)	Labai stipriai (4 balai)
1.	Esu sunerimęs					
2.	Mane ima žiovulys					
3.	Prakaituoju					
4.	Mano akys ašaroja					
5.	Mano nosis "bėga"					
6.	Mano oda pašiurpusi					
7.	Drebu					
8.	Jaučiu karščio bangas					
9.	Jaučiu šalčio bangas					
10.	Man gelia kaulus ir raumenis					
11.	Negaliu išbūti vienoje vietoje					
12.	Jaučiu šleikštulį					
13.	Vemiu					
14.	Mano raumenys trūkčioja					
15.	Jaučiu pilvo spazmus					
16.	Jaučiuosi išsekęs					
Stulpelio suma:						
Bendra balų suma:						

Planinės stacionarinės detoksikacijos nuo opioidų (receptinių ir nelegalių) protokolo

3 priedas

ABSTINENCIJOS SUNKUMO SKALIŲ VERTINIMO LAIKAS

Para	I		II		III		IV	
Valanda	10:00	20:00	10:00	20:00	10:00	20:00	10:00	20:00
SOWS	+	+	+	+	+	+	+	+
OOWS	+	+	+	+	+	+	+	+

Planinės stacionarinės detoksikacijos nuo opioidų (receptinių ir nelegalių) protokolo

4 priedas

SKIRTINGŲ RECEPTINIŲ OPIOIDŲ DOZIŲ MORFINO EKVIVALENTAI

Receptiniai opioidai	Dozė ekvivalentiška Sol. Morphyni sulphate 10 mg i/m	
	Peroralinė dozė (PO)	Injekcinė dozė (IM/IV/SC)
Morfinas	30 mg (60 mg)	10 mg
Kodeinas	180 – 200 mg	120 mg
Fentanilis	Netaikomas	0,1 mg (100 mcg)
Hidrokodonas	30 mg	Netaikomas
Hidromorfonas	7,5 mg	1,3 – 1,5 mg
Levorfanolis	4 mg	2 mg
Meperidinas	300 mg	75 – 100 mg
Metadonas	10 – 20 mg	5 – 10 mg
Oksikodonas IR[1]	20 – 30 mg	Netaikomas
Oksikodonas CR[2]	40 mg	Netaikomas
Oksimorfonas	10 mg	1 mg

[1]IR – greito atpalaidavimo
[2]CR – kontroliuojamo atpalaidavimo

3. QUALITY OF LIFE SF-36V2™ QUESTIONNAIRE IN LITHUANIAN LANGUAGE

JŪSŲ SVEIKATA IR GEROVĖ

Šiais klausimais norima išsiaiškinti Jūsų požiūrį į savo sveikatą. Ši informacija padės suprasti kaip jaučiatės ir kaip jums pavyksta užsiimti įprasta veikla.
Ačiū, kad dalyvaujate apklausoje!

Prašome atsakyti į kiekvieną klausimą pažymint vieną ☒ langelį, geriausiai atitinkantį Jūsų atsakymą.

1. Jūsų sveikata Jūsų nuomone apskritai yra:

Puiki	Labai gera	Gera	Nebloga	Bloga
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Kaip apskritai vertintumėte <u>dabartinę</u> savo sveikatą <u>lygindami su sveikata prieš metus</u>?

Dabar daug geresnė nei prieš vienerius metus	Dabar šiek tiek geresnė nei prieš vienerius metus	Maždaug tokia pati kaip prieš vienerius metus	Dabar šiek tiek blogesnė nei prieš vienerius metus	Dabar daug blogesnė nei prieš vienerius metus
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Šiais klausimais teiraujamasi apie veiklą, kuria užsiimtumėte įprastą dieną. Ar jūsų dabartinė sveikata varžo šią veiklą? Jei taip, tai prašome nurodyti kaip:**

	Taip, labai varžo	Taip, truputį varžo	Ne, visai nevaržo
a Energinga veikla, tokia kaip bėgimas, sunkių daiktų kilnojimas, daug jėgų reikalaujantis sportavimas	☐ 1	☐ 2	☐ 3
b Nuosaiki veikla, tokia kaip: patraukti stalą, stumti dulkių siurblį, dirbti sode arba važiuoti dviračiu	☐ 1	☐ 2	☐ 3
c Kilnoti arba nešti maisto pirkinius	☐ 1	☐ 2	☐ 3
d Užlipti keletą laiptų maršų	☐ 1	☐ 2	☐ 3
e Užlipti vieną laiptų maršą	☐ 1	☐ 2	☐ 3
f Pasilenkti ar klauptis	☐ 1	☐ 2	☐ 3
g Nueiti daugiau nei kilometrą	☐ 1	☐ 2	☐ 3
h Nueiti kelis šimtus metrų	☐ 1	☐ 2	☐ 3
i Nueiti vieną šimtą metrų	☐ 1	☐ 2	☐ 3
j Maudytis ar apsirengti	☐ 1	☐ 2	☐ 3

4. Ar dažnai per pastarąsias 4 savaites susidūrėte su kuriais nors išvardytais sunkumais darbe ar kitoje jums įprastoje kasdienėje veikloje dėl fizinės sveikatos problemų?

	Visą laiką	Labai dažnai	Kartais	Beveik niekada	Niekada
a Mažiau laiko skyrėte darbui ar kitai veiklai	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Atlikote mažiau nei norėtumėte	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Buvote apribota (-as) kažkokiamedarbe arba kitoje veikloje	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Kilo sunkumų atliekant darbą ar kitoje veikloje (pavyzdžiui, reikėjo daugiau pastangų)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. Ar dažnai per pastarąsias 4 savaites susidūrėte su kuriais nors išvardytais sunkumais (pavyzdžiui, prislėgta nuotaika ar nerimas) darbe ar kitoje jums įprastoje kasdienėje veikloje dėl bet kokių emocinių problemų?

	Visą laiką	Labai dažnai	Kartais	Beveik niekada	Niekada
a Mažiau laiko skyrėte darbui ar kitai veiklai	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Atlikote mažiau nei norėtumėte	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Atlikote darbą ar užsiėmėte kita veikla ne taip rūpestingai, kaip įprasta	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. Kaip per <u>pastarąsias 4 savaites</u> Jūsų fizinė sveikata arba emocinės problemos trukdė Jūsų normaliai visuomeninei veiklai kartu su šeima, draugais, kaimynais arba bendrų interesų grupėmis?

Visiškai ne	Truputį	Vidutiniškai	Gerokai	Ypatingai
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. Kokį <u>kūno</u> skausmą Jūs patyrėte per <u>pastarąsias 4 savaites</u>?

Jokio	Labai nesmarkų	Nesmarkų	Vidutinišką	Smarkų	Labai smarkų
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. Kaip per <u>pastarąsias 4 savaites</u> <u>skausmas</u> trukdė Jūsų normaliam darbui (apimant darbą ne namuose ir namų ruošą)?

Visiškai ne	Truputį	Vidutiniškai	Gerokai	Ypatingai
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. **Šie klausimai yra apie tai, kaip Jūs jautėtės ir kaip klostėsi Jūsų reikalai per <u>pastarąsias 4 savaites</u>. Kiekvienam klausimui prašome pasirinkti vieną atsakymą, tiksliausiai apibūdinantį Jūsų savijautą. Kiek laiko per <u>pastarąsias 4 savaites</u>…**

	Visą laiką	Labai dažnai	Kartais	Beveik niekada	Niekada
a Ar jautėtės gyvybingas?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Buvote labai susinervinusi (-ęs)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Jūs jautėtės taip nusiminusi (-ęs), jog niekas negalėjo pakelti Jums nuotaikos?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Jūs jautėtės rami (-us) ir taiki (-us)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Jūs buvote labai energinga (-as)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Jautėtės nusiminusi (-ęs) ir prislėgta (-as)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Jūs jautėtės išsekusi (-ęs)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Buvote laiminga (-as)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Jūs jautėtės pavargusi (-ęs)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. **Kiek laiko per <u>pastarąsias 4 savaites</u> Jūsų <u>fizinė sveikata arba emocinės problemos</u> trukdė Jūsų visuomeninei veiklai (tokiai kaip draugų, giminaičių lankymas ir pan.)?**

Visą laiką	Labai dažnai	Kartais	Beveik niekada	Niekada
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. Ar Jums yra TEISINGAS arba NETEISINGAS <u>kiekvienas</u> iš šių teiginių?

	Neabejotinai teisingas	Labiau teisingas nei neteisingas	Nežinau	Labiau neteisingas nei teisingas	Neabejotinai neteisingas
a Atrodo, kad aš susergu šiek tiek lengviau nei kiti žmonės	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Aš esu tokia (toks) pat sveika (-as) kaip bet kuris mano pažįstamas	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Aš manau, kad mano sveikata pablogės	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Mano sveikata yra puiki	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Ačiū, kad atsakėte į šiuos klausimus!

ABOUT THE AUTHOR

NAME: Gabija Laubner – Sakalauskienė

CONTACT INFORMATION:

- Clinic of Anesthesiology and Intensive Care, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania
- Email: gabija.laubner@mf.vu.lt, gabija.laubner@gmail.lt
- Mob. ph. +37069844708

NATIONALITY: Lithuanian

EDUCATION:

- 1998 – 2004 Vilnius University, Faculty of Medicine, MD
- 2004 – 2005 Vilnius University, Faculty of Medicine, General Internship
- 2005 – 2008 Vilnius University, Faculty of Medicine, Residency of Clinical Toxicology
- 2008 – 2010 Vilnius University, Faculty of Medicine, Residency of Anesthesiology and Intensive Care

CURRENT WORKPLACE:

- Republican Vilnius University Hospital – Head of the Acute Poisoning, Toxicology and Intensive Care and Resuscitation Units; doctor anesthesiologist-intensivist; clinical toxicology doctor
- Vilnius University, Faculty of Medicine, Clinic of Anesthesiology and Intensive Care – Junior Lecturer and Supervisor of Medical Residents.

SCIENTIFIC ASSOCIATIONS

- Member of European Association of Poisons Centers and Clinical Toxicologists
- Member of Lithuanian Clinical Toxicology Association
- Member of Lithuanian Society of Parenteral and Enteral Nutrition
- Member of Lithuanian Society of Anesthesiology and Intensive care

SCIENTIFIC INTERESTS:

Acute intoxications, toxicological intensive care, chemical dependences, methods of rapid drug detoxification, renal replacement methods, clinical nutrition.

PUBLICATIONS:

- Griškaitė, P., Kvaščevičienė, E., & Laubner Sakalauskienė, G. (2025). Cocaine-Induced Posterior Reversible Encephalopathy Syndrome (PRES): A Case Report Highlighting Neurological and Clinical Outcomes. *Acta Medica Lituanica*, *32*(1), 201-209. https://doi.org/10.15388/Amed.2025.32.1.20
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- Laubner Sakalauskienė, G., Stražnickaitė, I., Miškinytė, S., Zdanavičius, L., Šipylaitė, J., & Badaras, R. (2025). Baseline Vitamin D Levels on Quality of Life and Pain Perception Among Patients with Chronic Pain with Long-Term Prescription Opioid Use: A Prospective Study. *Journal of clinical medicine*, *14*(2), 645. https://doi.org/10.3390/jcm14020645
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- Martyna Jauniškytė, Unė Jokimaitytė, Gabija Laubner, Lina Radevičiūtė and Robertas Badaras Profile of Patients Presenting with Acute Seizures: Is Alcohol-Related Seizures a Big Problem in Lithuania?, EC Neurology 12.9 (2020): 122-130.
- Laubner Gabija, Gintautaitė Gabija, Badaras Robertas Challenges in the diagnostics and management of hydrochlorothiazide-induced severe hyponatremia in a habitual beer drinker, Acta medica Lituanica Vol 27, No 1 (2020)

APIE AUTORĘ

VARDAS, PAVARDĖ: Gabija Laubner Sakalauskienė

INFORMACIJA KONTAKTAMS:
Telefonas +37069844708
El. pašto adresas: gabija.laubner@mf.vu.lt, gabija.laubner@gmail.com

DABARTINĖ DARBOVIETĖ IR PAREIGOS

- Respublikinė Vilniaus universitetinė ligoninė, Ūminių apsinuodijimų ir Toksikologijos reanimacijos ir intensyvios terapijos skyrių vedėja, gydytoja anesteziologė reanimatologė, klinikinės toksikologijos gydytoja
- Vilniaus Universitetas Medicinos fakultetas, Anesteziologijos ir reanimatologijos klinika, jaun. asistentė ir gydytojų rezidentų vadovė

VEIKLOS SRITIS, NURODYTA LICENCIJOJE, LICENCIJOS DATA BEI NUMERIS

- klinikinė toksikologija MPL 10901, išduota 2008-06-25
- anesteziologija reanimatologija MPL 15955, išduota 2010-07-07

IŠSILAVINIMAS

- 2021 – 2025 Doktorantūros studijos Vilniaus Universitete
- 2008 – 2010 Vilniaus Universitetas, Medicinos fakultetas, anesteziologijos ir reanimatologijos rezidentūra
- 2005 – 2008 Vilniaus Universitetas, Medicinos fakultetas, klinikinės toksikologijos rezidentūra
- 2004 – 2005 Vilniaus Universitetas, Medicinos fakultetas, internatūra
- 1998 – 2004 Vilniaus Universitetas, Medicinos fakultetas, gydomosios medicinos studijos
- 1986 – 1998 Vilniaus Radvilų vidurinė mokykla

DARBO PATIRTIS

2015 11 – iki dabar	Respublikinė Vilniaus Universitetinė ligoninė, Ūminių apsinuodijimų ir Toksikologijos RIT skyrių vedėja

2010 09 – iki dabar	Vilniaus Universitetas, Medicinos fakultetas, jaun. asistentė, rezidentų vadovė
2010 07 – iki dabar	Respublikinė Vilniaus Universitetinė ligoninė, gydytoja anesteziologė reanimatologė
2008 06 – iki dabar	Respublikinė Vilniaus Universitetinė ligoninė, klinikinės toksikologijos gydytoja
2007 04 – 2015 11	Apsinuodijimų kontrolės ir informacijos biuras, Ektremalių sveikatai situacijų centras, specialistė toksikologė
2006 03 – 2008 06	Respublikinė Vilniaus Universitetinė ligoninė, gydytoja asistentė

MOKSLINĖS DRAUGIJOS

- 2020 05 – 2024 05 EAPCCT (European Association of Poisons Centers and Clinical Toxicologists) valdybos narė
- 2018 – 2021 Pasaulio sveikatos organizacijos (PSO) ekspertė
- 2017 – iki dabar European Association of Poisons Centers and Clinical Toxicologists (EAPCCT) narė
- 2014 – 2021 European Society of Intensive Care Medicine narė
- 2012 – 2022 European Society of Clinical Nutrition and Metabolism narė
- 2010 – 2022 Lietuvos Parenterinės ir Enterinės mitybos draugijos narė
- 2006 01 – iki dabar Lietuvos Klinikinės Toksikologijos draugijos narė
- 2010 09 – iki dabar Lietuvos Anesteziologų ir Reanimatologų draugijos narė

PUBLICATIONS ON THE DISSERTATION TOPIC

1. Laubner Sakalauskienė, G., Stražnickaitė, I., Miškinytė, S., Zdanavičius, L., Šipylaitė, J., & Badaras, R. (2024). Impact of Prescription Opioid Detoxification on Quality of Life and Pain Levels. *Clinics and practice*, *14*(4), 1529–1537. https://doi.org/10.3390/clinpract14040123
2. Laubner Sakalauskienė, G., Stražnickaitė, I., Miškinytė, S., Zdanavičius, L., Šipylaitė, J., & Badaras, R. (2025). Baseline Vitamin D Levels on Quality of Life and Pain Perception Among Patients with Chronic Pain with Long-Term Prescription Opioid Use: A Prospective Study. *Journal of clinical medicine*, *14*(2), 645. https://doi.org/10.3390/jcm14020645

PRESENTATIONS ON THE DISSERTATION TOPIC

1. Laubner Sakalauskienė, G., Stražnickaitė I. *"Influence of Vitamin D Concentration on Detoxification and Quality of Life in Prescription Opioid-Dependent Patients"*. Joint International Meeting: 22nd EAA Congress, 15th ISGA Congress, 5th International Conference of Evolutionary Medicine, August 24-27, 2022.
2. Laubner Sakalauskienė, G., Stražnickaitė, I., Miškinytė, S., Zdanavičius, L., Šipylaitė, J., & Badaras, R. *"Change of Quality of Life in Patients with Chronic Pain with Prescription Opioid Usage After Opioid Detoxification"*. BaltanestIC 2023 - *11th International Baltic Congress of Anaesthesiology and Intensive Care*, Tartu, Estonia, September 28-30, 2023.
3. Laubner Sakalauskienė, G., Badaras, R. *"Opioid (Non)Addiction and (In)Fidelity"*. Lithuanian Pain Society Congress *"Integral Care in Pain Medicine"*, Klaipėda, Lithuania, October 6, 202.
4. Laubner Sakalauskienė, G., Stražnickaitė, I., Miškinytė, S., Zdanavičius, L., Šipylaitė, J., & Badaras, R. *"Change of Quality of Life in Patients with Chronic Pain with Prescription Opioid Usage After Opioid Detoxification"*. European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) Congress, Munich, Germany, May 30, 2024.
5. Laubner Sakalauskienė, G., Stražnickaitė, I., Miškinytė, S., Zdanavičius, L., Šipylaitė, J., & Badaras, R. *"Change of Quality of Life in Patients with Chronic Pain with Prescription Opioid Usage After Opioid Detoxification"*. International Scientific Conference

"Evolutionary Medicine: How Evolutionary Thinking Can Contribute to the Medical and Health Sciences: The 6th International Conference", Vilnius, Lithuania, June 18-21, 2024.

6. Laubner Sakalauskienė, G., Badaras, R. *"Detoxification in Opioid Use Disorder"* at the Annual Nordic Poisons Centres Meeting, Porvoo, Finland, September 17-19, 2024.

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To support academic integrity and enhance clarity, the large language model ChatGPT (OpenAI; query 20 Jan 2025) was used exclusively in the literature-review section for two purposes: (i) to identify passages that might unintentionally paraphrase source material too closely, and (ii) to assist with English grammar and academic style refinement.
All suggestions were carefully evaluated and revised by the author, who bears full responsibility for the final content and scholarly rigor of the thesis.

NOTES

Vilniaus universiteto leidykla
Saulėtekio al. 9, III rūmai, LT-10222 Vilnius
El. p. info@leidykla.vu.lt, www.leidykla.vu.lt
bookshop.vu.lt, journals.vu.lt
Tiražas 25 egz.