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Understanding Opioid Therapy in Chronic Pain

Assessment, Lived Experience and Conceptions

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Abstract

Ljungvall, H. 2021. Understanding Opioid Therapy in Chronic Pain. Assessment, Lived Experience and Conceptions. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1733. 73 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1169-2.

The overarching aim of this thesis was to improve the understandings of opioid therapy for chronic non-cancer pain (CNCP) by examining the feasibility of different assessment methods of substance use, and opioid use disorder (OUD), and exploring the sense-making of opioid therapy in CNCP.

Methods: In study I, the reliability of the Addiction Severity Index Self-Report form (ASI-SR) was assessed by the agreement (intraclass correlation (ICC)) between the composite scores (CS) of the ASI interview and the ASI-SR, internal consistency of the CS subscales measured with Cronbach's α, and sensitivity and specificity of the alcohol and drug CS's, using Receiver Operating Characteristics analyses. Study II was a feasibility study of the U-PAIN cohort. Cohen's κ, PABAK, and ICC were used to assess the agreement between self-reported data on opioid use and data from medical records. In study III, interpretative phenomenological analysis was used to explore the lived experience of managing CNCP with opioids. In Study IV, phenomenography was used to explore physicians' understandings of prolonged opioid prescribing practices.

Results: In study I, 6/7 domains the ICC for the ASI interview and ASI-SR were good to excellent. Internal consistency was acceptable for 5/7 of the domains. Alcohol- and drug CS's predicted clinical substance dependence diagnoses. In study II, the agreement between self-reported opioid use and prescribed dose, and the agreement between OUD according to DSM-5 and clinical ICD-10 opioid dependence diagnoses, were almost perfect. In study III, opioids were used to regain control over the pain, but opioid use could also be experienced as a downward spiral of pain, dependence, and stigmatization. In study IV, specifics of a patient could justify opioid therapy. Insufficient follow-up, ignorance about pain management and opioids, an obligation to treat patients' pain, and lack of alternative treatments, were understood to drive continued opioid prescribing practices.

Conclusion: The studies suggest that the examined assessment methods of self-reported opioid use were feasible for assessing patterns of opioid use. To manage CNCP pain with opioids was experienced and conceptualized as a balancing act between pain control and quality of life, and aversive effects of opioids, e.g., OUD and stigmatization.

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“All we wanted was a little relief”
Pain Killers
Brian Fallon

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Ljungvall H, Persson A, Åsenlöf P, Heilig M, Ekselius L. Reliability of the Addiction Severity Index self-report form (ASI-SR): a self-administered questionnaire based on the Addiction Severity Index composite score domains. Nord J Psychiatry. 2020;74(1):9-15.

II Ljungvall H, Lind A-L, Zetterberg H, Wagner S, Karlsten R, Heilig M, Ekselius L, Åsenlöf P. Feasibility of the U-PAIN Cohort Study: Assessment of Acceptability, Recruitment and Data Collection in a Sample of Patients with Chronic non-cancer pain in Tertiary Care. *Manuscript*

III Ljungvall H, Rhodin A, Wagner S, Zetterberg H, Åsenlöf P. "My life is under control with these medications": an interpretative phenomenological analysis of managing chronic pain with opioids. BMC musculoskeletal disorders. 2020;21(1):61.

IV Ljungvall H, Öster C, Katila L, Åsenlöf P. "Opioids are opioids": A phenomenographic analyses of physicians' understandings of what makes the initial prescription of opioids become long-term opioid therapy. *Submitted*

Contents

Abbreviations

ACC	Anterior Cingulate Cortex
ASI	Addiction Severity Index
ASI-SR	Addiction Severity Index Self-Report
AUDIT	Alcohol Use Disorder Identification Test
BNST	Bed Nucleus of the Stria Terminalis
CeA	Central Amygdala
CNCP	Chronic Non-Cancer Pain
COMM	Current Opioid Misuse Measure
CS	Composite Score
DIRE	Diagnosis Intractability Risk Efficacy Instrument
DS	Dorsal Striatum
DSM	Diagnostic and Statistical Manual of Mental Disorders
HPC	Hippocampus
IASP	International Association for the Study of Pain
ICC	Intra Class Correlation
ICD	International Statistical Classification of Diseases and Related Health Problems
LTOT	Long-Term Opioid Therapy
M.I.N.I.	The Mini-International Neuropsychiatric Interview
MME	Oral Morphine Milligram Equivalents
NAc	Nucleus Accumbens
OFC	Orbital Frontal Cortex
ORT	Opioid Risk Tool
OUD	Opioid Use Disorder
PABAK	Prevalence-Adjusted Bias-Adjusted Kappa
PFC	Prefrontal Cortex
PROM	Patient Reported Outcome Measures
ROC	Receiver Operating Characteristics
SOAPP	The Screener Opioid Assessment for Patients with Pain
SUD	Substance Use Disorder
Thal	Thalamus
TLFB	Time Line Follow Back interview

1 Introduction

Opioids have been used since ancient times to alleviate pain or induce euphoria, and opioid addiction constitutes the prototype for substance use disorders. With the emerging opioid crisis in the U.S., and a rise in prescription opioid related deaths in Sweden, there is a growing concern regarding the use of opioids in the management of chronic non-cancer pain.

In contrast to the well-established opioid epidemic in the U.S., little is known about the current use of prescribed opioids in Sweden, especially about the use of opioids for chronic non-cancer pain. There are indisputable risks associated with long-term opioid use, and little evidence about its long-term effectiveness in non-cancer pain. Nevertheless, patients with chronic non-cancer pain are still started on opioids, and some individuals remain on opioid therapy over time. To enable safe and effective pain treatment for those suffering from chronic non-cancer pain, we need to understand who might benefit from opioid treatment, but also how to mitigate risks associated with opioids and not expose an already vulnerable group of patients to further harm. It is important to explore what factors influence prescribing behavior to start patients with chronic non-cancer pain on opioids and establish how to properly assess those who are already receiving opioids.

This thesis comprises four scientific studies that examine assessment of substance use in tertiary care settings; moreover, it explores the sense-making of managing chronic non-cancer pain with opioids, from the patients' and the healthcare providers' perspectives.

Section 2 provides a background on chronic non-cancer pain, opioid use disorder, and opioid therapy for chronic non-cancer pain, by reviewing the research literature. Section 3 comprises the rationale for the thesis and section 4 presents the overarching aim with the thesis. Section 5 presents an overview of the methods chosen for the different studies, followed by section 6 where the results of the studies are presented. In section 7, the results will be discussed and interpreted in relation to the original aim of the thesis. Furthermore, methodological considerations will be discussed, as well as the clinical implications and future research in the field of chronic non-cancer pain and opioid therapy. This will be followed by a summary in Swedish and the four scientific papers included in the thesis.

2 Background

2.1 Pain

To feel pain is crucial and has a protective role in warning of impending or actual tissue damage. Pain stimuli lead to innate reflexes as well as learned behaviors, aiming to avoid further damage (1). When a stimulus is perceived as a threat, the organism is primed to learn and adapt behavior to avoid the threat. If pain is experienced as threatening, it will have a great impact on learning and subsequently on behavior. How the pain is experienced is subjective and hard to measure or define objectively. The International Association for the Study of Pain (IASP) (2) defines pain as: "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage," and is expanded upon by the addition of six key notes and the etymology of the word pain for further valuable context:

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
- Through their life experiences, individuals learn about the concept of pain.
- A person's report of an experience as pain should be respected.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

2.2 Chronic non-cancer pain

Chronic non-cancer pain is a common condition affecting a large proportion of the population in Sweden, as well as citizens of the world, and is a leading contributor to disability and disease burden globally (3, 4).

A newly structured classification of chronic non-cancer pain was presented by IASP in 2019. This classification distinguishes chronic primary and chronic secondary pain syndromes and integrates existing pain diagnosis. It provides definitions and characteristic features of the respective diagnoses, according to the content model of the WHO for ICD-11, including the severity

of pain, its temporal course, and psychological and social factors. Chronic primary pain is defined as "pain in one or more anatomical regions that persists or recurs for longer than 3 months and is associated with significant emotional distress or functional disability (interference with activities of daily life and participation in social roles) and that cannot be better accounted for by another chronic non-cancer pain condition" ((5) p.21). Chronic secondary pain syndrome originates from other disorders, where pain at first is a symptom. Pain becomes relevant as a concomitant diagnosis when the chronic non-cancer pain ends up being a problem in its own right (5).

A combination of structural changes in the nervous system, psychological and social factors contribute to the development of several chronic non-cancer pain conditions (6, 7). They arise at the level of the spinal cord, via nociceptive signal transduction, and at the level of the brain circuits mediating reward, motivation, and cognition, via expectancy, interpretation, and emotional coloring (8). Pain is perceived differently in individuals depending on the experienced threat levels identified from the environmental context or prior experiences, and influence the subjective pain experience (9).

Common symptoms and behaviors in patients with chronic non-cancer pain include depression, avoidance, and hypersensitivity to pain (10, 11).

Pain avoiding behaviors, often relevant when the pain is acute, can worsen the problem in the case of chronic non-cancer pain. If the pain is interpreted as dangerous, eliciting catastrophic thoughts, it can result in a vicious cycle of maladaptive safety-seeking behaviors such as avoidance and hypervigilance, preventing participation in daily activities and physical rehabilitation. This may lead to increased pain sensitivity (12) and worsening of the physical condition (13). The unsuccessful struggle to control or reduce pain, may actually worsen the pain experience, and get in the way of people suffering from pain from accessing things that are important to them such as work, family and friends (14). Therefore, management of the patient's suffering from chronic non-cancer pain requires an interdisciplinary approach that includes assessment and treatment of biological, psychological, and social factors that may contribute to the disability caused by the chronic non-cancer pain, including pharmacological interventions as part of the treatment (7, 15, 16).

2.3 Opioid use disorder

One of the well-known risks associated with long-term opioid therapy, is opioid addiction, hereinafter equated with DSM-5 criteria of moderate-severe opioid use disorder (17, 18) as described in Figure 1.

Only a minority of people who try opioids develop addiction. It has been estimated that 20-30% of those who self-administer heroin will progress to opioid addiction (19, 20). About one-third of individuals with chronic non-cancer pain who are exposed to prescription opioids for longer than three months will develop problematic opioid use, and about one in ten will progress to opioid addiction (21). Various factors, including genetic, personal, psychological, and social, influence the risk of developing opioid use disorder (22, 23).

Opioid addiction is a severe condition associated with high mortality; and, opioids, both prescription opioids and heroin, together with cocaine, are the drugs most commonly associated with unintentional drug overdoses worldwide (24).

Opioid addiction is often a chronic condition that involves impairments in physiological, psychological, and social functioning (25). It is characterized by a substantial loss of control over use, indicated by compulsive opioid use with escalating doses, despite a desire to stop taking the opioids (18). Moreover, it is often associated with continued use, despite known adverse consequences (17).

Addictive drugs, such as opioids, activate reward regions of the brain. The function of the reward system is to promote activities that contribute to the survival of the species, such as eating nutritious food, mating, nursing offspring, and other social behaviors. These fundamental functions are linked with feelings of pleasure, which reinforce the behavior (26, 27). The release of dopamine in the mesolimbic system provides a “reward prediction error” - signal, which is critical for associative learning. This signal occurs when the reward exceeds the expected outcome, and promotes association of reward-predictive cues with approach behavior (28). The release of dopamine induced by addictive drugs exceeds the dopamine release induced by natural reinforcers by far (29). This contributes to behaviors related to addiction, such as mental pre-occupation of the drug and loss of control (30).

DSM-5 Opioid use disorder – Diagnostic criteria

1. Taking the opioid in larger amounts or for longer than you're meant to.
2. Wanting to cut down or stop using opioids but not managing to.
3. Spending a lot of time getting, using, or recovering from use of opioids.
4. Cravings and urges to use opioids.
5. Not managing to do what you should at work, home, or school because of opioid use.
6. Continuing to use, even when it causes problems in relationships.
7. Giving up important social, occupational, or recreational activities because of opioid use.
8. Using opioids again and again, even when it puts you in danger.
9. Continuing to use, even when you know you have a physical or psychological problem that could have been caused or made worse by opioids.
10. Needing more opioids to get the effect you want (tolerance). Do not apply under medical supervision.
11. Development of withdrawal symptoms, which can be relieved by taking more opioids. Do not apply under medical supervision.

Two or three symptoms indicate a mild substance use disorder, four or five symptoms indicate a moderate substance use disorder, and six or more symptoms indicate a severe substance use disorder. Items 10 and 11 are excluded if the drug is for medical use as prescribed.

ICD-10 Opioid dependence - Diagnostic guidelines

a) a strong desire or sense of compulsion to take the substance;

b) difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use;

c) a physiological withdrawal state when opioid use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for opioids;

d) evidence of tolerance, such that increased doses of opioids are required in order to achieve effects originally produced by lower doses;

e) progressive neglect of alternative pleasures or interests because of opioid use, increased amount of time necessary to obtain or take the substance or to recover from its effects;

f) persisting with opioid use despite clear evidence of overtly harmful consequences, such as, depressive mood states consequent to periods of heavy opioid use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

A definite diagnosis of dependence should be made only if three or more of the symptoms have been present together at some time during the previous year.

Figure 1 Opioid use disorder according to DSM-5 and opioid dependence according to ICD-10.

Addiction is often described as an acquired disorder of the brain and can be conceptualized as three recurring stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation - that worsens over time because of changes in the brain's reward and stress systems (18, 31), illustrated in Figure 2.

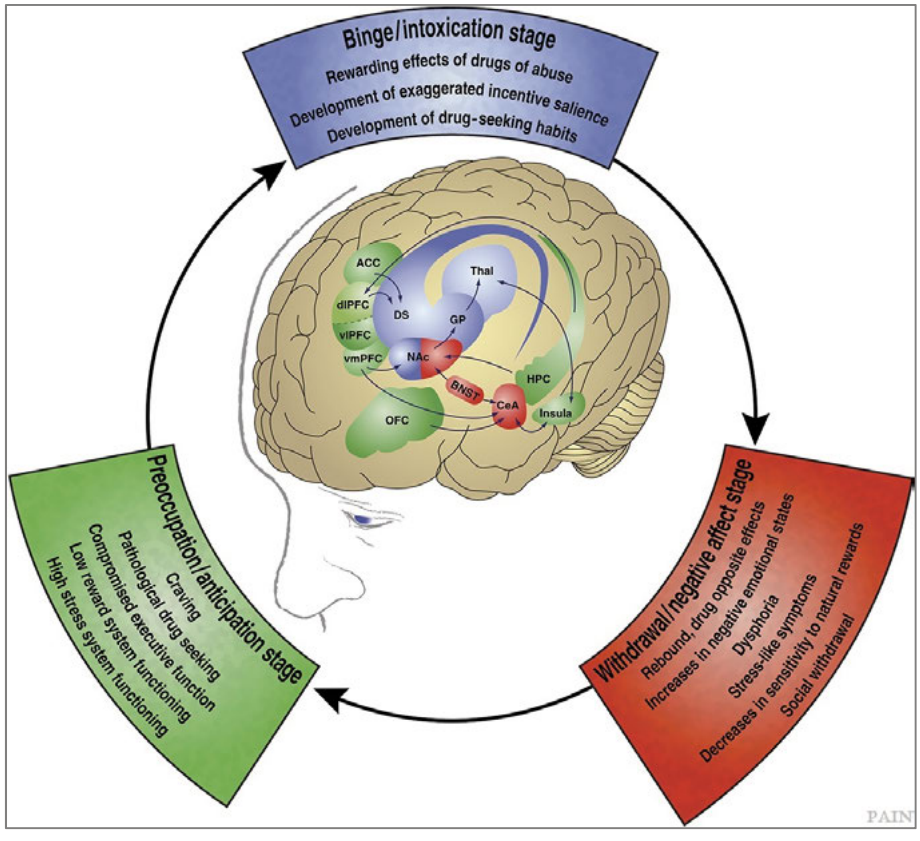

Figure 2 Model of interacting circuits in the development of addiction. The overall neurocircuitry domains correspond to 3 functional domains: binge/intoxication (reward and incentive salience: basal ganglia [blue]), withdrawal/negative affect (negative emotional states and stress: extended amygdala and habenula [red]), and preoccupation/anticipation (craving, impulsivity, and executive function: PFC, insula, and allocortex [green]). It is proposed that for patients receiving opioids for the treatment of pain, the withdrawal/negative affect stage (stage 2 of addiction) can be the main entry point to the addiction circuits. ACC, anterior cingulate cortex; BNST, bed nucleus of the stria terminalis or extended amygdala; CeA, central amygdala; DS, dorsal striatum; HPC, hippocampus; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PFC, prefrontal cortex; Thal, thalamus (32).

Pleasurable experiences of opioids are most apparent in the early stages of opioid use, as described above. Over time, after repeated exposure, the patient develops an opioid tolerance, which results in a decreased therapeutic effect. Consequently, higher doses of the opioid are required to achieve the desired effect. Adaptations occur within cells and circuits stimulated by the drug, resulting in tolerance and physical dependence (33). If the opioid user stops taking opioids, there will be signs of withdrawal due to hyperexcitability of the nervous system. Opioid withdrawal is very intense, characterized by both physical and affective features, i.e., anhedonia, nausea or vomiting, muscle pain, diarrhea, chills, insomnia, dilated pupils, runny nose and goosebumps. The symptoms in the acute phase of withdrawal vary in severity and duration, depending on duration, dose, and type of opioid used (34). Further, the activation of the brain regions involved in stress and negative emotions results in negative mood and enhanced sensitivity to stress (18).

During the withdrawal stage, negative, rather than positive, reinforcement mechanisms become dominant in promoting further drug use (31). This phenomenon, also called "the dark side of addiction," has been suggested as a mechanism that plays a major role in promoting opioid addiction, especially in individuals with chronic non-cancer pain. The sensitivity to stress and the negative affective states that arise during the acute phase of withdrawal can persist over time, into protracted abstinence. Furthermore, opioid craving and other conditioned responses to drug-associated cues, such as arousal, are measurable long after signs and symptoms of withdrawal have subsided. Stimuli that promote drug craving include re-exposure to small doses of the drug, i.e., "priming," pain, or stress, and these remain powerful triggers of relapse long after the acute withdrawal symptoms have subsided. Thus, both long-lasting neuronal adaptations, and long-term memories contribute to the chronicity of addiction (18, 30, 32, 35).

2.4 Opioid therapy for chronic non-cancer pain

The use of opioids in the treatment of chronic non-cancer pain has increased during the past few decades in most parts of the Western world. Opioids are effective for acute and post-operative pain, and they can be indispensable in the palliative treatment of cancer pain. However, the evidence for long-term opioid therapy for chronic non-cancer pain is scarce (36-39). Long-term is here defined as opioid therapy > 90 days. Opioids may provide benefits in terms of pain relief and physical functioning, but the magnitude is likely to be small and decrease over time (40). In well selected and monitored patients with chronic low back, neuropathic, and osteoarthritis pain, long-term opioid therapy can be beneficial over time. However, these findings are based on open label extension studies, and therefore cannot be extrapolated to other chronic non-cancer pain conditions and routine clinical care (41).

Furthermore, in a study by Krebs et al. (42), treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months, in patients with moderate to severe chronic back pain or hip or knee osteoarthritis pain.

The well-known risks associated with long-term opioid therapy are physical dependence, opioid use disorder, cognitive dysfunction, opioid induced endocrinopathy, and increased morbidity and mortality (43-45). Definitions of physical dependence, opioid use disorder, and addiction are presented in Figure 3.

Physical opioid dependence: Physical dependence is defined as tolerance to the effects of opioids when these are administered continuously over an extended period of time, and emergence of withdrawal symptoms upon rapid cessation or reduction in exposure to opioids, or exposure to an opioid antagonist. Physical dependence is thought to reflect neurobiological adaptations that include down-regulation of opioid receptor availability or signaling.

Opioid use disorder: A diagnostic term in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), referring to recurrent use of opioids that cause clinically and functionally significant impairments, such as health problems, disability, and failure to meet major responsibilities at work, school, or home. Depending on the level of severity, this disorder is classified as mild, moderate, or severe.

Opioid addiction: A term used to indicate the most severe, chronic stage of opioid-use disorder, in which there is a substantial loss of self-control, as indicated by compulsive drug taking despite the desire to stop taking the drug. In the DSM-5, the term *addiction* is synonymous with the classification of moderate to severe substance use disorder.

Figure 3 Definitions of Opioid Dependence, Opioid Use Disorder, and Opioid Addiction
(18, 19, 46).

Because of the risks associated with opioids, they are not recommended as first-line treatment for chronic non-cancer pain (36, 47), and the majority of patients initiated on opioids terminate treatment themselves because of side-effects or insufficient pain-relief (41, 48). Those who use opioids for > 90 days, report significant pain-relief in several studies, whereas findings regarding disability and quality of life are ambiguous (38). On a group level, improvement in disability and health is not associated with long-term opioid therapy; moreover, individuals treated with opioid therapy have worse pain and more activity interference; and are less able to return to work, than individuals that are not treated with opioids (49-52). This probably reflects confound by indication, and an adverse selection of individuals receiving opioids for chronic pain. They may be suffering from more severe pain and have higher levels of comorbidity and psychosocial stress, which probably

contributes to the maintenance of pain and disability associated with continued opioid use (49, 53, 54).

Nevertheless, prescription rates of opioids have skyrocketed in North America, Western Europe, and Australia (36). How common opioid therapy is probably varies depending on regional differences in healthcare organizations, available treatments, and settings (55, 56).

In a Norwegian population of individuals with chronic non-cancer pain, 3% were on long-term opioid therapy and 12% used opioids occasionally (57). A Danish population study found that 7% of individuals with chronic non-cancer pain were on long-term opioid therapy (58). In a large U.K. population-based cohort, 11% of those reporting any chronic non-cancer pain reported opioid use, and one in three participants reporting wide-spread chronic non-cancer pain, i.e., > 7 pain sites or all over, reported using opioids (59). In 2017, more than 17% of Americans had at least one opioid prescription filled, with an average of 3.4 opioid prescriptions dispensed per patient (60). Furthermore, in the last quarter of a century, there has been dramatic news headlines in the U.S. reporting the results of overtreatment with opioids, including misuse, addiction, and opioid related deaths (61, 62). However, during the last couple of years, there has been a decrease in the prescription of opioids, especially related to a decrease in opioid treatment for acute pain (63, 64). It is possible that this may have reduced the overdose deaths from prescription opioids, but instead there has been an increase in heroine and fentanyl overdose deaths (65).

In Sweden the annual prevalence of opioid prescription did not change much during 2006-2017 (66). However, there were significant shifts in the choice of opioids, with an increase in e.g., oxycodone and morphine (67, 68). The potential consequences of this shift and how opioid prescribing practices for chronic pain in Sweden are linked to an increase in opioid dependence diagnoses and opioid related deaths over the last few decades needs to be further studied (69).

About 15% of opioid naïve patients in Sweden were dispensed opioid medication more than once after their initial opioid prescription, and the dispensation rates increases with increasing age. Notably, among individuals who during the last 12 months have been dispensed opioids > 5 times, or have had several prescribers, the proportion of individuals with substance use disorder increases (68). It is not possible to establish from these data whether, in these individuals, the recurrent opioid prescriptions contribute to the development of substance use disorder, or whether these criteria capture individuals who have an established substance dependence/disorder that results in them seeking out repeated prescriptions (68).

2.4.1 The complexity of chronic non-cancer pain and long-term opioid therapy

Whether or not pain relief is achieved, opioids used continuously over time will have effects, beyond analgesia. The ability to feel pleasure, to socialize, and to evaluate and prioritize in life may be compromised, even though this will not necessarily lead to addiction (27, 32).

As described, both chronic non-cancer pain and opioid use disorder in its moderate- severe forms are, to some extent, disorders of the brain, characterized by impaired hedonic capacity and high levels of stress reactivity. Furthermore, both pleasure and pain are highly involved in motivating behavior, through positive and negative reinforcement, thus promoting behaviors relevant in both opioid use disorder and chronic non-cancer pain (8).

As stated above, dependence, i.e., tolerance and withdrawal, reflects adaptions to continuous opioid use, and does not necessarily reflect development of opioid use disorder. However, withdrawal symptoms include worsening of pain. Also, when tolerance has been developed withdrawal symptoms will persist unless the opioid dose is increased. This leads to a vicious cycle, in which withdrawal leads to increasing pain that requires higher opioid doses (27, 70). Patients on long-term opioid therapy may experience withdrawal, rather than a deteriorating pain condition, when their pain increases. Withdrawal pain is not only physical, but also emotional (71), and becomes entwined with the depression and reward deficiency associated with chronic non-cancer pain (32). Furthermore, high opioid doses may lead to opioid induced hyperalgesia, a sensitization process in which opioids cause pain hypersensitivity (72). Thus, opioids might have a paradoxical effect on pain and aggravate a pain syndrome. On the other hand, chronic non-cancer pain can become a drug cue when opioid and dopaminergic interactions lead to attentional hypervigilance for pain, which triggers opioid cravings.

Dysfunctional connectivity between self-referential and cognitive control networks in the brain, and dysregulation of stress and reward circuitry, are present in both chronic non-cancer pain conditions and opioid use disorder, where one condition might exacerbate the other (70).

2.5 Assessment of problematic opioid use in individuals with severe chronic non-cancer pain

2.5.1 Risk factors for opioid use disorder

Risk factors for opioid use disorder in patients with chronic non-cancer pain include past or current substance use disorders and associated social environments, heritability, co-morbid psychiatric disorders, younger age, and past or

current exposure to sexual or physical abuse (22, 73, 74). There are no gender differences when it comes to the degree of aberrant drug related behavior in men and women with long-term opioid therapy, but they do differ in risk factors. Specifically, women endorse more emotional issues and affective distress than men, and men endorse more problems related to illicit substance use, alcohol use, and criminal behavior (75).

Receiving opioids from several prescribers is associated with opioid use disorder and is also a risk factor for opioid related overdose death (76). The risk for opioid related overdoses increases with combinations of opioids, or combinations of opioids and benzodiazepines (77-79).

2.5.2 Assessment methods

As described above, regular opioid use may over time cause tolerance and withdrawal, even in patients who comply with prescribed doses and only use opioids as medically indicated. Therefore, in patients prescribed opioids or benzodiazepines who comply with prescribed doses, the DSM-5 eliminates tolerance and withdrawal as diagnostic criteria of opioid use disorder. Instead, the diagnosis is then based on the remaining criteria, which reflect maladaptive drug related behaviors (See Figure 1). However, symptoms corresponding to these criteria may be difficult to establish in patients with chronic pain, in whom the maladaptive behaviors are often manifested e.g., by doctor shopping, loss of -, or repeated request for early prescriptions (80). Further, the medication can have priming effects, and the pain is a constant trigger for opioid use. Therefore, it is hard to distinguish if drug-seeking behaviors are driven by drug cravings or uncontrollable pain (46, 81). Nevertheless, what promotes the behavior is often linked to the alleviation of experienced pain (82).

Considering the risks associated with long-term opioid therapy, it is of utmost importance to evaluate, in each case, the benefit vs risk balance associated with the treatment. If this balance is negative, e.g., if there are no evident benefits, the opioid therapy should be stopped before the patient develops opioid dependence. The nature of symptoms that might indicate potential problems related to opioid use will be a function of intersecting emotional, social, and biological changes. Thus, detection of potential benefits or problems related to opioid use cannot be determined without comprehensive, recurring assessments (83).

Methods that can be used by clinicians to assess risk behavior in conjunction with opioid therapy are urine toxicology tests to screen for illicit drug use, pill counts, or prescription monitoring strategies. However, the evidence for accuracy of these methods is scarce (84). Other assessment alternatives are different self-report measures, i.e., self-administered forms, and structured or semi-structured interviews.

Several screening instruments have been introduced in recent years to identify patients for whom opioids are not suitable for long-term pain therapy. Established tools for assessing risks for problematic opioid use in individuals with chronic pain include: The Screener and Opioid Assessment for Patients with Pain (SOAPP) (SOAPP-R); the Opioid Risk Tool (ORT); and the Diagnosis, Intractability, Risk, Efficacy (DIRE) instrument. The current opioid misuse measure (COMM) is a self-report measure of risk for maladaptive opioid behavior among individuals with chronic pain who are prescribed opioids for pain. It was developed to complement predictive screeners of opioid misuse and periodically assess a patient's risk for opioid misuse (85). However, the psychometric properties of many of these questionnaires are weak and have neither been established in accordance with principles of evidence-based medicine (84), nor been tested under Swedish conditions. Hence, there is no single test or instrument that can reliably identify patients at high vs low risk of developing problematic opioid use if opioid therapy is initiated, or identify those who need increased monitoring during treatment (61, 84, 86, 87). Furthermore, standardized assessments of benefits with opioid therapy beyond pain relief are warranted.

Contrary to the lack of validated instruments to assess opioid use in populations with chronic pain, there are several validated instruments for identifying and measuring severity of substance use disorders. In such populations with substance use disorders, the Addiction Severity Index (ASI) is an established multidimensional instrument, widely used all over the world, in research, clinical assessments, and during treatment evaluations (88-91). The ASI is a standardized semi-structured interview used for assessing severity and problems in different functional domains associated with substance use disorders (92, 93). The psychometric properties of ASI are well investigated, and it has been found to have satisfactory validity and reliability (93, 94).

The ASI could be a useful instrument for multidimensional assessment of patients with chronic pain where opioid treatment is considered, and could also be used for the multidimensional evaluation of ongoing opioid therapy (95). However, the ASI interview is time-consuming. It takes between 45-60 minutes to conduct an interview, followed by 20-25 minutes of administrative work (93). One strategy used to reduce the time and costs associated with administering the ASI interview is the development of client self-administered versions of the ASI, either in paper and pencil or computer-based formats (96-98). One example of a self-administered version of the ASI is the ASI Self-Report form (ASI-SR). The ASI-SR is a self-administered form based on interrelated 30-days items within the interview domains (98).

Another instrument for standardized assessment of substance use disorders and other psychiatric disorders is the Mini-International Neuropsychiatric Interview (M.I.N.I.) for DSM-5 (99). The M.I.N.I. is a structured diagnostic interview for the most common psychiatric disorders, designed for multicenter clinical trials and epidemiological studies, but also used in non-research

clinical settings (100). The M.I.N.I. allows for administration by non-psychiatrists and it can be used in different clinical settings and with different populations (100). Section (J) assesses drug use disorders, including opioid use disorder, according to the DSM-5 criteria. However, M.I.N.I. is designed to assess illicit, or non-medical drug-use, which should be considered when using it for assessing opioid use disorder in a sample of patients with chronic pain and opioid therapy.

2.6 Theoretical framework

2.6.1 The biopsychosocial model

"To provide a basis for understanding the determinants of disease and arriving at rational treatments and patterns of healthcare, a medical model must also consider the patient, the social context in which he lives, and the complementary system devised by society to deal with the disruptive effects of illness, that is, the physician role and the healthcare system. This requires a biopsychosocial model" ((101) p.132).

The biopsychosocial model views illness as a result of the interaction of physiologic, psychological and social factors (102). This makes it possible to explain the individual experience of health and illness.

The biopsychosocial model also incorporates emerging knowledge in genetics and neuroscience. For instance, in the field of addiction (35, 103), modern neuroscience is integrated to better understand the physiological dynamics that sustain craving and maladaptive behaviors and how biological factors influence psychological and social behaviors. Conversely, social and behavioral factors can act on the brain to influence health, illness, and even death (102). The integration of social, psychological and biological processes is critical for the understanding of chronic non-cancer pain and opioid therapy. It can guide clinicians in how to use opioids for chronic non-cancer pain, and in the treatment of patients with chronic non-cancer pain and opioid use disorder.

2.6.2 Phenomenology and second order perspective

As discussed above, the boundaries between the biological, psychological, and social are artificial. Experiences, such as pain, or craving and loss of control in addiction, always involves biochemical processes, sensations, actions and environmental factors that are intertwined, and inseparable in a constant loop of interactions. Most experiences are both intra- and interpersonal, thus relational, and emerges as processes of sense-making through a lived body inseparable from the world that we shape and that shapes us (104). However, the biopsychosocial model can lead to pain or addiction being viewed in a

fragmented manner, resulting in the perpetuation of dualistic and reductionist beliefs (105); moreover the patient's problems might get separated into two or three separate domains (bio, psycho, or social). This could prevent a dynamic integration aligned with the first-person's embodied experience (105). For example, when pain becomes chronic, it shifts the brain's representation from nociceptive to emotional circuits (106) and progresses from pain to suffering. This is an experience in many dimensions, not only in the brain. It is partly existential, definitely contextual, and can be hard to capture within the natural scientific research models. Pain, experienced from a first-person perspective, can be viewed not only as something that is happening inside the body but also as a relational and embodied process of sense-making, where objects from the environment and other people are a part of the experience (104, 105). Sense-making is the process through which people give meaning to experiences, then enacted in behavior. Sense-making is an intentional and normative engagement with the environment, and it is about transforming the world into a place of salience meaning, and value (107, 108). It can be explained as the meaning-making and decision-making that people engage in when what they experience does not align with their expectations of the world without a plausible explanation. When this happens, peoples' identities are challenged. By generating narratives, people give meaning to these incoherent experiences, thus reconfiguring their identities and finding order and coherence in their world (109). Participatory sense-making occurs when people engage in interactions that produce meaning that could not be produced by either individual alone. This is particularly relevant when considering the patient-clinician relationship and the meaning of the patient's pain and pain treatment (105).

In the health sciences, phenomenology has been used in qualitative research to obtain an in-depth understanding of the elusive and ambiguous phenomenon of pain. Phenomenology seeks to explicate the "lived experience" of a phenomenon under study, thus turning from facts to meanings (110, 111).

In the second order perspective, the researcher is primarily interested in how phenomena are conceived and understood (112). Our conceptions of, and knowledge about, the world is based on interpreted data from our senses, and on our personal history. This will affect how we interpret and experience the world. Therefore, it can be assumed that people with different experiences will understand and interpret the world differently, thus different worlds appear, with similarities and differences between them (113). The second order perspective can reveal human experience and reflect the world or phenomena as they are understood and conceptualized (114). This can add to the body of knowledge on how and what we experience and understand within the framework of healthcare (114).

3 Rationale for the thesis

This thesis is part of a larger project examining benefits and risks with long-term opioid therapy. The project is part of the U-PAIN research program at Uppsala University and the Pain Centre at Uppsala University Hospital. U-PAIN is an interdisciplinary research program that comprises an infrastructure for interdisciplinary and translational pain research of methods for pain diagnostics, treatment and rehabilitation.

As described, there is still a dearth of knowledge regarding long-term opioid therapy and its effect on pain, social activities, family, work ability, and cognitive functions. Altogether, a complex picture emerges of plausible interactions between the biopsychosocial risk factors for chronic non-cancer pain and problematic opioid use. Further, for a well selected group of patients with pain, long-term opioid therapy may actually work. However, very little is known about how to identify individuals who benefit from long-term opioid therapy in an early stage of treatment. In most guidelines, it is recommended to monitor patients on opioids carefully, especially those who are at risk for developing problematic opioid use (61). In the clinical setting, several behaviors associated with problematic opioid use are difficult to distinguish, particularly since no evidence-based method for a comprehensive biopsychosocial assessment is available. This, in turn, impedes any clinical efforts to offer an evidence-based treatment on an individual level, where benefits and problems associated with opioid therapy are evaluated with reliable methods. Thus, a tool for systematic, multidimensional assessment that can guide treatment efforts, additional diagnostic work, or both, is urgently needed.

Unlike illicit drug-use, prescription opioid use for chronic non-cancer pain is an interaction between the patient and the prescribing physician, where both parties contribute to whether or not the treatment will succeed. Therefore, long-term opioid therapy for chronic non-cancer pain needs to be explored with a range of different methods and strategies, and from different perspectives (36).

4 Aims

The overarching aim of this thesis was to improve the understanding of opioid therapy for chronic non-cancer pain by examining the feasibility of different assessment methods for substance use, and opioid use disorder, and explore the sense-making of opioid therapy for chronic non-cancer pain through the patients', and the healthcare providers' experiences.

The specific objectives of the studies were:

Study I: The objective was to investigate if a Swedish version of the ASI-SR offers a viable alternative to the ASI interview for assessing current substance use and related problems.

Study II: The objective was to examine the acceptability of study participation and feasibility of recruitment, data collection, and outcome measures of the U-PAIN cohort.

Study III: The objective was to explore the lived experience of managing chronic non-cancer pain with opioids, and to understand the sense-making of opioids as a long-term treatment from a first person's perspective.

Study IV: The objective was to explore prescribers' understanding of what makes initial prescription of opioids become long-term-opioid therapy.

5 Methods

This thesis includes four studies. Their design and outcomes are described in Table 1.

Table 1 Design, sample size, participants, and outcome variables of the four studies.

STUDY	DESIGN	PARTICIPANTS (N)	OUTCOME VARIABLES
I	Psychometric study (testing reliability)	Individuals seeking specialized treatment for SUD[1] (59)	Agreement between, and differences of, the ASI[2] and ASI-SR[3] CS and acceptability of the ASI-SR, internal consistency, sensitivity and specificity for SUDs
II	Internal feasibility study of a prospective cohort	Individuals seeking specialized treatment for severe chronic non-cancer pain (64)	Acceptability of study participation and feasibility of recruitment, data collection methods, and outcome measures
III	Qualitative interview study (Phenomenological Interpretative Analysis)	Individuals with chronic non-cancer pain and LTOT[4] in tertiary pain care (10)	The lived experience of managing chronic non-cancer pain with LTOT
IV	Qualitative interview study (Phenomenography)	Attending physicians in primary and specialized care (15)	Understandings of what makes initial opioid prescriptions become long-term opioid therapy

[1] *Substance Use Disorder*

[2] *Addiction Severity Index*

[3] *ASI-Self Report form*

[4] *Long-Term Opioid Therapy (opioids > 90 days)*

5.1 Assessment of substance use

Study I and study II examined structured methods to assess substance use in clinical settings. Study I was a reliability study of a Swedish version of the ASI-SR with the main objective to examine the agreement between the ASI-SR and the ASI interview.

Study II was an internal feasibility study of the U-PAIN cohort examining acceptability of study participation and feasibility of recruitment, data collection and outcome measures.

The U-PAIN cohort is a project with the overall aim to prospectively identify those with chronic non-cancer pain and long-term opioid therapy. These individuals either benefit from long-term opioid therapy or are at risk for problematic opioid use. The project was initiated at the Uppsala Pain Centre in collaboration with Uppsala University, and it includes a large prospective clinical cohort with a target number of 1,000 patients with chronic non-cancer pain who were referred to secondary and tertiary pain care. Specifically, the project includes (1) a cross-sectional study of baseline characteristics and (2) a prospective, longitudinal cohort study over a 5-year period for prediction of risks and benefits with long-term opioid therapy with endpoint measures every 12 months. The aim is to prospectively identify patterns of opioids use, including dose, duration, way of administration, and type of opioid, and to establish predictors of different courses of opioid use, including 1) non-adherent or maladaptive opioid use, here defined as opioid use disorder according to the DSM-5 criteria, and 2) beneficial use, i.e., increased ability to work and health related quality of life.

Main research questions are:

1. What are the characteristics of those who *do not* have any symptoms of opioid use disorder at baseline, and what variables predict their future:
   Opioid-related behaviors? b) Work ability, activity interference, quality of life, and pain?
2. What are the characteristics of those who have a mild, moderate, or severe opioid use disorder, respectively, at baseline and what variables predict their future:
   Opioid-related behaviors? b) Work ability, activity interference, quality of life, and pain?

Potential predictors and co-variates are grouped as follows: (1) Individual factors and demographic variables, (2) Pain characteristics, (3) Psychiatric comorbidity and susceptibility for addiction, (3) Cognitive-behavioral variables, and (4) Physical functioning. The objective is to identify the most salient predictors from each group and combine them into a final model with the best goodness of fit. Data collection methods are described in Table 2.

Table 2 Variables and measures for the cohort study

Variables	Measures	Baseline	Follow-up [1]
Diagnostic criteria opioid use disorder according to DSM-5	The Mini-International Neuropsychiatric Interview	x	x
Work ability	Work Ability Index	x	x
Sick-leave	Swedish Social Insurance Registers	x	x
Social support	MOS Social Support Survey	x	
Pain severity and interference	The Brief Pain Inventory	x	x
Health-related quality of life	EQ-5D-5L	x	x
Patient's Global Impression of Change	PGIC		x
Physical activity, eating, smoking, drinking	Lifestyle-habits The National Board of Health and welfare	x	x
Screening alcohol, illicit drugs	AUDIT, DUDIT	x	
Socioeconomics, significant others and family	Medical records, questionnaire	x	
Personality traits	Swedish Scale of Personalities (SSP)	x	
Anxiety and Depression	Generalized Anxiety Disorder 7 item Scale, Patient health questionnaire-9	x	
Catastrophizing	The Pain Catastrophizing Scale	x	
Self-efficacy	Pain Self-Efficacy Questionnaire	x	
Trauma	Checklist for life events	x	
Fear of movement/(re)injury	The Tampa Scale of Kinesiophobia	x	
Balance	MiniBesTest	x	
Walking speed	10-meter walking test	x	

5.1.1.1 Measures

In study I, the ASI interview and the ASI-SR were used. The ASI interview assesses severity and problems in seven functional domains: physical health, employment/support status, alcohol use, drug use, legal status, family/social functioning, and psychiatric health. It is designed to evaluate patients' recent, past 30 days, and lifetime functional status in the seven domains covered (92, 93). Current functional status can be assessed by mathematically calculated composite scores (CS), ranging from 0-1.00, with higher values indicating more severe problems. The CSs are based on interrelated items within a specific domain and are suitable for evaluating change over time as clinical or research outcomes (92), and the ASI-SR is based on these items (98, 115). The ASI-SR was translated following the specifications provided by RAND Health (116).

Finally, for the purposes of this study, three items on acceptability were added. Participants were asked whether it was easy to understand the ASI-SR items, to fill out the form, and whether the items were relevant. Response alternatives were Yes, No, and No Opinion.

For descriptive purposes the Alcohol Use Disorders Identification Test (AUDIT) (117) and the Drug Use Disorder Identification Test (DUDIT) (118) were used, and are further described in paper I.

In study II, feasibility of recruitment was assessed by using the recruitment and refusal rates for enrollment, retention rate at the one-year follow-up, and sample characteristics collected from an online questionnaire as well as medical records.

Feasibility of data collection was measured by completion rates of the different study procedures described in Table 2, as well as validation checks of collected data regarding the self-reported opioid use.

To validate data collection methods regarding opioid use patterns, agreements between the categories were examined based on: self-reported opioid use and categories based on the prescribed opioid dose retrieved from the medical records, and self-reported opioid dose and prescribed opioid dose retrieved from medical records, and self-reported opioid dose for week 1 and week 4.

The categories used to describe opioid use are defined and described in paper II.

Self-reported opioid use (dose, route of administration and number of days last 30 days), was assessed with a structured interview: the Time-line follow back (TLFB) (119-122), which is further described in paper II. Opioids were stratified as the type of opioid, route of administration, and dose converted to oral morphine milligram equivalents (MME) (123).

To examine the feasibility of opioid use disorder according to DSM-5 as the outcome measure, we assessed:

a) The number of individuals meeting the opioid use disorder criteria according to DSM-5, and

b) The agreement between moderate- severe opioid use disorder and clinical diagnoses for opioid dependence according to ICD-10, retrieved from the medical records (124).

Opioid use disorder was assessed by a modified version of the drug use disorder section (J) of the Swedish M.I.N.I. for DSM-5 (99). The M.I.N.I. (J) assesses the most common categories of drugs, including both prescribed and illicit controlled substances. For the purpose of this study, the drug use disorder section was modified to assess current as well as life-time drug use, and medical as well as non-medical use. Additional interviewer information was added to clarify that if participants reported using opioids as prescribed, questions regarding desire to take a lesser amount would be coded "No", even if the participant endorsed a desire to take less but took the prescribed dose because of increased pain if they did not take the opioid. Before the interview, trained research staff showed participants a list of substances and read the following instructions: "I am going to show you and read to you a list of drugs. The list also includes some medicines. Please describe your use of the listed drugs and medicines, even if the medicine was prescribed to you by a doctor and used accordingly. I will ask you to describe life-time use, and your use during the past 12 months."

Additional outcome measures for the U-PAIN study that were assessed in the feasibility study are described in paper II.

Acceptability of study participation in study II, was measured with a 10-item Likert scale, the U-PAIN acceptability form, constructed for the purpose of the feasibility study, which is further described and depicted in paper II. A score of 1 indicated total agreement and a score of 5 indicated total disagreement, and a score < 3 on an item was considered acceptable. For two items assessing respondent burden, items 7 and 8, a higher score indicated lesser respondent burden.

5.1.1.2 Procedures

In study I, participants were recruited randomly from the consecutive intake of patients to an addiction clinic. About 20 percent of the eligible sample were approached with information letters and an appointment for the interview. The research visit, comprising completion of the ASI interview and the ASI-SR, was scheduled before their first clinical consultation. There was no intended selection based on choice of drug.

All interviews were conducted by the same interviewer who had appropriate ASI training and previous clinical experience of conducting ASI interviews. The interviewer was blinded to the participants' ASI-SR answers while conducting the interviews. The order of the two different ASI assessments was

counterbalanced (ASI interview first: n=31; ASI-SR first: n=29), and the participants did not receive any assistance from the staff in completing the ASI-SR.

In study II, participants filled out an online questionnaire comprising questions regarding demographic and 12 computerized PROMs, accessed through a secure personal log in on the Swedish Healthcare Guide's digital platform, before the research visit. The PROMs were used for both clinical purposes and as research data. During the research visit, participants completed the structured interviews, TLFB and M.I.N.I.; underwent physical performance tests; provided blood samples; and filled out six additional computerized study specific PROMs, including the U-PAIN acceptability form.

5.1.1.3 Statistics

Statistical analyses were conducted with Statistical Package for the Social Sciences (SPSS) (IBM SPSS Statistics for Windows, Version 23. Armonk, NY: IBM Corp) in study I, and with SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) in study II.

Calculation of the CSs in study I followed standard procedures (92, 115, 125). When calculating the drug CS, only illicit or non-medical drug use were included in the analyses.

In study I, the agreement between the ASI interview's CSs and ASI-SRs CSs was evaluated on an individual basis by intraclass correlation analysis (ICC). The ICC coefficient is considered poor if lower than 0.6 (126). However, for this study, we chose the stricter cut-off values suggested by Hahn et al. (127), because individual clinical decisions require more precise instruments than research assessing differences between groups. Hence, the ICC coefficient was considered poor if lower than 0.70, moderate or good between 0.71 and 0.89, and excellent between 0.9 and 1.00 (127). Average measures of ICCs were used because the interviewer was blinded to the answers generated in the ASI-SR, and no interaction effect between the raters was assumed. On group level, the Wilcoxon signed rank test was used since data were not normally distributed. Receiver Operating Characteristics (ROC) analyses were used to investigate sensitivity and specificity in identifying participants who had been given a clinical ICD diagnosis of substance dependence.

In study II, ICC single measures and absolute agreement were used for assessing the agreement between self-reported opioid dose in week 1 and prescribed dose according to the medical records, and the agreement between self-reported dose in week 1 and week 4. Here, the ICC coefficient was considered poor if < 0.40, fair 0.40–0.59, good 0.60–0.74, and excellent between 0.75–1.00 (126). To examine the agreement between categories based on current opioid use according to self-reported dose vs. prescribed dose, and agreement between the structured interview establishing opioid use disorder according to DSM-5 and the clinical opioid dependence diagnosis according to ICD-10 derived from medical records, Cohen's Kappa (κ) was used. κ is a

coefficient for rater agreement considering chance agreement. Values for κ range between − 1 and + 1, with + 1 indicating the total agreement between outcomes. The agreement is considered as poor at a value of 0, as slight when κ = 0–0.20, as fair when κ = 0.21–0.40, as moderate when κ = 0.41–0.60, as substantial when κ = 0.61–0.80, and as almost perfect when κ = 0.81–1 (128, 129).

As a low number of opioid use disorder diagnoses was expected in our sample, an alternative calculation of κ was also used: The prevalence-adjusted bias-adjusted Kappa (PABAK). PABAK takes into account the categorization by the interview and the prevalence of the clinical diagnosis (130).

Internal consistency was evaluated using Cronbach's α in both study I and study II. The α coefficient was considered acceptable if above 0.70 (131).

5.2 Sense-making of opioid therapy for chronic non-cancer pain

Study III and IV were qualitative studies exploring the sense-making of chronic non-cancer pain in opioid therapy through lived experience and conceptions.

5.2.1.1 Participants and procedures

In studies III and IV purposeful sampling was applied, using posting, gatekeepers and official contact information to contact potential participants. The settings and recruitment processes are further described in papers III and IV. Eligible for participation in study III were individuals 18-65 years of age with chronic non-cancer pain and long-term opioid therapy, currently in employment or work rehabilitation, and with work experience. In study IV attending physicians with experience of prescribing opioids were eligible for participation. A variation in experiences of opioid prescribing practices was sought, why participants were recruited from different medical disciplines, healthcare settings, and from diverse regions in Sweden.

5.2.1.2 Data collection and analysis

Semi-structured interview guides using open-ended questions were used for the interviews in both study III and study IV. The interview guides were used in a way to promote openness and allowed the participants to discuss questions that were most pertinent to them regarding their experiences of pain and opioid therapy. The interviewer was free to probe further on subjects generated during the interviews that were consistent with the aim of the study, using repetition, request for clarification or elaboration, and confirmation as probing strategies to avoid ambiguity and enable an interpersonal and flexible interview, being sensitive to each interviewee (132). The interviews were audio recorded

and transcribed verbatim for analysis. The interview guides were developed with guidance from the literature regarding qualitative methods, and important topics were established by going through current literature on research regarding opioid prescribing practices, and long-term opioid therapy for pain (132).

Before analyzing the data, the researchers bracketed their preconceptions to enable an explorative approach, with emphasis on the participants' lived experience and understandings (112, 114).

In study III, interpretive phenomenological analysis (IPA) was used for analyzing the data according to Smith et al. (133). For detailed information, see paper III. Emergent themes, sub-themes, and super-ordinate themes were developed through a thorough reading of the transcripts and initial notes. After each transcript was analyzed, the analysts met to discuss the themes assigned to the transcript. Through this procedure, the themes could be developed further, enabling coders to consider the transcripts from different perspectives and staying close to the text and the participants' accounts. When analyzing subsequent cases, efforts were made to bracket prior ideas and themes emerging from the previous transcripts. After completion of a separate analysis of every transcript, a cross-case analysis was conducted using the same strategy as for the individual transcripts. Shared themes across cases, in accordance with the purpose and aim of this study, were identified, and corresponding text sections from the transcripts were assigned thereto.

In study IV, phenomenography was used for analyzing the data. The analysis was done consecutively during the data collection by two separate researchers, consistent with the constant comparative process and the seven analysis steps outlined by Dahlgren et al. (134) described in paper IV. Recruitment continued until categorical saturation was reached, i.e., no new categories were identified during the analyses (135). An additional researcher read five transcripts to check for consistency between the data and the categories. Finally, an outcome space was constructed, representing the logical relationship between the categories and describing the similarities and differences within and between the categories, according to the phenomenographic methodology (136, 137).

5.3 Ethical Considerations

There are several ethical issues to consider when conducting research with human subjects, and additional considerations apply to studies that involve treatment seeking individuals in a clinical setting. Study participation involves time-consuming activities, and in this type of research participants are often asked to share private information about themselves. Thus, one of the most urgent ethical issues for the studies in this thesis is that of intrusiveness and personal integrity. Therefore, it is important to protect the privacy of the participants and for the researchers to be aware of the ethical aspects when

handling sensitive data. In a research setting, this means offering a non-judgmental environment, where the research staff is professional, respectful, and yet compassionate, when interacting with the participants. When this is achieved, participants often appreciate the opportunity to talk to an interested independent listener paying attention to their story. This can help the participant to develop new perspectives on their lived experiences. It can also be an opportunity for the participants to advocate for the self, and generate a feeling of being able to influence future healthcare procedures (138).

To minimize the risk of exposing participants to unnecessary discomfort, or harm, it is important to conduct research in accordance with the Helsinki declaration. This means that every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information. The researchers also have to make sure that each study participant provides informed consent to participate, and is well informed about the study and the right to end participation at any time (139).

In a time when the well-identified risks associated with long-term treatment using opioids are widely discussed, different perspectives on managing chronic non-cancer pain with opioid therapy are vital.

All studies included in this thesis have been approved by ethical review boards, studies I-III by the Regional Ethical Review Board in Uppsala, and study IV by the Swedish Ethical Review Authority. All participants got written information about the study in which they participated. Moreover, the studies were explained verbally to eligible participants immediately prior to data collection giving the participants an opportunity to ask questions about the study before they gave their informed consent.

6 Results

The result section comprises a summary of the most important findings in the different studies.

6.1 Assessment of substance use

6.1.1 Recruitment, completion rates, and characteristics

In study I, 59 (35%) of the 168 individuals that were approached chose to participate in the study.

The mean age of participants was 46.2 years (SD 13.9). A majority of the participants were male (66%) and had alcohol as their primary drug (63%). Five participants (8%) reported prescription drugs as their primary drug, i.e., opioids or benzodiazepines, and 14 (24%) reported regular use of illicit drugs. Forty-four (75%) had completed high school, and 38 (64%) were employed, and 40 (68%) lived alone. Fifty percent reported prior experience of treatment for alcohol problems and 29 % for drug problems.

In study II, 65 participants were consecutively recruited, and the first follow-up was completed approximately 12 months after the base-line visit. The recruitment process, participant and refusal rates, and completion rates of the different research procedures are described in Figure 4.

The mean age of participants in study II was 50.3 years (SD 14.5), and all participants had at least one chronic non-cancer pain diagnosis according to ICD-10. A majority of the participants were women (56%), and about half (52%) attended out-patient care. Forty-eight (75%) had completed high school, and seventeen (26%) were employed or studied full-time. Thirty-eight (59%) were either retired or on long-term sick-leave (> 3 months). Baseline score values of outcome measures for the U-PAIN cohort are further described in paper II.

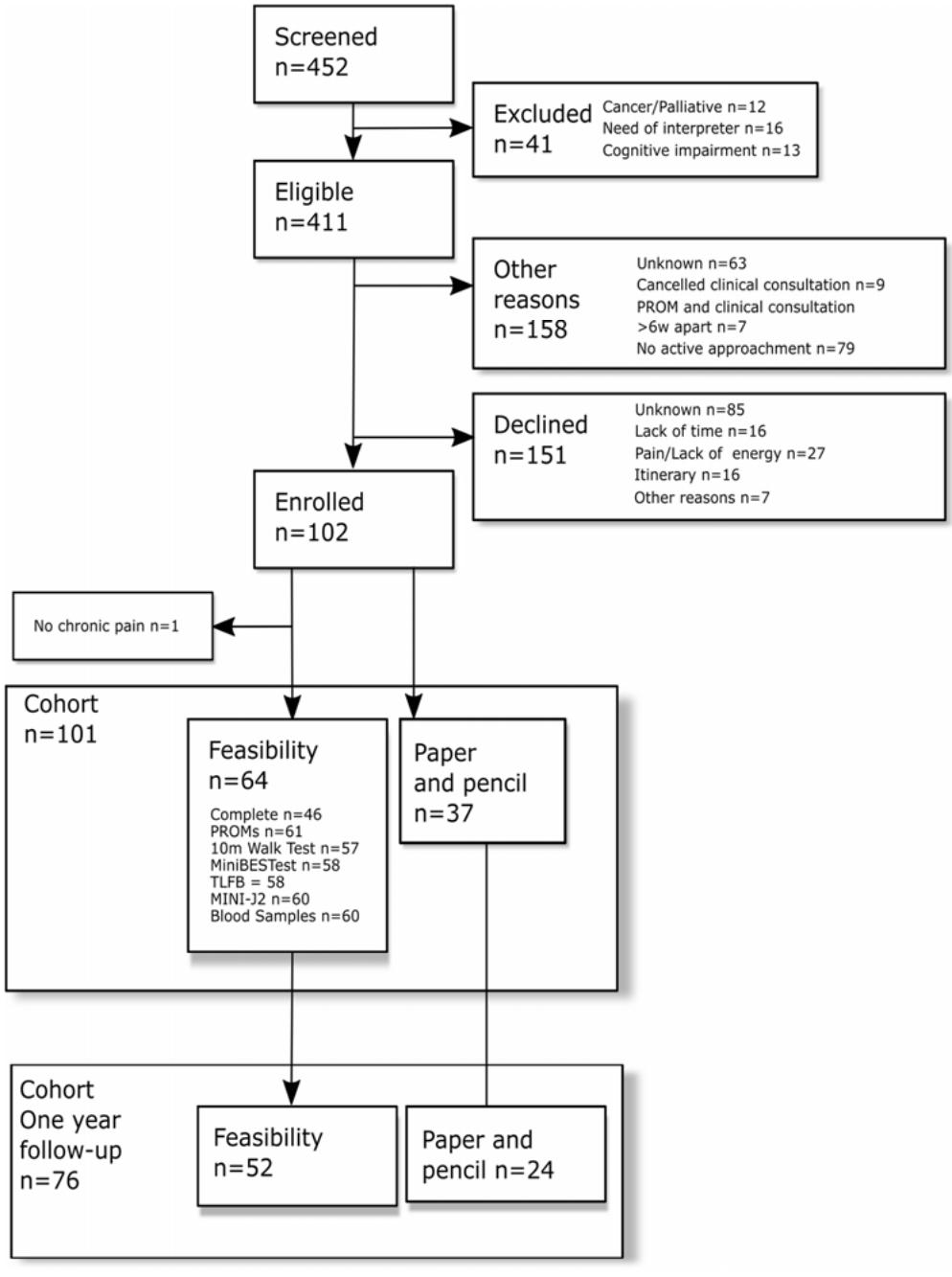

Figure 4 Number of eligible patients, recruitment and refusal rates, follow-up rates, and completion rates of PROMs, protocolized tests and interviews, in study II.

6.1.2 Self-reported opioid use and opioid use disorder

In study I, 20 (34%) participants reported opioid use during the past 30 days, of which 12 (20%) individuals had prescribed opioids.

Thirty-seven (58%) of the participants in study II reported any opioid use and 28 (44%) reported regular long-term opioid use. About 30% of those using opioids met the criteria for any opioid use disorder, of which 3 (8%) met the DSM-5 criteria for moderate or severe opioid use disorder. One-third of the participants were prescribed both opioids and benzodiazepines. Opioid use is described in Table 3.

Table 3 Sample characteristics regarding opioid use and opioid use disorder study II (N= 64)

Opioid use	***n (%*)***
Use of opioids	62
No use	25 (39)
Short-term or intermittent use	9 (14)
Long-term use with low to moderate doses (< 100 MME[1])	21 (33)
Long-term use with high doses (> 100 MME)	7 (11)
Opioid + benzodiazepines	7 (11)
Several opioids + benzodiazepines	13 (20)
Opioid Use Disorder (DSM-5)	60
No	49 (76)
Any	11 (17)
Mild	8 (12)
Moderate	1(2)
Severe	2 (3)
Tolerance[2]	11 (17)
Withdrawal[3]	7 (11)

**% of total sample*
[1] Oral morphine milligram equivalents
[2] Overlap 7 with any opioid use disorder, 4 with no opioid use disorder diagnoses
[3] Overlap 3 with any opioid use disorder, 4 with no opioid use disorder diagnoses

6.1.3 Agreement and reliability

In study I, the agreement between the ASI-SR and the ASI CSs measured with ICC was good to excellent for all domains, except for the family/social domain where the agreement was low. There were no significant differences between the ASI interview and the ASI-SR CSs, and there were no differences based on whether the participants completed the ASI-SR before or after the ASI interview.

For the ASI-SR CSs, Cronbach's α varied between 0.92 for the alcohol domain and 0.50 for the family/social domain.

Data comparing the ASI interviews and the ASI-SRs CSs respectively, internal consistency and reliability measured by Cronbach's α are presented are presented in Table 4.

Table 4 Comparisons between the ASI and the ASI-SR composite scores (CS), with respect to Cronbach's α, intraclass correlation coefficient (ICC), and score values in study I.

ASI Domain	Cronbach's alpha		ICC	n[1]	Score Values				
	ASI	ASI-SR			ASI CS		ASI-SR CS		
					Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	p-value[2]
Medical	0.85	0.77	0.86	52	0.39 (0.32)	0.33 (0.68)	0.38 (0.29)	0.38 (0.43)	0.67
Employment	0.70	0.64	0.94	50	0.48 (0.35)	0.50 (0.70)	0.47 (0.35)	0.50 (0.65)	0.15
Alcohol	0.92	0.92	0.98	50	0.41 (0.34)	0.31 (0.58)	0.37 (0.33)	0.23 (0.58)	0.31
Drugs	0.83	0.82	0.97	52	0.10 (0.15)	0.00 (0.23)	0.09 (0.14)	0.00 (0.15)	0.30
Legal	0.74	0.82	0.94	53	0.03 (0.11)	0.00 (0.00)	0.04 (0.12)	0.00 (0.00)	0.14
Family/social	0.64	0.50	0.61	52	0.22 (0.20)	0.18 (0.31)	0.17 (0.16)	0.16 (0.25)	0.07
Psychiatric	0.82	0.85	0.92	49	0.32 (0.24)	0.29 (0.43)	0.32 (0.25)	0.30 (0.45)	0.28

[1]*Pairs with no missing items in each domain*

[2]*Wilcoxon signed rank test*

The results in study II supported the use of self-reported measures for assessment of opioid use. Categories based on self-reported opioid use and categories based on prescribed dose and duration showed almost perfect agreement (κ=0.91) as measured with Cohen's κ. Furthermore, the agreement, measured with ICC, single measures, was excellent for both self-reported average opioid dose in week 1 and prescribed dose (ICC=0.86), and for the self-reported average opioid dose in week 1 and week 4 (ICC=0.79).

The number of identified opioid use disorder diagnoses according to DSM-5 exceeded the number of clinical opioid dependence diagnoses retrieved from the medical records. The agreement between opioid use disorder according to DSM-5 and clinical ICD-10 diagnoses for opioid dependence was fair when

measured with Cohen's κ (κ= 0.38), but almost perfect when measured with PABAK (κ= 0.90).

6.1.4 Sensitivity and specificity

Additional results, not presented in paper I, are the sensitivity and specificity analyses, examined with ROC analyses, as described in Figure 5. The ASI-SR alcohol- and drug CSs predicted clinical ICD-10 diagnoses for alcohol and drug dependence. With a cut-off value of 0.3, there was a sensitivity of 93% and a specificity of 89% of subsequent alcohol dependence diagnoses. With a cut-off value of 0.1, there was a sensitivity of 83% and a specificity of 95% for any drug dependence diagnoses, illustrated in Figures 5.

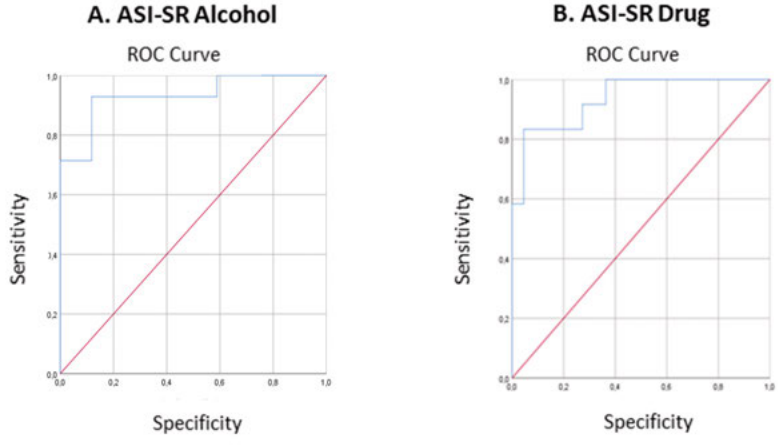

Figure 5 ROC curves for alcohol dependence diagnoses according to ICD-10 (n=31) and alcohol CS, and for drug dependence diagnoses according to ICD-10 (n=34) and drug CS**

**Cases used for the ROC-analyses of subsequent alcohol dependence and drug dependence diagnoses had complete CS data and had undergone psychiatric diagnostic assessment within three months of completion of the ASI-SR.*

6.1.5 Acceptability

In study I, feasibility and acceptance for the ASI-SR was good, and 50 participants (85%) found the ASI-SR easy to understand, 46 participants (78%) found the ASI-SR easy to complete, and 40 participants (68%) found the ASI-SR items to be relevant. The remaining participants were either neutral to, or did not answer, these questions.

In study II, participants reported acceptable satisfaction with their participation in the research study. A majority of the participants, 52 (81%), reported that they agreed or strongly agreed with the statement that they had received

sufficient information prior to the research visit, and 48 (75%) agreed or strongly agreed with the statement that it was easy to find the online PROMs and 41 (64%) with that it was easy to complete them. Sixty participants (94%) agreed or strongly agreed with the statement that interaction with research staff was good. Fifty-four (84%) agreed or strongly agreed that the research visit worked well in practice and 49 (76%) that the research visit required a reasonable amount of time (76%). Fifty-nine (92%) agreed or strongly agreed with the statement that they, on the whole, were satisfied with their participation in the research study.

6.2 Sense-making of opioid therapy for chronic non-cancer pain

6.2.1 Lived experience of managing chronic non-cancer pain with opioids

In study III, ten individuals with chronic non-cancer pain and long-term opioid therapy were interviewed. The demographics and medical data for the participants in study III are further presented in paper III.

Three super-ordinate themes emerged from the analyses: *Without opioids, the pain becomes the "boss"*; *Opioids as a salvation and a curse*; and *Acknowledgement of the pain and acceptance of opioid therapy enables transition to a novel self.*

The first theme represents that without opioids, the pain invades and takes over one's life. Life represents both the inner and the outer world, the life-world, which gets altered by pain.

The pain made the participants lose their identity and agency in the life-world. This is relevant for the understanding of why the participants chose to use opioids, in spite of the potential risks associated with opioid therapy. Thus, both pain and opioids had to be under control, to enable a life worth living. It was important for the participants to preserve or regain a "true" self, not altered by opioids or pain.

The second theme illustrates the paradoxical effects of opioids. Despite the beneficial relief of unbearable pain, opioids also generated problems such as dependence, addiction, and stigma. Those afflicted with addiction described a total loss of control, with escalating opioid doses and intensified pain. In some cases, methadone or buprenorphine agonist therapy became a turning point. It allowed a gradual decrease in the opioid dose, once the vicious circle of tolerance, withdrawal, and pain was broken.

Other participants emphasized that they were not addicted to the opioids. To them, opioids were not associated with euphoria, feelings of pleasure, or

loss of control. Instead, they viewed tolerance and withdrawal as natural consequences of long-term opioid use.

Not all participants accepted physical dependence as a part of their treatment, and they were intimidated by the long-term consequence of opioid use, i.e., tolerance and dependence. To them, it was important to know that they could get off the opioids whenever they wanted to.

The third theme exposes the lived experience of being a patient with chronic pain using opioids. It could be difficult to get an understanding for the pain and suffering, and many of the participants experienced that they had to justify their need for opioid medication, by convincing the healthcare providers of the severity of the pain. In contrast, when the pain was validated and taken seriously, the participants experienced how they could start to accept the pain, and the opioid therapy, and start a transition to a novel version of the self.

6.2.2 Understandings and conceptions about opioid prescribing practices and long-term opioid therapy

In study IV, fifteen attending physicians were recruited and interviewed. Information about the participants is further described in paper IV. The prescribers were situated in different healthcare regions, i.e., six in Uppsala, three in Stockholm, one in Östergötland, two in Jämtland-Härjedalen, and three in Västerbotten.

Six categories were identified: *The addictive opioid, The deserving patient, The lost patient, The ignorant prescriber, The compassionate prescriber*, and *The exposed prescriber* illustrating six ways of understanding what drives opioid prescribing practices from a prescriber's perspective. We clarified the differences in conceptions among the categories through three main contributors related to opioid therapy: prescriber's characteristics, patient's characteristics, and the healthcare organization.

The categories and how they are related to each other are depicted in the outcome space in Figure 6.

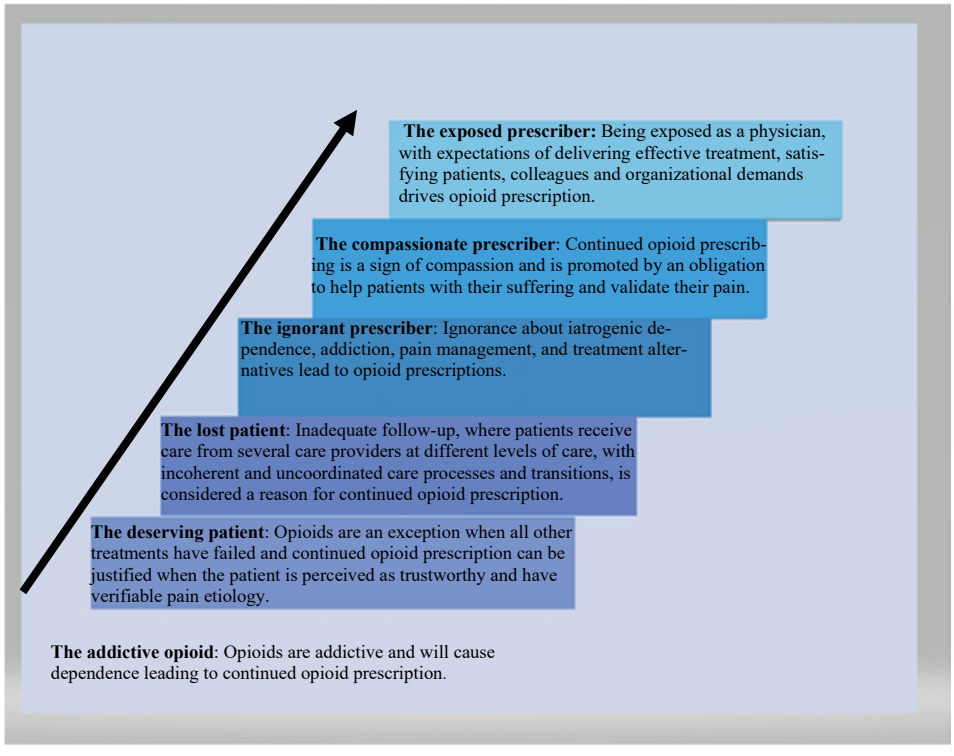

Figure 6 The outcome space illustrates the logical relationships between the categories. The categories are depicted as a hierarchy of six levels of understanding, ranging from the most rudimentary or basic level to the most complex level of understanding of how the interaction of patient's and prescriber's characteristics, together with the healthcare organization contribute to continued opioid prescription. The understanding and experience of opioids as addictive is the first level and the premise, the framework of understanding, and the other categories are defined as related, but qualitatively different parts of what makes the initial prescription of opioids become long-term opioid therapy.

Opioids were not considered as being suitable for long-term treatment, due to their addictiveness. The prescriber was thought to have a responsibility to inform patients about the risks with long-term use and explain when and how the opioids were supposed to be used. Even though opioids were seen as addictive, opioids *should* be used when clinically indicated. This could entail use for acute and post-operative pain and cancer pain. However, opioid therapy could also be an alternative for chronic pain when the pain was verified through objective findings and all other treatments had failed. If so, patients were to be perceived as trustworthy with no signs of current opioid abuse, and they should adhere to their treatment plans. Rules, as well as boundaries, were to be set out by the prescriber to avoid excessive opioid prescription. However, being able to assess whether a patient has a problematic opioid use and evaluate the putative beneficial effects of opioid therapy was conceived as

difficult. Furthermore, inadequate patient follow-up prevented the prescriber from following the patient over time and provide long-term and sufficient treatment. Thus, patients on opioids could be passed on from one prescriber to the next, without any plan for the opioid therapy or opioid cessation. To inherit patients on opioids was experienced as an ethical dilemma when the prescriber disagreed with the long-term opioid therapy for the chronic pain. However, often a pragmatic approach was described, prioritizing the patient-clinician relationship over opioid cessation, especially in cases where the patient used opioids as prescribed.

Prolonged opioid prescription was also conceptualized as a sign of ignorance and lack of knowledge about iatrogenic dependence, addiction, and pain management. Furthermore, the experience of feeling obligated to help patients with their suffering could result in opioids being initiated on the wrong indications, e.g., existential pain or mental illness, because the prescriber was emotionally affected by the patient's pain and suffering. Prescribing opioids could be understood as a sign of compassion and a way to validate the patient's pain, a sometimes misdirected benevolence. In situations where the prescriber perceived a responsibility for the patient's suffering, e.g., when patients with chronic pain, on opioids, suffered from iatrogenic opioid dependence with pain originating from healthcare related complications, treating the patients with opioids was understood as a way to redeem the damage done.

Being exposed as a physician, with expectations of delivering effective treatment, while satisfying patients, colleagues, and organizational demands could also drive continued opioid prescribing practices. In difficult and sometimes threatening situations where patients demanded refills of opioid prescriptions, it could be easier to just continue prescribing the opioids – a short-term solution for a long-term problem, helping the prescriber to avoid the patient's aversion and save time and effort.

7 Discussion

The studies in this thesis contributes with new insights on opioid therapy for chronic non-cancer pain in a Swedish healthcare context, and the findings are complements to previous research in this field. The European situation differs from that in North America. However, the different experiences and insights can promote an understanding of the difficulties associated with the treatment of chronic non-cancer pain with opioids, and the limitations and putative benefits of long-term opioid therapy (27).

7.1 Assessing opioid therapy for chronic non-cancer pain

As described, assessing if patients are suitable for opioid therapy or evaluating the effects of ongoing opioid therapy is challenging (87, 140). There is an ongoing discussion on how relevant the different diagnostic criteria for opioid use disorder or opioid dependence are, and how to apply them in a population with chronic non-cancer pain and opioid therapy.

The development of assessment methods for problematic prescription opioid use is not only relevant from an academic perspective, but it also has strong clinical significance. As Jane C. Ballantyne illustrated in her special commentary in PAIN 2015 (140), it is difficult to know when the physical dependence that arises in patients with long-term opioid therapy becomes addiction. How can impaired control over opioid use, compulsive opioid use, craving after opioids, and continued use in spite of adverse effects be defined in persons with opioid therapy and pain? And when and how do we determine when patients should be offered addiction treatment for their opioid dependence? This needs to be investigated further, and a variety of assessment tools, translated and adapted for Swedish conditions need to be validated in samples of individuals with chronic non-cancer pain in different clinical settings, to enable feasible, yet comprehensive enough, assessment and evaluation methods of opioid therapy. Here, the ASI-SR is one interesting option, given its multidimensional construct.

The results in Study I suggest that a self-administered form, based on the composite score items of the ASI, provides information about current substance use and related problems similar to that obtained through an interviewer

based ASI assessment. The ASI-SR demonstrated excellent discrimination between individuals with and without different substance use disorders, based on the ROC analyses. Even though this is an enriched population seeking treatment for substance use disorders, about half of the sample used for the ROC analyses did not have any alcohol use disorder diagnoses. In addition, about two thirds did not have any drug use disorder diagnoses, suggesting that ASI-SR works very well for assessing substance use disorders. Furthermore, considering the complexity of managing patients with chronic non-cancer pain, much of the information collected from the ASI-SR, such as medical and psychiatric problems, employment status, legal and family problems could help healthcare providers to conduct comprehensive risk assessments and treatment plans, as part of the routine care. The composite scores of the seven domains can also be compared for individual patients before, during and after treatment as well as among groups, facilitating treatment evaluation (92). It must be kept in mind that the ASI-SR was tested on a population with substance use disorders, which is why the results should not be extrapolated to a population with chronic non-cancer pain and need to be further validated in a population with chronic non-cancer pain and opioid therapy. However, the ASI has been used in samples with chronic non-cancer pain, and chronic non-cancer pain and substance use disorder, in previous studies (95, 141).

The TLFB was used for assessing self-reported opioid use. The results suggest that data were reliable. These observations are in line with previous research on self-reported substance use, especially regarding prescribed medications used regularly (142, 143). The TLFB made it possible to detect patterns of intermittent and regular use that could not have been retrieved from registers or medical records, supporting the use of self-reported data for the cohort studies. Furthermore, it allowed the participants to describe and elaborate on their opioid use facilitating an intersubjective understanding of when and how the opioids were used.

A little more than half of the participants with chronic non-cancer pain reported using opioids for pain management, and the high prevalence of opioid use in our sample is similar to what has previously been described in patients treated in specialized pain care (56, 144). It is noteworthy that almost one-third of the sample recruited from the pain center were prescribed both benzodiazepines and opioids, despite the known risks of this combination (76).

The presence or absence of opioid use disorder was evaluated with a modified version of the Swedish M.I.N.I. (J) interview performed by trained research personnel (87, 124). The rate of individuals meeting the DSM-5 opioid use disorder criteria among those reporting opioid use in the sample is similar to what has been found in other populations with chronic non-cancer pain and long-term opioid therapy. However, the proportion varies greatly depending on the method used for assessment and the criteria used to establish a diagnosis (21, 73, 87). The different diagnostic definitions in use make comparison of results challenging (145). However, our results suggest that the modified

version of M.I.N.I. (J) assesses opioid use disorder accurately in our sample. More individuals met the criteria for any opioid use disorder according to DSM-5, than the ICD-10 criteria for opioid dependence reported in the medical records. This is expected, since the ICD-10 opioid dependence criteria, similar to DSM-IV, correspond to moderate - severe opioid use disorder, rather than any opioid use disorder (146, 147). This was further supported by the almost perfect agreement between moderate - severe opioid use disorder and clinical opioid dependence diagnoses according to ICD-10.

Following the instructions for DSM-5 and rater instructions in M.I.N.I. (J), tolerance and withdrawal were excluded as criteria if the opioids were used as prescribed. Not all patients meeting any opioid use disorder criteria reported withdrawal and tolerance to opioids. Conversely, not all patients reporting withdrawal or tolerance met the criteria for any opioid use disorder, which is compatible with the construct of excluding these criteria in patients with opioid therapy (148). Before the DSM-5, the DSM-IV distinguished between substance abuse and dependence. The two disorders were assumed to be related, but DSM-IV placed dependence above abuse in a hierarchy by stipulating that abuse should not be diagnosed when dependence was present. The dependence diagnosis represented a strength of the DSM-IV approach to substance use disorders and was highly reliable (149). In the DSM-5 substance abuse and dependence were merged into a single diagnostic category, substance use disorder, where two or more symptoms fulfill the DSM-5 criteria for substance use disorder for the specified substance (148). Concerns that the threshold of two or more criteria is too low have been expressed, and that mild substance use disorder would have questionable clinical significance, and allows so much heterogeneity that the clinical and research utility of the diagnostic category would be compromised (150). However, moderate-severe opioid use disorder corresponds to DSM-IV opioid dependence, similar to ICD-10 opioid dependence criteria (146, 147), making it possible to assess severity and clinical implications for different treatment strategies. Furthermore, the lower threshold for the DSM-5 opioid use disorder diagnosis, compared to ICD-10 and DSM-IV opioid dependence diagnoses, may contribute to an earlier detection of problematic opioid use, guiding healthcare providers in clinical decision-making and leading to strategies such as closer monitoring, safer prescribing practices, and prioritizing non-opioid treatment alternatives.

The results suggest that with minor revisions of the M.I.N.I. (J), and training of research personnel, some of the difficulties in applying the DSM-5 opioid use disorder criteria to patients with chronic non-cancer pain and receiving opioid therapy may be overcome, while maintaining the credibility and standardization of the DSM-5 criteria.

Interviewer-administered assessment tools are typically psychometrically superior to self-administered questionnaires under research conditions with trained interviewers (151), but adherence to methodological standards is less reliable in regular clinical practice (151-153). It has been argued that the

difficulty in applying the DSM-5 opioid use disorder criteria to patients who are prescribed opioids for pain increases when the healthcare provider has inadequate training in pain and addiction medicine (154). This was something that was described in both study III and study IV. Specifically, patients described how they felt incriminated and accused of being addicts when they requested opioids for their pain, and they did not feel that their problems were taken seriously. When they met a healthcare provider who they felt was knowledgeable in both pain and opioid therapy, they were more inclined to adhere to treatment and try different strategies. The prescribers described similar problems concerning difficulties in assessing patients regarding opioid therapy, and communicating with patients about opioids, without offending or stigmatizing them. A picture of tacit assessments emerged, where the clinicians avoided uncomfortable uncertainties regarding adherence and maladaptive opioid related behaviors to come out in the open, resulting in a mutual feeling of distrust. Integrating structured standardized assessment methods, e.g., self-administered questionnaires or structured interviews, may facilitate communication about opioids and reduce the stigma related to opioid use. Self-administered questionnaires may be an alternative in settings where the time required to train staff and conduct interviews is considered prohibitive and thereby facilitate systematic, quantitative assessment, with little if any penalty in terms of psychometric performance (151). Structured interviews may, on the other hand, enable a therapeutic alliance and offer both the healthcare provider and the patient an opportunity to elaborate on their experience of the treatment offered and on what different alternatives are available.

Conducting structured assessments in a non-stigmatizing way may also make both the healthcare providers and the patients aware of problems related to opioid use, and thereby affect opioid related behaviors and decision-making, promoting safer opioid use and prescribing practices (87, 155). The ASI-SR, and the structured interviews TLFB and M.I.N.I. (J) were well accepted by the participants, suggesting that they offer ways to assess and communicate about opioid therapy without offending the patients.

7.2 Sense-making of opioid therapy for chronic non-cancer pain

In studies III and IV, the sense-making of opioids for chronic non-cancer pain was explored through lived experience and conceptions.

Opioids for chronic non-cancer pain was described as an exception, when all other treatments had failed. Opioids were seen as addictive and associated with abuse and related problems. Thus, opioids should not be prescribed without close monitoring from knowledgeable healthcare providers, and the benefits of opioid therapy had to be significant to justify continued treatment.

Opioid therapy was experienced as balancing between risks and beneficial effects, congruent with other qualitative research on chronic non-cancer pain and opioid therapy (156-159).

Pain as an intrusive experience was evident in many of the participants' narratives. The pain prevented the wanted life and the wanted self. This wanted self was often regarded as the true self, similar to what is described as the ideal (how one would like to be) and ought self (what one and others think one ought to be) according to the self-discrepancy theory (160). Living with pain was recounted as an existential void where agency and meaning were lost. Opioids could make the pain less intrusive, more predictable, and controllable, and decreased the discrepancy between the pain-afflicted self and the true self. This seemed to enable the participants to regain existential meaning and renegotiate their previous self, thus defining a novel sense of self. Therefore, opioids were accepted as a necessity for a tolerable quality of life, even though a life without opioids was also sought. However, abstention from opioids was not the main goal. Instead, functional goals were the first priority, e.g., being able to return to work, to function as a parent, and to engage in activities important for creating a meaningful life. The participants also made a distinction between physical dependence and addiction, where dependence was accepted as a tolerable side-effect among the pain sufferers, while the prescribing physicians were more concerned about dependence and addiction. This is consistent with other findings, where patients consider pain-relief to be more important than opioid dependence, while physicians report more concerns about physical dependence and problematic opioid use (161-164).

Nevertheless, a downward spiral of escalating pain and uncontrollable opioid use, was described by some of the participants using opioids for managing pain. Here, poor pain relief, rather than craving for the drug, led to drug-seeking behaviors. This is similar to what has been called "pseudo addiction," a clinical concept that has been questioned, not the least due to the opioid epidemic in the U.S. and the related over-prescription of opioids (81, 165, 166). However, problematic opioid use, driven by pain rather than drug cravings, is consistent with the concept of refractory opioid dependence in patients with chronic pain, introduced by Ballantyne and colleagues (32). They propose that the brain adaptations that arise in individuals with long-term medical opioid use are comparable to those that arise in patients with non-medical opioid use. The consequences will be very similar to those accounted for in study III. Therefore, if problems should arise for patients prescribed opioid therapy, the solution cannot be abandoning or rejecting them, as they struggle with their pain, and with established dependence. Instead, alternative treatments should be offered, e.g., other pharmacological treatments, multi-modal pain rehabilitation, opioid cessation, and if that fails, opioid agonist therapy with buprenorphine or methadone (167, 168).

Here, the pain in combination with escalating opioid use caused considerable limitations in the patient's life, pre-occupied the conscious mind, and

limited social interactions and pleasurable experiences. Furthermore, both opioid use disorder and chronic non-cancer pain, and in particular their combination, may be experienced as shameful and stigmatizing (169, 170), which contributed to individual suffering and difficulties in receiving adequate treatments and help (171).

Using opioids to control or treat pain is similar to what is described as a moral struggle by Edwards et al. (172). Opioid therapy for chronic non-cancer pain seemed to underline the moralistic aspects of using an addictive drug for pain treatment, for both patients and healthcare providers. The prescribers experienced an ethical dilemma in providing a treatment associated with known risks and few benefits, while trying to maintain a therapeutic alliance with the patient. This created a conflict between a compassionate opioid prescribing practice and a fear of subjecting patients or the community to risks and harm, similar to what has been described in previous research (159, 173, 174). On the other hand, a moralistic view of opioids seemed to increase the inclination of physicians to focus on either the use of opioids or the chronic non-cancer pain, instead of both, creating a reductionist approach (171). The focus on the risks associated with opioids can be perceived as an under-recognition and under-treatment of pain and as an inability of healthcare providers to show compassion for the suffering. Here, this resulted in conflicts and feelings of distrust and abandonment, and sometimes hopelessness. Instead of getting acknowledgement for the complexity of uncontrollable pain and opioid use as a shared problem pertinent for both parties to solve, the repeated contacts with medical care were seen as drug-seeking behaviors and malingering, rather than a legitimate cry for help. However, when the participants in study III, felt that they were being met with compassion and had their suffering acknowledged and validated, they experienced feelings of hope which enabled a transition to a novel version of self and life. What the participants describe is an example of how patients and their healthcare providers engage in participatory sense-making, creating a narrative for the opioid therapy and pain without shame and stigma (105, 108).

Prescribing opioids as a way to express compassion and validate patients was not unproblematic for the prescribers. It could be difficult to meet a suffering patient because of the expectations, stemming both from the patient and from the prescriber him/herself, to relieve the suffering and pain. Relational continuity and shared decision-making could outweigh the inconvenience and the feeling of inadequacy that occurred when denying a patient continued opioid therapy, thus leading to continued opioid prescribing practices. Allowing compassion related processes to guide clinical decision-making has been associated with successful clinician-patient interactions (175), and can enable a patient-centered care. However, using opioids as a way to validate patients and express compassion is problematic if the opioids are not clinically indicated.

Both studies III and IV illustrate how clinician-patient interaction and shared decision-making is impeded by incongruent care-transitions, ignorance about pain, pain management and opioids. Furthermore, a perceived lack of time, resources, and treatment alternatives prevented evidence-based practice, and a person-centered care, despite the common understanding that healthcare providers should strive for a person-centered approach when treating patients. Person-centered care has been prioritized on the agenda of policy makers as a means to empower patients and improve health outcomes (176, 177). Patient-centered care involves considering the biological, psychological and social aspects of patients' health, seeing the 'patient-as-person', recognizing that illness has a personal meaning, and striving for a sharing of power and responsibility between the healthcare provider and the patient. In summary, the healthcare provider should be sensitive to the patient's need for information and sharing in the decision-making. Further, a therapeutic alliance between the healthcare provider and the patient, should be sought, with common goals of therapy. An intersubjective understanding of the patient's experience and an awareness of how the healthcare provider's own subjectivity may influence his or her decision-making when practicing medicine, is a prerequisite for a person-centered care (178). However, the healthcare organization disenabled the physicians to follow patients over time, thus impeding them to take full responsibility for the patient's opioid treatment, leading to uncertainties regarding the opioid therapy. This was experienced as aggravating shared decision-making regarding the opioid therapy, e.g., try alternative treatments to opioids and discontinuation of opioid treatment, which is consistent with previous research (179, 180). It also made it harder to communicate about opioids without making the patients feel offended or stigmatized. The findings illustrate how healthcare providers tend to use ground rules, generic information about risks, or reference to guidelines and clinical regulations instead of using a compassionate person-centered approach with shared decision-making when denying patients increased or continued opioid prescriptions. These findings are consistent with previous research (163, 181-183). Lecturing patients and using generic information, as opposed to offering individual counseling, may disempower and invalidate, rather than educate, the patient. Altogether, the findings reveal how complex it is to provide a safe and evidence-based care, and still be able to validate the pain, show compassion as well as convey to the patients that they are being cared for (184, 185).

7.3 Methodological considerations

The current thesis has several limitations that need to be considered when interpreting the results.

7.3.1.1 Internal and external validity

Several methodological issues related to the design of the studies could have affected the results. In study I, the ASI interview and ASI-SR were completed on the same occasion, which could bias the responses. Nonetheless, because the order of the questions is not the same in the ASI-SR as in the ASI interview, and the number of items and questions asked in the interview is much larger, we believe this confound is less likely. This is supported by the observation that there was no order effect on the outcomes.

In both study I and study II, clinical diagnoses were used for assessment of reliability, and the results should be interpreted with some caution. Considering the number of sources of error that can occur during the clinical diagnostic process, the reliability and validity of clinical diagnoses, especially regarding substance use disorders, vary considerably (186). However, in study I, the substance use disorder diagnoses were established in a specialized addiction medicine clinic, suggesting reliable and valid diagnoses. In study II, the lack of gold standard for assessing opioid use disorder in patients with prescription opioids and chronic non-cancer pain impedes valid comparisons between constructs and assessment methods. This could have been overcome using inter-rater assessments or intra-rater test-retest assessments, but that was not considered feasible due to staff and respondent burden, given the already strenuous research protocol.

In study II, no item in the U-PAIN acceptability form asked specifically about the structured interviews assessing opioid use. However, the participants rated their experience of the data collection procedures, and interaction with research staff, and had a possibility to write an additional comment. No participant commented on the interviews, and the participants were overall satisfied with the research visit, suggesting that the TLFB and the M.I.N.I. (J) were well accepted.

The large proportion of eligible individuals who were approached that did not consent to participate and the small sample sizes in the studies, raises concerns about external validity in studies I and II.

The low participation rate in study I, together with the small sample size of comparably well-educated treatment seeking participants (187), recruited at a single site, limits generalizability. Compared to other Swedish ASI samples, our participants reported similar severity regarding substance use, and psychiatric symptoms, although they reported fewer problems regarding employment, legal, and family and social relationships (187, 188). This result is not surprising, given that much of the ASI data in Sweden have been retrieved from social services and the criminal justice system.

Although the results from study I are based on a sample from tertiary healthcare they cannot, as mentioned earlier, be generalized to a population with chronic non-cancer pain, since the ASI-SR was tested in a substance use disorder population, with only a small proportion of the participants with

prescription opioid use disorder. Concerning the participation rate in study I, it is fairly typical for what is seen in substance use disorder populations (189), and recruitment was made consecutively to enable variation in the sample.

In study II, the low participation rate and the limited exploration of demographic factors other than age, gender, or care unit, for those who did not consent to participate limit the generalizability of the findings. For the future cohort study, a more thorough characterization of non-participants will be required to enable strategies for adjustments of possible selection bias (190). Furthermore, the small sample sizes may jeopardize the statistical validity in studies I and II. However, for detecting an ICC of 0.85, assuming a power 80%, α=0.05 and acceptable ICC (q0) set to 0.70 is achieved, a sample of 53 persons would be sufficient (191). Moreover, the number of subjects required in a 2-rater study to detect a statistically significant κ ($p \leq 0.05$), with 80% power, at a proportion 10% of positive diagnoses, assuming the null hypothesis value of Kappa to be 0.40, is 39 (192), suggesting the sample sizes in both studies I and II were adequate for measuring agreement and reliability.

7.3.1.2 Trustworthiness, credibility and transferability

In studies III and IV, qualitative methods were chosen to explore opioid therapy for chronic non-cancer pain from both the patients' and the healthcare providers' perspectives. Qualitative method helps bridge the scientist - practitioner gap, by systematically illuminating individual experience in the healthcare context. Furthermore, qualitative method allows an immersive exploration, and an intersubjective understanding of the complex chronic non-cancer pain and opioid therapy phenomenon.

Procedures to enhance the standards of rigor, trustworthiness, credibility and transferability were used in the qualitative studies. These included engaging in reflexivity throughout the research process. The interviewer established the credibility of the findings by summarizing and clarifying ambiguous or indistinct statements during the interviews, and semi-structured interview guides were used to ensure consistent probing among all participants (193). The interviewer and the analysts were trained in qualitative methods and experienced in carrying out qualitative research. Trustworthiness was also established by using a multi-analyst, interdisciplinary triangulation, and through a thorough literature review to identify any gaps in the existing literature regarding chronic non-cancer pain and opioid therapy. To reduce the influence of the literature on the thematic and categorical construction, the literature reviews for comparative analyses with existing research were conducted after the data were analyzed. Auditability was established by consistently following the format for coding and sampling, as suggested for IPA and phenomenography (133, 134, 194). Fittingness, or the transferability of findings, was confirmed by comparative analysis of the findings with existing literature. However, there are still limitations that need to be addressed.

In study III, recruitment of participants went through gatekeepers, entailing a risk that participants were chosen for other qualities than being suitable for this study, e.g., a good relationship with a gatekeeper or good treatment response. Still, all our participants had long histories of opioid therapy, and a variety of experiences related to pain and opioid treatment, generating data with richness and depth.

In study IV, all but one interview, were conducted by telephone which could have affected the quality of the data. However, telephone interviews enabled recruitment of participants from different regions of Sweden, and facilitated participation, hence the participants could schedule an interview at their convenience, both regarding time and place. Furthermore, the participants were allowed to choose the mode of interview administration, and attending physicians are often confident in communicating by telephone. Given that the phenomenographic analysis relies heavily on transcripts, nonverbal data may not actually be used. Also, unlike in face-to-face interactions, everything has to be articulated in a telephone interview. This need for full articulation may contribute to much richer transcripts for analysis (195). This was supported by the richness and depth of the data generated by the interviews, enabling a thorough exploration of conceptions related to opioid prescribing practices.

In study III, the findings were based on a small selected group of individuals with chronic non-cancer pain treated in tertiary care, thus, results, should not be generalized to all patients with chronic non-cancer pain and opioid therapy or to other clinical settings. In accordance with the IPA methodology, with detailed accounts of individual experiences, empirical generalizability was not sought; rather we sought a theoretical transferability, where the reader can make links between the findings, the extant literature, and their own professional experience (133).

In study IV, the findings were based on a small selected group of prescribers from different medical specialties. Given the difficulties in recruiting participants, especially from primary care, some perspectives and variations of the phenomenon might be unexplored. Nevertheless, the fifteen participants had a long experience of prescribing opioids, as well as a variety of experiences related to pain management. Furthermore, the study included a diverse group of prescribers from different specialties and settings, generating a wide range of variation in understandings of what makes initial prescription of opioids become long-term opioid therapy. Recruitment continued until categorical saturation was achieved, suggesting an adequate number of participants.

Qualitative research is at times limited in its transferability. Nevertheless, concepts such as stigma, the pain afflicted self, patient safety, person-centeredness, need for knowledge, and how individual- and organizational factors contribute to clinical decision-making, are similar for patients and healthcare professionals, regardless of the healthcare setting (196). Thus, the lived experiences and understandings of managing chronic non-cancer pain with long-

term opioid therapy, emerging from the narratives included in this thesis, may be transferable to other contexts and settings.

7.3.2 Ethical reflections

Persons suffering from substance use disorders and chronic non-cancer pain disorders are often viewed as having character flaws, leading to shame and stigma. Thus, it was crucial to have an ethical awareness and to protect the participants' privacy and integrity when conducting the studies. All studies in this thesis required a lot of time and engagement from the study participants. Therefore, it was important to establish that participants were confident in study participation and that they were comfortable with sharing the requested information. This was ensured by transparent recruitment procedures, and the participants in studies I–III were assured that their decision whether or not to participate in the research study would not affect their future care.

When doing the research interviews, the interviewer used a compassionate approach to establish a trustful relationship with the participants, where the interviewer and the participant were equals. By promoting openness and transparency during the interviews, the participants could choose what information to share and to discuss matters pertinent to them and their experiences.

One ethical aspect of using standardized and structured assessment methods is that it enables a fair and open assessment, that is not only based on the healthcare provider's own subjective attitude to opioid therapy. This can empower the patient and promote a shared decision-making. It can also ensure a more equal care, based on the evaluation of the treatment outcome, and not based on the patient-healthcare provider relationship.

7.4 Future research

The large individual variation in response to opioid treatment is well-known, but it remains largely unknown to what extent this variation is a determinant of individual risk and benefit. The ongoing U-PAIN cohort, which is the context of study II in this thesis, offers a thorough biopsychosocial characterization of enrolled participants and the possibility to examine predictors of risks as well as benefits of opioid therapy. The U-PAIN cohort can contribute to a better understanding of factors that help identify patients who are safe candidates for opioid treatment and those who are not. The project can contribute with a scientifically valid biopsychosocial screening algorithm based on the results of the comprehensive data collection. The advantage with this approach is that it will enable an assessment of opioid therapy with regard to functional outcomes, beyond mere measures of pain severity and opioid use disorder. This offers a possibility for tailored treatment strategies. Identification of patients at risk of iatrogenic opioid use disorder can help avoid this

complication, while allowing for safe prescription of opioids in tertiary care settings to those who have good therapeutic effect of opioids with low risk of developing opioid use disorder. It could also contribute to the establishment of a gold standard for assessing problematic opioid use in the context of long-term opioid therapy and chronic pain.

Furthermore, studies on long-term opioid therapy with regard to benefits and risks, which also examine how this differs between different levels of care, medical specialties, and healthcare providers, are called for.

Finally, the results of this thesis suggest that structured assessment of opioid therapy enables a non-stigmatizing communication about opioids. This hypothesis should be tested using qualitative, observational, and experimental designs. However, before this can be examined, assessment tools, such as the ASI-SR, need to be translated, adapted for Swedish conditions, and validated in different samples of individuals with chronic non-cancer pain.

7.5 Conclusions

The studies suggest that the examined assessment methods of self-reported substance and opioid use were feasible for monitoring patterns of prescription opioid use. To manage chronic non-cancer pain with opioids was experienced and conceptualized as a balancing act between pain control, together with improvement of function and quality of life, and aversive effects of opioids such as dependence, opioid use disorder, along with stigma, and shame.

- The ASI-SR was found to be a feasible and reliable alternative to the ASI for assessing current patient functioning and evaluation of problematic alcohol and drug use.
- The U-PAIN protocol was well accepted and feasible for recruitment, and data collection, but participation rates were low. The use of both the TLFB and the modified version of the M.I.N.I. (J) was feasible and well accepted for the assessment of self-reported opioid use patterns in patients with chronic non-cancer pain in a specialized care setting.
- The lived experience of managing chronic non-cancer pain entailed the importance of control, regarding both pain and opioid use. To accomplish this, trust between patients and healthcare providers was essential for satisfactory treatment.
- Long-term opioid therapy was explained as the last resort when all other treatments had failed because of the negative pharmacological side effects of opioids, including opioid use disorder. Measurable improvements in function and quality of life were understood to justify the long-term use of opioids. Factors contributing to clinically unindicated continued opioid prescribing practices were understood as characteristics of both the patient and the prescriber, and the healthcare organization.

7.6 Clinical implications

The ASI-SR, and the structured interviews, TLFB and M.I.N.I. (J), may provide methods to assess and communicate about opioid therapy without offending the patients. They offer an opportunity to have a broad implementation of structured, quantitative assessments of patients with chronic non-cancer pain and opioid therapy, seeking treatment in regular clinical care. Broadly implementing this type of strategies is critical for allowing treatment interventions to be matched with individual patient needs and for evaluating the extent to which these interventions result in an improvement. Thus, they can provide tools for risk mitigation strategies and treatment evaluation, which can be applied before and during opioid therapy. Furthermore, structured assessments may facilitate an intersubjective understanding of the patient's experience of the treatment offered. If there is no evidence of significant benefit from the opioid therapy, the prescriber should provide support to the patient to taper the opioids, given the known risks associated with long-term opioid therapy.

The results in this thesis underline the stigma related to chronic non-cancer pain, and especially chronic non-cancer pain and opioids. It highlights the importance of an ethical awareness on the part of the healthcare providers, treating an already vulnerable group.

In summary, measures of the opioid therapy's effectiveness, a choice of alternative evidence-based treatments, and accurate information about the treatments proposed from knowledgeable healthcare providers, are required to enable safe and clinically relevant opioid therapy. The aim should be to provide a person-centered care, where the therapeutic alliance lies not in agreement, but in respect for the patient's experience, so that treatment can be on the basis of a shared reality and not that of misunderstandings.

8 Svensk sammanfattning

Långvarig opioidbehandling, här definierat som opioidanvändning i mer än tre månader, har ökat lavinartat i västvärlden under de senaste tre decennierna. Inte minst på grund av den så kallade opioidkrisen i USA, där alltför vidlyftig opioidförskrivning bidragit till situationen, har opioidbehandling vid långvariga smärttillstånd blivit alltmer kontroversiellt och ifrågasatt. Även om situationen i Europa och i Sverige inte går att jämföra med den nordamerikanska, så har erfarenheterna därifrån belyst riskerna med överförskrivning av opioider. Dessutom är evidensen för den kliniska nyttan med långvarig opioidbehandling vid kroniska smärttillstånd begränsad.

Denna avhandling ingår i ett större projekt som undersöker fördelar och risker med långvarig opioidbehandling. Projektet är en del av forskningsprogrammet U-PAIN vid Uppsala universitet och Smärtcentrum, Akademiska sjukhuset. U-PAIN är ett tvärvetenskapligt forskningsprogram för klinisk och translationell smärtforskning.

Det övergripande syftet med avhandlingen var att bidra med kunskap om långvarig opioidbehandling vid kroniska icke-maligna smärttillstånd, genom att undersöka olika bedömningsmetoder för substansanvändning och opioidbrukssyndrom, samt utforska patienters och vårdgivares upplevelser och erfarenheter av - samt uppfattningar om - opioidbehandling vid långvarig smärta.

Studie I var en reliabilitetsstudie av en svensk version av självskattningsformuläret Addiction Severity Index Self-Report form (ASI-SR). Genom att jämföra resultaten från ASI-SR och den svenska ASI intervjun, undersöktes om ASI-SR ger likvärdig information som intervjun. Vidare undersöktes intern reliabilitet, samt sensitivitet och specificitet för kliniska substansbruksdiagnoser. Femtionio individer som sökte vård på en beroendepsykiatrisk klinik rekryterades till studien.

Studie II var en intern feasibility-studie av en prospektiv kohortstudie: U-PAIN-kohorten. Syftet med kohorten är att identifiera prediktorer som kan identifiera vilka som riskerar att utveckla problematiskt opioidbruk, och vilka som kan ha nytta av långvarig opioidbehandling. Syftet med feasibility-studien var att undersöka hur rekrytering, datainsamlingsmetoder och utfallsmått fungerade. Sextiofyra deltagare med långvarig icke-malign smärta rekryterades från ett multidisciplinärt smärtcentrum. För att samla in data om opioidbruk användes strukturerade intervjuer som validerades mot diagnos- och förskrivningsdata inhämtat från deltagarnas patientjournaler.

Studie III och IV var kvalitativa intervjustudier. I studie III användes tolkande fenomenologi för att utforska upplevelsen av att hantera långvarig smärta med opioider. Tio individer med långvarig smärta och opioidbehandling intervjuades. I studie IV användes fenomenografi för att utforska 15 specialistläkares uppfattning om vad som bidrar till att tillfällig opioidförskrivning övergår till långvarig behandling.

Överenstämmelsen mellan ASI-SR och ASI intervjuns resultat var god, och den interna reliabiliteten var acceptabel för 5/7 domäner. ASI-SR visade även god sensitivitet och specificitet för kliniska substansbruksdiagnoser.

Självrapporterade data gällande opioidanvändning överensstämde väl med data som inhämtats från patientjournaler. ASI-SR och de strukturerade intervjuerna som undersökte opioidanvändning var väl accepterade av studiedeltagarna.

Att hantera långvarig smärta med opioider upplevdes som att balansera smärtlindring mot risker förenade med opioidanvändning. Upplevda negativa aspekter av opioidbehandling var opioidberoende, känslor av skam och upplevd stigmatisering. Opioider uppfattades som det sista behandlingsalternativet när alla andra behandlingar misslyckats. Opioidbehandling upplevdes dock i vissa fall som livräddande, där opioiderna var det enda som möjliggjorde ett fungerande liv. Därför kunde mätbar smärtlindring, samt förbättring av funktion och livskvalitet rättfärdiga långvarig opioidbehandling.

För att balansera risker och fördelar med opioidbehandling bör denna utvärderas regelbundet. Sådan utvärdering bör ske på ett icke-stigmatiserande sätt och främja en intersubjektiv förståelse av patientens situation. Det behöver inte betyda att vårdgivare och patient alltid måste vara överens, men behandlingsinsatserna bör bygga på en respekt för patientens upplevelse och erfarenhet, för att möjliggöra en person-centrerad vård, där vården är baserad på en gemensam bild av verkligheten och inte på missförstånd eller misstänksamhet.

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