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LOW-DOSE METHADONE AS ADD-ON TO ONGOING OPIOID TREATMENT IN CANCER-RELATED PAIN

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THESIS FOR DOCTORAL DEGREE (PhD)

By

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To my family

"If you make listening and observation your occupation, you will gain much more than you can by talk."

Robert Baden-Powell, founder of the scout movement

ABSTRACT

Background: In complex cancer-related pain in imminently dying patients, even high doses of ordinary opioids may have an insufficient effect. The addition of low-dose methadone to another ongoing opioid has been proposed as a treatment option. The aims of this thesis were to study different aspects of low-dose add-on methadone to another ongoing opioid in specialized palliative care in Sweden.

Patients, methods and results: In Study I, the medical records of 80 patients prescribed low-dose add-on peroral methadone to an ongoing opioid were assessed retrospectively. Eighty percent reached better pain control. Delirium and sedation increased near the end of life, but no serious adverse events were registered. In Study II, data on 4780 patients from 60 specialized palliative care units were analyzed. Methadone was safely prescribed, even in home care, to 8.6% of the patients (n=410), 96% of whom received it as a low-dose add-on for complex pain. In total, 94% were reported to benefit. Study III was a qualitative study to explore different aspects of methadone use. Semi-structured interviews were conducted with 30 physicians in specialized palliative care and pain medicine. Attitudes to methadone were reported not to affect its use as an analgesic and methadone was reported to achieve a best effect in situations of long-term opioid use with insufficient pain improvement and cases with central sensitization. Pain from skeletal metastases in the spine or pelvis were described to benefit particularly well. Cancer of the prostate, breast, kidney, pancreas, and sarcoma were reported as typical benefitting diagnoses. In Study IV, the daily symptoms of 93 imminently dying patients prescribed pain management via continuous subcutaneous infusion were followed. Improvement of pain, but unchanged prevalence of delirium, regardless of age, was seen in all patients. Low-dose add-on methadone was safely used in the patients with the highest initial pain. The daily median start dose of methadone in all studies was reported as 5 mg, increasing to a maximum of 20 mg.

Discussion: Studies I-IV report that dying patients with complex cancer-related pain may obtain improved pain control from low-dose add-on methadone to another ongoing opioid, with limited side-effects. Attitudes to methadone seem not to be an obstacle to its use. Continuous subcutaneous infusion of opioids, including low-dose methadone, can effectively and safely reduce pain in the imminently dying patient without an increase of delirium, regardless of age. Overall, low-dose add-on methadone may be considered a valuable tool for pain management in selected patients with cancer-related complex pain in specialized palliative care.

LIST OF SCIENTIFIC PAPERS

This doctoral thesis is based on the following four original papers, referred to in the text by their Roman numerals (I-IV):

I. Furst P, Lundstrom S, Klepstad P, Runesdotter S, Strang P.
Improved Pain Control in Terminally Ill Cancer Patients by Introducing Low-Dose Oral Methadone in Addition to Ongoing Opioid Treatment.
Journal of palliative medicine. 2018;21(2):177-81.

II. Furst P, Lundstrom S, Klepstad P, Strang P.
The Use of Low-Dose Methadone as Add-On to Regular Opioid Therapy in Cancer-Related Pain at End of Life: A National Swedish Survey in Specialized Palliative Care.
Journal of palliative medicine. 2020;23(2):226-32.

III. Furst P, Lundstrom S, Strang P.
Methadone in Swedish specialized palliative care - Is it the magic bullet in complex cancer-related pain?
PloS ONE. 2020;15(4):e0230845.

IV. Furst P, Lundstrom S, Klepstad P, Strang P.
Continuous subcutaneous infusion for pain control in dying patients: experiences from a tertiary palliative care center.
Manuscript. (Accepted for publication in BMC Palliative Care, Nov. 5, 2020)

ADDITIONAL PAPER NOT INCLUDED IN THE THESIS

Strang P, Fürst P, Schultz T.

Excess deaths from COVID-19 correlate with age and socio-economic status. A database study in the Stockholm region

Ups J Med Sci. 2020 Nov;125(4):297-304.

CONTENTS

LIST OF ABBREVIATIONS

AIP	Ambulatory Infusion Pump
b.i.d.	Prescribed twice a day
CAM	The Confusion Assessment Method
COX	Cyclooxygenase
CSCI	Continuous Subcutaneous Infusion
CYP	Cytochrome-P Enzyme
DSM	The Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
ECOG	The Eastern Cooperative Oncology Group
ELQ	End-of-life questionnaire
ESAS	The Edmonton Symptom Assessment Scale
IASP	The International Association for the Study of Pain
IPOS	The Integrated Palliative Care Outcome Scale
IQR	Inter Quartile Range
IV	Intravenous
M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide
MEDD	Morphine Equivalent Daily Dose
MET	Methadone group
MMT	Methadone Maintenance Therapy
NMET	Non-methadone group

NMDA	N-methyl-D-aspartate (receptor)
NRS	Numeric Rating Scale
OIBD	Opioid Induced Bowel Dysfunction
OIH	Opioid-induced hyperalgesia
PPI	Proton Pump Inhibitors
QTc	Q-T Time (on ECG, c=corrected for heart rate)
RASS	The Richmond Agitation and Sedation Scale
SC	Subcutaneous
SR	Sustained-Release
SRPC	The Swedish Register of Palliative Care
VAS	Visual Analogue Scale
WHO	The World Health Organization

1 PERSONAL INTRODUCTION

As a newly trained physician around the turn of the millennium, I had a hard time deciding the direction that my career should take, and I worked as an anesthesiologist, pediatrician, and internist. For some time, I also worked as physician in the archipelago of northernmost Norway. Back home, by chance, I started working with people dying of cancer who were cared for in their own homes, i.e., in specialized palliative home care. The work was very challenging and combined many exciting medical disciplines such as pharmacology, physiology, psychiatry and communication skills. Above all, together with the team, I was able to make a difference for these suffering patients and their families, who often felt abandoned by the rest of the healthcare system. The job felt very meaningful. I had found my medical direction, and I wanted to continue working with these patients. Through the specialty of geriatrics, I became a specialist in palliative medicine.

Cancer-related pain is usually a symptom that must be alleviated before one can even consider helping patients with their other problems. Supportive talks are not an option when the patient is in severe pain that takes all his or her attention.

Still, pain can be different even in cancer. Working in a palliative care service at Nacka hospital in the middle of the 00s I found the cancer-related pain in some patients harder to treat than usual, the regular drugs did not help. In complex cases where I struggled to provide good analgesia, there was always the possibility that pain relief was difficult to reach because of existential, psychological, social, or other factors. Sometimes, however, I felt this could not be the only explanation.

In connection with some of these more complex pain situations, I had contact with the pain clinic at Södersjukhuset hospital. They sometimes recommended the addition of a low dose of methadone to the patients' already ongoing opioid. In some cases, this regimen did not help, in other cases it seemed to contribute to a much better analgesia.

When I started working at Stockholm Sjukhem in 2011, it turned out that the physicians there had, since the middle of the 00s, following the publication of Mercadante et al., also used low doses of methadone in a similar way [1]. My curiosity was thus aroused. I wanted to find out more about the use of low-dose add-on methadone, but the existing literature on the subject was limited.

Thanks to the unique expertise in palliative research available at the research department at Stockholm Sjukhem, together with a warm and welcoming attitude, I had the opportunity to

transform my curiosity about low-dose methadone into a graduate program as a doctoral student.

2 BACKGROUND

A top priority for both dying patients and their families is a pain-free status at the end of life [2]. In its definition of palliative care the WHO emphasizes the importance of identifying physical and other symptoms in order to prevent and relieve suffering [3]. The adequate control of pain and other symptoms in patients with life-threatening diseases, resulting in improved quality-of-life for both patients and their families, is important [3]. To achieve this goal, effective treatment options are needed.

Opioids are the basis for the relief of moderate to severe cancer-related pain [4]. Sometimes rotation from one opioid to another can contribute favorably to further improved pain relief [5]. Methadone is an opioid that, due to its unique pharmacodynamic properties, is occasionally turned to for managing complex cancer-related pain. Its complex pharmacology presupposes knowledgeable and experienced users, familiar with the drug. This can be a barrier to its use and therefore safe alternative methods, to take advantage of the properties of methadone, would be of great value in achieving better pain relief for some patients.

This literature review aims at providing a background for understanding the mechanisms and effects behind the novel use of low-dose methadone as an add-on to other regular opioids for pain management in end-of-life cancer patients.

2.1 CANCER-RELATED PAIN

Management of pain is a common clinical problem in cancer patients. In a review of 122 articles van den Beuken - van Everdingen et al. reported that cancer-pain prevalence, despite treatment, was 40% after curative treatment, 55% during anticancer treatment, 66% in advanced, metastatic, or terminal disease and 51% in all cancer stages. Thus indicating that pain treatment for cancer patients remains suboptimal [6].

Moreover, untreated pain has been reported to accelerate death by limiting mobility, increasing physiological stress, and increasing the risk of complications, e.g., pneumonia and thromboembolism [7, 8]. Nevertheless, pain management in palliative care patients with advanced cancer has improved over the last few years due to a better understanding of pain mechanisms, new guidelines, and attempts to tailor a mechanism-based treatment targeting each pain component (e.g., nociceptive somatic, nociceptive inflammatory, neuropathic pain etc.) [4, 6, 9-11].

2.1.1 Pain, definitions

In July 2020, the International Association for the Study of Pain (IASP) introduced a new definition of pain, replacing the previous one that had been unchanged since 1979 [12]. More than before, the new definition emphasizes the individual's own experience of pain.

Pain: an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.

Six key notes are associated with this definition:

- 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 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; an inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

Other essential definitions are:
Nociceptive pain: pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.

Neuropathic pain: pain caused by a lesion or disease of the somatosensory nervous system

2.1.2 Pain assessment at the end of life without self-reporting

In most settings pain intensity is assessed with, for example, a visual analogue scale (VAS) or a numeric rating scale (NRS) [13]. However, as their disease progresses, the dying patient's ability to verbalize pain deteriorates. The delirium prevalence in cancer patients in a palliative setting is reported to be between 13 and 42% and may increase to 88% at the end of life [14-17]. The absence of reported pain does not necessarily mean that the patient is not experiencing pain or that the pain has resolved. Therefore, when assessing pain in dying patients who have had pain in the past and for whom it has become more difficult to communicate, it must be assumed that the pain is still present [18].

Due to the practical difficulties of studying pain in imminently dying patients, this is an under-researched area, a gap in the knowledge that needs to be covered.

2.1.3 Complex pain

The term complex pain in this text, although not an official term, refers to pain that is refractory or partially refractory to first-line treatments, but often involves both nociceptive and neuropathic pain components and where central sensitization plays an important role. Examples of first-line treatments are opioids and/or COX-inhibitors for nociceptive continuous visceral cancer-related pain and gabapentin and/or amitriptyline for neuropathic cancer-related pain [19, 20].

Moreover, there are novel treatments emerging in regards to nociceptive inflammatory and/or neuropathic pain, e.g., a Swedish group reported that supplementation with vitamin D may reduce opioid consumption in patients with cancer-related pain and concomitant vitamin D deficiency [21-23].

Opioids are often effective as first line treatments in nociceptive cancer-related pain but have variable and often inadequate effects on neuropathic and mixed nociceptive-neuropathic pain. For the treatment of neuropathic pain components in cancer, which partially differs from the treatment of neuropathic pain in non-cancer conditions, opioids are often combined with tricyclic antidepressants, gabapentin or pregabalin and/or serotonin-noradrenaline reuptake inhibitors as well as with steroids and non-steroid anti-inflammatory drugs in cases with inflammatory components [24].

2.1.4 Central sensitization

Complex pain is often due to a combination of nociceptive and neuropathic pain mechanisms and management often remains a challenge [25-27]. Central sensitization can cause an accelerated state of pain despite no progressive tissue damage and is defined by IASP as an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input [12, 28-30].

This central sensitization, which is associated with a decreased opioid sensitivity, is partly mediated by activation of the N-methyl-D-aspartate (NMDA) receptor [31, 32]. There is also evidence that NMDA receptors are involved in the development of allodynia, hyperalgesia, opioid tolerance and opioid resistant neuropathic pain [33].

Recent research has proposed the possibility that neurons can fine-tune NMDA receptor signaling by shifting the ratio of the expressed four subunits that compose NMDA receptors,

so called GluN subunits [34]. Thus, the selective expression of NMDA receptors containing distinct GluN isoforms provides new opportunities to study functional properties relevant to neuronal receptors [34].

2.1.5 Opioid rotation and opioid combination therapy

Rotation to another opioid is an option when the first-line opioid provides inadequate pain-relief or intolerable adverse effects. The success rate has varied from 50-80%, but only when rotating to methadone a reduction in morphine equivalent daily doses (MEDD) could be seen, indicating that methadone has properties that differ from other opioids [35-37]. An additional important explanation for why opioid rotation can be successful is that there often may exist a cross-tolerance between opioids, meaning that the new opioid has a better analgesic effect than expected from equianalgesic tables. Therefore, a lower start dose is often chosen with reduced adverse effects [38].

An example of a clinical situation where morphine adverse effects may occur due to accumulation of the renally eliminated morphine metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) is in progressive terminal renal impairment at the end of life. M6G contributes to analgesia but M3G is more associated with central adverse adverse effects, such as delirium and myoclonus, and the development of opioid tolerance [39]. Rotation from morphine to oxycodone, fentanyl, hydromorphone or methadone may then improve the analgesic effect and reduce adverse effects, even in the severely ill patient [40].

However, a review by Schuster et al. in 2018 confirmed the stated findings in the Cochrane review from 2004 that, although widely practiced, robust evidence for the benefit of opioid rotation is still lacking, mainly due to methodological limitations [41, 42].

Combining two opioids is another theoretical option for improving analgesia aimed at limiting the development of opioid tolerance and decreasing opioid adverse effects. The rationale comes from laboratory research that reported an additive analgesic effect when methadone was combined with oxycodone and fentanyl, while combination with morphine or diamorphine revealed even a synergistic effect [43].

Overall, the evidence concerning opioid combination therapy is limited and there is so far, mainly due to practical and patient safety reasons, only a weak recommendation to support it [44].

2.1.6 Opioid-induced hyperalgesia (OIH)

Opioids that are intended to abolish pain can sometimes unexpectedly aggravate it instead, particularly in cases of rapid opioid dose escalation. In particular, opioids generating active metabolites, such as morphine-3-glucurionide, have been associated with OIH [45, 46]. NMDA receptors are thought to play a role and the addition of NMDA-receptor inhibiting drugs, together with a reduction of the opioid dose, can significantly diminish the worsened state [47-54].

2.2 METHADONE

The opioid methadone was synthesized by Hoechst in Germany in 1938, initially in the search for a spasmolytic drug, and its analgesic properties were not primarily appreciated at the time. The name derives from fragments of its chemical name: 6-di**methy**l**a**mino-4,4-**d**iphenyl-3-heptan**one** [55]. Methadone is used for methadone maintenance therapy (MMT) of both opioid use disorder and chronic pain patients and is recognized as an important analgesic drug [56, 57].

2.2.1 Pharmacodynamics

Methadone has unique analgesic properties. It stimulates both regular mu, kappa and delta opioid receptors, has N-methyl-D-aspartate (NMDA) receptor inhibiting effects and affects the reuptake of serotonin and norepinephrine in the pain modulating descending tracts in the medulla [31, 58-60]. The *R*-isomer of methadone has opioid receptor affinity, and the *S*- and *R*-isomers have comparable NMDA receptor antagonism [60]. It is the *S*-isomer of methadone that is a potent inhibitor of serotonin and norepinephrine uptake [60]. Methadone binds to the NMDA receptor to the same degree as ketamine [60].

2.2.2 Pharmacokinetics

Methadone is a lipophilic opioid with high oral bioavailability, generally over 85%. The recommended parenteral dose is usually, not least because of safety reasons, 50-80% of the oral dose [60, 61]. By analogy, the established recommendation for conversion from parenteral to oral methadone has been 1:2. However, recent research suggests that the analgesic effect may be maintained, while the risk of drug-related adverse reactions such as drowsiness and myoclonus may be reduced, with a more conservative parenteral to oral conversion ratio of 1:1.2 [62].

Oral administration is followed by rapid gastrointestinal absorption with measurable plasma levels at 30 minutes. The peak plasma levels after a single oral dose occur at four hours and

begin to decline 24 hours after dosing [60]. Methadone is metabolized in the liver mainly via CYP3A4, and with a lesser involvement of CYP2D6 and CYP2C8, and 20-50% is excreted via the kidneys, the rest via feces [60, 63-65]. In anuric patients, elimination is exclusively via the fecal route. Dosage adjustment is not required in renal insufficiency, nor in hemodialysis. Additionally, methadone does not appear to produce active, potentially toxic metabolites [60, 65].

Racemic methadone has a biphasic elimination with a rapid initial distribution phase within 2-3 hours, followed by a prolonged terminal elimination phase, the half-life varying greatly in length from 5 to 130 hours with a mean of approximately 20-35 hours [60, 66]. The biphasic elimination contributes to the fact that despite the long half-life, the drug's analgesic effect at the start of the treatment is only 5-6 hours and with longer treatment the effect lasts for 8-12 hours [67]. The half-life is shorter in subjects on chronic methadone therapy, probably due to autoinduction of methadone's metabolism. It is generally considered that a steady state is reached after 3 to 5 times the half-life for a drug, after regular dosing is started. It therefore may take from one day to several weeks to reach steady-state levels of methadone [66].

2.2.3 Methadone as a long-acting agent

Methadone is considered a long-acting agent [68]. Before the oral slow-release preparations of opioids were introduced in the late 1980s, methadone was occasionally used for long-term relief of opioid-sensitive nociceptive pain when a more long-lasting effect was wanted. Because a primary μ-receptor effect was then sought, relatively high doses were required. A standard dosing schedule was 10 mg up to every 4-5 hours for the first 24 hours before switching to dosing three times a day [69]. During the first few days of treatment, the duration of analgesia did not differ significantly between morphine and methadone but became more pronounced with long-term treatment [70].

2.2.4 Methadone as an analgesic in cancer-related pain

Today, methadone is internationally recommended as a second-line opioid in the management of cancer-related pain [71]. It is predominantly used for switching from another opioid to improve the balance between analgesia and adverse effects [71]. The combination of opioid agonism, no active metabolites, as well as NMDA receptor inhibition, could potentially provide analgesic effects with fewer adverse effects than other opioids [67]. However, several reviews have reported high-dose methadone in cancer-related pain to be similar or better in effect compared with both morphine and transdermal fentanyl, but with a higher frequency of somnolence and dropouts from studies [35, 36, 65, 71-74]. The need for

dose escalation of methadone over time is usually limited [71, 73, 75]. Despite some evidence for an analgesic effect in chronic neuropathic pain [76], the Cochrane reviews from 2017 concerning methadone for cancer pain and neuropathic pain in adults could not draw any final conclusions regarding differences in efficacy or safety between methadone and a placebo, other opioids, or other treatments [77]. This was mainly due to small and low-qualitative studies.

Methadone is often considered as an alternative or complement to other opioids when they do not have the expected effect, which can often be due to the fact that the pain is not purely sensitive to μ-receptors, and other mechanisms also need to be taken into account, such as inhibiting NMDA receptors [71].

2.2.5 Practical obstacles

Despite its reported unique properties, many clinicians are reluctant to use methadone because of its complex pharmacokinetics and numerous drug interactions [66].

In some patients, even low doses of methadone can result in an opioid overdose [78]. It is known that pain stimulates the respiratory drive in the respiratory center in the brain stem [79, 80]. If methadone is given for pain that has insufficiently responded to regular opioids but responds well to the partially unique properties of methadone, probably particularly NMDA receptor inhibition, it may contribute rapidly to better pain relief. If good pain relief is obtained and the stimulating effect of the pain on the respiratory tract hence decreases, the risk of overdose with subsequent respiratory depression increases [79, 80]. It seems that even low doses of add-on methadone can have this effect and may thus contribute to a relative opioid overdose when combined with high doses of common opioids (such as morphine, oxycodone, hydromorphone, or fentanyl). A similar effect may be seen in individuals who are methadone naïve because they metabolize methadone more slowly than patients using methadone regularly [61].

Furthermore, conversion from another opioid to methadone demands caution since the potency ratio from morphine to methadone varies and can be difficult to predict, exemplified by Ripamonti et al. who found a conversion dose ratio from 2.5:1 to 14.3:1 in patients with advanced cancer taking a pre-rotation MEDD of 145 mg opioid per day [81]. However, conversion ratios are in general dose-dependendent in relation to MEDD and there are practically useful conversion tables that can be applied. In all studies in this thesis, MEDD were calculated according to guidelines from the MD Anderson Hospital (Houston, TX) [82].

Clinicians may also hesitate to prescribe methadone as an analgesic due to the social stigma surrounding its use in the treatment of heroin (diamorphine) abuse [83].

2.2.6 Adverse effects of methadone

Mu-receptor related adverse effects of opioids are equally common with methadone, including constipation, OIBD (opioid induced bowel dysfunction), delirium, sedation, nausea, hypotension, miosis, and respiratory depression. [65, 67, 71, 72, 77, 84].

Long-term opioid treatment may also have endocrine effects. Rhodin et al. compared chronic pain patients treated with strong opioids, mostly methadone, for more than one year with a control group of chronic pain patients without opioid treatment [85]. Differences were found regarding the pituitary-gonad and pituitary-adrenal axis, including prolactin levels, indicating an opioid effect causing endocrine dysregulation. Typical symptoms were sedation, sweating, sexual dysfunction, gynecomastia, and low physical and emotional functions. An important finding was that function and quality of life was better in the control group of pain patients despite no differences in pain between the two groups.

2.2.7 Interactions with other drugs

Many medications can increase or decrease levels of methadone in the body. Weschules et al. found in a review of 200 articles that the evidence base associated with methadone drug interactions is underdeveloped in general, as most of the references found were case reports or case series from the MMT population, which may differ significantly from the cancer pain population [86]. Further, they highlighted that genetic polymorphism associated with the cytochrome-P enzymes (CYP) may have a bearing on methadone-related drug interactions [86].

Besides absorption, distribution and elimination, inhibitors and inducers of the CYP450 enzyme system are of importance for the metabolism of methadone [66]. Administration of CYP450 inhibitors will reduce methadone's metabolism, resulting in increased methadone levels. CYP450 inducers will have the opposite effect, which may even present as opioid abstinence symptoms.

Examples of drugs that may increase methadone concentration include antibiotics (ciprofloxacin, erythromycin, trimethoprim), antidepressants (citalopram, fluoxetine, sertraline, paroxetine), antifungals (fluconazole, ketoconazole), benzodiazepines (midazolam, diazepam, alprazolam), cardiac drugs (verapamil, nifedipine, amiodarone), NSAIDs

(celecoxib), neuroleptics (haloperidol), PPIs (omeprazole, esomeprazole, lansoprazole), TCAs (amitriptyline) and cannabinoids.

Medications that may decrease methadone concentration comprise anticonvulsants (phenytoin, carbamazepine, phenobarbital), antiretroviral agents (nevirapine, rifampin) and St John's Wort. [66, 87].

2.2.8 QTc prolongation

Prolongation of the QTc interval can potentially result in fatal cardiac arrhythmia, Torsade de Pointes, though it is very rare. Several drugs often used in specialized palliative care have QTc prolonging effects, such as neuroleptics, antidepressants, octreotide and methadone [88]. There are conflicting reports concerning the correlation between the total daily methadone dose and prolongation of the QTc interval [89-95]. QTc prolongations of >500 ms are considered to be clinically significant [96, 97]. Patients with cancer often already have an increased risk of QTc prolongation due to cardiotoxic chemotherapy, use of QTc prolonging medications, radiotherapy to the chest and electrolyte disturbances [98]. Lovell et al. found that clinically significant QTc prolongation was present in 10% of cancer patients using oral methadone regardless of a low (mean 14.4 mg) or high (mean 86 mg) dose [97]. In methadone maintenance programs for opioid use disorder, ECG monitoring is typically initiated at the start of treatment and is then regularly performed in patients on high doses (>100 mg daily) or in the presence of other QT interval prolongation risk factors, including heart or liver disease, electrolyte abnormalities, concomitant treatment with CYP 3A4 inhibitors, or other drugs with the potential to cause QT interval prolongation [99]. Overall, a dose higher than 30 mg of methadone daily seemed to add a risk of cardiac arrhythmia, but the benefits of methadone should greatly outweigh the risks of QTc prolongation, especially in patients receiving palliative care where doses of methadone often are 5-20 mg daily and ECG monitoring is usually not recommended [97, 100, 101].

2.2.9 The non-oral route

There are several reliable administration routes of methadone as the patient approaches the end of life and the oral route is no longer available. Conversion to intermittent IV or SC injections or continuous infusion via a syringe driver, are convenient in the palliative care setting. Unfortunately, SC methadone has been associated with subcutaneous erythema [102]. However, if the infusion site is rotated every one or two days or if the methadone is diluted, these reactions tend to be mild and manageable [103-106]. It has been reported in Germany that the levo-rotatory form of methadone (l/*R*-methadone) is not associated with local

toxicity, but the drug is not commercially available [107]. Methadone tablets or enemas that can be given rectally are often absorbed within 30 minutes and have a reliable oral to rectal dose ratio of 1:1. Oral solution can be used for sublingual or buccal administration effectively, but is limited by volume constraints (1-1.5 mL) [108].

2.2.10 Ambulatory use

There are concerns about methadone's safety for outpatient use in palliative care. Overall, there are only a few reports on methadone use in outpatient clinics or home care. The studies are almost exclusively about opioid rotation to methadone, which in an ambulatory outpatient setting appears to be safe, with typical success rates of 70-80% and final methadone doses well below 100 mg daily [109-115]. Hawley et al. reported few adverse effects and only 2.3% hospital admissions when slow transition to methadone was practiced in their outpatient palliative cancer clinic [116]. In a prevalence study on 21,219 hospice patients in a home-care setting in Philadelphia, methadone accounted for 1.7% of all long-acting opioid prescriptions during the study period [117].

2.2.11 Methadone in the elderly person

Reports indicate that frail elderly patients should be initiated on much lower doses of methadone, perhaps as low as 0.5 mg daily in the oldest population, although starting doses of 2.5 mg b.i.d. are commonplace, which is still a low dose [82, 118, 119]. This could be due to age-related changes including increased fat composition and age-related decreases in activity of CYP enzymes responsible for methadone metabolism, both of which contribute to a prolonged half-life for methadone. Especially in elderly individuals, "starting low and going slow", with a close follow-up, is central for the safe use of methadone [87].

2.2.12 Low-dose methadone as an add-on to regular opioid therapy

In patients with poor analgesic benefit after opioid dose escalation, the practice has long been to attempt a complete switch to methadone, with other opioids only being used for breakthrough pain [116]. In 2004, Mercadante et al. described a successful "opioid semi-switching" regime aimed at breaking opioid escalation and regaining analgesia in 14 patients with cancer-related pain who had raised their opioid doses more than 100% in the last week, where fentanyl or methadone, in an initial equivalent dose of 20 % of the previous regime, was added [1].

The next reports concerning adjuvant use of methadone as a low-dose add-on to an ongoing opioid therapy were the letters by McKenna et al. in 2011 and Haughey et al. in 2012,

reporting 10 and 3 cases, respectively [120, 121]. The idea was that low-dose methadone can be safely and successfully used as a co-analgesic to another opioid if introduced cautiously, thereby benefitting from the NMDA-receptor antagonism, without having to do a complete switch to methadone in the usual manner and simultaneously minimizing the risks associated with methadone's complex pharmacology. This simpler regimen was thought to potentially be of particular use in palliative care services managing severe pain in the outpatient setting [120].

There are a few rather small retrospective cohort studies [122, 123] that typically describe 2.5-5 mg b.i.d. of oral methadone added safely to a regular opioid for analgesia in complex cancer-related pain. Methadone doses are stabilized at 10-15 mg daily within a week, and improved pain control is reported in 49-75% of the cases. In a recent study from 2019, Chary described the use of an ultralow add-on regime, starting with 1 mg daily and increasing the daily dose by 1 mg once a week up to a maximum of 20 mg methadone daily, with a slow onset of analgesia [124]. Furthermore, Courtemanche et al. observed a plateau in response to an increasing methadone dose, suggesting that patients who responded to a low dose of methadone might not experience a further reduction in pain intensity if the methadone dose was increased, compared with if maintained at the same level [123].

At our own institution, the first clinical attempts to use methadone as an add-on drug were carried out about 15 years ago. The add-on low-dose methadone regimen is promising and could have the potential to change future medical practice, thereby improving quality-of-life for numerous patients.

2.2.13 Knowledge gap

The studies conducted on low-dose add-on methadone have shown promising results. The two larger studies of Wallace and Courtemanche are both retrospective observational studies that reported analgesic effect in some patients who received the treatment [122, 123]. The patients often had several months left to live. Courtemanche made an attempt to seek characteristics for those patients who seemed to benefit from low-dose add-on methadone. With multivariate analysis it was shown that subjects with a higher pain score intensity at initiation were more likely to respond to adjuvant methadone with analgesia during the first week, the only association found. Patients who had already responded to a low dose of methadone did not appear to benefit from a further dose escalation.

In all, this leads to questions as to whether the use of low-dose add-on methadone in patients with cancer-related pain can be successfully used even during the last days of life. Due to the

methodological difficulties of studying pain in imminently dying patients, this is an under-researched area. Would imminently dying patients benefit from add-on methadone and are there patients who benefit from it better than others? Which doses are adequate in dying patients? If low-dose add-on methadone is already an established treatment: how common is it, who prescribes it and to whom and how? What do dosages, opioid combinations and adverse effects look like? Can low-dose add-on methadone be safely used in home care? If methadone is best known in the context of opioid withdrawal, can attitudes toward methadone affect the conditions for using it for pain in palliative care? Thus, effects, adverse effects, prevalence of use, indications, practical use, and attitudes to methadone need to be further explored.

In addition, if low-dose add-on methadone is a good treatment, may it then be continued parenterally without risk of increased adverse effects, should the oral route become unavailable during the last days of life?

2.3 THE SWEDISH REGISTER OF PALLIATIVE CARE (SRPC)

The SRPC is a national quality register that contributes to the research and development of palliative care in Sweden [125]. The registration is made by the responsible staff through an online end-of-life questionnaire (ELQ) after the death of a person. The ELQ provides information concerning, for example, demographics, diagnoses, prevalence, and changes of either severe pain, breakthrough pain, anxiety, dyspnea, nausea, delirium, or death rattles during the last week of life. The questions reflect quality of care delivered during the last week of life, irrespective of age, diagnosis, or care setting. In 2016, when Study II was initiated, 10.8% of the 91,029 persons who died in Sweden were enrolled in specialized palliative care and registered in the SRPC, which corresponds to 90-100% of all patients that died in specialized palliative care [126]. In total, 64% of all deaths during 2016 were reported to the SRPC [126].

Since, anecdotally, low-dose methadone as an add-on is practiced by an increasing number of physicians nationally, particularly in palliative care, there is a need for further exploration of this topic. The SRPC network is well suited to provide the basis for investigations of prevalence and indications for low-dose methadone add-on therapy in cancer-related pain.

2.4 QUALITATIVE RESEARCH

Well-validated instruments are preferably used in quantitative research, e.g., in quality of life studies. A validated instrument has high validity (it measures well what it is intended to measure in a given context), reliability (the instrument produces consistent and reproducible

results) and sensitivity (the ability to find differences between groups). A disadvantage of such instruments with predefined questions best suited for a given context, is the risk of missing important aspects not asked about. For example, the same questions can be perceived, evaluated, and answered completely differently by a cancer patient when early on in the course of the disease, or when being close to the end of life.

Qualitative research methods can explore, uncover, describe, and understand what lies behind phenomena about which little is known and may often be used in the early phase of a study to explore an area on first entry into the field to obtain clarity or to clarify hypotheses [127]. Qualitative research that explores a partially unknown phenomenon is often a basis for planning a quantitative study. Qualitative research delineates different aspects of a phenomenon, whereas subsequent quantitative research quantifies the aspects.

However, qualitative research also has other areas of use. For instance, the qualitative method can be used to deepen the knowledge about outliers. As mentioned above, a predefined questionnaire risks missing unexplored areas. For example, the important aspects are known for a certain phenomenon which is then examined quantitatively with a questionnaire. If the vast majority respond positively to a central question and perhaps just five percent answer negatively, then interviews with these outliers can provide important knowledge about why the question did not suit them.

Qualitative methods can be very useful to produce new ideas and there is space within the research structure to explore new ideas as they arise [127]. Used along with other types of research it also gives additional perspectives on the problem, i.e., it can produce results that directly represent how people think and feel.

2.4.1 Qualitative interviews

In healthcare research, both semi-structured and in-depth interviews are common methods for data collection. In semi-structured interviews, a prepared interview guide with open-ended questions is applied. Follow-up questions are then used to further explore the phenomenon of interest [128-130]. To explore an issue in-depth, but perhaps not cover as many aspects, in-depth interviews can be used. The questions in such an interview should be open-ended, often neutral, sensitive and not difficult to understand [129]. The most important aspect during the interview is to try to capture as many details as possible and make sure to find and investigate new and unexplored information [129]. Instead of taking notes, audio recording of the interview can be a good way for the interviewer to both capture details and be able to be more

engaged during the interview. The recording is then transcribed verbatim or in a near-verbatim mode [131].

2.4.2 Sampling

Sampling in qualitative research is not based on the same scientific assumptions as in quantitative research. Quantitative research often uses total cohorts or large randomized samples and calculates probabilities. In qualitative research, where the goal is often to capture as many nuances of a phenomenon as possible, purposeful sampling is a common technique often used to identify and select information-rich cases [129].

There are various purposeful sampling techniques such as single significant cases sampling (to reach a more thorough understanding of the person), comparison focused sampling (people are selected to be compared and to find differences among them) and group characteristic sampling (cases are selected to create a group as rich as possible in information). One variant of group characteristic sampling is the so-called maximum variation sampling, where people are selected in order to find as varied characteristics as possible, but also common patterns.

In qualitative research, the sample sizes are often smaller than in quantitative research, typically 10-25 cases and the sample size is often not predetermined. Instead, an important concept is saturation, originally a concept in grounded theory [132]. Saturation roughly means that further data collection from additional cases does not provide much more new essential information and that the collection therefore can be completed [133].

2.4.3 Analyzing qualitative data

There are different approaches to analyzing qualitative data. Qualitative content analysis, which was used in this thesis, is a method used to explore the content and meaning of a text by systematically searching for and classifying data and ultimately shaping overarching themes based on the common data [128]. It is a step-by-step analysis that usually starts with reading the transcribed text repeatedly to really immerse oneself in it. Then meaning units are identified, i.e., short text segments representative of different aspects in relation to the research question. The meaning units are given short new names, codes, which are then compared and grouped into categories, i.e., groups with codes that have something in common. Finally, themes are searched for, i.e., threads through the data with a common underlying meaning [128, 134, 135]. In an inductive analysis, the data is interpreted bottom-up to create new concepts and categories that can be used to classify phenomena that have not yet been described or delimited in a precise way [129, 135]. In contrast, a deductive, or

abductive, approach means that data is analyzed based on an already existing theoretical framework, top-down [129, 135]. Additional important terms are latent and manifest. In latent analysis, the underlying meaning of the text is searched for and interpreted, while manifest analysis is more descriptive in its nature and focuses more on what the informants really said and stays close to the text [134].

To conclude, the choice of qualitative method is based on the research question and the type of phenomenon that is analyzed. The researcher, therefore, has to take into account different considerations such as the depth of the analysis, i.e., a descriptive analysis (mainly manifest data) or an interpretative analysis (latent data) and whether theories already exist that are useful as a theoretical framework for the analysis. If so, then a hermeneutic approach is possible for example, or, if the focus is on the process rather than the content, then Grounded theory could be an option.

2.4.4 Trustworthiness

Qualitative research is often based on texts originating in interviews or observations. A text always involves multiple meanings and there is always some degree of interpretation when approaching a text [134]. This is essential when discussing the trustworthiness of findings in qualitative content analysis [134].

Graneheim et al. described how research studies must be evaluated in relation to the procedures used to generate the findings to be as trustworthy as possible [134, 136]. The concepts of *credibility*, *dependability* and *transferability* were used to describe various aspects of trustworthiness in qualitative research [134].

Credibility is about how well the data and analysis really address what was intended to be investigated [134]. It starts with the structure of the study, for example how and in what context one intends to select participants and collect the data. Informants with different experiences increase the opportunity to shed light on different aspects. Then it is important to choose the most appropriate meaning units and categorize and create themes that cover the data. Credibility is also the demonstration of how to assess similarities and differences between categories, for example by presenting representative quotations from the transcribed text [134]. Another way is to seek agreement on how data is sorted among co-researchers, experts and participants [134].

Dependability is how much both the data collection and the researcher's decisions change during the analysis process [134]. Interviews and observations are developing processes

where the researcher continuously gains new insights about the phenomenon being studied and which can then influence follow-up questions or limit the focus of observation.

Transferability is the extent to which the results can be transferred to other settings or groups [134]. Here, researchers can only make suggestions, but it is the reader's decision whether the results can be transferred to another context. This is facilitated by providing a clear description of the participants' context, selection and characteristics, data collection and analysis process [134]. Also, a complete presentation of the results along with appropriate quotes improves the transferability.

In summary: whereas validity is a strength (informants narrate a picture that is valid to them) in qualitative research, results are not easily generalizable due to the methodological assumptions and, especially, due to the need of using purposeful sampling strategies. However, data may be transferable to similar contexts and in some cases also beyond the original context [127]. One example is the concept of SOC (sense of coherence) that was coined by Aaron Antonovsky. His original study was on females who survived Nazi camps, but since then, the concept of SOC has been applied to various contexts within health care.

In this thesis, qualitative research methods were required to enable an exploration of the attitudes and opinions of physicians, patients and their families regarding methadone and its potential role and current use.

3 AIMS

The overall goal of this thesis was to study the use of low-dose methadone in addition to other ongoing opioid treatments for complex cancer-related pain in specialized palliative care in Sweden.

The specific objectives of Studies I-IV were:

I. To investigate whether a low-dose add-on of methadone to another ongoing opioid therapy could contribute to pain relief in dying patients with complex cancer pain, as well as examining the possible adverse effects in the form of sedation, delirium and/or respiratory depression.

II. To investigate the use of methadone in specialized palliative care in Sweden and specifically explore the frequency of use, indications, doses, opioid combinations and adverse effects when using low dose methadone in combination with other opioids at the end-of-life.

III. With the aid of semi-structured interviews, to broaden and deepen the understanding of attitudes about, potential significance of and practical aspects regarding the use of methadone for pain in specialized palliative care. Further, to identify new areas of future research.

IV. To prospectively study analgesic and adverse effects when prescribing subcutaneous infusion via an ambulatory infusion pump to imminently dying patients in specialized palliative care with a special focus on add-on low-dose methadone.

4 MATERIALS AND METHODS

4.1 OVERVIEW

An overview of the materials and methods used in the studies in this thesis is provided in Table 1.

Table 1. Overview of materials and methods used in Studies I - IV

	Study I	Study II	Study III	Study IV
Design	Retrospective observational	Retrospective observational	Qualitative interview study	Prospective observational
Data source	Stockholms Sjukhem charts 2006-2013	Swedish Registry of Palliative Care 2017-2018	Physicians in specialized palliative care 2017-2018	Patients at Stockholms Sjukhem 2019-2020
Study time	Retrospective, already deceased	Retrospective, already deceased	When at work	End-of-life
Outcome	Intensity of pain Opioid doses incl. methadone Adverse effects	Prevalence, indications and reported effects Opioid doses incl. methadone Adverse effects	Attitudes to, indications for and practical use of methadone	Level of pain and other symptoms Opioid doses incl. methadone Adverse effects
Pain measurements	Interpretation of case records and VAS/ESAS, when available	VAS/NRS, ESAS or IPOS	-	IPOS
Methods of analyses	Wilcoxon signed-rank test, Chi-square test, Fisher's exact test	Chi-square test, T-test, Mann-Whitney U-test, Wilcoxon signed-rank test	Qualitative conventional content analysis	T-test, Chi-square test, Mann-Whitney U-test, Wilcoxon signed-rank test

4.2 STUDY DESIGN

This thesis includes four studies, all performed within specialized palliative care. Study I is a retrospective observational study that assesses pain, opioid doses, and adverse effects. Study II is also a retrospective observational study examining the prevalence of, indications for, doses of and reported effects of methadone treatment for pain. Study III is a semi-structured interview study to explore attitudes to and practical aspects of methadone for pain. Study IV is a prospective observational study to investigate symptoms, opioid doses including methadone doses and adverse effects in pain relief delivered via continuous subcutaneous infusion.

4.3 DATA SOURCES

4.3.1 Medical records - TakeCare

TakeCare is a single-sign-on medical system for medical records [137]. It connects staff to all other systems and handles electronic medical records, with one shared record per patient. TakeCare covers 90% of the care providers in Stockholm County [137].

4.3.2 The Swedish Register of Palliative Care

The Swedish Register of Palliative Care (SRPC) was established in 2005 and is based on a validated on-line end-of-life questionnaire (ELQ) with 30 questions that is completed soon after the death of a patient by the nurse or physician in charge. The questions reflect quality of care delivered during the last week of life. The SRPC is a national quality register and in 2019, it covered 60.2% of all deaths and close to all of the deaths in specialized palliative care in Sweden [125]. An important purpose of the registry is to contribute to research and development of palliative care in Sweden.

4.4 STUDY POPULATION

4.4.1 Study I

For the purpose of Study I, all deceased patients at the specialized palliative care unit at Stockholm Sjukhem Foundation who, during the years 2006-2013, received treatment with methadone for pain relief were identified within the TakeCare medical record system. The unit is a tertiary palliative care center for patients over 18 years of age and most patients suffer from advanced cancer. All identified patients who were prescribed a peroral add-on of low-dose methadone to another ongoing opioid therapy for cancer-related pain, constituted the study population.

4.4.2 Study II

For the purpose of Study II, all known specialized palliative in-care and home care units in Sweden using the SRPC were invited to participate by having an additional questionnaire added to their regular ELQ. This additional on-line survey covered the use of methadone in individual patients and was completed by the responsible registered nurse or physician. The participating units contributed to data collection for twelve months, with starts from January to June 2017. All patients registered by the participating units during the study period constituted the study population.

4.4.3 Study III

For the purpose of the qualitative Study III, we intended to capture the width of the information the participating informants could contribute to. Thus, the participants were selected with purposeful maximum variation sampling among physicians in active clinical service in specialized palliative and pain care in Sweden. We aimed for as much variation as possible in terms of age, gender, geographical place of work, level of education and experience. The prospective informants were contacted via email. Everyone who was contacted chose to participate in the study. The interviews were conducted at each informant's workplace from November 2017 to February 2018. The number of informants in the study was largely determined by when “saturation” began to be achieved, i.e., when the data obtained in each additional interview did not contribute to additional information of value and when increasingly clear patterns in the collected data could be seen. Saturation began to appear around 15 interviews and was clear at about 20 interviews. The data collection was continued to a total of 30 interviewed physicians in order to be able to assess with greater certainty that further aspects did not appear. Informed consent was obtained from the participants.

4.4.4 Study IV

For the purpose of Study IV, participation was asked of imminently dying patients who were neither sedated nor unconscious and who were prescribed continuous subcutaneous infusion (CSCI) for symptom control while admitted to the specialized palliative care in-patient unit at Stockholms Sjukhem. Informed consent was obtained from each patient and, thereafter, the patients were monitored for symptoms and medication daily until the end of life. Since this was a descriptive study no sample size was calculated.

4.5 DATA COLLECTION

4.5.1 Study I

In Study I, the data collection was exclusively performed using a manual review of medical records from deceased patients, covering the time from three days before methadone was initiated up to and including seven days after initiation. Background data were obtained from the medical records regarding, for example, demography and disease, the use of opioids and other medications.

Furthermore, two independent physicians read each patient record individually and, using a structured template developed for the study, made assessments from the records regarding pain type and intensity (no / mild, moderate or severe) that the patient appeared to have experienced during each separate day. In order to estimate the consistency of the pairwise assessments, the two physicians then compared their assessments. In 69% of the assessments, they had made exactly the same grading of pain intensity, a similar assessment (one pain level difference or less on a single day) in 25% and in only 6%, did the assessed pain levels differ by two steps. The deviating assessments were discussed together and after this the assessors agreed on all the pain assessments, which are presented in the study. Similarly, the presence or absence of confusion/delirium (based on DSM-IV criteria), sedation, and respiratory depression were assessed.

4.5.2 Study II

In Study II, data were used from both SRPC's regular ELQ and from the supplementary survey, which was mandatory to complete for participating units over a twelve-month period.

The regular ELQ, which in specialized palliative care in Sweden is completed for 90-100% of individual patients and covers the patient's last week of life, provides data concerning demographics, diagnosis, prevalence and changes in pain and other symptoms, i.e., nausea, dyspnea, anxiety or death rattles. It also reports whether validated assessment instruments for pain and other symptoms were used.

The supplementary survey questionnaire was designed to specifically examine the methadone use of each individual patient initiated on the drug during their time in specialized palliative care. The questions were developed through discussion by an expert group consisting of physicians with a broad expertise in pain treatment and pain research that included a professor of palliative medicine, an author of books on pain, a specialist in palliative medicine, an algologist, an anesthesiologist, a geriatrician, and an oncologist. Preliminary

questions were tested in a pilot study and revised three times before the study was launched. The questionnaire included questions about the indications and doses of methadone and other opioids. The effects on pain and possible adverse effects were based on patient-reported outcome measures and were transferred by the reporting staff to a four-point Likert scale where the effect of the methadone initiation was assessed on a scale from very good to no effect at all. Adverse effects were rated as present or not. In addition, the questionnaire included questions concerning the medical experience of the prescribing physician and whether any other specialist physician had been consulted regarding the use of methadone. (See Appendix I for the supplementary survey questionnaire of Study II)

4.5.3 Study III

In Study III, data was collected in the form of semi-structured interviews that were audio-recorded and then transcribed verbatim. Initially, the interview guide was pilot tested on two informants. The questions concerned attitudes to methadone and their prescription of methadone for pain in specialized palliative care. Question examples include: “Describe any occurring prejudices about methadone that you have encountered [in colleagues, staff, patients or their next of kin]”, “Tell me about your experience of treating pain over the years”, and, for physicians positive to methadone use: “Describe a patient who you would expect to benefit from the use of methadone for analgesia”. The open-ended character of the questions allowed, when needed, for follow-up questions. Also, further questions were added, and new emerging areas of interest were explored. The interviews lasted for 30-55 minutes. (See Appendix II for the semi-structured interview-guide of Study III)

4.5.4 Study IV

The patients in Study IV were at the absolute end of life with a gradual deterioration in the general condition to be expected. Therefore, it was a basic condition that the daily assessments of the patients' symptoms could be performed regardless of whether the patients could participate or not. The proxy version of the Integrated Palliative Care Outcome Scale (IPOS) was used to estimate patients’ symptoms and relatives' concerns. The Richmond Agitation and Sedation Scale (RASS) was used for assessing level of patient alertness, the Eastern Cooperative Oncology Group (ECOG / WHO) for performance status and the Confusion Assessment Method (CAM) instrument was used for assessing delirium. The patient's responsible registered nurse for the day completed the instruments after caring for the patient during his or her work shift. (See Appendix III for the start protocol of Study IV)

4.6 MEASUREMENTS OF SYMPTOMS AND ADVERSE EFFECTS

NRS/VAS, ESAS or IPOS constituted the basis for the evaluations of pain intensity and adverse effects in Studies I, II and IV. In Study I, a supplementary study-specific template was used for the assessment of the patients. Additionally, in Study IV, RASS, ECOG/WHO and CAM were used for assessments of adverse effects and other symptoms.

In Study II, pain intensity and adverse effect-reports were, in 84% of patients, based on NRS/VAS, ESAS or IPOS evaluations.

For missing data in Studies I and IV, last observation carried forward was practiced.

4.6.1 Study-specific template

In Study I, the information concerning the patients' intensity of pain and the occurrence of delirium and sedation were collected retrospectively from the medical records. Due to sparse registration, VAS/NRS registrations were not a reliable source of information. Therefore, in addition, the assessing researchers used a template as follows:

With few or no descriptions of oral complaints (awake patients) or pain behavior (anxiety, grimaces, etc. in unconscious patients) the pain was classified in the records as none or mild. The need for single extra doses of analgesics, a few complaints of pain or a more regular pain behavior (unconscious patients), was judged as moderate pain. Descriptions of significant pain or use of regular rescue doses was considered as presence of severe pain. Whether delirium was present or not was classified based on the DSM IV criteria. In the same way, sedation was judged as either no sedation or any degree of sedation. The assessments of respiratory depression related to respiratory rate, and impaired respiration was considered to exist if there were notes from physicians or registered nurses about clinical signs of respiratory depression (e.g. "breathing slowly" or "only eight breaths per minute").

In order to strengthen the assessments, the templates were used by two independent reviewers (physicians) who performed their assessments separately and then compared their findings. In cases of initial disagreement, the patient was discussed, and a consensus was found.

4.6.2 Visual Analogue Scale (VAS) and Numeric Rating Scale (NRS)

The Visual Analogue Scale (VAS) and the Numerical Rating Scale (NRS) are 11-point graded (0 = no symptom, 10 = worst possible) scales for the self-reporting of pain or other symptoms in cognitively intact adults. Of these, NRS is recommended on the basis of higher compliance rates, better responsiveness, and ease of use relative to VAS, especially in elderly persons [13].

4.6.3 Edmonton Symptom Assessment Scale (ESAS)

ESAS is a clinical tool to document the symptom burden in patients with advanced cancer admitted to a palliative care unit covering pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, feeling or well-being and an optional category, often used for sleep or constipation [138]. Over the years, ESAS has evolved. Initially, each symptom was assessed in a VAS (visual analogue scale) format, but this has today often been replaced by the 11-point NRS (numeric rating scale) format. A one step change is considered a minimal clinically important difference [139].

4.6.4 Integrated Palliative Care Outcome Scale (IPOS)

IPOS consists of 10 questions regarding symptoms, anxiety, anxiety in relatives, feelings of being at peace, need for information and practical problems [140]. There is a patient-reported version and a staff version (proxy rating). The questions are answered on five-point Likert scales. The staff version enables assessment even when the patient is unable to self-report and was used consistently throughout Study IV. IPOS was used to prospectively assess patients' symptoms and relatives' concerns, as well as the variables for pain and anxiety on a daily basis. The assessments referred primarily to the patient's situation during the past 24 hours. IPOS has been validated in Swedish and is widely used in specialized palliative care in Sweden [141].

4.6.5 Richmond agitation and sedation scale (RASS)

The RASS is a 10-point scale assessing level of consciousness and agitation, ranging from +4 (combative) to -4 (unarousable). Zero means alert and calm and corresponds to the neutral level [142]. RASS was originally developed for intensive care but has been validated for patients being treated with palliative sedation and is reliable for patients both with and without sedative drugs. RASS has no subscales, is fast, clear and easy to use. It has a high inter-rater reliability and high validity with other scales [142]. It is available in Swedish [143].

4.6.6 ECOG/WHO

Performance status according to ECOG/WHO is a simple scale without subscales developed for cancer patients that indicates an assessment by a physician or nurse regarding the patient's general condition. The scale comprises six steps from 0 (manages all activity without limitation) to 5 (dead) [144].

4.6.7 Confusion Assessment Method (CAM)

CAM is an instrument consisting of four questions to assess whether delirium is present or not in a patient, based on DSM criteria [145]. It is short and fast, validated, and frequently used in research. It has been translated into Swedish. CAM is not considered appropriate for grading the severity of delirium [146].

4.7 DATA ANALYSES

4.7.1 Statistical methods

The statistical analysis used in the studies are listed in Table 1. Overall, standard descriptive statistics were used for patient characteristics, including presentation of medians with interquartile ranges and means with standard deviation.

Comparisons

In Studies I, II and IV, t-tests were used for the calculations of statistical significance between groups with normally distributed data. Otherwise, non-parametric tests were used, Chi-square for comparison of proportions or Fisher's exact test for small groups. The Mann-Whitney U test was used for comparing independent groups and the Wilcoxon signed-rank test for dependent groups, respectively. In all calculations a p-value < 0.05 was considered statistically significant.

4.7.2 Qualitative content analysis

A qualitative conventional content analysis in accordance with the description of Hsieh et al. was performed [128]. This method is often applicable when there is only a limited amount of literature or theory about a phenomenon. The analysis followed the following steps:

1. In order to delve deeper into and become better acquainted with the material, the texts were read through several times.
2. The text was then read carefully word for word to identify meaning units, i.e., words or text segments, important patterns and subjects of potential interest with respect to the research question. The short segments were given short names, as preliminary codes.
3. Based on meaningful differences and similarities, the preliminary codes were sorted into groups, ie., preliminary categories. As far as possible, the informants' verbatim formulations were used.
4. The preliminary categories were compared and then carefully examined to find the core meaning. They were also compared to detect any overlap.

5. Finally, the preliminary categories were combined and four final categories or themes, were created. These four final categories represented different aspects of the underlying meanings of what the informants had presented.
6. The final categories were discussed by the researchers and revised as needed to achieve agreement.

The free software OpenCode 4.0 from Umeå University was used to manage the data [147].

4.8 ETHICAL APPROVAL

Ethical approval for all four of the studies was obtained from the Regional Ethical Review Board in Stockholm with the following diary numbers:

- Study I: 2013/1814-31/2, 2014/835-32
- Study II: 2015/1486-32
- Study III: 2017/2302-32
- Study IV: 2018/2103-31/1, 2019-06234

5 RESULTS

5.1 STUDY I

Of the 4233 patients who were cared for during the study period, 165 were prescribed methadone in any form for pain and, in 80 of these, as *peroral* add-on of low-dose methadone to another ongoing opioid therapy for cancer-related pain. These 80 patients made up the study population. A majority were women (64%), the mean age was 68 years and the most common cancer diagnoses were of urogenital, gastrointestinal, pulmonary or breast origin. One patient had local disease only, the rest metastatic disease. Half of the patients had a documented pain mechanism, in 80% it was neuropathic or mixed neuropathic and nociceptive.

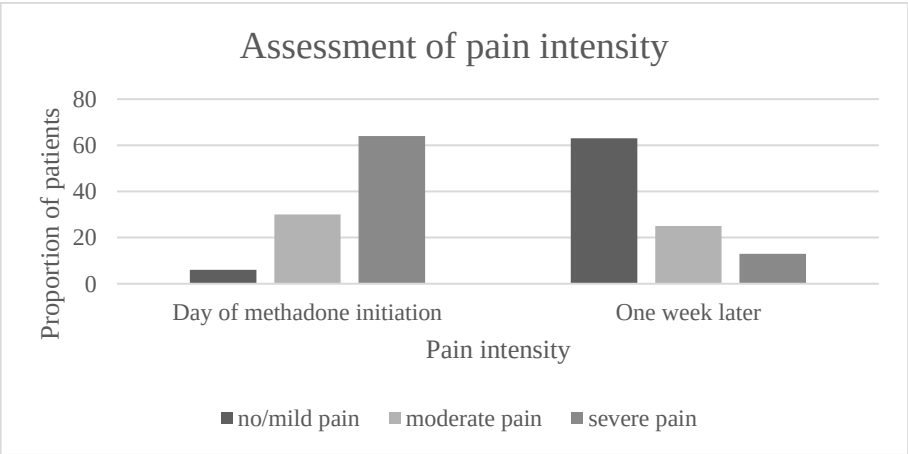
At the time of methadone initiation, regular opioids used were oxycodone (38%), morphine (36%), fentanyl (19%) and hydromorphone (8%). The median total MEDD of opioids (except for methadone), i.e., regular and rescue-doses, was 290 mg (IQR 505).

The median dose of methadone was 10 mg (IQR 5) on the first day and still 10 mg (IQR 10) one week later. However, the methadone dose was increased in 67% of the patients during the week. During the same period, the total median MEDD of other opioids decreased to 250 mg (IQR 358).

5.1.1 Change in pain

As many as 80% of the patients were assessed to have reached better pain control during the period from when methadone was initiated until one week later ($p < 0.001$). The proportions of patients who were assessed to have no or mild, moderate, and severe pain changed from 6%, 30% and 64% to 63%, 25% and 13%, respectively ($p < 0.001$).

FIGURE 1.



5.1.2 Adverse effects

As expected in end-of-life care, both delirium and sedation increased during the last weeks of the patients' lives, which constituted the study period. The increase was significantly more pronounced in patients with a survival time of less than 14 days, i.e., 80% of the patients with shorter survival were assessed as sedated or delirious. There were only severe symptoms in 17% and 21% of the patients with shorter survival, respectively, and there was no report of respiratory depression. Due to methodological reasons, it could not be distinguished as to which proportions methadone and the dying process contributed to sedation and delirium.

5.2 STUDY II

In total, 133 specialized palliative in-care and home care units in Sweden were invited. With a good geographical representation from throughout the country (Figure 2), 60 (45%) units chose to participate. During the study period, a total of 10,058 ELQs were registered nationally. Of these, 4780 ELQs were registered by the participating units, corresponding to 48% of all deaths of patients admitted to specialized palliative care during the study period. Methadone was initiated in 410 (8.6%) patients. These patients constituted the study population.

FIGURE 2. GEOGRAPHICAL REPRESENTATION OF SPECIALIZED PALLIATIVE CARE UNITS PARTICIPATING IN STUDY II

Each dot represents one of the 60 participating specialized palliative care units in Sweden (some of the dots are overlapping, especially in the Stockholm region).

The mean age of the patients who were initiated on methadone was 68 years and 41% were women. In those who did not receive methadone, the mean age was 74 years and 55% were women. In one third of the patients methadone was initiated in home care. Eighty-seven and 82 percent had a cancer diagnosis in the methadone and non-methadone groups, respectively.

5.2.1 Indications

In the 410 patients who had been initiated on methadone, 96% were prescribed low-dose methadone as add-on to another ongoing opioid. The most common indication (74%) was unsatisfactory pain control with the current analgesic therapy. The underlying pain mechanism had been assessed in almost all patients (96%). Of these, 70% had mixed neuropathic and nociceptive pain, 16% neuropathic pain, 11% nociceptive, and uncertain mechanism in 3%. Methadone was used as the primary opioid for neuropathic pain in 17% of the patients.

Validated instruments for assessing the level of pain were used in 84% of the patients and instruments for assessment of other symptoms in 50%. Forty-six percent had a reported pain level exceeding 6 out of 10 on VAS/NRS, ESAS (or IPOS) at least once during their care period. In 94%, methadone was reported to have added a good or very good analgesic effect.

5.2.2 Methadone and other opioids

Methadone was used for a median of 21 days (mean 48). In 86% of patients the reason for discontinuation of methadone was death, but in 10% it was due to an inability to swallow tablets at the end of life.

The most common regular ongoing opioid combined with methadone was fentanyl, used by half of the patients. One third (32%) used oxycodone, 11% morphine, 6% hydromorphone, 1% ketobemidone and 0.3% buprenorphine. For doses of regular opioids and methadone, see Table 2.

TABLE 2. OPIOID DOSES IN STUDY II

	Daily opioid doses (mg) at initiation of methadone	Daily opioid doses (mg) during the last 24 hours
Median MEDD (IQR)	184 (IQR 155)	199* (IQR 150)
Median methadone dose	5 (IQR 5)	10*** (IQR 10)

* $p < 0.05$; *** $p < 0.001$

Methadone doses were increased in 70% of the patients during the study period. At initiation, peroral methadone twice daily was the most common prescription, but during the last 24 hours intermittent SC injections two times per day dominated. Only 2% of the patients were prescribed continuous SC or IV infusion of methadone during the last 24 hours.

5.2.3 Adverse effects

In the vast majority of patients (80%) there were no reported adverse effects. In 8.5% sedation and in 7.3% delirium was reported. During the last 24 hours, opioid doses were higher in delirious than non-delirious patients (median MEDD 242 mg vs 195 mg) while the opposite was true for methadone doses (10 mg vs 15 mg). There were no serious cases of respiratory depression.

5.3 STUDY III

In Study III a qualitative method was used. With the aid of semi-structured interviews, attitudes, significance, and practical aspects of methadone use in specialized palliative care were explored. Of the 30 physicians interviewed, 22 were women, the mean age was 53 years and their experience in palliative or pain medicine ranged from 8 months to 40 years.

Main categories and subcategories in Study III
Attitudes
Physicians and staff
Attitudes among patients and relatives
Indications
Mechanism-based prescription
End-of-life situations with short life expectancy
Practical use
Low-dose add-on strategy
Effects and adverse effects
Initiation, settings
The dying patient
Refractory pain situations

5.3.1 Attitudes

According to the descriptions made by the informants, association with substance use disorder occurred, especially among patients and relatives but, in general, attitudes to methadone were not described as an obstacle to its use.

Attitudes to methadone as an analgesic varied. Among physicians and other staff, some were skeptical that methadone had any unique properties compared with other opioids, while others were almost over-optimistic about the possibilities of methadone.

Among some palliative care physicians, methadone was described as almost a magic bullet, while others emphasized the risk of overconfidence in an individual drug and the risk of neglecting other therapeutic options. The latter perception occurred among pain physicians who, although partially recognizing a unique role of methadone, had not seen long lasting effects. The differing views on the benefits of methadone were explained by the palliative physicians being due to the fact that they saw dying patients more often and that they therefore usually worked with shorter time perspectives.

[Palliative specialist:] "But, I have seen how they [the pain specialists] have struggled with the same patients that we have later achieved analgesia for. No, we usually do not involve them, only when intrathecal catheters are required. Otherwise not, since we have a better understanding of these things [=in this special context]. I know—I am not being very humble [in this matter]."

[Pain specialist:] "Sometimes you see a remarkably good short-term effect of a low dose [methadone]as add-on. But I don't think the effect will last.. . .//. . .In the selected group of patients that I meet, it is extremely rare that you see any differences [in pain] when you discontinue methadone treatment [after a longer period of treatment], it makes no difference."

5.3.2 Indications

Methadone was highlighted as having the greatest significance primarily in two situations: First, in the treatment of long-term severe cancer-related pain in palliative care, especially in situations with a rapid increase in opioid doses with only a limited effect on the pain control. Second, in situations with complex pain at the absolute end of life where rapid effect against mixed nociceptive and neuropathic pain was required. In both cases, low-dose add-on to another opioid was advantageously used as the routines for insertion and dose increases were considered simple.

[Palliative specialist:] "First you just raise the basic dose of opioids, but when you start coming up in dose and it does not help then I would immediately say to try methadone, just because it influences neuropathic pain . . .//. . . It is fantastic, I could sell it.

Combining a low dose of methadone with another opioid for mixed pain was sometimes perceived as having an unexpectedly rapid and good effect, similar to the effect seen with ketamine, but the advantage of tablet treatment with methadone was emphasized as important.

"Some patients improve. They get a better pain effect than you would expect from five milligrams, if you see what I mean."

Others that could benefit from methadone, according to the informants, were elderly patients or patients with renal failure.

About half of the patients who received combination therapy with methadone were perceived to reach improved pain control. Their pain preceding the treatment was typically described in terms of "wind-up", "central sensitization", "exhausted pain system", "receptor fatigue" and "opioid tolerance". Pain originating from skeletal metastases or pathological fractures as well as pain from the spine or pelvis was described to benefit extra well. Cancer of the prostate, breast, kidney, pancreas, and sarcoma were mentioned as typical examples of diagnoses where analgesic effect could be seen.

5.3.3 Practical use

A much-discussed aspect of prescribing methadone was the risk of delayed respiratory depression and this was given as a recurring reason for the use of low-dose add-on methadone. The purpose of the methadone use was to achieve NMDA-receptor inhibition.

The dosing strategy appeared very similar at many palliative care units. Usually 2.5 mg of methadone two or three times daily was added to an ongoing opioid treatment. After about 2-7 days, the methadone dose was increased, if needed. Often, dose increase stopped at 5 mg twice daily and sometimes at 10 mg twice daily. Higher dosing was seldom used since it was not considered to provide an additional analgesic effect.

The analgesic effect often appeared within a few hours or a day. With improved pain control, the risk of adverse effects, especially sedation, increased instead. Experienced physicians often perceived occurring sedation as an effect of the already ongoing high-dose opioid treatment and recommended therefore, at the first signs of analgesic effect of the methadone introduced, the dose of regular opioid to be reduced by 25-30%.

"If you have a pain that is almost not morphine sensitive at all, you can increase to very high opioid doses and still have a normal respiration [as pain is a strong stimulus for the brain

stem]. If you then add something [addressing another pain mechanism] that makes you pain free, you still have the high [opioid] dose and the whole problem [with adverse effects] emerges."

If the regular opioid treatment was not reduced, effects and adverse effects were seen to appear in a certain order, often 2-4 days after the initiation of methadone. First there was reduced pain, then cognitive impairment, then sedation and finally respiratory depression.

When the patient was imminently dying and had difficulty swallowing, the tablets were usually discontinued. Intermittent methadone injections were then used and sometimes methadone was added to a CSCI. However, sometimes methadone was completely discontinued.

Add-on methadone was also reported to be safely initiated in the home environment if good and daily contact, by visits or telephone, could be maintained with the patient or their relatives for 3-5 days after the methadone initiation.

5.3.4 Refractory pain situations

According to the informants, methadone, although a valuable tool in the treatment arsenal for individual patients, was not the solution to all complex pain situations with often several different pain mechanisms involved. Death anxiety, existential suffering and social pain were highlighted as major challenges and these conditions were described as difficult to master with drugs alone.

"Severe pain is a matter of so many different components, not only physical pain. The physical pain itself is often the simplest part, whereas the existential and the psychosocial components are the most difficult."

5.4 STUDY IV

The last study in this thesis was a prospective observational study. Of 321 potentially eligible patients, 93 were eventually included. Most of the dropouts, 88%, were due to a certain amount of gatekeeping: they were considered too fragile, in a physical or psychological sense, by the staff. Twelve percent of the patients abstained from participation. The participants were followed until death, a median of four days. Inclusions were performed from 1 February 2019 to 22 January 2020. Mean age was 76 years and 57% were women.

5.4.1 Indications for CSCI

The most common indications for transition to CSCI were difficulty swallowing tablets at end of life, and to improve pain control when oral medication was considered to be having an insufficient effect. In two thirds of the patients the pain mechanisms were assessed as mixed neuropathic and nociceptive.

5.4.2 The main study group

The forty-seven patients who survived for three days or more after the initiation of CSCI were selected as the main study group to study the effects and adverse effects of the analgesic regime. This cohort included patients receiving low-dose midazolam for anxiety, but not for sedation. The median survival in this cohort was 5 days (mean 9).

The subgroup of patients in this group who were prescribed methadone by CSCI were also studied separately.

5.4.3 Analgesics and analgesic effect

At the time of initiation of CSCI, patients used a mean of 1.7 non-opioid/adjuvant analgesics such as steroids, COX inhibitors, antidepressants or gabapentinoids. All were prescribed opioids: oxycodone (61%), morphine (23%), fentanyl patches (14%) and hydromorphone (2%). At initiation, the total median MEDD, excluding methadone, was 123 mg (IQR151) and after three days 150 mg (IQR 210). Improved pain control was seen after initiation of CSCI. In three days, the IPOS 5-point pain scores decreased, from a mean of 2.2 (median 2) to a mean of 1.5 (median 2) ($p \leq 0.001$), and the proportion of patients judged to be overwhelmingly affected by pain decreased, from 45% to 19% ($p \leq 0.001$).

5.4.4 Adverse effects

The patients were nearing end of life and levels of alertness decreased significantly over time, while the doses of sedative midazolam and performance status did not change significantly. At initiation of CSCI, 30% of the patients were judged to have delirium and 52% anxiety. The proportion with delirium did not change significantly, neither for patients younger nor older than 75 years of age, while the proportion with anxiety was halved ($p < 0.05$). Local erythema occurred around the SC needle in three patients, of whom one was prescribed methadone. All three had had the needle for at least five days and the erythema disappeared within a day after changing the injection site.

5.4.5 Patients receiving methadone

Thirteen patients were prescribed methadone as add-on to another opioid in CSCI (MET) and their characteristics differed from those who did not receive methadone in CSCI (NMET): the median survival time from the initiation of CSCI was 14 versus 4 days ($p = 0.044$), initial median MEDD of opioids was 240 mg versus 113 mg ($p = 0.004$), and severe/overwhelming pain was seen in 77% versus 32% ($p = 0.009$) in the MET and NMET groups, respectively. Alertness decreased significantly in both groups over time. Otherwise, no significant differences were seen between MET and NMET regarding doses of midazolam, performance status, anxiety, or prevalence of delirium.

The median daily dose of methadone was unchanged at 5 mg (IQR 5).

One patient had an episode with respiratory ratio < 8 breaths/min, that passed without any need for intervention and the patient survived for four more days.

6 DISCUSSION

In this thesis, I have focused on the use of low-dose methadone as an add-on to another ongoing opioid therapy to relieve complex cancer pain in dying patients. In our studies, we examined how low-dose methadone was used clinically and we assessed its effects and adverse effects. Further, we investigated to what extent, and how, methadone was used in specialized palliative care in Sweden today, including its use in continuous subcutaneous infusions with ambulatory infusion pumps for the most severely ill patients at the absolute end of life. In order to deepen the knowledge concerning the attitudes and opinions regarding methadone, in particular as a low-dose add-on, and to identify future areas in need of further research, we also, as a complement to the quantitative studies, conducted semi-structured interviews with physicians in specialized palliative and pain care in Sweden. The following discussion first presents the overall findings and interpretations, then clinical implications, and, finally, the methodological aspects.

6.1 FINDINGS AND INTERPRETATIONS

6.1.1 Indications for low-dose add-on methadone in specialized palliative care

The subjects of primary interest in our studies were some of the most severely ill people in society: patients dying from advanced cancer with complex pain not responding adequately to commonly used analgesic methods. In such circumstances, physicians then do their best to find new treatment options. Possibly based on knowledge of methadone's partly unique pharmacological properties and anecdotal evidence, there has in recent years been a growing interest among physicians in specialized palliative care to use methadone for complex cancer-related pain.

Methadone is an opioid that, in itself, when referring to its μ-receptor effect, does not provide better pain relief than other opioids in common cancer-pain situations where a low dose of opioid, e.g. morphine, is already enough to achieve good analgesia [71, 73, 148]. For the vast majority of patients with cancer-related pain, strong opioids provide satisfactory analgesia.

Unfortunately, regular opioids are not sufficient in all situations. In certain types of pain, additional analgesic therapy may be needed, for example in case of severe mixed nociceptive and neuropathic pain or in situations where opioid doses have needed to be increased rapidly without providing much better pain relief. These are situations where central sensitization of the nervous system can be suspected to be a contributing factor to the complexity of the pain.

Central sensitization is, at least partly, related to activation of NMDA receptors and leads to reduced thresholds (allodynia), increased responsiveness and prolonged aftereffects to noxious stimuli (hyperalgesia) [30]. NMDA receptors also seem to be involved in the development of opioid tolerance [33]. In selected cases, drugs that inhibit NMDA receptors appear to be able to reduce the effects of central sensitization [149, 150]. The opioid methadone is sometimes successfully used in these situations.

As an alternative to carrying out a full, and potentially complicated, conversion to methadone as the single opioid, a method introducing a low-dose add-on of methadone to the ongoing opioid therapy has been used. Interestingly, this method proved to be applied in several specialized palliative care units in Sweden. In Study II, we found that during 12 months of study time, methadone for pain was prescribed to 8.6% of the patients cared for in the participating specialized palliative care units.

In Studies I, II and IV we could see that in 70-80% of the cases where the pain mechanisms had been assessed, the indication for introducing the regimen with low-dose add-on methadone to another opioid was either a complex pain with mixed nociceptive and neuropathic components that was difficult to manage, or a purely neuropathic pain. This finding was also supported in interviews with physicians in Study III, who described that these mixed types of pain, in addition to existential pain and death anxiety, are considered the most complex pains to treat in specialized palliative care, but that a low-dose add-on of methadone in these situations is considered a rapid and effective way to achieve a sometimes almost unexpectedly effective pain relief in a safe way.

Previous studies have shown that 49-75% of patients who were prescribed low-dose add-on methadone for cancer-related pain achieved an improved pain control within one week to one month after initiation of the treatment [122-124]. The patients we studied were relatively closer to the end of life and did also generally seem to be in a more severe pain situation at the time of methadone initiation. However, we obtained similar results: in Study I, 80% had achieved improved pain relief after one week and in Study II it was reported that as many as 96% of the patients reached improved pain control after the introduction of methadone. In Study III, a recurring description by the informants was that about half of the patients who were prescribed low-dose add-on methadone also had an improved analgesic effect, sometimes even described as an unexpectedly good effect.

It is not fully clear why we observed such relatively high proportions of successful treatment in our studies compared to what is seen in the existing literature. Our quantitative Studies I, II

and IV, were descriptive and not designed to answer the question of which patients benefited the most from methadone.

However, one partial explanation may be that successful treatment is largely dependent on the initial selection of patients who are offered the treatment. The fact that we had a larger proportion of patients who were reported to have had an improved analgesic effect in our studies than what was previously reported, may be due to the fact that we did not focus solely on pain intensity, i.e. "severe pain". The main focus was on pain analysis and pain mechanisms.

This became clearer in the interviews in Study III where the physicians described that the pain conditions that responded best to methadone tended to have been present for a longer time period and did not respond well to increased opioid doses. The informants used explanatory models in which concepts such as "central sensitization", "exhausted pain system" and "opioid tolerance" were mentioned as possible underlying mechanisms. They also gave examples of locations where these pains often occurred, such as pain arising from skeletal metastases or pathological fractures and pain from the spine or pelvis. The specific cancer diagnoses mentioned were prostate, breast, kidney, pancreas, and sarcoma. Just over half of the patients in Study I had at least one of these cancer diagnoses. To the best of our knowledge, except for the occurrence of severe pain [123], there are no previous descriptions of which patients could potentially benefit most from low-dose add-on methadone.

Laboratory tests have previously shown a synergistic analgesic effect between methadone and morphine, but only an additive analgesic effect in combination with fentanyl or oxycodone [43]. Despite this, no clear pattern was seen in how strong opioids were combined with methadone in any of the present studies. The two most common regular drugs combined with methadone were: in Study I oxycodone and morphine, in Study II fentanyl and oxycodone and in Study IV hydromorphone and oxycodone. In Study II, it was reported that 74% of the prescriptions of low-dose add-on methadone were made due to insufficient pain control from the ongoing treatment with a strong opioid. Since better pain control was reported to be achieved after initiation of low doses of methadone, a possible explanation could be that the additional analgesic effect was to a certain extent due to the NMDA receptor inhibitory properties of methadone.

In Study III, the emergence of central sensitization was mentioned as a possible underlying explanation to more complex pain. Drugs with an NMDA inhibitory effect, such as ketamine or 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), can reduce the effects of

central sensitization and contribute to better pain relief in intractable chronic pain, although the evidence in cancer pain is not unequivocal, partly due to difficulties in studying these patients [149-152]. It also appears that the administration of ketamine over a short period of time improves analgesia more effectively than lower doses for longer durations [150]. This is of course of uncertain significance for methadone, but in addition to its μ-receptor inhibitory effect, methadone also has an NMDA receptor inhibitory effect [31, 58, 60]. By fine tuning the NMDA receptor subunits, neurons seem to be able to alter the functional properties of neuronal receptors [34]. Subtype-specific agonists for NMDA receptor glycine binding sites could be a possible, but so far not established, explanation behind the differing effects between different NMDA-inhibiting drugs [153].

The addition of methadone to an ongoing opioid therapy has been associated with lower escalation rates or even decreased doses of opioid [1]. This was partially seen in our studies, as well. In Study I, there was a 14% reduction of MEDD after one week and in Study II an 8% increase after a median of 21 days. In Study IV, there was a 25% increase of MEDD over three days, which may possibly be explained by these patients being in an imminently dying state. These were patients with severe pain, indicated by their generally high doses of opioids and, so far, the methadone treatment had only lasted a few days.

Based on previous knowledge and our findings it is therefore not unreasonable to assume that methadone can also affect a condition with central sensitization. How long the effect of add-on low-dose methadone lasts is unclear and, in the sparse literature available, the effect has been described as lasting for anywhere between a week up to at least several months [122-124]. Also, in our qualitative Study III, some informants described that improved pain relief could exist for weeks to months after initiation of low-dose add-on methadone, even possibly after the add-on with methadone had ended and only the original opioid remained.

One way to exemplify this could be to compare it with a situation where an ongoing analgesic treatment with methadone as the sole opioid, not low-dose add-on, was suddenly stopped. The pain would then return quickly. Thus, a possible explanation for why increased pain is not seen when a successful low-dose add-on methadone therapy is discontinued may be that it is due to the NMDA inhibitory effect that the low-dose add-on methadone primarily contributed to, resulting in a decreased central sensitization and “wind-down”. Once analgesic control is achieved, the goal is reached.

The age distribution in Studies I, II and IV was a consistently mean 68 years for the patients who were prescribed methadone. For those who did not receive methadone, the mean ages

were 74 and 78 years in Studies II and IV, respectively. In both studies, the age difference was significant ($p < 0.001$ and $p < 0.05$, respectively). The gender distribution was more varied. In Studies II and IV, about 40% were women and, in Study I, 64%. Previous studies on low-dose add-on methadone have not described groups both with or without methadone treatment in the same way as in our Studies II and IV, but in Wallace et al. patients prescribed low-dose add-on methadone were a mean of 63 years of age and 75% were women [122]. Similarly, in Courtemanche et al. the mean age was 60 years and 42% were women [123]. The underlying reasons behind, and the clinical significance of, these differences are not evident based on current knowledge.

These studies provide pieces of the puzzle to be placed into the larger picture. It is still not certain whether methadone has a better analgesic effect than other opioids, as our studies were not designed to answer this particular research question. Despite this, it is likely that the mechanisms behind complex pain are the most important to address first. The adequate drug is then selected based on the pain mechanism. In the context of very seriously ill patients with severe cancer-related pain, NMDA receptor inhibition with methadone is an attractive alternative, especially in the form of low-dose add-on to another ongoing opioid. It appears to be an easy and safe way to initiate and use methadone, even in homecare, provided that there is a good level of knowledge and experience and good follow-up.

6.1.2 Attitudes, opinions and perceptions

In general, people's attitudes towards methadone used for analgesia is an unexplored area. Methadone maintenance therapy is known to be associated with opioid use disorder [83]. This can be both socially stigmatizing and adversely affect the use of methadone in specialized palliative care [83]. An important conclusion from Study III was that the interviewed physicians had not perceived that negative attitudes towards methadone were a problem, neither among physicians, staff, patients nor their relatives, and that the sparse negative attitudes did not preclude an analgesic use of methadone. Rather, there was an almost surprisingly positive attitude. Low-dose methadone treatment was reported by palliative care physicians to be a valuable, easier, and safer method to take advantage of methadone's special analgesic properties.

6.1.3 Adverse effects and safety aspects

In Study III, the interviewed physicians emphasized, more than anything else, that the risk of opioid overdose is considered the greatest risk of using methadone for pain. Although the μ-receptor mediated inhibitory effect on pain comes quickly, within hours, it may take several

days before the full effect of NMDA receptor inhibition occurs. Pain effectively stimulates the respiratory center of the brain [79, 80]. This means that in patients with pain, opioid doses can often be increased significantly even in those with not very opioid-sensitive pain, without entailing a greater risk of respiratory depression. If, on the other hand, the pain subsides suddenly, such as when an NMDA inhibitory effect sets in, then the stimulation of the respiratory center ceases and the risk of sudden respiratory depression occurs. It is worth noting that despite the prevalent concern, no severe respiratory depression due to opioid overdose was reported in any of the Studies I-IV, possibly, because the Swedish palliative care community has learned to reduce the total daily dose of the primary opioid after a few days if an analgesic effect is seen with the add-on therapy.

Opioids have certain μ-receptor-related adverse effects as a class and methadone is no exception. In all four studies, typical opioid-adverse effects were described as the most common, although in Study II it was shown that 80% of the patients were not judged to have any significant adverse effects at all. Examples of opioid-related adverse effects are constipation, delirium, sedation, nausea, hypotension, miosis, and respiratory depression. Mild adverse effects can often be prevented, for example with antiemetics, laxatives, etc. [65, 67, 71, 72, 77].

The results are somewhat scattered regarding the prevalence of sedation and delirium in methadone treatment. In Studies I and IV, an increased incidence of sedation was noted seven and three days after methadone initiation, respectively, while in Study II, a lower proportion of patients with sedation was seen than in both Study I and other previous studies [123]. Perhaps because of the accepted strategy to reduce the primary opioid after two to three days. Study I showed that sedation, as expected, was more common in patients with a short remaining survival time.

Delirium was also more common near the end of life in the patients with per oral methadone in Study I, while the patients who received methadone via CSCI in Study IV did not have an altered incidence of delirium, even regardless of age. This is an interesting finding that strengthens the idea that drug administration via CSCI at the end of life, even to elderly patients, is beneficial for symptom relief. No unequivocal conclusion can be drawn from this material as to whether methadone contributes to more or less sedation and delirium than other opioids. Other factors, such as proximity to the end of life, are probably of importance.

There is a risk of cardiac arrhythmias due to QTc prolongation in cancer patients in general, both due to medication and other antitumor treatments [89-95, 97]. Methadone doses above at

least 30 mg are considered to increase the risk of negative QTc effects [89-95, 97]. This means that low-dose add-ons for patients in palliative care, usually around 5-20 mg daily, appear to be a safer alternative than higher doses. The benefit of this treatment can be considered to outweigh the risks and a possible explanation as to why ECG monitoring is not generally recommended in palliative care [97, 100, 101].

6.1.4 The practical use of low-dose add-on methadone in specialized palliative care

The required frequency of methadone dosing varies significantly depending on the desired effect. If methadone is used as a primary opioid, a my-receptor effect is sought, and higher doses are needed. Dosing of 10 mg tablets up to every four to five hours during the first days may be required, usually followed by three times daily [69]. Previous reporting has described how there was no significant difference in analgesic effect during the first few days, whether morphine or methadone was administered, while there was a marked difference in long-term treatment [69, 70].

Study III was important because, even though we already examined doses and administration with the questionnaire in Study II, we wanted to be more confident that we covered all the aspects, not least so as to be able to design future studies. According to the physicians in Study III, they prescribed low-dose add-on methadone to ongoing opioid treatment primarily for the purpose of achieving NMDA receptor inhibition, i.e., to reduce an increasing opioid tolerance or to remedy a condition with central sensitization. The practical aspects of achieving this were mainly concerned with how to start the treatment and then how to prescribe and follow-up to minimize the risks of serious adverse effects, in particular, severe respiratory depression. In Study II, as many as 96% of the patients who received methadone in specialized palliative care in Sweden did so in the form of a low-dose add-on. In earlier studies the initial doses of methadone added to an ongoing opioid varied between 1-10 mg daily, usually b.i.d. [120-124]. In our Studies I, II and IV, the median starting dose, and also the reported starting dose in Study III, was consistently 5 mg daily, most often as 2.5 mg twice daily. In case of insufficient analgesic effect, the dose was increased after about two to seven days to 5 mg b.i.d., and rarely to more than 10 mg twice daily, as reported in Studies I-III. Thus, a starting dose of 2.5-5 mg during the first 24 hours should be considered an appropriate dose as a balance between the desired rapid effect and the need to minimize the risk of serious adverse effects, with the lowest doses used for the elderly and the most fragile individuals.

Courtemanche et al. described that further increasing the methadone dose to patients who had responded with analgesia within a week from initiation, did not result in further pain reduction [123]. Methadone doses in our studies most often remained unchanged over time after the initial increases. This, together with the stable or even decreased doses of other regular opioids after methadone initiation, given how severely ill the patients were, makes the properties of methadone even more interesting.

If the initiation of low-dose methadone resulted in the intended effect, the improved analgesia came within hours or a day. The informants in Study III described how they then first used to see an improvement in pain, and then sometimes a delayed cognitive impairment and later sedation. Being aware of this order in the onset of adverse effects, it was a well-established perception among experienced palliative physicians that it was often necessary to reduce the regular opioid dose, by about 25-30% to reduce the risk of opioid overdose when analgesia occurred. There were descriptions of situations where methadone was initiated in patients whose pain, up to that time, had not responded very well to opioid treatment. In some cases, the pain then seemed to subside rapidly followed by relatively rapid subsequent symptoms of opioid overdose. This was reported as the main reason why the physicians often chose to start with doses as low as 2.5 mg x 2 in the first few days.

As reported in Study II and by some informants in Study III, it can be stated that initiation and use of low-dose methadone is done routinely in outpatient palliative care and is appreciated by the patients as it means that they do not have to be admitted to hospital to benefit from methadone treatment for pain.

Overall, our studies support the conclusions of the American Academy of Hospice and Palliative Medicine from 2018, that safety of methadone is well established in cancer pain management [154]. Low-dose add-on to another opioid appears to be a safe method of offering the benefits of methadone while minimizing the risk of potential adverse effects, even in home care. Still, methadone prescription should be carried out by experienced pain and palliative care providers with careful dose titration and clinical monitoring, considering the individual patient´s total situation [154].

6.1.5 Low-dose add-on methadone in the imminently dying patient

In the imminently dying patient the oral route may be unreliable due to a reduced ability to swallow and absorb drugs. In the patients prescribed methadone in Study II, it was reported to be used in 86% of cases until end of life, and during the last 24 hours parenterally in at least 50%. In 10% of patients, per oral methadone was discontinued without being replaced with a

parenteral preparation. Only 0.5% were reported as receiving methadone via continuous SC or IV infusion. In Study III, the physicians described how intermittent injections of methadone could be successfully given twice daily, but some also described how they were uncertain about possible adverse effects, e.g., sedation if methadone were to be given as CSCI. Several informants mentioned that they would like to use methadone in CSCI if they knew more. Others described CSCI containing methadone as both effective and complication-free. Altogether, these findings led to the setup of Study IV aimed at further exploring the use of low-dose add-on methadone via CSCI at the end of life.

In the dying patient, continuous opioid infusion is beneficial in terms of both analgesic effect and avoidance of peaks and troughs in serum concentration [155-157]. Also, opioids and benzodiazepines in adequate doses via CSCI do not shorten life [156, 158, 159]. In Study IV, in addition to CSCI providing good pain control without increasing delirium, we also found that low-dose add-on methadone was successfully used in patients with severe pain and already on high doses of strong opioids, without an increase of adverse symptoms or any serious adverse effects that required special treatment. Thus, there are good reasons to use CSCI in dying patients and, if necessary, include low-dose add-on methadone.

The marginally longer survival of the patients who received add-on low-dose methadone in CSCI, as described in Study IV, was notable. However, it was probably due to the patient's severe illness with increased pain that resulted in an earlier CSCI prescription. Unpublished data from Study I showed similar results between our unmatched groups: a median survival of 13 days for all patients on the ward, and 28 days for those who were prescribed a low-dose add-on of methadone.

An additional explanation for the overall relatively sparse use of methadone in CSCI, as indicated in Study II, may be the risk of skin adverse effects, such as SC erythema [102]. Erythemas are uncommon at SC injections of methadone 10 mg/ml in volumes < 2.5-3 ml per day [154, 160]. They usually fade away rapidly with rotation of the injection site [103-105, 160]. The few adverse effects seen at the SC injection site in Study IV were all judged to be due to the fact that at least five days had passed since the last rotation of the injection site, rather than the methadone infusion itself. Thus, low-dose add-on methadone in CSCI should not be withheld from patients because of fear of dermal adverse effects.

6.2 CLINICAL IMPLICATIONS

In specialized palliative care in Sweden, a low-dose add-on of methadone to another opioid seems to be an established treatment that is appreciated and regularly used mainly by specialists in palliative medicine, even for patients in palliative home care.

Low-dose add-on methadone may be considered in situations with complex cancer-related pain of long duration involving central sensitization, or in situations with a rapid escalation of opioid doses. According to the clinical experience expressed by the clinicians in Study III, the greatest probability of successful treatment seemed to be in bone pain from metastases and pathologic fractures in the spine or cancer-related pain from the pelvis. Specific diagnoses were metastatic cancer of the prostate, breast, kidney and peritoneal carcinosis, as well as pancreatic cancer and sarcomas.

The evidence for low-dose add-on methadone in complex cancer-related pain is still limited. It is therefore not possible to issue unambiguous clinical recommendations for how this treatment method should be used. On the other hand, based on both the literature and the results in Studies I-IV, it is possible to describe how the practical application in specialized palliative care in Sweden appeared, mainly according to the specialist physicians in Study III. In this way, everyone can draw their own conclusions about how this treatment model can be used.

The indications for treatment were reported to be either need for improved pain control in complex cancer-related pain or marked development of opioid tolerance. It was important to minimize the risk of undiagnosed opioid overdose, both for patients who were cared for in specialized palliative care units and in home care. More severe adverse effects in the form of cognitive effects, sedation or impaired breathing were reported to occur usually within 2-4 days after initiation or dose increase of add-on methadone. However, due to the long half-life, adverse effects could occur much later, especially if no dose reduction of the regular opioid was done when the patient began to experience improved pain relief.

A common starting dose for low-dose add-on peroral methadone was 2.5 mg x 2. In complete absence of effect, the responsible physician could consider prescribing a first dose increase after 3-4 days and in case of partial effect, the dose could be increased after 5-7 days. Especially in home care, for safety reasons, it was common to wait up to seven days before considering a dose increase, depending on the treatment response. Dose increases were usually done in steps of 5 mg per day to a maximum of 10 mg twice daily. After every dose increase the analgesic effect was evaluated, as above.

Daily follow-ups were usually performed by either a registered nurse or physician, both after initiation and after every dose increase. Follow-up in home care was often in the form of home visits but if there were cognitively intact relatives in the patient's home, a telephone call could sometimes replace personal visits. If there was improved analgesia, a further dose increase of methadone was postponed and the responsible physician considered a dose reduction, usually with about 25-30% of the regular opioid, to avoid adverse effects.

6.3 METHODOLOGICAL CONSIDERATIONS

6.3.1 Internal validity

Internal validity means how well a study measures what it is intended to measure, i.e., absence of systematic errors. The systematic errors remain the same regardless of sample size, as opposed to random errors which decrease by increasing sample size. There is high internal validity if there is a low risk of systematic errors that affect the results. Three main groups of systematic errors, or bias, are usually described: selection bias, information bias and confounding [161]. Studies I, II and IV were descriptive and did not use sampling but aimed at total cohorts.

Selection bias

Selection bias is referred to as the error introduced when the study population does not correspond to the non-study population, that is the participants are not representative of the whole target population. In cohort studies, selection bias means that the exposed and unexposed group are different in another way than the exposure being studied. Selection bias is a systematic error that occurs during recruitment or when deciding which patients are to stay in the study [161, 162].

Study I was a total cohort including all patients introduced on an oral dose of methadone during the study period identified from medical records and, in principle, all eligible patients were likely included. However, it was likely that the patients from the very beginning had in some way been selected by their physicians to be prescribed low-dose add-on methadone.

To the total cohort in Study II, all specialized palliative care units in Sweden affiliated to the Swedish Register for Palliative Care were invited to the 12-month survey and 45% chose to participate, possibly units already experienced with methadone and possibly with a relatively positive attitude to methadone. In participating units, completion of the questionnaire was mandatory in patients using methadone, reducing selection.

Selection bias can occur in registers if some groups are registered less often than others. The SRPC has a coverage rate of 90-100% in specialized palliative care and is cross-checked weekly with the Swedish Tax Agency's population register and annually with The National Cause of Death Register which, together, entails a low degree of selection and errors among the registered subjects [125].

Study III was a qualitative study, and no statistics were performed. A max variation sampling was aimed at. All physicians invited to be interviewed participated as informants.

Study IV was a total cohort, but for organizational reasons inclusion was limited to daytime. In addition, imminently dying patients were studied and less than a third of eligible patients were eventually included. Of patients not included, nine out of ten was due to difficulty in giving informed consent and because of gatekeeping, where staff were especially prone to withhold certain patients for psychological, rather than medical reasons. In one tenth, the patients abstained. These factors introduce selection and affect the internal validity. Methadone was found to be prescribed to patients with the most severe pain, also affecting selection in this group.

Information bias

Information bias, or misclassification bias, means a systematic error in the measurement or classification of the participants in the study. This can occur when the information collected differs for different participants [161, 162]. Participants in a cohort study that are excluded due to loss to follow-up are one example.

It is difficult for patients to estimate symptoms during the last weeks of life, mainly due to debilitation, delirium and lowered levels of consciousness [16]. This needed to be addressed in the studies as there were generally, at least for research purposes, consequently insufficient systematic assessments of pain and adverse effects in the medical records. In Study I, a predefined protocol was used to assess pain and adverse effects. The medical records were reviewed by two physicians individually, who also followed-up and discussed until they agreed on all assessments. The questionnaire in Study II was pilot-tested in one palliative care unit before it was launched in the main study. In Study II, the registered nurse or the responsible physician completed both the SPRC’s ELQ and the methadone survey after the death of each individual patient. As far as possible, the information provided was based on patient reported outcomes, but was otherwise up to the individual physician or registered nurse to reproduce as accurately as possible, based on the team's opinion and documentation in the medical records, possibly introducing recall bias. The relatively sparse occurrence of

systematic symptom assessments in the medical records is due to the nature of the matter: the scales usually presuppose intact cognition and full alertness in the patients, not so often seen in end of life care. However, VAS/NRS, ESAS or IPOS was used for pain evaluation in 84% of patients and validated tools for assessment of symptoms in 50%.

In Study IV, the patients were so seriously ill that validated observer ratings had to be used. Even if observer ratings do not directly reflect the patients' experiences, they still enable studies in acutely dying patients during their very last days of life [163]. Both Studies I and IV were performed at Stockholm Sjukhem palliative care department and primarily reflect the experiences in this environment.

Confounding

Confounding means "confusion of effects", that is, finding a connection, but for the wrong reason, and can occur when the cause of a particular treatment is also a prognostic factor for the study results. A confounder is thus a factor that disturbs both the exposure and the result but is not a causal factor. Randomization and matching can prevent confounding. Statistical analysis can also adjust for confounders [161, 162].

In all four studies, the most important confounder was probably that patients were close to the end of life, in many cases in the terminal dying phase. In Study I, we tried to get around this in part by describing the occurrence of delirium and sedation separately for patients with more or less than 14 days survival. In Studies I, II and IV we lacked the opportunity to correct for the influence of social, psychological or existential factors that also affect human behavior [164, 165]. Another confounder is the μ-receptor mediated analgesic effect common to all opioids.

6.3.2 Random errors and precision

Random errors are the influence of chance. Random errors are tested with significance analysis and described with p-values. The p-value indicates the probability that the null hypothesis, which assumes that there is no difference between the groups, is rejected even though it is true. In medical research, a p-value of < 0.05 is often used as a significant level. However, other possible levels can be used, such as < 0.01 or < 0.001 [162].

In our studies, p-values were used to describe the degree of assertiveness in indicating differences after statistical analysis that compared dependent or independent groups.

6.3.3 Assessments of symptoms

In the four studies, treatment of complex pain was studied in individuals who are in the final stages of life due to a serious illness. This poses already well-known methodological challenges when patients' opportunities to actively participate in data collection are rapidly limited when the deterioration occurs [16].

To enable the study of even the most severely ill individuals, various methods have been used to circumvent and minimize the need for patient participation. In Study I, the medical records from deceased patients were assessed in a systematic way by two physicians individually, who also compared their results and reasoned until consensus was reached. Study II benefited from the good coverage rate in the SRPC and healthcare professionals reporting their assessments of dying patients' last days. In Study III, physicians in specialized palliative care were interviewed about their own perceptions, but also about the perceptions of other staff, patients, and their relatives. Finally, in Study IV, validated questionnaires were used for proxy estimates performed by registered nurses. This ensured continuity even in the absolute final stages of life.

6.3.4 External validity

In a quantitative method, external validity means whether the results from a study can be generalized to another population [162].

Studies I, II and IV describe total cohorts. The results from these studies can be used to plan future prospective studies involving patients in specialized palliative care. Another way of generalizing the results from Studies I, II and IV can be inspired by qualitative research: the reader can, by comparing the described conditions for each study, e.g., demographic and healthcare data, draw conclusions as to how the study results can be interpreted and applied in their own context.

6.3.5 Trustworthiness

In qualitative research, the term trustworthiness is used in much the same way as validity and reliability in quantitative research. Trustworthiness is thus about whether the results of the study can be trusted and used. The three terms commonly used for trustworthiness are credibility, dependability and transferability [134], which is applicable to the qualitative Study III.

Credibility

Credibility is about how well the data and analysis really address what was intended to investigate [134].

The purpose of the study was to explore both positive and negative attitudes as well as opinions and practical aspects regarding the use of methadone in specialized palliative care in Sweden. To capture as many aspects as possible, the informants were selected through purposeful maximum variation sampling, mainly regarding age, gender, geographical representation, level of education and experience of palliative medicine or pain medicine. The number of informants was limited by when additional interviews did not appear to contribute any additional new essential information, often described with the term saturation and judged to be reached approximately after 15-20 interviews. Another 10 interviews were conducted however to ensure, as far as possible, that no new valuable information was found.

Dependability

Dependability is how much both the data collection and the researcher's decision change during the analysis process [134]. Through interviews and observations, the researcher continuously gains new insights into the phenomenon being studied. This in turn can affect both the focus and follow-up questions.

The interview guide was pilot tested on two participants. Open-ended questions with appropriate follow-up questions were asked and additional questions were also added. When new areas of interest were discovered, they were also explored. During the interviews, similar questions were asked several times in different ways in order to better ensure that different aspects had been sufficiently elucidated and discussed.

We described the different steps and nomenclature used during the analysis, which was performed according to Hsieh [128]. To name the meaning units, the exact words from the interviews were used as short codes, so as not to lose any important meaning. The researchers also analyzed relevant parts of the interviews and compared the results. In a blinded sample control comprising 30 citations, the supervising researcher chose the same code as the first researcher in as many as 97% of the cases, even though the supervising researcher also had double-coded 17% of the longer citations. The final categories were discussed among the researchers and revised to find common formulations, rather than a consensus. To enable readers to assess similarities and differences and to illustrate the categories, representative quotes from the text were presented. During the analysis for Study IV, the most obvious and

common themes were attitudes, indications, practical use, and refractory pain situations which thus formed the basis for the analysis and reporting.

Transferability

Transferability means the extent to which the results of a qualitative study can be applied outside the study and is similar to the concept of external validity used in quantitative research [134]. It is up to the reader to transfer the results to another context.

To enable an assessment of transferability in Study III, we described the research team, participant selection, setting, data collection, analysis, and factors relevant for trustworthiness.

7 CONCLUSIONS

The following conclusions can be drawn from the studies included in this thesis:

• A considerable proportion of patients with complex cancer-related pain at the end-of-life who received add-on low-dose methadone in combination with another ongoing opioid treatment seemed to experience rapidly decreasing pain.

• Low-dose methadone treatment was reported by palliative care physicians to be a valuable, easy, and safe method to take advantage of methadone's special analgesic properties.

• In specialized palliative care in Sweden, the addition of low-dose methadone to another ongoing opioid for cancer-related pain is an emerging treatment option that is appreciated and regularly used by, in particular, specialists in palliative medicine, even for patients in palliative home care.

• Although methadone is sometimes associated with the treatment of substance use disorders, the informants reported that there were few negative attitudes among physicians, patients, or their relatives towards methadone use for pain treatment and that this did not constitute an obstacle to its acceptance.

• According to the informants, low-dose methadone may contribute to improved pain relief in selected patients with certain diagnoses, especially in situations of complex pain involving central sensitization.

• Continuous subcutaneous infusion of opioids is an effective way to reduce pain in the imminently dying patient without any increased adverse effects in the form of delirium or respiratory depression.

• For complex cancer-related pain, low-dose methadone in combination with another opioid can be successfully and safely used in continuous subcutaneous infusions at the end-of-life.

8 FUTURE RESEARCH

Adding low-dose methadone to another ongoing opioid treatment may help to relieve pain in selected patients with severe and complex pain. However, so far, the research carried out on this subject, including this thesis, is primarily of an observational and descriptive nature. It is not yet possible to say that the excellence of low-dose add-on methadone has been established. In 2019, Chalker wrote in a review of the efficacy of low-dose and/or adjuvant methadone in palliative medicine that, although promising, the evidence base for adjunct methadone in populations with palliative care needs is limited and has methodological shortcomings [166]. Any recommendation in clinical practice should, therefore, be interpreted with caution. Thus, although potentially effective as an adjuvant, it will not be substantiated until further evidence arises [166].

An important future study should be a sufficiently powered, double-blinded randomized controlled study (RCT) comparing add-on low-dose methadone with the add-on of another low dose opioid, i.e. morphine, to selected patients with complex pain where the proposed NMDA-related mechanism is at least theoretically of importance. This would have the potential to provide further answers to what the real effect of methadone is when the μ-receptor stimulating effect is excluded.

A study that non-selectively included all patients with morphine-sensitive pain would carry some risk that any NMDA receptor-related effect would be more difficult to identify behind the opioids' common μ-receptor stimulating effect. Therefore, to increase the precision, the patient selection could be based on the preliminary findings from this thesis, in particular on the qualitative Study III that described the possible pain mechanisms, specific diagnoses and localizations that seemed to be the most susceptible to low-dose add-on methadone treatment.

Additional topics that any future research could potentially address are:

- Are there differences in the effect of low-dose add-on methadone depending on the mechanism and duration of pain and on the cancer diagnosis?
- How long does the presumed effect of add-on methadone last? After how long could the add-on treatment be discontinued, and the patient still benefit from a continued analgesic effect?
- If an NMDA receptor inhibitory effect of methadone is desired, is dosing twice or three times daily more effective, or does it even matter?

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Lågdos metadon som tilläggsbehandling till pågående opioidbehandling vid cancerrelaterad smärta

9.1 BAKGRUND

Smärta är vanligt vid långt gången cancersjukdom. Lyckligtvis har smärtbehandlingarna förbättrats under senare år. För de flesta patienter som lider av avancerad cancersjukdom nära livets slut fungerar idag smärtlindringen bra. Man försöker alltid att skräddarsy smärtlindringen efter mekanismen som orsakar smärtan. Ibland kan det räcka med enkla preparat som paracetamol, naproxen eller ibuprofen, trots att man kanske har spridning till skelettet. Då väljer man det. Många behöver emellertid också behandling med morfingruppens preparat, det som kallas för starka opioider. Med hjälp av opioider blir de flesta smärtfria, utan att bli trötta av medicineringen.

Tyvärr finns det en grupp patienter som inte blir smärtfria, ens med ganska höga morfindoser. Det kan bero på att man har flera smärtor samtidigt, med flera bakomliggande smärtmekanismer. Morfin och andra starka opioider som verkar via morfinreceptorn, det som heter μ-receptorn på vetenskapligt språk, fungerar vid många smärtmekanismer men inte alla.

I vissa fall uppstår en komplex smärta som till exempel kan bero på att man, förutom den vanliga värken som beror på vävnadsskada, också har fått inslag av nervsmärta. Ett komplext smärttillstånd kan också bero på att det uppstått på grund av det som på vetenskapligt språk kallas för central sensitisering. Enkelt uttryckt innebär det att smärtsystemet blivit överkänsligt. Smärtimpulser som normalt skulle ha bromsats långt innan de nådde hjärnan och därmed långt innan man upplevde smärta, flödar nu fritt upp till hjärnan och ger svåra smärttillstånd, där morfin inte räcker till. Det beror på att det här flödet underlättas av att en viktig receptor, NMDA-receptorn, blivit aktiv. Om man kan hämma den receptorn, kan man också minska smärtan.

Läkemedel som hämmar NMDA-receptorer verkar kunna minska sensitiseringen av nervsystemet och göra att smärtan blir mer känslig för morfin igen. Ett sådant läkemedel är metadon, ett läkemedel annars kanske mest är känt vid heroinavvänjning.

Metadon verkar till en del smärtlindrande på samma sätt som morfin, men kan alltså också hämma NMDA-receptorer. Därför kan det hjälpa till att lindra komplex cancerrelaterad smärta. Metadon har också en del nackdelar, bland annat lång och varierande halveringstid i

kroppen som gör att det är svårstyrt. Det kan ta flera dagar eller veckor innan man når stabila koncentrationer i blodet. Den smärtstillande effekten blir svår att förutsäga. Metadon påverkar också många andra läkemedel. En del biverkningar, som till exempel andningsdepression, kan komma med fördröjning. Man behöver ha mycket erfarenhet för att ordinera metadon.

Vid komplex cancerrelaterad smärta eller när vanliga opioider verkar ha tappat effekten, har erfarna läkare ibland prövat att byta opioid till just metadon. Man har förstås varit medveten om de risker som behandling med metadon kan medföra och ett annat sätt att använda metadon har därför kommit att prövas, särskilt inom specialiserad palliativ vård. Istället för att helt och hållet byta till metadon, har man istället lagt till en låg dos av metadon till den redan pågående opioidbehandlingen. Detta för att försöka dra nytta av metadonets unika smärtlindrande egenskaper och samtidigt minska risken för allvarliga biverkningar.

Syftet med denna avhandling var att studera olika aspekter av tilläggsbehandling med låg dos av metadon till en annan pågående opioid, inom specialiserad palliativ vård i Sverige. Fyra studier har utförts.

9.2 METODER OCH RESULTAT

I studie I granskades journalerna för de 4233 patienter som vårdats i livets slutskede på Stockholm Sjukhems palliativa klinik under åren 2006–2013 och av dem hade 165 ordinerats metadon. Av dessa inkluderades de 80 patienter som ordinerats en låg dos av oralt metadon som tillägg till en pågående opioidbehandling mot komplex cancerrelaterad smärta. Fördjupad journalgranskning visade att 80 procent av patienterna bedömdes ha uppnått en signifikant bättre smärtkontroll inom en vecka efter att man hade lagt till låg dos av metadon. De biverkningar som sågs var inte andra än de man hade kunna vänta sig med vanligt morfin och inga allvarliga biverkningar registrerades.

I studie II användes under 12 månader en tilläggsenkät till Svenska Palliativregistret där läkare och sjuksköterskor vid 60 specialiserade palliativa vårdenheter i hela Sverige rapporterade in data om 4780 avlidna patienter. Av dessa hade 410 (8,6%) ordinerats metadon, i 96% av fallen som lågdos i tillägg till annan opioid. Metadon användes i snitt i tre veckor (medianvärde) och i 86% av fallen till livets slut. Vanligaste orsaken var komplex cancerrelaterad smärta. Hela 94% av de patienter som ordinerades metadon rapporterades ha fått en bättre smärtlindrande effekt. Biverkningarna var få och inga var allvarliga.

Studie III var en kvalitativ studie med syfte att undersöka olika attityder, åsikter, betydelse och praktiska aspekter kring användning av metadon för smärtlindring i livets slut. Semi-strukturerade intervjuer genomfördes med 30 läkare som arbetade inom specialiserad palliativ vård eller smärtvård i Sverige. Intervjuerna skrevs ut och texterna analyserades med konventionell kvalitativ innehållsanalys.

Det visade sig att, enligt läkarna, attityder eller åsikter inte utgjorde något hinder för användning av metadon mot smärta. Metadon rapporterades återkommande användas och fungera framför allt vid långdragen opioidanvändning med otillräcklig effekt och central sensitisering vid komplexa cancerrelaterade smärtor i ryggrad eller bäcken. Typiska diagnoser var skelettmetastaser av prostata-, bröst- eller njurcancer men även bukspottkörtelcancer eller sarkom.

Läkarna beskrev hur de genom att starta med låga doser av metadon och sedan öka doserna stegvis, kunde få bra smärtlindrande effekt och samtidigt undvika allvarliga biverkningar, även vid användning i hemsjukvård. Om metadon började ge bra smärtlindrande effekt inom några dagar minskade de ofta dosen av den redan pågående opioiden med 25-30% för att minimera risken för opioidöverdosering. Den smärtlindrande effekten rapporterades sitta i åtminstone veckor eller månader och det var i de flesta fall tillräckligt inom specialiserad palliativ vård. En del läkare var närmast okritiskt positivt inställda till metadon, medan andra varnade för övertro på enskilda preparat och för risken att förbise andra behandlingsalternativ.

I studie IV följdes de dagliga symtomen hos 93 döende patienter som behövde få sina symptomlindrande läkemedel tillförda kontinuerligt subkutant med hjälp av en läkemedelspump. Orsaken var oftast ökande svårigheter att svälja tabletter på grund av försämrat allmäntillstånd i livet slut eller behov av bättre smärtlindring. Överlevnaden var i snitt fyra dygn (medianvärde). Smärtlindringen förbättrades signifikant hos patienterna när den subkutana tillförseln startade utan att förekomsten av förvirring ökade, oavsett ålder. Låg dos av metadon användes även i en del av de subkutana läkemedelspumparna och man kunde se att det gavs framgångsrikt främst till patienter som från början bedömdes ha mycket svår smärta, utan att allvarliga biverkningar uppstod.

Startdosen per dygn av metadon rapporterades i alla studier vara i median 5 mg, som ofta ökades till 10 mg och maximalt 20 mg, per dygn. Tilläggsbehandling med lågdos metadon gavs vanligen uppdelat på två doser per dygn.

9.3 DISKUSSION OCH SLUTSATSER

Patienterna i dessa fyra studier var bland samhällets allra svårast sjuka; personer döende på grund av avancerad cancersjukdom med komplexa smärtor som inte lindras tillräckligt bra med de vanliga smärtstillande läkemedlen.

I studie I-IV beskrevs att vissa patienter med svårbehandlad komplex cancerrelaterad smärta verkade kunna få förbättrad smärtlindring genom tillägg av en låg dos metadon till den opioid som de redan använde. Metoden användes återkommande inom specialiserad palliativ vård i Sverige, där nästan en tiondel av patienterna ordinerades metadon. Attityder till metadon verkade inte utgöra något hinder för dess användning. Genom att starta med låga doser och sedan öka stegvis med flera dagars intervall verkade metadon kunna introduceras på ett säkert vis. Kontinuerlig subkutan tillförsel av opioider, inklusive låg dos av metadon, kunde effektivt och säkert minska smärtan hos döende patienter utan ökad risk för förvirring, oavsett ålder.

Sammantaget kan tilläggsbehandling med låg dos metadon betraktas som ett värdefullt verktyg för smärtlindring hos utvalda patienter med komplex cancerrelaterad smärta inom specialiserad palliativ vård.

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12 APPENDICES

12.1 APPENDIX I. SUPPLEMENTARY SURVEY TO THE SRPC'S ELQ (STUDY II)

This methadone survey was filled in online and dealt with the following points:

Fick patienten metadon ordinerat för smärtbehandling i någon form (inte för behandling av beroende) under tiden som din enhet hade ansvar för patienten?

□ Ja – övriga metadonfrågor gås igenom □ Nej – hela enkäten är klar

Varför ordinerades metadonbehandling mot smärta?

□ Otillräcklig smärtlindring trots höga opioiddoser

□ Otillräcklig smärtlindring trots höga opioiddoser i kombination med läkemedel mot neuropatisk smärta (t.ex. gabapentin, amitriptylin)

□ Störande biverkningar av andra opioider

□ För behandling av smärta som varit svårbehandlad på annat sätt

□ Byte till metadon som enda opioid

□ Primärbehandling mot neuropatisk smärtkomponent

□ Annan anledning. Vilken?

Bedömd huvudsaklig fysiologisk smärtmekanism

□ Nociceptiv smärta □ Neuropatisk smärta

□ Blandad nociceptiv och neuropatisk smärta □ Oklar smärtmekanism

□ Smärtmekanismen ej bedömd

Läkaren som initierade behandlingen med metadon är

□ Icke-legitimerad läkare □ Legitimerad läkare □ ST-läkare □ Specialistläkare

Läkaren som initierade insättningen av metadon har

□ Stor erfarenhet av metadon □ Begränsad erfarenhet av metadon

□ Ingen erfarenhet av metadon

Skedde behandlingen i samråd med en eller flera andra läkare?

□ Ja □ Nej

Med vem skedde samrådet?

□ Annan specialistläkare med palliativmedicinsk kompetens

□ Annan specialistläkare med smärtmedicinsk kompetens

□ Annan specialistläkare

Var gavs de första doserna av metadon?

□ På specialiserad palliativ slutenvårdsavdelning

□ På ordinarie sjukhusavdelning

□ På kommunalt boende

□ I specialiserad palliativ hemsjukvård

□ I allmän hemsjukvård

Datum då metadonbehandlingen startades

Startdos (mg/dygn)

Administrationssätt vid start

□ Peroralt □ Subkutant □ Intravenöst

Doseringstillfällen per dygn

□ 1 □ 2 □ 3

□ Gavs som kontinuerlig infusion □ Gavs enbart vid behov

Har dygnsdosen av metadon ändrats under vårdtiden?

□ Ja □ Nej

Vid hur många tillfällen ändrades metadondosen under vårdtiden?

Dygnsdos metadon under det sista dygnet som metadon administrerades (mg/dygn)

Administrationssätt, sista dygnet

□ Peroralt □ Subkutant □ Intravenöst

Antal doseringstillfällen för metadon under det sista dygnet som metadon administrerades

□ 1 □ 2 □ 3 □ Gavs som kontinuerlig infusion □ Gavs enbart vid behov

Metadonbehandlingen avslutades

□ I samband med dödsfallet □ Annat datum

Datum då metadonbehandlingen avslutades

Anledning till att metadonbehandlingen avbröts?

□ Ingen effekt □ Biverkningar □ Annat, vilken annan anledning

Hade patienten någon annan samtidig opioidbehandling?

□ Samtidig opioidbehandling första dygnet (ange substans och dygnsdos)

□ Samtidig opioidbehandling vid behov sista dygnet (ange substans och sammanlagd dygnsdos)

□ Ingen annan opioidbehandling än metadon

Effekten av metadonbehandlingen på patientens smärta

□ Mycket god □ God □ Måttlig □ Ingen alls

Biverkningar relaterade till metadonbehandlingen

□ Inga biverkningar □ Förstoppning □ Illamående □ Konfusion

□ Sedering □ Andningspåverkan □ Fall □ Annan, vilken?

Sammantaget, bedömer du att insättningen av metadon var till nytta för denna patient?

□ Ja □ Nej

Kommentar:

12.2 APPENDIX II. SEMI-STRUCTURED INTERVIEW PROTOCOL (STUDY III)

The questions below were only initial questions, with the possibility to follow-up questions, depending on the initial response. When needed, the questions were modified to suit the actual interview situation.

Berätta om dig själv och din medicinska bakgrund.

Berätta om din erfarenhet av att behandla smärta genom åren.

Hur stor erfarenhet har du av att hantera svåra fall? Om du har det, hur mycket erfarenhet har du? Har du utvecklat några egna strategier (för komplex smärtbehandling)?

Vilken erfarenhet har du av att använda metadon i smärtbehandling, om någon? Utveckla.

Om du använder metadon, vad överväger du innan du sätter in det på en patient?

Tycker du att du har tillräckliga kunskaper och erfarenhet för att förskriva metadon? Beskriv!

Vilka smärtmekanismer anser du är de viktigaste för att välja metadon?

Beskriv en patient som du skulle förvänta dig kan dra nytta av insättning av metadon mot smärta.

När det gäller metadonanvändning: hur är den allmänna kunskapsnivån bland dina kollegor och hur använder de metadon, tycker du?

Hur uppfattas metadon bland dina kollegor – finns positiva eller negativa attityder?

Skulle du rekommendera en ny kollega att förskriva metadon? Varför eller varför inte?

Hur ser kunskapen ut om metadon bland övrig personal?

Beskriv eventuella förekommande fördomar om metadon som du har stött på [hos kollegor, personal, patienter eller deras närstående].

Kommer du ihåg något fall där metadonbehandling resulterade i en oväntat god smärtlindring?

Kommer du ihåg något fall där metadonanvändning blev särskilt problematisk [oavsett orsak]?

Slutligen, om eller när smärtlindring erhålls hos en patient med ett ovanligt svårt smärtsyndrom - vad betyder det i stort [för patienten, familjen, personalen och för dig själv]?

12.3 APPENDIX III. START PROTOCOL (STUDY IV)

The start protocol referred to the patient's situation just before the CSCI was initiated. The start protocol was thus filled in only once. Every subsequent day thereafter, the daily protocol was filled in. The only difference between the start protocol and the daily protocol was the first page where the latter did not include the questions about indication for CSCI and type of pain. In the daily protocol, on the page with the pain drawing, was also to be marked each day the current insertion place for the SC needle for the CSCI.

OBSERVERA! Fyll i detta fullständigt **INNAN** patienten erhåller pump!!

□ Patienten avstår
□ Kan ej ge medgivande

(OBS! Skriv ändå namn och personnr/etikett!)

Startprotokoll

Pumpstudien

Fullständigt ifyllt protokoll lämnas i låda märkt ”Pumpstudien – ifyllda protokoll”
på avdelningens expedition

Frågor? Kontakta Per Fürst

0739-17 74 73

per.furst@stockholmssjukhem.se

Patient

Plats för namnetikett

Personnummer:

_____

Datum:__-__ -__ Avdelning: _____

Klockan: _____:_____

1. Lägg in att ”fylla i dagligt protokoll” i ”Att göra” i TakeCare

2. Indikation för insättning av smärtpumpen

- Sväljsvårigheter på grund av försämrat allmäntillstånd
- Sväljsvårigheter av medicinska skäl, t.ex. stroke
- Hinder i magtarmkanalen
- Otillräcklig effekt av pågående smärtmedicinering
- Biverkningar av pågående smärtmedicinering
  - Ange biverkan_____
- Annat, nämligen_____

3. Smärttyp

- ☐ Nociceptiv
- ☐ Neuropatisk
- ☐ Blandad
- ☐ Annan, nämligen: _____

4. Aktuell andningsfrekvens (andetag/minut)

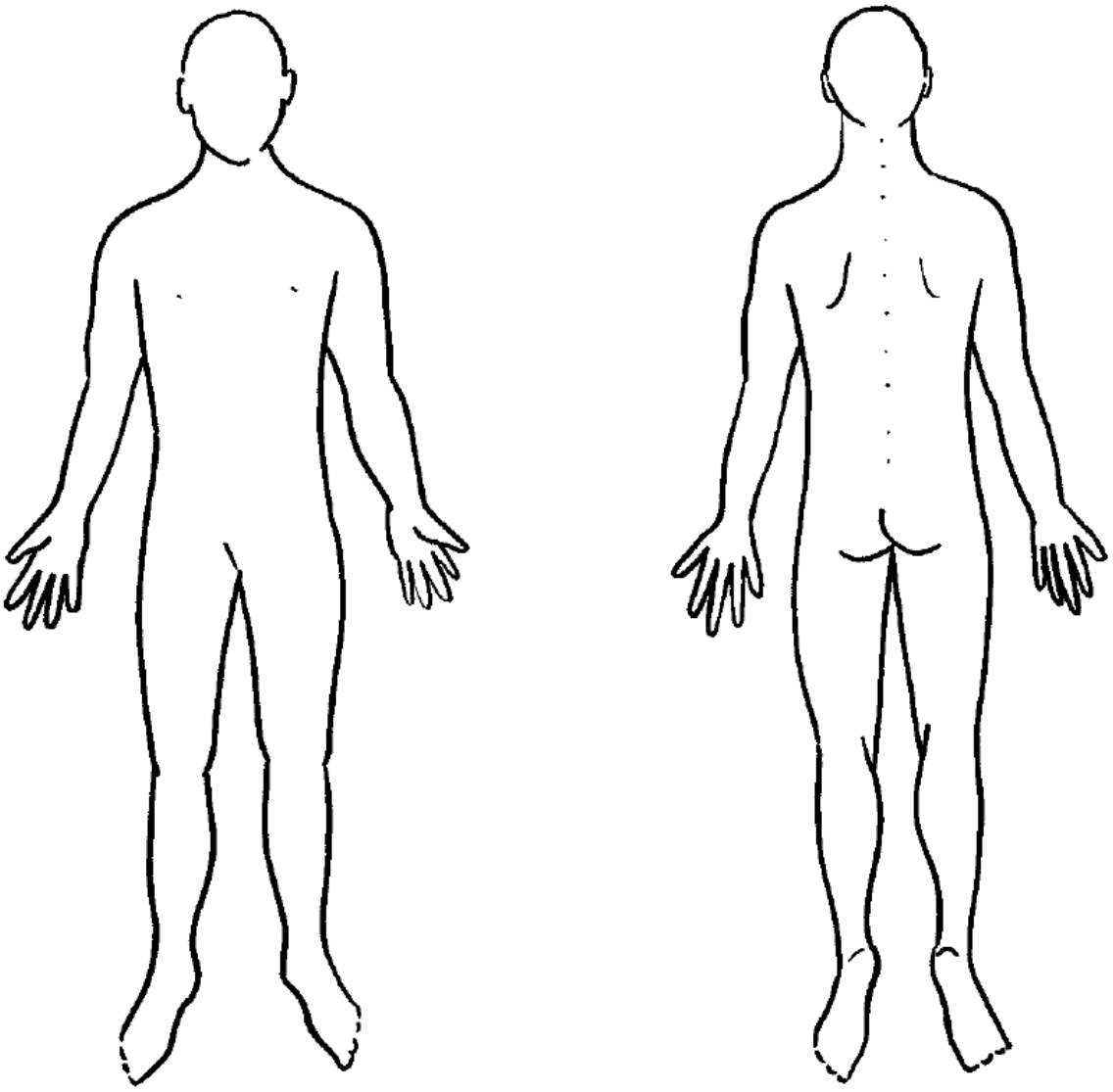
- ☐ Hög >16
- ☐ Normal 12–16
- ☐ Sänkt <12
- ☐ Låg <8

4. Smärta och hudirritation

☐ Markera med skuggning /////// ungefär var den mest besvärande smärtan funnits senaste dygnet

☐ Markera med ring **O** var eventuella relevanta hudirritationer finns. Beskriv dem kort, skriv intill markeringen

☐ Andra avvikelser av intresse
(fritext):_____



5. IPOS
(fylls i av undersökaren med fokus på det senaste dygnet)

1. Vilka har patientens huvudsakliga problem eller bekymmer varit de senaste 3 dagarna?

1._____

2._____

3._____

F2. Vänligen markera den ruta som bäst beskriver hur patienten har påverkats av nedanstående symtom de senaste 3 dagarna.

	Inte alls	*Lite*	*Måttligt*	*Mycket*	*Värsta tänkbara*	*Kan inte bedömas (t.ex. medvetslös)*
Smärta	0☐	1☐	2☐	3☐	4☐	☐
Andnöd	0☐	1☐	2☐	3☐	4☐	☐
Svaghet eller bristande energi	0☐	1☐	2☐	3☐	4☐	☐
Illamående	0☐	1☐	2☐	3☐	4☐	☐
Kräkningar	0☐	1☐	2☐	3☐	4☐	☐
Dålig aptit	0☐	1☐	2☐	3☐	4☐	☐
Förstoppning	0☐	1☐	2☐	3☐	4☐	☐
Ont eller torr i munnen	0☐	1☐	2☐	3☐	4☐	☐
Dåsighet	0☐	1☐	2☐	3☐	4☐	☐
Nedsatt rörlighet	0☐	1☐	2☐	3☐	4☐	☐
Eventuella andra symtom:						
1._____	0☐	1☐	2☐	3☐	4☐	☐
2. _____	0☐	1☐	2☐	3☐	4☐	☐
3._____	0☐	1☐	2☐	3☐	4☐	☐

Under de senaste 3 dagarna:

	Nej, inte alls	*Vid enstaka tillfällen*	*Ibland*	*Ofta*	*Ja, hela tiden*	*Kan inte Bedömas (t.ex. medvetslös)*
F3. Har han/hon känt ångest eller oro över sin sjukdom eller behandling?	0☐	1☐	2☐	3☐	4☐	☐
F4. Har någon av hans/hennes närstående känt oro eller varit bekymrad för patienten?	0☐	1☐	2☐	3☐	4☐	☐
F5. Anser du att patienten känt sig nedstämd?	0☐	1☐	2☐	3☐	4☐	☐

	Ja, hela tiden	*Ofta*	*Ibland*	*Vid enstaka tillfällen*	*Nej, inte alls*	*Kan inte Bedömas (t.ex. medvetslös)*
F6. Anser du att han/hon känt lugn och ro inombords?	0☐	1☐	2☐	3☐	4☐	☐
F7. Har patienten berättat för sina närstående hur han/hon mår? (i den utsträckning som han/hon önskat)	0☐	1☐	2☐	3☐	4☐	☐
F8. Har patienten fått så mycket information som han/hon önskat?	0☐	1☐	2☐	3☐	4☐	☐

	Har fått hjälp/ Inga problem	*Har Oftast fått hjälp*	*Har Delvis fått hjälp*	*Har knappast fått hjälp*	*Har inte fått hjälp*	*Kan inte Bedömas (t.ex. medvetslös)*
F9. Har han/hon fått hjälp med praktiska problem? (problem som uppkommit i samband med sjukdomen)	0☐	1☐	2☐	3☐	4☐	☐

6. Richmond Agitation-Sedation Scale (RASS)

Kryssa för bästa alternativet som beskriver senaste dygnet

□	+4	Stridslysten. Uppenbart stridslysten eller våldsam, direkt fara för personal.
□	+3	Mycket agiterad. Drar i eller drar ut tub/katetrar eller har ett aggressivt beteende mot personal.
□	+2	Agiterad. Frekventa oavsiktliga rörelser eller dålig följsamhet med ventilator.
□	+1	Rastlös. Ängslig eller orolig men ej aggressiva eller kraftfulla rörelser.
□	±0	Alert och lugn.
□	-1	Slö. Ej helt alert men upprätthåller (mer än 10 sekunder) vakenhet med ögonkontakt vid tilltal.
□	-2	Lätt sederad. Kortvarig (mindre än 10 sekunder) vakenhet med ögonkontakt vid tilltal.
□	-3	Måttligt sederad. Någon form av rörelse (men ingen ögonkontakt) vid tilltal.
□	-4	Djupt sederad. Ingen respons vid tilltal men någon form av rörelse vid fysisk stimulering.
□	-5	Ej väckbar. Ingen respons vid tilltal eller fysisk stimulering.

7. Performance enligt ECOG - Allmäntillstånd

Kryssa för bästa alternativet som beskriver senaste dygnet

□	0.	Klarar all normal aktivitet utan begränsning
□	1.	Klarar inte fysiskt krävande aktivitet men är uppegående och i stånd till lättare arbete.
□	2.	Är uppegående och kan sköta sig själv men klarar inte att arbeta. Är uppe och i rörelse mer än 50 % av dygnets vakna timmar.
□	3.	Kan endast delvis sköta sig själv. Är bunden till säng eller stol mer än 50 % av dygnets vakna timmar.
□	4.	Klarar inte någonting. Kan inte sköta sig själv. Är bunden till säng eller stol.
□	5.	Död

8. Confusion Assessment Method (CAM)

(Bedömningen gäller senaste dygnet. Familjemedlem eller vårdpersonal utfrågas vanligtvis)

1. *Akut debut eller fluktuerande förlopp*

☐ *ja* ☐ *nej* Finns det tecken på att en akut förändring skett i patientens mentala status i jämförelse med patientens normaltillstånd?

☐ *ja* ☐ *nej* Har det onormala beteendet fluktuerat, d.v.s. har det eventuellt varit helt borta, eller varierat i svårighetsgrad?

2. *Störning i uppmärksamhet*

☐ *ja* ☐ *nej* Har den undersökta svårt att fästa uppmärksamheten, är han t.ex. lätt distraherad eller har han svårt att hålla sig till det som diskuteras?

3. *Splittrad tankeförmåga*

☐ *ja* ☐ *nej* Är patientens tankar splittrade, osammanhängande, med t.ex. irrande eller irrelevant tal, är tankeflödet oklart eller ologiskt eller växlar konversationen oförutsägbart från en sak till en annan?

4. *Förändrad medvetandegrad*

☐ *ja* ☐ *nej* Är patientens medvetandegrad annat än normal? Utvärdering av patientens medvetandegrad: normal, alert (överkänslig mot omgivningens stimuli), dåsig (lättväckt) eller medvetslös (kan inte väckas).

-Slut-