Prevalence and pharmacological treatment of pain in patients with cancer

The role of opioids with and without NMDA receptor affinity

Johan Haumann

Prevalence and pharmacological treatment of pain in patients with cancer

The role of opioids with and without NMDA receptor affinity

Prevalentie en farmacologische behandeling van kankergerelateerde pijn

De rol van opioïden met en zonder affiniteit voor de NMDA receptor

ISBN 978-90-830376-0-8

Design Daphne van Langen – www.raza.nl
Printed by Print Service Ede – www.proefschriftenprinten.nl

Prevalence and pharmacological treatment of pain in patients with cancer

The role of opioids with and without NMDA receptor affinity

Prevalentie en farmacologische behandeling van kankergerelateerde pijn

De rol van opioïden met en zonder affiniteit voor de NMDA receptor

Proefschrift
ter verkrijging van de graad van doctor
aan Maastricht University
op gezag van de Rector Magnificus, Prof. dr. Rianne M. Letschert
volgens besluit van het College van Decanen,
in het openbaar te verdedigen op:
woensdag 8 januari 2020 om 14.00 uur

door

Johan Haumann
Geboren te Senanga, Zambia

Promotiecommissie

- Promotor: Prof. Dr. E.A. Joosten
- Copromotores: Prof. Dr. M.H.J Van den Beuken – Van Everdingen
  Dr. S.M.J. Van Kuijk

Beoordelingscommissie

- Prof. Dr J. Van Zundert (voorzitter)
- Dr. Y. Van der Linden (LUMC)
- Prof. Dr. B. Tan
- Prof. Dr. V.C.G. Tjan - Heijnen
- Prof. Dr. K. Vissers (UMCN)

General Introduction

1. Cancer-induced Pain and its pharmacological treatment

The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[1] The pain pathway relays action potentials from peripheral nociceptors via the dorsal horn to the brain. Imminent tissue damage activates nociceptors, which are specialized endings of the nociceptive afferent fibers. The information (action potentials) is then transmitted via the spinal dorsal horn to the brain. In the brain the nociceptive stimulus is registered as pain with its sensory, emotional, cognitive and social components. Pain serves an important protective function: diseases that disrupt the nociceptive pathway and result in anesthesia can cause deformations due to untreated fractures, burn related injuries and osteomyelitis. Small wounds go unnoticed, are not cared for and can infect.[2-4]

From a mechanistic point of view various cellular processes are involved along the pain pathway when nociceptive input is transmitted to the brain. When nociceptive signals are transmitted to the brain and the pain is registered in the somatosensory cortex the individual can respond. This protective response is needed for survival and protection. Understanding the transmission of the nociceptive signal is important because pharmacological interventions often modulate this signal. The network of nociceptive afferents and cells in the spinal dorsal horn is often referred to as the spinal pain gate and if this gate is closed no information can further be transferred to the higher brain areas. Closing the spinal pain gate with pharmacological tools is an important strategy in the treatment of pain. The neurotransmission between nociceptive afferents and the second order neurons in the dorsal horn is known to be a complex interaction between inhibitory and excitatory neurotransmitters and their receptors. Important neurotransmitters involved in the transmission of nociceptive information are glutamate and aspartate. Several receptors for glutamate have been identified, including the N-Methyl-D-Aspartate (NMDA) receptor and the alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor.[5,6] The AMPA receptor is activated by glutamate release of the activated nociceptive afferents, and upon continuous activation the NMDA receptor becomes involved as well. The activation of the NMDA receptor lowers the threshold for signal transduction resulting in more action potentials (information) forwarded to the brain. In other words the spinal pain gate is open, a process referred to as central sensitization.[7]

Based on the different mechanisms and the cellular processes involved, pain can be discriminated in two predominant types: nociceptive and neuropathic pain. Nociceptive pain is pain that arises from actual or threatened damage to non-neural tissue and is due to activation of nociceptors (IASP definition).[1] Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system.[1] Because these types of pain have different underlying mechanisms it seems logical that these different pain types respond distinctively to pharmaceutical treatments.

When pain is experienced by a patient with cancer this pain is often referred to as cancer pain. The simplicity of the term hides the complexity of the underlying problem. For instance, a patient suffering from pain due to bone metastases is suffering from a different pain type as the patient suffering from neuropathic pain due to chemotherapy, however both are included in the term cancer pain. Therefore the term cancer pain should no longer be used, instead it is preferred to discriminate between nociceptive and neuropathic pain and with that describe the actual pain syndrome the patient with cancer is suffering from. This will improve understanding of the

underlying pain syndrome, and should assist in the optimal choice of pharmaceutical treatment related to the type of pain this specific patient is suffering from.

Pain in the cancer patient is a major problem. Irrespective of the disease state 38% of all
9 patients with cancer report moderate to severe pain.[8] Pain is an important cause for a decreased quality of life for the patient with cancer, it is described as distressing, and even intolerable in 33% of the patients with cancer.[9] The prevalence of pain has not decreased when comparing the decade 2005-2014 to the decades 1966-2005.[8,10] This despite the fact that according to the literature pain in the cancer patient is described to be relatively easy to treat. The WHO pain ladder is a simple algorithm for the treatment of pain in cancer patients.[11] (*Figure 1*) This algorithm was first published in 1986 and since then little has changed. Briefly: the cancer patient with pain should first be treated with a non-opioid pain pharmaceutical such as paracetamol or an NSAID (*step 1*). When step 1 does not result in significant pain relief next steps are use of a weak (*step 2*) or a strong opioid (*step 3*). Implementation of this algorithm has been shown to result in clinical significant pain relief in 70-90% of the patients.[12] The simplicity and effectiveness of this algorithm makes us wonder why cancer patients are still suffering from pain. Currently, over half of the cancer patients with an advanced disease state are suffering from moderate to severe pain.[8]

2. Opioid therapy

The stepwise approach of the WHO pain ladder (*Figure 1*) is easy to follow. Reaching the 3rd step in this algorithm (use of strong opioids) it is advised to use an opioid that is easily available and an opioid the clinician is experienced with.[13] The strong opioid is not specified in this algorithm. Multiple Cochrane reviews were unable to show clinical relevant differences between opioids in effectiveness in pain in cancer patients.[14-19] The only difference between various opioids seems to be their side effect profile, which favors transdermal fentanyl patch when compared to oral morphine in terms of constipation.[19,20] Various meta-analyses could not provide scientific evidence on the preference of one strong opioid over the other in the treatment of pain in the cancer patient. Nevertheless it should also be indicated that these meta-analyses made clear that research so far is relatively weak. The conclusion of the Cochrane review on opioids for cancer pain even states that " the amount and quality of evidence around the use of opioids for treating cancer pain is disappointingly low".[21] The fact that between 6–19% of the patients treated with opioids suffer from intolerable side-effects and as a consequence stop their medication due to these side-effects could be an important reason for sustained pain in the cancer patient.[21]

An option in the treatment of opioid-induced intolerable side effects is opioid rotation. The rotation from one opioid to another may result in a reduction in side effects and improved pain relief, which subsequently may increase the chance of success of the opioid therapy.[22] Although opioid rotation is an accepted method to achieve pain relief including an acceptable side effect profile, it must be stressed that the procedure to find an equi-analgesic dose of a different opioid during the rotation is not supported by solid evidence.[23]

Commonly used opioids, like fentanyl and oxycodone directly activate opioid receptors.[24] The most important opioid receptor in the pain pathway is the μ-opioid receptor. Once activated this receptor will hyperpolarize the cell membrane through the activation of calcium and potassium channels. This hyperpolarization will result in an increased threshold of the neuron. This will result in a decreased glutamate release, and via this mechanism the conduction of nociceptive information will decrease.[25,26] Methadone is a strong opioid which has NMDA antagonist qualities

as well. The additional effect of methadone on the NMDA receptor could provide additional effect on certain pain states such as neuropathic pain.[27,28] It should nevertheless be stated that the use of methadone is complex due to its pharmacokinetic profile and many interactions.[29,30]

From this we hypothesize that due to the effect on both the mu-opioid receptor and the NMDA receptor methadone will result in superior pain relief in patients with pain in which the NMDA receptor is involved such as neuropathic pain.

3. Thesis Outline

The aims of this thesis are:

1. to understand why the prevalence of pain in cancer patients has not reduced over the last decade as compared to the decades before.
2. To examine if it is possible to improve the treatment of pain in patients with cancer by discriminating between neuropathic and nociceptive pain. To do so the effect of methadone with its dual mechanism compared to presently commonly used opioids will be examined. Then following research questions are formulated:
   - RQ1 Why is the prevalence of pain in cancer patients not reduced in the decade 2005-2014 as compared to the decades 1966-2005?
   - RQ2 Is methadone superior to fentanyl in head-and-neck-cancer patients with neuropathic pain?
   - RQ3 Is methadone superior/inferior to fentanyl in head-and-neck-cancer patients with nociceptive pain?
   - RQ4 Can we predict which patient will benefit from opioid therapy?

In Chapter 2 we address RQ1 and describe the prevalence of pain in cancer patients. The prevalence of pain in cancer patients in the years 1966-2005 is compared to the prevalence of pain in cancer patients in the decade 2005-2014. Possible causes and explanations for this ongoing problem are reviewed, with a focus on the lack of improvement in the prevalence of cancer related pain despite the increased attention on cancer related pain.

In Chapter 3 we address RQ2 and performed a Randomized Controlled Trial (RCT) which allows to study the pain relieving effect of methadone versus fentanyl in a patient population with neuropathic pain due to head-and-neck cancer.

Based on the RCT design as described in Chapter 3 we perform a non-inferiority study (see RQ3) which focuses on the effect of methadone versus fentanyl in a patient population with nociceptive pain due to radiation induced mucositis in a population with head-and-neck cancer (Chapter 4).

In view of RQ4 we aim to develop a predictive model for the probability of clinical success of opioid therapy in nociceptive and neuropathic pain due to head-and-neck cancer based on data as collected in the RCTs (see Chapter 3 and 4).

In Chapter 5 a prediction model is presented which consists of four parameters: age of the patient, duration of pain, neuropathic pain and treatment with methadone.
In order to evaluate the generalizability of our results in a different patient population we describe

a protocol to investigate the difference between methadone and oxycodone in a population with cancer induced bone pain. This study protocol for a randomized controlled trial is presented in chapter 6.

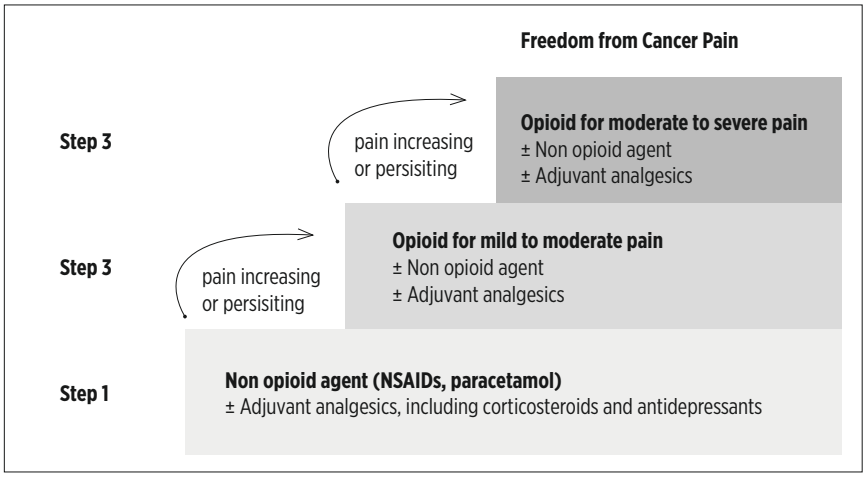


Figure 1. WHO's cancer pain ladder for adults. This pain ladder is an easy to use algorithm to treat pain. When treating a patient with pain the first step is to start with a non-opioid, such as an NSAID or paracetamol. If this proves ineffective the second step is to add a weak opioid. In pain due to cancer this step is mostly skipped. The third step is to add a strong opioid such as morphine, fentanyl or oxycontin. [31]

1. **definition pain** iasp. https://www.iasp-pain.org/education/content.aspx?ItemNumber=1698#Pain.

2. **Goldberg YP**, **MacFarlane J**, **MacDonald ML**, et al. Loss-of-function mutations in the Nav1.7 gene underlie congenital indifference to pain in multiple human populations. *Clin Genet* 2007; **71**(4): 311-9.

3. **Piazza MR**, **Bassett GS**, **Bunnell WP**. Neuropathic spinal arthropathy in congenital insensitivity to pain. *Clin Orthop Relat Res* 1988; (236): 175-9.

4. **Cox JJ**, **Reimann F**, **Nicholas AK**, et al. An SCN9A channelopathy causes congenital inability to experience pain. *Nature* 2006; 444(7121): 894-8.

5. **Mao J**, **Price DD**, **Hayes RL**, **Lu J**, **Mayer DJ**, **Frenk H**. Intrathecal treatment with dextrorphan or ketamine potently reduces pain-related behaviors in a rat model of peripheral mononeuropathy. *Brain Res* 1993; 605(1): 164-8.

6. **Sher GD**, **Cartmell SM**, **Gelgor L**, **Mitchell D**. Role of N-methyl-D-aspartate and opiate receptors in nociception during and after ischaemia in rats. *Pain* 1992; **49**(2): 241-8.

7. **Basbaum AI**, **Bautista DM**, **Scherrer G**, **Julius D**. Cellular and molecular mechanisms of pain. *Cell* 2009; **139**(2): 267-84.

8. **van den Beuken-van Everdingen MH**, **Hochstenbach LM**, **Joosten EA**, **Tjan-Heijnen VC**, **Janssen DJ**. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage* 2016; **51**(6): 1070-90 e9.

9. **Breivik H**, **Cherny N**, **Collett B**, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. *Ann Oncol* 2009; **20**(8): 1420-33.

10. **van den Beuken-van Everdingen MH**, **de Rijke JM**, **Kessels AG**, **Schouten HC**, **van Kleef M**, **Patijn J**. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007; **18**(9): 1437-49.

11. **Ventafridda V**, **Saita L**,**Ripamonti C**, **De Conno F**. WHO guidelines for the use of analgesics in cancer pain. *Int J Tissue React* 1985; **7**(1): 93-6.

12. **Carlson CL**. Effectiveness of the World Health Organization cancer pain relief guidelines: an integrative review. *J Pain Res* 2016; **9**: 515-34.

13. **Caraceni A**, **Hanks G**, **Kaasa S**,et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol* 2012; **13**(2): e58-68.

14. **Nicholson AB, Watson GR, Derry S, Wiffen PJ**. Methadone for cancer pain. *Cochrane Database Syst Rev* 2017; **2**: CD003971.

15. **Bao YJ**, **Hou W**, **Kong XY**, et al. Hydromorphone for cancer pain. *Cochrane Database Syst Rev* 2016; **10**: CD011108.

16. **Schmidt-Hansen M**, **Bennett MI**, **Arnold S**, **Bromham N**, **Hilgart JS**. Oxycodone for cancer-related pain. *Cochrane Database Syst Rev* 2015; (2): CD003870.

17. **Schmidt-Hansen M**, **Bromham N**, **Taubert M**, **Arnold S**, **Hilgart JS**. Buprenorphine for treating cancer pain. *Cochrane Database Syst Rev* 2015; (3): CD009596.

18. **Wiffen PJ**, **Wee B**, **Moore RA**. Oral morphine for cancer pain. *Cochrane Database Syst Rev* 2016; **4**: CD003868.

19. **Hadley G**, **Derry S**, **Moore RA**, **Wiffen PJ**. Transdermal fentanyl for cancer pain. *Cochrane Database Syst Rev* 2013; (10): CD010270.

20. **Wang DD**, **Ma TT**, **Zhu HD**, **Peng CB**. Transdermal fentanyl for cancer pain: Trial sequential analysis of 3406 patients from 35 randomized controlled trials. *J Cancer Res Ther* 2018; **14**(Supplement): S14-S21.

21. **Wiffen PJ**, **Wee B**, **Derry S**, **Bell RF**, **Moore RA**. Opioids for cancer pain - an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2017; **7**: CD012592.

22. **Mercadante S**. Opioid rotation for cancer pain: rationale and clinical aspects. *Cancer* 1999; **86**(9): 1856-66.

23. **Vissers KC**, **Besse K**, **Hans G**, **Devulder J**, **Morlion B**. Opioid rotation in the management of chronic pain: where is the evidence? *Pain Pract* 2010; **10**(2): 85-93.

24. **Azzam AAH**, **McDonald J**, **Lambert DG**. Hot topics in opioid pharmacology: mixed and biased opioids. *Br J Anaesth* 2019; **122**(6): e136-e45.

25. **Knezevic NN**, **Yekkirala A**, **Yaksh TL**. Basic/Translational Development of Forthcoming Opioid- and Nonopioid-Targeted Pain Therapeutics. *Anesth Analg* 2017; **125**(5): 1714-32.

26. **Yaksh TL**. Pharmacology and mechanisms of opioid analgesic activity. *Acta Anaesthesiol Scand* 1997; **41**(1 Pt 2): 94-111.

27. **Gorman AL**, **Elliott KJ**, **Inturrisi CE**. The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett* 1997; **223**(1): 5-8.

28. **Ebert B**, **Andersen S**, **Krogsgaard-Larsen P**. Ketobemidone, methadone and pethidine are non-competitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. *Neurosci Lett* 1995; **187**(3): 165-8.

29. **Kharasch ED**, **Regina KJ**, **Blood J**, **Friedel C**. Methadone Pharmacogenetics: CYP2B6 Polymorphisms Determine Plasma Concentrations, Clearance, and Metabolism. *Anesthesiology* 2015; **123**(5): 1142-53.

30. **Fredheim OM**, **Moksnes K**, **Borchgrevink PC**, **Kaasa S**, **Dale O**. Clinical pharmacology of methadone for pain. *Acta Anaesthesiol Scand* 2008; **52**(7): 879-89.

31. WHO's cancer pain ladder for adults. 1986. https://www.who.int/cancer/palliative/painladder/en/.

II

Pain prevalence in cancer patients: status quo or opportunities for improvement?

J. Haumann; E. A. Joosten, PhD,
M.H.J. van den Beuken-van Everdingen, MD, PhD

Current opinion in supportive and palliative care
2017 Jun;11(2): 99-104

Abstract

Purpose of review: Cancer incidence increases worldwide and thus more patients will suffer from cancer related pain. As cancer related pain severely affects quality of life, the decrease of pain should be of high priority for every clinician. In the last decade attention for cancer related pain and for its' treatment has increased, and new pharmacological based treatment options became available. This gave reason to hypothesize a decrease in pain prevalence in cancer patients over the last decade.

Recent findings: Despite increased attention to cancer related pain, pain prevalence in cancer patients has not significantly changed over the last decade as compared to the four decades before. This absence of change might be due to comorbidities cancer patients have, but also to undertreatment of pain, due to a lack of knowledge and pain measurement. Other factors underlying this absence of change are the use of incorrect co-analgesics in the case of treatment of neuropathic pain, as well as the present absence of potent analgesics with little side effects.

Summary: Consistent screening of pain in cancer patients and consequent correct treatment of pain might result in an impressive decrease in cancer related pain. For further reduction of pain new pharmacological analgesics need to be developed.

1. Introduction

Cancer has become the leading cause of death and morbidity in the world, with 14 million new cases and 8 million cancer related deaths in 2012.[1] The incidence of cancer is expected to increase by about 75% over the two next decades according to the International Agency for Research on Cancer (IARC). This increase in cancer patients will increase the demand for clinical expertise in the treatment of cancer. Beside treatment of cancer itself, there will be an increase in associated complaints. As up to 70% of patients with cancer suffer from pain,[2] it is impossible to treat a cancer patient without addressing pain. Pain is a major factor affecting the patients' quality of life and it is associated with numerous psychosocial responses.[3,4] Pain related to cancer is described as a distressing, and even an intolerable aspect of cancer by over 33% of cancer patients.[5] As adequate treatment of pain results in a clinically relevant improvement in the quality of life, it is an imperative that every clinician treating cancer patients can address and treat pain.[6]

A systematic review on pain prevalence in cancer patients was published in 2007. This review concluded that no progress in the treatment of cancer related pain had been made in the four decades preceding that publication. Since then a lot has happened, and attention for cancer related pain has increased. In 2008 the International Association for the Study of Pain (IASP) launched the global year against cancer pain, which raised awareness for cancer related pain. More research on cancer related pain has been instigated, resulting in an increased understanding of cancer related pain mechanisms such as pain due to bone metastases.[7] The increased attention for cancer related pain, in combination with new insights in pain mechanisms and the development of new drugs for cancer related pain such as the rapid onset opioids for breakthrough pain, gave hopeful reasons to expect a decrease in the prevalence of cancer related pain. However, a systematic review and meta-analysis of literature published between 2005 and 2014 showed that pain continues to be a prevalent symptom in patients with cancer and that the prevalence of pain in patients with cancer has not decreased.[8] In this review we focus on the reasons behind the still inacceptable high prevalence of pain in patients with cancer, and the opportunities to decrease pain in cancer patients.

2. Developments in Pain Prevalence

In the period 1966-2005 the overall prevalence of pain in patients after curative therapy was reported to be 33%, 59% in a cancer patient population on anticancer treatment, 64% in a cancer patient population with advanced, metastatic or terminal disease and 53% in a cancer patient population with all stages of cancer. [2]

In a follow up analysis the prevalence of pain in cancer patients (2005-2014) was reported by 39.3% of patients after curative therapy, 55.0% of patients on anticancer treatment, 66.4% of patients with advanced disease and 50.7% of patients with all stages of cancer.[8]

Further analyses on the intensity of pain in cancer patients showed that moderate to severe pain (NRS >4) was not evaluated in patients after curative therapy in the time-period 1966-2005, in the population on anticancer therapy 36% of the patients suffered from moderate to severe pain. In the patient population with advanced disease 45% of the patients suffered from moderate to severe pain, and in the patient population with all stages of cancer moderate to severe pain was reported by 31% of the patients. Moderate to severe pain was reported by 27.6, 32.4, 51.9 and 33.1% respectively (*see Table 1*) based on articles published in 2005-2014. These numbers indicate that pain prevalence and pain intensity did not decrease in the last ten years as compared to the 40 years before.

At the same time an increase in awareness of pain in cancer patients was noticed. This conclusion is based on the fact that the first systematic review (1966-2005; 40 years) included 54, whereas the second (2005-2014; 10 years) included 122 published articles of sufficient quality. Despite an increase in awareness of cancer related pain, studies show that pain and severe pain have not decreased in patients suffering from cancer.

3. Causes for lack of improvement

Increased awareness alone is not enough to establish a decrease in the prevalence of pain in cancer patients. Greco et al showed in two systematic reviews that undertreatment of cancer related pain according to the pain management index (PMI) has decreased from 43% in 2008 to 32% in 2014. Although this shows a decrease of 25% in undertreatment of pain in cancer patients, still a staggering 32% of cancer patients with pain remain undertreated.[9, 10]

It is of importance to note that it remains difficult to correctly treat pain in specific groups of cancer patients. For instance, the coexistence of renal impairment, which was shown to affect up to 20% of the cancer population,[11] will complicate pharmacological pain therapy. Renal impairment results in altered metabolism of opioids, therefore complicating opioid treatment for pain. Although fentanyl, sufentanil or alfentanil are advised in the treatment of cancer related pain in the patient with renal impairment [12] there is hardly any clinical evidence to support this. In fact, there is very limited evidence for opioid treatment of cancer related pain in the patient with renal impairment at all.[13] Furthermore, the use of analgesics, such as NSAID's or gabapentin will be restricted in cancer patients with renal impairment thereby further complicating pain therapy in these patients. As many cancer patients nowadays suffer from comorbidities, because of increased age, it is necessary to further investigate the effects of comorbidities on pain perception, and on the pharmacological therapy of pain.

4. Can we do better?

The World Health Organization (WHO) has developed a well-known treatment algorithm

for patients with cancer related pain, the WHO pain 3-step-ladder (Figure 1). This simple, straightforward treatment algorithm was presented in 1986, and is still relevant. The use of the WHO pain ladder has been shown to result in adequate pain relief in 20-100% of the patients.[14] This range is quite wide, and depends on the definition of success. When an NRS <4 is used to define success, 50-90% of the patients can be treated successfully with the WHO pain ladder, with one study reporting 81% success in patients without incidental pain, but only 50% success in a subpopulation with incidental pain.[15] Other studies reporting success in 72%-90% of the patients.[16-18] These numbers seem to indicate that it should be possible to provide sufficient pain relief using the WHO ladder in a substantial part of the patients with cancer related pain.

Although the WHO ladder is an easy to follow treatment algorithm for use in pain therapy, there is still room for debate. One general question is to start a weak opioid or a strong opioid at step two. Recently there is good evidence to suggest the start of a strong opioid at step two.[19] Previously published research however showed a higher incidence of side effects when step 2 was omitted.[20]

Another debate is the use of non-steroidal anti-inflammatory drugs (NSAID's) at step one of the WHO pain ladder, as long term use of NSAID's is associated with severe side effects due to its effects on renal and platelet function, and its toxicity on gastrointestinal tract mucosa. There seems to be little evidence on the effectivity of NSAID's in treatment of pain in cancer related pain. Based on one retrospective study it is impossible to provide a solid advice on the use of NSAID's in the treatment of pain in cancer patients.[21] Also subject for debate is the benefit of additional application of paracetamol with opioids at step three for which the evidence is 'weak if any'.[22]

Finally, interventional procedures, such as epidurals and nerve blocks were not incorporated in the original WHO cancer related pain ladder, even though some specialists suggest these should be implemented and become step four in the pain ladder. The lack of the incorporation of interventional pain therapy in the WHO ladder for treatment of cancer related pain results in less awareness, and possibly less use of these therapies. Furthermore, these interventions should not be considered as "step 4" in the pain ladder, as this would suggest to use them only when opioïds do not provide sufficient pain relief. These interventions can result in improved pain control when performed in an earlier stage.[23,24]

5. Pain types

The optimal treatment of pain depends on the cause of the pain. If pain is caused by actual or threatened damage to non-neural tissue and is due to activation of nociceptors the pain is defined as nociceptive pain. Severe nociceptive pain should be treated with opioids, and, if possible, by treating the cause of the damage. However, if the pain is caused by a lesion or disease of the somatosensory nervous system the pain is neuropathic. An analysis of the literature shows that 31.4% of cancer patients suffer from neuropathic pain.[25] A recent survey of 50 Italian palliative care centres even showed a mean reported prevalence of (partly) neuropathic pain of 44.2%. In this survey neuropathic pain was combined with mixed pain.[25]

As opioids often fail to treat neuropathic pain satisfactory,[26] adjuvant analgesics are often necessary. The pharmacological drugs to treat neuropathic pain can be divided into four categories: 1. anticonvulsants; 2. antidepressants; 3. NMDA receptor antagonists and 4. other adjuvant analgesics. A systematic review on the pharmacological treatment of neuropathic cancer

related pain showed only low to very low quality evidence for pain relief with all pharmacological agents. The authors made strong recommendations to prescribe an anticonvulsant or an antidepressant (amitriptyline or a Selective Noradrenaline Reuptake Inhibitor (SNRI)) in case of
19 combined nociceptive and neuropathic pain if opioids alone do not provide the wanted effect, and in the case of non-chemotherapy-induced neuropathic pain.[27] The European Federation of Neurological Societies (EFNS) strongly advices to use opioids as a second or third line therapy, as well as to use anti-epileptics and antidepressants as a first line therapy for non-cancer related neuropathic pain.[28] It should be taken into account that even these first line therapies for treatment of neuropathic pain have a relative high failure rate, and do come with side effects. Hence, new and potent analgesics to treat neuropathic cancer related pain are urgently needed. In this respect methadone might become an interesting option. It has been shown in a recent trial that cancer patients with a neuropathic pain component responded better to methadone than to the opiate fentanyl in terms of pain relief.[29] In addition methadone was not inferior to fentanyl in patients with nociceptive pain as shown in a yet unpublished part of the same trial (manuscript submitted). On the other hand no difference in effect between methadone and other opioids in the treatment of cancer related pain has been shown in other studies.[30] However these studies did not differentiate the cancer related pain patients into those with nociceptive, neuropathic or mixed pain. The combination of these findings in neuropathic and in nociceptive cancer related pain patients show that methadone is a very good candidate for the treatment of cancer related pain with an important neuropathic pain component.

6. Barriers for optimal treatment of cancer related pain

One of the most important barriers for optimal treatment of cancer related pain is a consistent lack of knowledge of physicians, nurses and patients. For instance many physicians and policy makers are still unfamiliar with the WHO pain ladder for treatment of cancer related pain, despite the fact that this algorithm is well validated and also around for 30 years.[31,32] A review article by Kwon[33] addresses this lack of knowledge, and describes that many physicians are very cautious in prescription of opioids (as part of the WHO-ladder of pain treatment in cancer related pain patients) because of fear for side effects, tolerance and addiction. Furthermore, in specific cancer patients emotional distress might be considered as the cause of the pain, which results in psychological counselling instead of prescribing pain medication. From this we suggest that knowledge of the WHO ladder of pain treatment in cancer related pain patients should be educated and trained as much as possible. Nevertheless it is obvious that even despite the simplicity of the pain ladder, correct use and adherence to the WHO-ladder continues to be a problem for many physicians.

Another barrier for optimal treatment of pain in cancer patients is the lack of consistent assessment of pain in cancer patients. A lack of pain assessment is a problem according to 63% of a sample of physicians.[34] In the Netherlands pain in cancer patients is not systematically registered,[35] which might lead to undertreatment of pain which could consequently lead to high pain scores in the cancer patient population. Consistent assessment of pain is an easily achievable goal as modern technology rapidly develops. Telemonitoring, or remote patient monitoring, of pain is a potential method to empower the patient to express his or her pain. An automated alarm when the patient's pain scores are high triggers a nurse to contact the patient, or the pain is assessed by calling the patient. Using telemonitoring or experience sampling techniques

a patient should not have to wait for a long period to adjust medication, which leads to better pain management index (unpublished results), or to a lower ratio of patients with moderate to severe pain.[36,37]

Other, patient related, barriers for poor pain control in patients with cancer are the patients' believes that pain is inevitable and uncontrollable.[38] Furthermore, patients and their direct family and carers struggle with their communication of pain and misconceptions about analgesic use, which can lead to a reluctance to opioid use.[39] Education for patients and their caregivers could improve the success of pain management. Patient education should be focused on self-empowerment.[40] For family caregivers a face-to-face educational intervention, combined with written information and contact information for reinforcement and review has the potential to improve self-efficacy, and change faulty believes about medication and cancer related pain.[41]

7. Literature and data handling

As mentioned, the attention for cancer related pain has increased over the last ten years, with more and more papers on cancer related pain being published. The increase in available data on pain in patients with cancer has not resulted in better pain control in these patients. Sauzet and colleagues[42] performed a systematic review of longitudinal randomized controlled trials in cancer related pain. They report that many of these trials analyse their data sub-optimally which includes: not correcting for baseline data, dichotomization of the main continuous outcome, aggregation of longitudinal data, cross sectional analyses at each time point, and failure to provide an effect size were frequent sources of suboptimal data handling. Correct data handling is important to provide the best available answers based on the available data. From this it is hoped that better handling of the data will result in more conclusive answers, which then might result in better pain treatment in cancer patients.

8. Conclusion

Attention for cancer related pain has increased in the last ten years, but this has not resulted in lower prevalence of pain in patients with cancer. The increased attention to cancer related pain as can be deduced form the increased number of published papers on this subject and this then needs to be followed by an increase in awareness of cancer related pain in practice by the clinician. Every clinician treating patients with cancer should be aware that pain is an important factor affecting patients' quality of life. Therefore, pain should be systematically monitored in cancer patients. To facilitate treatment of pain in cancer patients a protocol for cancer related pain, which could be the WHO pain ladder or a local adaptation of this ladder, should easily be available for every clinician. Furthermore, differentiation of pain in neuropathic, nociceptive or mixed type should be addressed. Finally the protocol for cancer related pain should include treatment with adjuvant analgesics, and a reminder to consider interventional pain therapy.

	Cured patients	On anticancer therapy	Advanced disease	All stages
Pain prevalence ‘66 - ‘05	35	59	64	53
Pain prevalence ‘05 - ‘14	39	55	66	51
Moderate severe ‘66 - ‘05	–	36	45	31
Moderate severe ‘05 - ‘14	28	32	52	33

Table 1. Prevalence of patients suffering from pain, and moderate to severe pain

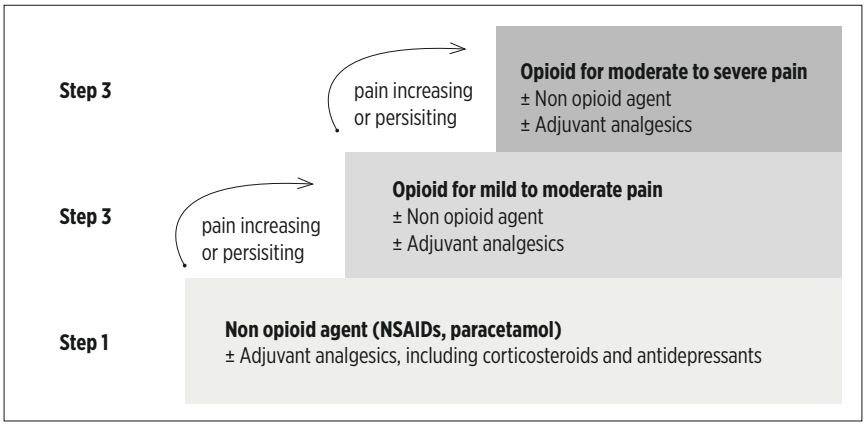


figure 1. WHO pain ladder

1. World Cancer Report. Geneva, Switzerland: World Health Organization Press; 2014.

2. **van den Beuken-van Everdingen MH**, **de Rijke JM**, **Kessels AG**, **Schouten HC**, **van Kleef M**, **Patijn J**. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007; **18**(9): 1437-49.

3. **Kroenke K**, **Theobald D**, **Wu J**, **Loza JK**, **Carpenter JS**, **Tu W**. The association of depression and pain with health-related quality of life, disability, and health care use in cancer patients. *J Pain Symptom Manage* 2010; **40**(3): 327-41.

4. **Porter LS**, **Keefe FJ**. Psychosocial issues in cancer pain. *Curr Pain Headache Rep* 2011; **15**(4): 263-70.

5. **Breivik H**, **Cherny N**, **Collett B**, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. *Ann Oncol* 2009; **20**(8): 1420-33.

6. **Puetzler J**, **Feldmann RE**, Jr., **Brascher AK**, **Gerhardt A**, **Benrath J**. Improvements in health-related quality of life by comprehensive cancer pain therapy: a pilot study with breast cancer outpatients under palliative chemotherapy. *Oncol Res Treat* 2014; **37**(9): 456-62.

7. **Mantyh PW**. Bone cancer pain: from mechanism to therapy. *Curr Opin Support Palliat Care* 2014; **8**(2): 83-90.

8. **van den Beuken-van Everdingen MH**, **Hochstenbach LM**, **Joosten EA**, **Tjan-Heijnen VC**, **Janssen DJ**. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage* 2016; **51**(6): 1070-90 e9.

9. **Greco MT**, **Roberto A**, **Corli O**, et al. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. *J Clin Oncol* 2014; **32**(36): 4149-54.

10. **Deandrea S**, **Montanari M**, **Moja L**, **Apolone G**. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol* 2008; **19**(12): 1985-91.

11. **Launay-Vacher V**, **Oudard S**, **Janus N**, et al. Prevalence of Renal Insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. *Cancer* 2007; **110**(6): 1376-84.

12. **Caraceni A**, **Hanks G**, **Kaasa S**, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol* 2012; **13**(2): e58-68.

13. **Sande TA**, **Laird BJ**, **Fallon MT**. The use of opioids in cancer patients with renal impairment-a systematic review. *Support Care Cancer* 2016.

14. **Carlson CL**. Effectiveness of the World Health Organization cancer pain relief guidelines: an integrative review. *J Pain Res* 2016; **9**: 515-34.

15. **Mercadante S**, **Maddaloni S**, **Roccella S**, **Salvaggio L**. Predictive factors in advanced cancer pain treated only by analgesics. *Pain* 1992; **50**(2): 151-5.

16. **Zech DF**, **Grond S**, **Lynch J**, **Hertel D**, **Lehmann KA**. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. *Pain* 1995; **63**(1): 65-76.

17. **SL Tsui KN**, **WS Chan**, **TY Chan**, **JR Lo**, **JCS Yang**. Cancer pain management: experience of 702 consecutive cases in a teaching hospital in Hong Kong. *Hong Kong Medical Journal* 1996; (2): 405-13.

18. **Bhatnagar S**, **Mishra S**, **Srikanti M**, **Gupta D**. Cancer pain management at a tertiary care cancer center in India–a retrospective analysis of 3,238 patients. *J Opioid Manag* 2008; **4**(6): 361-8.

19. **Bandieri E**, **Romero M**, **Ripamonti CI**, et al. Randomized Trial of Low-Dose Morphine Versus Weak Opioids in Moderate Cancer Pain. *J Clin Oncol* 2016; **34**(5): 436-42.

20. **Nunes BC**, **Garcia JB**, **Sakata RK**. Morphine as first medication for treatment of cancer pain. *Braz J Anesthesiol* 2014; **64**(4): 236-40.

21. **Shinde S**, **Gordon P**, **Sharma P**, **Gross J**, **Davis MP**. Use of non-opioid analgesics as adjuvants to opioid analgesia for cancer pain management in an inpatient palliative unit: does this improve pain control and reduce opioid requirements? *Support Care Cancer* 2015; **23**(3): 695-703.

22. **Nabal M**, **Librada S**, **Redondo MJ**, **Pigni A**, **Brunelli C**, **Caraceni A**. The role of paracetamol and nonsteroidal anti-inflammatory drugs in addition to WHO Step III opioids in the control of pain in advanced cancer. A systematic review of the literature. *Palliat Med* 2012; 26(4): 305-12.

23. **Brogan S**, **Junkins S**. Interventional therapies for the management of cancer pain. *J Support Oncol* 2010; **8**(2): 52-9.

24. **Wyse JM**, **Chen YI**, **Sahai AV**. Celiac plexus neurolysis in the management of unresectable pancreatic cancer: when and how? *World J Gastroenterol* 2014; **20**(9): 2186-92.

25. R**oberto A**, **Deandrea S**, **Greco MT**, et al. Prevalence of Neuropathic Pain in Cancer Patients: Pooled Estimates From a Systematic Review of Published Literature and Results From a Survey Conducted in 50 Italian Palliative Care Centers. *J Pain Symptom Manage* 2016; **51**(6): 1091-102 e4.

26. **McNicol ED**, **Midbari A**, **Eisenberg E**. Opioids for neuropathic pain. *Cochrane Database Syst Rev* 2013; (8): CD006146.

27. **van den Beuken-van Everdingen MH**, **de Graeff A**, **Jongen JL**, et al. Pharmacological Treatment of Pain in Cancer Patients: The Role of Adjuvant Analgesics, a Systematic Review. *Pain Pract* 2016.

28. **Attal N**, **Cruccu G**, **Baron R**, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; **17**(9): 1113-e88.

29. **Haumann J**, **Geurts JW**, **van Kuijk SM**, **Kremer B**, **Joosten EA**, van den Beuken-van Everdingen MH. Letter response: Methadone is superior to fentanyl in treating neuropathic pain in patients with head-and-neck cancer. *Eur J Cancer* 2016; **68**: 201-2.

30. **Nicholson AB**. Methadone for cancer pain. *Cochrane Database Syst Rev* 2007; (4): CD003971.

31. **Srisawang P**, **Harun-Or-Rashid M**, **Hirosawa T**, **Sakamoto J**. Knowledge, attitudes and barriers of physicians, policy makers/regulators regarding use of opioids for cancer pain management in Thailand. *Nagoya J Med Sci* 2013; **75**(3-4): 201-12.

32. **Tennant F**. **Tennant F**. Editor's memo: the WHO pain treatment 3-step ladder. Practic Pain Manage. 2015;15(3):1–4. *practical pain management* 2015; **15**(3): 1-4.

33. **Kwon JH**. Overcoming barriers in cancer pain management. *J Clin Oncol* 2014; **32**(16): 1727-33.

34. **Zhang Q**, **Yu C**, **Feng S**, et al. Physicians' Practice, Attitudes Toward, and Knowledge of Cancer Pain Management in China. *Pain Med* 2015; **16**(11): 2195-203.

35. **te Boveldt ND**, **Vernooij-Dassen MJ**, **Jansen A**, **Vissers KC**, **Engels Y**. Pain is not systematically registered in Dutch medical oncology outpatients. *Pain Pract* 2015; **15**(4): 364-70.

36. **Kim HS**, **Shin SJ**, **Kim SC**, et al. Randomized controlled trial of standardized education and telemonitoring for pain in outpatients with advanced solid tumors. *Support Care Cancer* 2013; **21**(6): 1751-9.

37. **Verhagen SJ**, **Hasmi L**, **Drukker M**, **van Os J**, **Delespaul PA**. Use of the experience sampling method in the context of clinical trials. *Evid Based Ment Health* 2016; **19**(3): 86-9.

38. **Jacobsen R**, **Moldrup C**, **Christrup L**, **Sjogren P**. Patient-related barriers to cancer pain management: a systematic exploratory review. *Scand J Caring Sci* 2009; **23**(1): 190-208.

39. **Miaskowski C**, **Dodd MJ**, **West C**, et al. Lack of adherence with the analgesic regimen: a significant barrier to effective cancer pain management. *J Clin Oncol* 2001; **19**(23): 4275-9.

40. **Marie N**, **Luckett T**, **Davidson PM**, **Lovell M**, **Lal S**. Optimal patient education for cancer pain: a systematic review and theory-based meta-analysis. *Support Care Cancer* 2013; **21**(12): 3529-37.

41. **Latter S**, **Hopkinson JB**, **Richardson A**, **Hughes JA**, **Lowson E**, **Edwards D**. How can we help family carers manage pain medicines for patients with advanced cancer? A systematic review of intervention studies. *BMJ Support Palliat Care* 2016; **6**(3): 263-75.

42. **Sauzet O**, **Kleine M**, **Williams JE**. Data in longitudinal randomised controlled trials in cancer pain: is there any loss of the information available in the data? Results of a systematic literature review and guideline for reporting. *BMC Cancer* 2016; **16**(1): 771.

III

Methadone is Superior to Fentanyl in Treating Neuropathic Pain in Patients with Head-and-Neck Cancer

J. Haumann; J.W. Geurts; S.M.J. van Kuijk;
B Kremer; E. A. Joosten;
M.H.J. van den Beuken-van Everdingen

European Journal of Cancer
2016 Sep; 65:121-129

Abstract

Background: Cancer related pain is still inadequately treated in up to 60% of cancer patients. Based on the additional effect on the N-Methyl-D-Aspartate receptor, we expected that methadone could provide better pain relief than fentanyl in cancer related pain with a neuropathic pain component.

Methods: A randomized controlled trial was performed with 52 strong opioids naive patients with head-and-neck cancer with substantial pain (pain Numerical Rating Scale [NRS] > 4) and a neuropathic pain component (Douleur Neuropathique [DN4] > 4). Twenty-six patients were treated with methadone and 26 with fentanyl. Patients were evaluated at 1, 3 and 5 weeks. The primary outcomes were reduction in average pain, clinical success (defined as 50% average pain decrease) and reduction in pain interference. Secondary outcomes were global perceived effect (GPE) and side-effects.

Findings: Reduction in NRS was higher with the use of methadone at 1, 3 and 5 weeks (pain change 2.9, 3.1 and 3.1) compared to fentanyl (1.4, 1.7 and 2.0). This difference was significant at 1 (p Z 0.011) and at 3 weeks (p Z 0.03). Clinical success (>50% improvement) was higher with methadone at 1 week (15% versus 50%, p Z 0.012). The change in pain interference, the GPE and side-effect profile were not significantly different between the groups.

1. Introduction

Up to 60% of patients suffering cancer-related pain are inadequately treated for their pain.[1,2] This prevalence is high and contradicts the statement by Meuser et al[3] that cancer related pain could be treated effectively (in 70 to 86% of patients), if the World Health Organization (WHO) ladder is used. As numerous studies and meta-analyses up till now show no clear benefit in pain relief for one opioid over the other, there is no consensus on the choice of strong opioid to start with at step 3 of the WHO ladder.[4-7] In order to minimize side effects and interactions, guidelines advise to prescribe an opioid one has clinical experience with. Other factors to keep in mind are ease of use and cost.

In current pain management, patients with cancer related pain are treated with an opioid irrespective of pain type (neuropathic, nociceptive, or mixed). Methadone is an opioid which has, besides an opioid receptor-mediated effect, an additional effect on the N-Methyl-D-Aspartate (NMDA) receptor.[8] The NMDA receptor is known to be important in central sensitization (CS).[9] CS is a process reported to be fundamental in development and maintenance of neuropathic pain. Hence, a combined targeting of the NMDA receptor and the opioid receptors might result in better pain relief in neuropathic pain patients. Currently, limited evidence is reported on the effect of Methadone over other opioids in treatment of neuropathic pain in both cancer and non-cancer patients.[10,11] To further confirm this randomized clinical studies are needed. A meta-analysis based on three studies on the effect of methadone in neuropathic non-cancer pain was inconclusive as data could not be pooled due to methodological differences.[12] Furthermore, studies were performed with methadone as a first line strong opioid in cancer patients, comparing methadone to other opioids but no significant difference in pain reduction or side effects was noted.[13,14] The latter might be explained due to the fact that these studies did not differentiate between neuropathic, nociceptive, or mixed pain types.

Given the dual mechanism of action of methadone on both the NMDA receptor and on the opioid receptors, we hypothesize that methadone is superior to fentanyl in alleviating pain in cancer patients with a neuropathic pain component. In order to test this hypothesis, a randomized

clinical trial was performed comparing the effect of methadone to transdermal fentanyl in patients with head-and-neck cancer suffering from neuropathic pain.

27

2. Methods

2.1 Study design

This study is part of a prospective single-`center, open label, randomized controlled trial (RCT) in which 52 patients were included with head-and-neck cancer related pain with a neuropathic pain component and 82 cancer patients with nociceptive pain due to radiotherapy. To answer the research question if methadone is superior in pain management for cancer patients with a neuropathic pain component data of the 52 neuropathic pain patients were used in the present analysis.

The RCT was approved by the local medical ethics committee of the Maastricht University Medical Center, and was registered at clinicaltrials.gov (identifier NCT01317589).

2.2 Patients

Patients were included in the study from May 2011 to July 2015. Patients were recruited at the outpatient clinic of the head-and-neck department of the oncology center of Academic Hospital Maastricht (MUMC+), a regional oncological center. Patients with histological proven head-and-neck tumors with moderate to severe neuropathic pain (≥ 4 on the standard Numerical Rating Scale (NRS), range 0-10, related to tumor or therapy and Douleur Neuropathique (DN4) ≥ 4), were included in the study after screening for eligibility criteria: age > 18; naïve to continuous strong opioids. Exclusion criteria were: illiteracy; surgery less than 7 days before the start of the study; pregnancy; contraindications for fentanyl or methadone; myasthenia gravis, and asthma. All patients gave written informed consent.

2.3 Randomization and masking

After informed consent patients were randomly assigned to the fentanyl or methadone group. The randomization was stratified by surgery, chemotherapy, and radiotherapy using software for randomization of clinical trials ALEA (version 2.2 CTCM/ALEA).

2.4 Procedures

2.4.1 Measurements

After informed consent, patients received a booklet with questions concerning demographics, pain, breakthrough medication use, opioid side effects, the patients' perceived effect of the therapy, depression, anxiety, and quality of life.

Pain was measured using the Brief Pain Inventory (BPI), which is a patient completed numeric rating scale that assesses the severity of pain and its impact on daily functioning via the seven item pain Interference Scale (general activity, mood, walking, relationships, sleep, normal work, and enjoyment of life).[15-17]

- *Daily breakthrough medication:* Patients were asked to document their breakthrough medication needed once a day in a diary.
- *Opioid side effects:* Opioid side effects (xerostomia, nausea, vomiting, constipation, somnolence and drowsiness) were scored on a four-point scale (1 to 4), where a score of 1 stands for "not at all", and 4 stands for "severe". Patients were asked if they suffered from a dry mouth, if they felt sleepy or

dull, if they felt dizzy or nauseated, and if they vomited, or were constipated. We dichotomized the data for severity. Scores 1 and 2 were referred to as minimal, and scores 3 or 4 were referred to as severe.

- *Global perceived effect (GPE):* GPE reflects a patient's belief about the efficacy of treatment.[18] GPE is a seven-point scale depicting a patient's rating of overall improvement. Patients rate their change as "complete pain relief", "much improved", "slightly improved", "no change", "slightly worsened", "much worsened", or "worse than ever".
- *Depression and Anxiety (Hospital Anxiety and Depression Scale):* The Dutch translation of the Hospital Anxiety and Depression Scale is validated to be used as a screening tool for depression and anxiety disorders.[19,20]
- *Quality of Life (EuroQol-5D):* The EuroQol 5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health. It provides a simple descriptive profile and a single index value for health status.[21]

The treating physician filled out the medical data form to obtain the following sets of measurements:

- *Neuropathic pain:* Type of pain will be measured by the Douleur Neuropathique (DN4) questionnaire. The DN4 is a validated questionnaire consisting of ten yes or no questions. One point is given for each yes. A cut-off value of ≥ 4 is used to discriminate between patients with and without neuropathic pain. The Dutch translation of the DN4 has been validated.[22] The medical examination part of the DN4 was performed by the physician.
- *Medical data (medical chart):* cancer type and location (lip, oral cavity, nasopharynx, hypopharynx, larynx, salivary glands, sinuses), date of diagnosis, treatment history (radiotherapy, current or more than 4 weeks ago / accelerated radiotherapy yes or no, bilateral radiotherapy yes or no, chemotherapy, current or more than 4 weeks ago), stage of disease (curative treatment, palliative treatment, palliative care), sort of pain (nociceptive, neuropathic, mixed), medication (including but not limited to neuropathic pain medication), possible opioid side effect symptoms (xerostomia, nausea, vomiting, constipation, somnolence, drowsiness), and grade of mucositis (Common Toxicity Criteria (CTC) criteria).

2.4.2 Protocol

Follow-up duration was five weeks, and patients were seen four times after informed consent was obtained. At baseline patients provided the demographic variables, the BPI, side effect questionnaires, HADS, and QoL. methadone 2.5 mg twice daily or fentanyl patch 12 μg/hr was prescribed (or the double doses when patients already used weak opioids), as well as fentanyl nose spray 50 μg or fentanyl sublingual 100 μg as necessary up to six times per day for breakthrough pain. Due to delivery problems with the methadone 2.5 mg tablets, the starting dose was altered to 2 mg twice daily later in the study.

Patients were allowed to take six breakthrough medications per 24 h. They were instructed to take a second dose of the breakthrough medication when no effect was present at 15 min after the first dose. The dose of the rapid onset opioids (ROO) is independent of the basis opioid dose. We titrated the basis opioid based on the patients story and breakthrough dose by increasing the daily dose with 50%. Because the lowest dose of the fentanyl patch is 12 μg/h, the dose could only be doubled. The breakthrough medication was titrated conform the instructions belonging to the individual preparations.

We reviewed the patients after 1 week. Methadone has a long and variable half-life and steady state is to be expected after 4-7 d, so we preferred not increasing the dose within a week. The patients received a 24/7 phone number to contact in case of trouble (side-effects/pain).

29 At 1, 3 and 5 weeks, patients filled in the BPI, side effect questionnaires, and GPE. The opioid dose in both groups was decreased with 30% when possible, or stopped if medication was at starting dose. Therapy discontinuation due to side-effects was assessed at every visit.

2.5 Outcomes

2.5.1 Primary outcomes

Primary outcome measures are the change in average pain, the proportions of patients reporting clinical success for average pain at 3 weeks, defined as a reduction of 50% in average pain score[23], and the change in pain interference after 3 weeks.

2.5.2 Secondary outcomes

Secondary outcomes included the time to achieve significant pain relief and GPE. Furthermore, side-effects and therapy discontinuation due to side-effects; mean increase of opioid dose measured by the opioids escalation index (maximal dose-starting dose/ starting dose) and use of breakthrough medication were used as secondary endpoints.

2.6 Outcomes

2.6.1 Statistical analysis

Baseline characteristics are reported as mean and standard deviation or absolute value and percentage. To compare the proportion of patients reporting clinical success at 3 weeks after randomization between the methadone and fentanyl groups, the Pearsons' Chi-squared statistic was used. The difference in change in pain interference was tested using the Student t test. In addition to univariable analyses of the primary outcomes, we performed multivariable analyses to correct for potential baseline differences despite randomisation and to increase precision in the estimation by using logistic and linear regression for the proportion of clinical success and change in pain interference, respectively. Missing data were imputed using multiple imputation, and data were analysed on an intention to treat basis (JH, JG, SK, MvdB).

2.6.2 Sample size calculation

A difference between the experimental and control means of 2 on the NRS score was considered clinically relevant. The estimated standard deviation of response on the NRS for pain was 3 (based on a pilot study, results not published). We aimed to include at least 48 experimental subjects and 48 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability of (power) 0.9. The Type I error probability associated with this test of this null hypothesis was 0.05.

3. Results

3.1 Study population

A total of 52 patients were included in the study. Of the 52 patients, 14 were treated with curative intent (4x surgery, 10x radiotherapy) and had treatment related neuropathic pain. Fourteen patients received palliative antitumor therapy, and 24 patients had far-advanced disease. The latter

two groups had combined nociceptive-neuropathic pain. For these groups it was not possible to differentiate between treatment-related or tumor-related pain. None of these patients had clinical important mucositis. Patients were treated with fentanyl(n=26) or with methadone (n=26) (*Figure 1*).

We observed a considerable response loss over the complete follow-up period, which was mostly due to intercurrent diseases and success of treatment (*Figure 1*). Eight patients (15 %) were lost to follow up at 3 weeks, and 18 patients (34 %) at 5 weeks. In the fentanyl group 18 patients started with 12 mcg/hr patches, and eight started with 25 mcg/hr patches. In the methadone group six patients started with a total of 4 mg per day, 16 patients started with 5 mg/day, and four patients with 10 mg per day.

The baseline characteristics were balanced between the two groups (*Table 1*). Especially the quality of life and the pain scores were equal in both groups. The use of prior opioid exposure, mostly codeine or tramadol, some used fentanyl spray or oxycodone for breakthrough pain without use of baseline opioids, was balanced as well (42.3% fentanyl vs. 46.2% methadone). There were slightly less males in the fentanyl group as compared to the methadone group (62% fentanyl vs. 73% methadone).

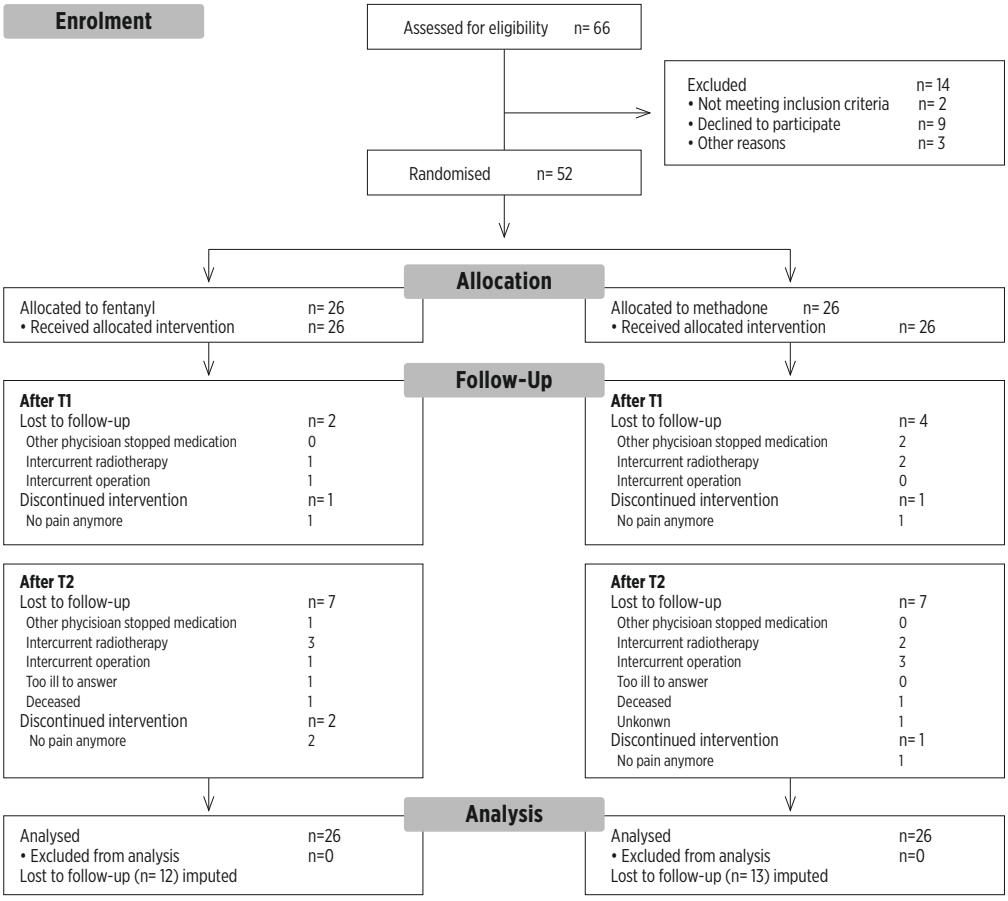


Figure 1. Flow diagram of enrolment

3.2 Decrease in Pain

At the primary end-point of 3 weeks the average NRS decreased from 6.3 to 4.5 in the fentanyl group versus from 6.3 to 3.2 in the methadone group (p = 0.042). The decrease in average NRS for all time points is shown in Table 2. Pain decrease occurred faster in the methadone group (mean NRS = 3.4) than in the fentanyl group (mean NRS = 4.9) (p = 0.011) in the first week. Based on an average pain of 4.2 (standard error of the mean (SEM) 0.36) in the fentanyl group and 3.2 (SEM 0.38) in the methadone group no significant difference (p=0.11) is noted at week 5.

	Fentanyl (n= 26)		Methadone (n= 26)	
	No*	%*	No*	%*
Age, years				
Median	66		64	
SD	9		9	
Male sex	16	62	19	73
Education				
Primary school	3	12	3	12
Secondary school	6	23	12	46
College/university	17	65	11	42
Employment status				
Working	0	0	3	12
Housewife / man	4	16	4	16
Old-age pension	12	46	11	42
Disability pension	8	32	2	8
Sick leave	1	4	4	16
Volunteer work	0	0	1	4
Living arrangements				
At home alone	9	35	5	19
At home with partner	17	65	21	81
Mean pain# (BPI)	6	2	6	2
Pain duration in months	4.5	5.8	4.0	5.9
Quality of life# (Eqol5)	.37	.34	.38	.33
Depression (HADS)				
No	7	27	8	31
Borderline	12	46	10	38
yes	7	27	8	31
Anxiety (HADS)				
No	12	46	9	35
Borderline	3	12	9	35
yes	11	42	8	30
Prior radiotherapy	11	42	15	58
Prior chemotherapy	5	19	6	23
Prior surgery	6	23	9	35
Anti-neuropathic co-medication^	8	31	9	35
Prior opioid exposure	11	42	12	46

Table 1. Baseline characteristics
Abbreviations: Eqol5, Euroquol 5; HADS, Hospital Anxiety and Depression Scale, depression/anxiety no 0-7 points, borderline 8-10, yes 11-21; BPI, brief Pain Inventory *Unless otherwise specified #Median and SD ^gabapentin, pregabalin or amitriptyline

3.3 Clinical Success

Clinical success, defined as a decrease of 50% in average NRS, was noted in 27% of the patients in the fentanyl group and in 44% in the methadone group (p=0.23) at three weeks (*Figure 2*). A 50% decrease in average NRS was achieved faster with methadone than with fentanyl. At 1 week 50% of the patients in the Met group and 15 % of the fentanyl group showed clinical success (p=0.012). This initial difference between the groups after one week diminished over the following weeks, as no significant difference was noted between the fentanyl and methadone groups at three and five weeks (49% methadone vs. 33% fentanyl p = 0.367).

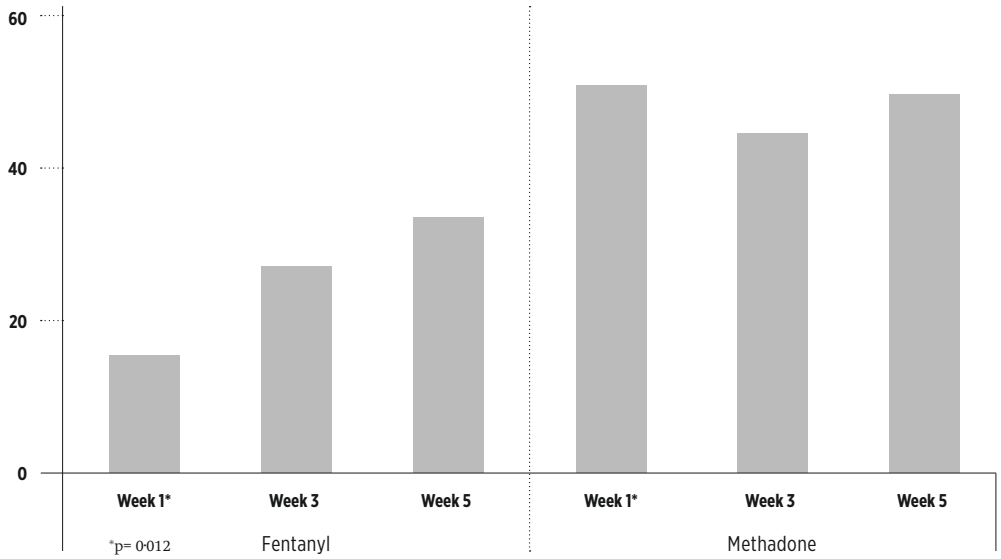


Figure 2: Percentage of clinical success, defined as a pain reduction of 50% in average pain.

3.4 Interference

The mean decrease in pain interference for patients treated with fentanyl at 3 weeks was 8.2 versus 15.7 for patients treated with methadone (p=0.29).The decrease in interference was consistent at all time points, and although not statistically significant, the decrease tended to be more prominent in the methadone group (*Table 2*).

	Week	Met	Fen	Δ (95% CI)	p	Δ* (95% CI)	p*
Change from	1	-2.89	-1.24	1.46 (0.33 - 2.59)	**0.011**	1.35 (0.33 - 2.37)	**0.010**
baseline NRS	3	-3.12	-1.74	1.37 (0.05 - 2.69)	**0.042**	1.30 (0.13 - 2.48)	**0.030**
	5	-3.10	-2.04	1.06 (-0.22 - 2.33)	0.106	1.00 (-0.10 - 2.11)	0.074
Change from	1	-15.65	-10.54	5.12 (-4.40 - 14.63)	0.292	5.43 (-4.46 - 15.32)	0.282
baseline	3	-15.69	-8.24	7.46 (-2.59 - 17.51)	0.146	8.17 (-2.09 - 18.43)	0.119
Interference	5	-18.71	-14.12	4.60 (-6.86 - 15.05)	0.389	5.26 (-5.41 - 15.92)	0.334

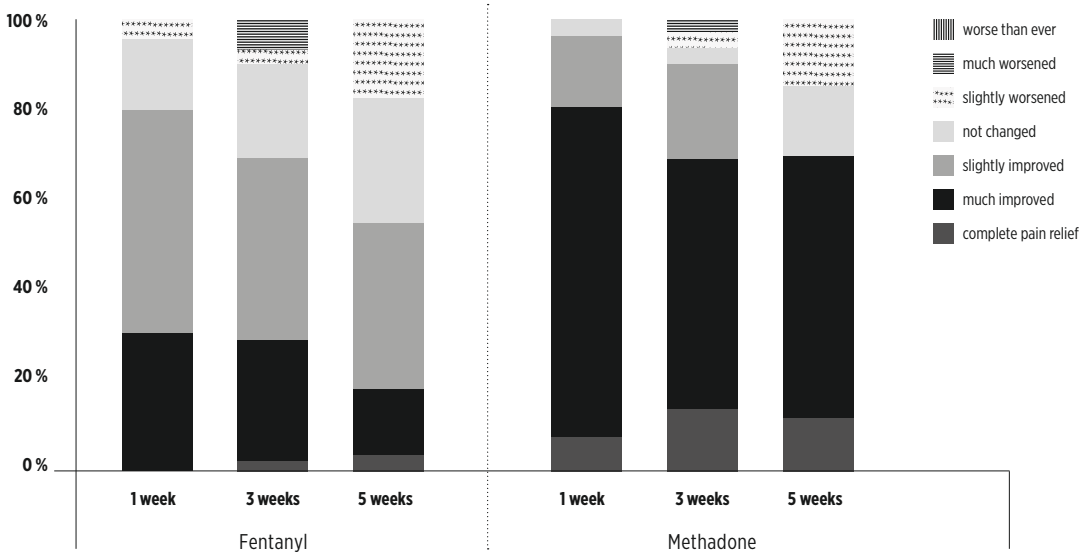
Table 2. Multivariable analysis.
p: p-value *Adjusted for age, gender, and baseline pain score NRS: Numeric Rating Scale
Met: Methadone Fen: Fentanyl Δ: Difference CI: Confidence Interval

3.5 Multivariate analyses

The multivariate analyses did not alter the primary outcomes significantly. No outcomes reached or lost their statistical significance in the multivariate analyses. See Table 2 for adjusted p-values.

3.6 Global Perceived Effect (GPE)

The GPE showed that in the fentanyl group 27% of patients reported to experience "much improvement" as compared to 56% of patients in the methadone group at 3 weeks. Fig. 3 shows the proportion of patients that scored one of the 7 items on the GPE scale at 1, 3 and 5 weeks. No statistical significant difference was noticed. (p = 0.084, p = 0.428, and p = 0.151, respectively). The percentage of patients that scored one of the 7 GPE scales. The differences do not reach statistical significance (p = 0.08, 0.43 and 0.15 respectively).



3.7 Side effects

No serious side effects were noticed in our study population, and deaths were related to normal disease progression. There was no drop out due to intolerable side effects. There was no significant difference between the groups in percentage of patients with severe side effects (i.e. score 3 or 4 on a 4 point scale of one of the side effects; dry mouth, sleepiness, dizziness, nausea, vomiting, constipation).

The most common side effect was dry mouth, 46 % of patients in the fentanyl group reported a dry mouth at 3 weeks and 35 % in the methadone group. Overall, about 70% of the patients complained about a severe dry mouth at any point in the study.

3.8 Opioid Increase Ratio

Patients in the fentanyl group experienced a slightly steeper, albeit not significant, increase in opioid dose over the weeks as compared to patients in the methadone group (1.2 vs 1.3 at one week, 1.5 vs 1.8 at three weeks, and 1.6 vs 2.2 at five weeks). The amount of breakthrough medication did not differ between the groups (Figures not shown).

4. Discussion

This RCT is the first to demonstrate that the use of methadone results in a better and faster pain relief in the treatment of oncological pain with a neuropathic component as compared to fentanyl.

The decrease in pain (NRS) in head-and-neck cancer patients with neuropathic pain receiving methadone is significantly higher at 1 and 3 weeks as compared to fentanyl treated patients .

Ample preclinical evidence exists that the NMDA receptor, a glutamate receptor abundantly present in the dorsal horn of the spinal cord, is essential for the development of CS and increased sensitivity in neuropathic pain.[24] Animal studies demonstrate an antihyperalgesic effect of NMDA-receptor blockers in models of inflammatory, neuropathic and ischemic pain.[25] A systematic review of the use of the selective NMDA-antagonist ketamine for the treatment of intractable chronic pain in cancer (five RCT's, six observational studies and one case series) concluded that ketamine may be an option, although strong evidence was lacking.[26]

Furthermore, results from a RCT by Salas et al. demonstrated the presence of responders and non-responders to ketamine.[27]

Methadone is a strong opioid with significant non-competitive NMDA-receptor antagonist qualities.[8,28] It is thus likely that methadone modulates the glutamate transmission at the (pain) gate in the spinal cord where nociceptive afferents pass their signal to the dorsal horn pain neurons via the AMPA and NMDA receptors. Hence, Methadone may not only modulate the opioid receptors known to be involved in neuropathic pain but may affect the increased synaptic plasticity of the NMDA receptor at the glutamatergic synapse or central nervous system during chronic neuropathic pain.

Many small studies and case-reports describe the successful rotation from different strong opioids to methadone.[29-35] A positive clinical response, better pain control, and/or less side-effects is seen in more than 50% of patients after rotation to methadone.[36,37]

The effect of methadone in cancer related pain was evaluated in two systematic reviews. The 2007 Cochrane review concluded that the efficacy of methadone is similar to morphine and this conclusion was based on nine RCT's.[4] It was then methadone that the efficacy of methadone is

similar to morphine although a differentiation between nociceptive and neuropathic pain was made in only one study.[13] When no difference between nociceptive and neuropathic pain was made, no difference in pain relief between morphine and methadone could be observed. With respect to the latter, it is important to realize that the investigators did not test for differences in patients with neuropathic pain specifically, but only used a subpopulation with a neuropathic component.[13]

In a recent systematic review, based on four RCT's published after the 2007 Cochrane review on the effect of methadone in cancer related pain management was evaluated.[38] Here no difference in effectiveness between methadone compared to other strong opioids was reported in two RCT's.[14,39] It should be noted that these RCT's did not differentiate between cancer patients with neuropathic pain or nociceptive pain. Two other RCT's used in this systematic review evaluated the effect of opioid rotation to methadone: in one study no conclusion on the efficacy of methadone in treatment of cancer related pain could be presented due to the number of dropouts[40], and the other reported a decrease in pain intensity switching from morphine to methadone and a patient preference for methadone.[41]

No differences in side-effect profiles between methadone and other strong opioids were reported.[4] It should be noted that a significant reduction in constipation and xerostomia in most patients was reported 7 days after rotating to methadone. From a group of 13 patients rotated from methadone to another strong opioids for the study, 12 had to be rotated back because of pain increase and dysphoric effects.[42]

Patient selection is of utmost importance in choosing methadone as first choice opioid in pain in patients with cancer. On theoretical basis (NMDA-receptor antagonism) is the superiority of methadone over other strong opioids only to be expected in continuous and massive nociception. The unique pharmacological properties make methadone a difficult drug in inexperienced hands. There is a large inter-individual variability in bioavailability (41 to 90%), possibly due to gene polymorphisms.[43] Furthermore, methadone is known to have a long and variable half-life (7 to 65 hours) influenced by urine pH, high protein binding (85 to 90%) and a distribution volume of 3.6 l/kg.[44] The metabolism of methadone by CYP 3A4 and 2B6 implies numerous drug-drug interactions and methadone prolongs the QTc-time with risk on torsades-de-points.[45] Therefore, the administration and management of methadone should be done, preferably in a pain clinic, by experienced pain physicians.

Compared to other studies we started with a relative low dose of methadone which might decrease the risk of severe side effects. Despite this relative low dose, we observed a good clinical outcome, with a very good patients' GPE. We therefore advise, based on our results, to start with a low dose in opioid naïve patients, and slowly increase the dose if and when necessary.

This study has some limitations. Although most participants were available for the analysis of short-term pain relief, we observed a significant loss to follow-up over the course of five weeks, which was in part due to treatment success. To compute unbiased estimates of treatment effects, to obtain the statistical precision that we needed to detect a clinically relevant difference and to make the intention-to-treat sample available for analysis we used multiple imputation. As compared to many other frequently used methods of handling missing data, multiple imputation yields correct standard errors and unbiased estimates when data are missing at random.[46]

In contrast to the original power calculation, we were unable to include 48 patients in each group. As stated after 4 years, we only included 52 patients. There are different explanations for

the relative low accrual: possibly, we overestimated the prevalence of neuropathic pain in patients with head-neck cancer, more patients than expected already received strong opioids (mostly via their general practitioner) and, possibly most important, the travelling distance to the university hospital. Our institution is a referral centre for a large region. When patients become palliative, they most often prefer to be referred to a physician in their region.

The power calculation we performed for this study was based on very limited data. Earlier studies comparing methadone to other opioids showed no significant differences. Furthermore, as far as we know no RCT's comparing methadone to other opioids in neuropathic pain have been published. Therefore, it was impossible to precisely estimate the expected difference. Our power calculation was based on an estimated standard deviation of 3 which finally proved to be less than 2 in our study. Despite the fact that the present study is underpowered we want to emphasize that our findings have significant clinical impact: a decrease in pain, during the first weeks of treatment is expected to result in a better quality of life for patients. In our opinion the profit of at least three weeks better pain relief is important for oncological patients, especially in view of the fact that they have short life expectancies.

It is obvious that our findings need to be further studied in other cancer patients with neuropathic pain. It is not clear if the findings, now restricted to head and neck cancer patients with neuropathic pain can be generalized for all cancer patients suffering from neuropathic pain. From a conceptual point of view, as the NMDA receptor is involved in neuropathic pain, it might be expected that methadone treatment will result in a better pain relief also in patients with different types of cancer with neuropathic pain.

The largest contribution of our RCT is that this study is the first to proof that the theoretical concept (and clinical experience) of involvement of the NMDA receptor specifically in neuropathic pain in patients with cancer holds through and should be targeted in treatment.

5. Conclusion

methadone is significantly better than fentanyl in the treatment of neuropathic pain in patients with head-and-neck cancer in terms of pain relief and time to achieve pain relief. In patients with oncological pain due to head-neck cancer with a neuropathic component methadone should be considered.

1. **van den Beuken-van Everdingen MH**, **de Rijke JM**, **Kessels AG**, **Schouten HC**, **van Kleef M**, **Patijn J**. High prevalence of pain in patients with cancer in a large population-based study in The Netherlands. *Pain* 2007; **132**(3): 312-20.

2. **Te Boveldt N**, **Vernooij-Dassen M**, **Burger N**, **Ijsseldijk M**, **Vissers K**, **Engels Y.** Pain and its interference with daily activities in medical oncology outpatients. *Pain physician* 2013; **16**(4): 379-89.

3. **Meuser T**, **Pietruck C**, **Radbruch L**, **Stute P**, **Lehmann KA**, **Grond S**. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain* 2001; **93**(3): 247-57.

4. **Nicholson AB**. Methadone for cancer pain. *The Cochrane database of systematic reviews* 2007; (4): CD003971.

5. **Hadley G**, **Derry S**, **Moore RA**, **Wiffen PJ**. Transdermal fentanyl for cancer pain. *The Cochrane database of systematic reviews* 2013; **10**: CD010270.

6. **Schmidt-Hansen M**, **Bromham N**, **Taubert M**, **Arnold S**, **Hilgart JS**. Buprenorphine for treating cancer pain. *The Cochrane database of systematic reviews* 2015; **3**: CD009596.

7. **Schmidt-Hansen M**, **Bennett MI**, **Arnold S**, **Bromham N**, **Hilgart JS**. Oxycodone for cancer-related pain. *The Cochrane database of systematic reviews* 2015; **2**: CD003870.

8. **Ebert B**, **Andersen S**, **Krogsgaard-Larsen P**. Ketobemidone, methadone and pethidine are non-competitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. *Neurosci Lett* 1995; **187**(3): 165-8.

9. **Zhou HY**, **Chen SR**, **Pan HL**. Targeting N-methyl-D-aspartate receptors for treatment of neuropathic pain. *Expert Rev Clin Pharmacol* 2011; **4**(3): 379-88.

10. **Gagnon B**, **Almahrezi A**, **Schreier G**. Methadone in the treatment of neuropathic pain. *Pain research & management : the journal of the Canadian Pain Society = journal de la societe canadienne pour le traitement de la douleur* 2003; **8**(3): 149-54.

11. **Rhondali W**, **Tremellat F**, **Ledoux M**, **Ciais JF**, **Bruera E**, **Filbet M**. Methadone rotation for cancer patients with refractory pain in a palliative care unit: an observational study. *Journal of palliative medicine* 2013; **16**(11): 1382-7.

12. **Haroutiunian S**, **McNicol ED**, **Lipman AG**. Methadone for chronic non-cancer pain in adults. *The Cochrane database of systematic reviews* 2012; **11**: CD008025.

13. **Bruera E**, **Palmer JL**, **Bosnjak S**, et al. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2004; **22**(1): 185-92.

14. **Mercadante S**, **Porzio G**, **Ferrera P**, et al. Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. *European journal of pain* 2008; **12**(8): 1040-6.

15. **Radbruch L**, **Loick G**, **Kiencke P**, et al. Validation of the German version of the Brief Pain Inventory. *Journal of pain and symptom management* 1999; **18**(3): 180-7.

16. **Wang XS**, **Mendoza TR**, **Gao SZ**, **Cleeland CS**. The Chinese version of the Brief Pain Inventory (BPI-C): its development and use in a study of cancer pain. *Pain* 1996; 67(2-3): 407-16.

17. **Caraceni A**, **Mendoza TR**, **Mencaglia E**, et al. A validation study of an Italian version of the Brief Pain Inventory (Breve Questionario per la Valutazione del Dolore). *Pain* 1996; **65**(1): 87-92.

18. **Farrar JT**, **Young JP** Jr, **LaMoreaux L**, **Werth JL**, **Poole RM**. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; **94**(2): 149-58.

19. **Spinhoven P**, **Ormel J**, **Sloekers PP**, **Kempen GI**, **Speckens AE**, **Van Hemert AM**. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychological medicine* 1997; **27**(2): 363-70.

20. **Zigmond AS**, **Snaith RP**. The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica* 1983; **67**(6): 361-70.

21. **EuroQol G**. EuroQol–a new facility for the measurement of health-related quality of life. *Health policy* 1990; **16**(3): 199-208.

22. **Van Seventer R**, **Vos C**, **Meerding W**, et al. Linguistic validation of the DN4 for use in international studies. *European journal*

of pain 2010; **14**(1): 58-63.

23. **Dworkin RH**, **Turk DC**, **Wyrwich KW**, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *The journal of pain : official journal of the American Pain Society* 2008; **9**(2): 105-21.

24. **Ji Y**, **Traub RJ**. Spinal NMDA receptors contribute to neuronal processing of acute noxious and nonnoxious colorectal stimulation in the rat. *Journal of neurophysiology* 2001; **86**(4): 1783-91.

25. **Swartjes M**, **Morariu A**, **Niesters M**, **Aarts L**, **Dahan A**. Nonselective and NR2B-selective N-methyl-D-aspartic acid receptor antagonists produce antinociception and long-term relief of allodynia in acute and neuropathic pain. *Anesthesiology* 2011; **115**(1): 165-74.

26. **Bredlau AL**, **Thakur R**, **Korones DN**, **Dworkin RH**. Ketamine for pain in adults and children with cancer: a systematic review and synthesis of the literature. *Pain Med* 2013; **14**(10): 1505-17.

27. **Salas S**, **Frasca M**, **Planchet-Barraud B**, et al. Ketamine analgesic effect by continuous intravenous infusion in refractory cancer pain: considerations about the clinical research in palliative care. *J Palliat Med* 2012; **15**(3): 287-93.

28. **Gorman AL**, **Elliott KJ**, **Inturrisi CE**. The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett* 1997; **223**(1): 5-8.

29. **Ripamonti C**, **Bianchi M**. The use of methadone for cancer pain. *Hematol Oncol Clin North Am* 2002; **16**(3): 543-55.

30. M**anfredi PL**, **Borsook D**, **Chandler SW**, **Payne R**. Intravenous methadone for cancer pain unrelieved by morphine and hydromorphone: clinical observations. *Pain* 1997; **70**(1): 99-101.

31. **Lawlor PG**, **Turner KS**, **Hanson J**, **Bruera ED**. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. *Cancer* 1998; **82**(6): 1167-73.

32. **Mercadante S**, **Casuccio A**, **Calderone L**. Rapid switching from morphine to methadone in cancer patients with poor response to morphine. *J Clin Oncol* 1999; **17**(10): 3307-12.

33. **Moryl N**, **Kogan M**, **Comfort C**, **Obbens E**. Methadone in the treatment of pain and terminal delirum in advanced cancer patients. *Palliat Support Care* 2005; **3**(4): 311-7.

34. **Mancini I**, **Lossignol DA**, **Body JJ**. Opioid switch to oral methadone in cancer pain. *Curr Opin Oncol* 2000; **12**(4): 308-13.

35. **Benitez-Rosario MA**, **Salinas-Martin A**, **Aguirre-Jaime A**, **Perez-Mendez L**, **Feria M**. Morphine-methadone opioid rotation in cancer patients: analysis of dose ratio predicting factors. *J Pain Symptom Manage* 2009; **37**(6): 1061-8.

36. **Quigley C**. Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev* 2004; (3): CD004847.

37. **Mercadante S**, **Bruera E**. Opioid switching: a systematic and critical review. *Cancer Treat Rev* 2006; **32**(4): 304-15.

38. **Good P**, **Afsharimani B**, **Movva R**, **Haywood A**, **Khan S**, **Hardy J**. Therapeutic challenges in cancer pain management: a systematic review of methadone. *Journal of pain & palliative care pharmacotherapy* 2014; **28**(3): 197-205.

39. **Lauretti GR**, **Rizzo CC**, **Mattos AL**, **Rodrigues SW**. Epidural methadone results in dose-dependent analgesia in cancer pain, further enhanced by epidural dexamethasone. *British journal of cancer* 2013; **108**(2): 259-64.

40. **Moksnes K**, **Dale O**, **Rosland JH**, **Paulsen O**, **Klepstad P**, **Kaasa S**. How to switch from morphine or oxycodone to methadone in cancer patients? a randomised clinical phase II trial. *European journal of cancer* 2011; **47**(16): 2463-70.

41. **Cubero DI**, **del Giglio A**. Early switching from morphine to methadone is not improved by acetaminophen in the analgesia of oncologic patients: a prospective, randomized, double-blind, placebo-controlled study. *Support Care Cancer* 2010; **18**(2): 235-42.

42. **Moryl N**, **Santiago-Palma J**, **Kornick C**, et al. Pitfalls of opioid rotation: substituting another opioid for methadone in patients with cancer pain. *Pain* 2002; **96**(3): 325-8.

43. **Kharasch ED**, **Regina KJ**, **Blood J**, **Friedel C**. Methadone Pharmacogenetics: CYP2B6 Polymorphisms Determine Plasma Concentrations, Clearance, and Metabolism. *Anesthesiology* 2015; **123**(5): 1142-53.

44. **Fredheim OM**, **Moksnes K**, **Borchgrevink PC**, **Kaasa S**, **Dale O**. Clinical pharmacology of methadone for pain. *Acta Anaesthesiol Scand* 2008; **52**(7): 879-89.

45. **Beuken-van Everdingen van den MHJ**, **Geurts JW**, **Patijn J**. Prolonged QT interval by methadone: Relevance for daily practice? A prospective study in patients with cancer and noncancer pain. *J Opioid Manag* 2013; **38**(3): 263-9.

46. Buuren van S. Flexible Imputation of Missing Data. ; 2012.

Methadone versus Fentanyl in Patients with Radiation Induced Nociceptive Pain with Head and Neck Cancer, a randomized controlled noninferiority trial

J. Haumann; S.M.J. van Kuijk; J.W. Geurts;
F.J.P. Hoebers; B. Kremer; E.A. Joosten;
M.H.J. van den Beuken-van Everdingen

Pain Practice, 2018 Mar; 18(3):331-340

Abstract

Background: Pain is still a burden for many patients with cancer. A recent trial showed superiority of methadone over fentanyl in neuropathic pain, and we expect that this finding could influence the number of patients treated with methadone.

Methods: We performed a randomized controlled noninferiority trial in patients with nociceptive pain. Eighty-two strong-opioid-naïve patients with head-and-neck cancer with substantial pain (pain numeric rating scale [NRS] score ≥ 4) due to radiation therapy were included. Forty-two patients were treated with methadone, and forty with fentanyl. Patients were evaluated at 1, 3 and 5 weeks. The primary outcomes were reduction in average pain and clinical success (50% pain decrease). We set the predefined noninferiority margin at 1 on the NRS scale and 10% clinical success. Secondary outcomes were pain interference, global perceived effect (GPE), side effects, and opioid escalation index.

Results: Noninferiority was shown for decrease in NRS for maximum and mean pain scores at 1 and 3 weeks. Noninferiority was shown for clinical success at 1 week only. The opioid escalation index was lower in the methadone group at 3 and 5 weeks as compared to fentanyl (1.44 vs. 1.99, p=0.004 and 1.50 vs. 2.32 p=0.013). The pain interference in the methadone group was significantly decreased at three weeks only. GPE and side effects were not different.

Conclusion: This is the first study to show non-inferiority of methadone compared to fentanyl at one and three weeks in the treatment of radiation induced nociceptive pain in patients with head-and-neck cancer.

1. Introduction

Pain continues to be an important burden for patients with cancer, and it is often undertreated.[1, 2] Meuser and colleagues showed that following the World Health Organization (WHO) 3-step analgesic ladder results in adequate pain relief in 70% to 86% of patients with cancer suffering from pain.[3] Until recently there was no strong preference for the choice of a specific opioid. Most studies showed no difference between opioids in terms of pain relief.[4-7] When constipation is assessed transdermal fentanyl seems to be the best choice.[8-10]

Recently it was shown that methadone is superior to fentanyl in patients with head-and-neck cancer with a neuropathic pain component.[11] Therefore, differentiating between neuropathic and nociceptive pain is important for adequate pain management. However, distinguishing between these types of pain can be complicated and mixed types are rather common, which could result in methadone treatment in patients with nociceptive pain as well.

The objective of this study is to evaluate whether methadone is not inferior to fentanyl with respect to pain relief in cancer patients with nociceptive pain. To test this, we performed a randomized noninferiority study in patients with head-and-neck cancer with nociceptive pain (such as painful radiation mucositis).

2. Methods

2.1 Study design

A single-center, open-label, randomized controlled, noninferiority trial was performed. The data for this study were collected as part of a randomized controlled clinical trial (RCT) to measure differences between methadone and fentanyl in patients with head-and-neck cancer. In this RCT patients with head-and-neck cancer and either nociceptive pain due to radiation mucositis

or with a neuropathic pain component were treated with either fentanyl or methadone. This trial was started with the hypothesis that patients with a neuropathic pain component would respond better to methadone as compared to fentanyl, and that this effect would be attenuated in a population with nociceptive pain. Before data analysis the choice was made to report the data as two separate studies, because this would better explain the differences than one study with subgroup analyses. The results from the patient population with a neuropathic pain component have already been published (Chapter 3).[11] In this study, patients with nociceptive pain due to radiation mucositis were analyzed. There was no overlap between the patient populations of both studies.

The study was approved by the local medical ethics committee of the Maastricht University Medical Center, and was registered at clinicaltrials.gov (identifier NCT01317589).

2.2 Patients

Patients were included in the study from May 2011 to July 2015. Patients with histological proven head-and-neck tumors undergoing (chemo-) radiation therapy, with moderate to severe pain (≥ 4 Numerical Rating Scale (NRS), range 0-10) were included in the study. Patients undergoing radiotherapy were treated by an oral hygienist with fluoride gel, saline, and soda mouthwash. When a fungal infection was expected fluconazole was started. If the patients suffered from pain they were treated with lidocaine gel, and according to the WHO pain ladder. When strong opioids were necessary for pain control, patients were referred to a palliative care specialist, and strong opioid therapy was started. These patients were included in the study after informed consent was obtained. All patients were included within 6 weeks of the start of radiotherapy. Eligibility criteria were: nociceptive pain due to radiation mucositis, age > 18; naïve to strong opioids; being able to read and fill out the questionnaires. Exclusion criteria were: surgery up to seven days prior to randomization, pregnancy, contraindications for fentanyl or methadone, myasthenia gravis, or asthma.

2.3 Randomization and masking

After informed consent was obtained, patients were randomly assigned to the methadone or fentanyl group. The randomization with stratification for accelerated radiotherapy (RT), concurrent chemotherapy during RT and treatment volume (unilateral vs bilateral RT) was performed using software for randomization of clinical trials ALEA (version 2.2 CTCM/ALEA).

2.4 Procedures

2.4.1 Measurements

Data for neuropathic and nociceptive pain was entered in separate databases. For this study all analyses were performed on data from patients with nociceptive pain due to radiation mucositis only. The diagnosis of nociceptive pain was made by an experienced palliative care physician. No DN4 score was used.

Patients received a booklet to fill out the following forms and questionnaires:

- *Demographic data (questionnaire):* gender, age, marital status and education level.
- *Pain (Brief Pain Inventory):* The Brief Pain Inventory (BPI) is a patient completed numeric rating scale that assesses the severity of pain and its impact on daily functioning, and has been validated in many languages.[12-14] The BPI includes the four item severity scale (worst pain,

least pain, average pain, and current pain) and the seven item pain Interference Scale (general activity, mood, walking, relationships, sleep, normal work, and enjoyment of life). Each item is scored on a numeric rating scale (NRS) ranging from 0 to 10 anchored at zero for "no pain'" and 10 for "pain as bad as you can imagine" for severity, and "does not interfere" to "completely interferes" for interference.

- *Daily Breakthrough Medication:* Patients were asked to document their break-through medication needed once a day in a diary.
- *Opioid side effects:* Opioid side effects (xerostomia, nausea, vomiting, constipation, somnolence, drowsiness) were scored on a 4 point scale, with a score of 1 meaning "not at all", and 4 meaning "severe".
- *Global perceived effect:* Patient's Global Perceived Effect (GPE) reflects a patient's belief about the efficacy of treatment.15 GPE is a 7-point scale depicting a patient's rating of overall improvement. Patients rate their change as "complete pain relief", "much improvement", "little improvement", "no change", "little deterioration", "severe deterioration" or "worse than ever".
- *Depression and Anxiety (Hospital Anxiety and Depression Scale):* The Dutch translation of the Hospital Anxiety and Depression Scale is validated to be used as a screening tool for depression and anxiety disorders. 16, 17
- *Quality of Life (EuroQol-5D):* The EuroQol 5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health. It provides a simple descriptive profile and a single index value for health status.18

The treating physician filled out the medical data form to obtain the following information:

- *Medical data (medical chart):* cancer type and location (lip, oral cavity, nasopharynx, hypopharynx, larynx, salivary glands, sinuses), date of diagnosis, treatment history (accelerated radiotherapy yes or no, bilateral radiotherapy yes or no, chemotherapy, current or more than 4 weeks ago), stage of disease (curative treatment, palliative treatment, palliative care), sort of pain (nociceptive, neuropathic, mix), medication, possible opioid side effect symptoms (xerostomia, nausea, vomiting, constipation, somnolence, drowsiness) and grade of mucositis (see Common Terminology Criteria for Adverse Events, version 4.0). The diagnosis mucositis was made by clinical history and oral inspection.

2.4.2 Protocol

The study duration was 5 weeks from the time of inclusion in the study, and patients were seen 4 times after informed consent was obtained. At t=0 patients provided the demographic data, as well as responses to the BPI, side effect questionnaires, HADS and EuroQoL 5D. Methadone 2,5 mg twice daily or fentanyl patch 12 μg/hr was prescribed, as well as fentanyl nose spray 50 μg or fentanyl sublingual tablet 100 mcg (lowest doses available in The Netherlands) as necessary up to 6x/day for breakthrough pain. Due to delivery problems with the methadone 2.5 mg tablets the starting dose was altered to 2 mg twice daily later in the study.

At 1 week, 3 weeks and 5 weeks after inclusion patients provided responses to the BPI, side effect questionnaires and GPE. If the average NRS pain score was >4, and the patient used breakthrough medication four times or more the opioid dose was increased with 50%. If the pain perceived was acceptable the opioid dose was reduced with 30%. Patients were able to contact someone at any time during the study if the pain was unbearable, or if side effects were noticed.

2.5 Outcomes

Primary outcome: Pain was measured on the NRS, and a reduction of the NRS of 50% was deemed as clinical success.

45 Secondary outcomes included pain interference; mean increase of opioid dose measured by the opioids escalation index (maximal dose-starting dose/ starting dose) and use of breakthrough medication; GPE; and the side effect profile using the side effect questionnaires;

2.6 Statistical analysis

Baseline characteristics of patients are shown in Table 1, stratified by group, as mean and standard deviation, or absolute value and percentage. To test for noninferiority of methadone, we computed the 95% confidence interval of the difference in NRS and success rate between methadone and fentanyl. The noninferiority margin was predefined in a consensus meeting before the data were available to the analyst as a difference in NRS score of 1. For the success rate (i.e. the proportion of patients experiencing a 50% reduction in average NRS), the non-inferiority margin was set at a difference of 10%. The noninferiority analysis was performed per-protocol since this is often more conservative, and an intention-to-treat analysis was performed as a sensitivity analysis.

To accommodate the sensitivity analysis, and to analyze all secondary outcomes, missing data were imputed using multiple imputation. The number of imputations was set to 10. Secondary outcomes are compared between groups with regular (i.e. superiority) testing on an intention-to-treat basis.

Differences in pain interference, opioid escalation, and GPE were tested using the independent t-test. Differences in the occurrence of symptoms were tested using the Chi-squared statistic.

Data imputation and analyses were performed using SPSS version 23. Results of the Chi-square analyses of the 10-fold imputed dataset were pooled using the package 'miceadds' in R, version 3.2.3 (Kiel, Germany).

2.6.1 Sample size calculation

The sample size calculation was performed for the neuropathic and nociceptive trials combined. A difference between the experimental and control means of 2 on the NRS score was considered clinically relevant. The estimated standard deviation of response on the NRS for pain was 3 (based on a pilot study, results not published). We aimed to include at least 48 experimental subjects and 48 control subjects in the combined studies to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability of (power) 0.9. After the start of the study, but before analyzing the data, the study was split into two parts. As a result, the current study is likely to have had less power than desired using the conventional 20% type-II error rate. As the power calculation was performed for the combined study the non-inferior margin was not incorporated at that time. Before analyzing the data we chose a conservative non-inferiority limit of only 1 point difference on the NRS score to test for non-inferiority of methadone over fentanyl.

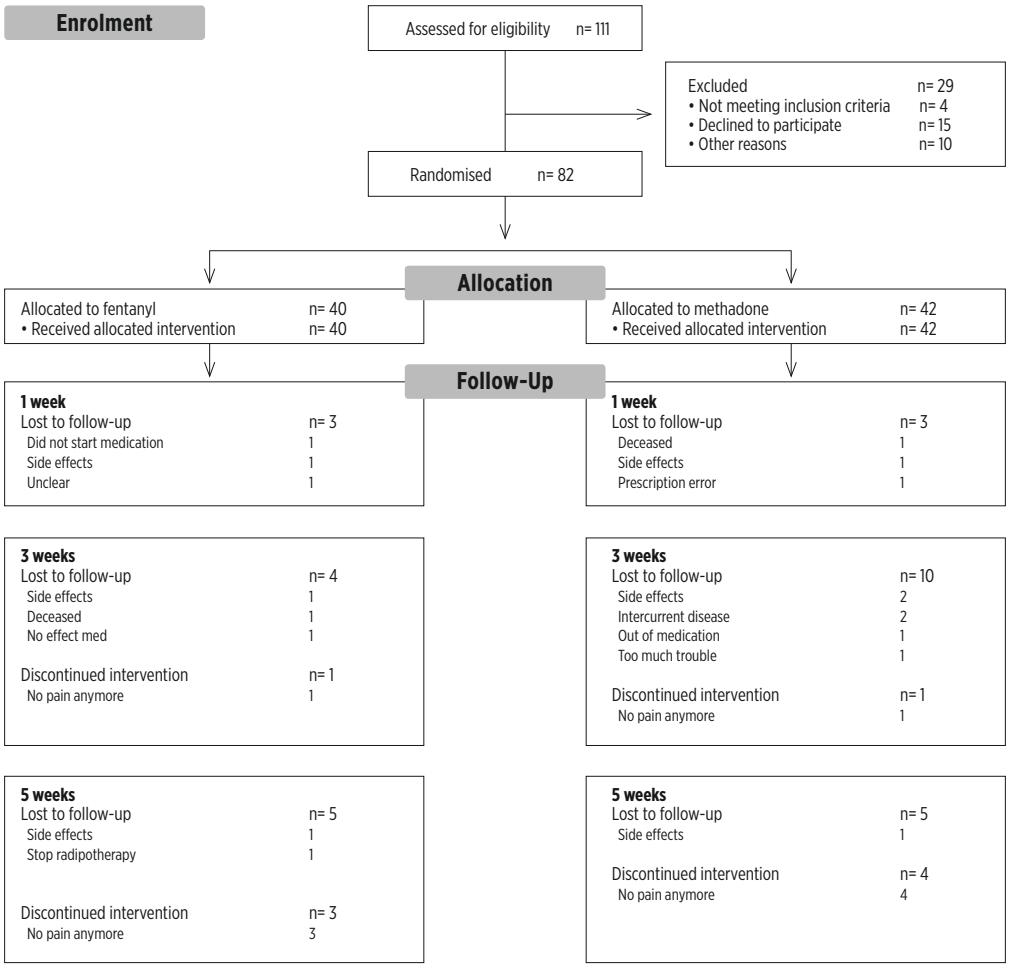
3. Results

3.1 Study Population

We included a total of 82 participants with nociceptive pain for this study. Forty participants were randomly allocated to the fentanyl group, 42 to the methadone group. Baseline characteristics

stratified for treatment allocation are presented in Table 1. We observed baseline imbalance with respect to the distribution of gender (72.5% male in the fentanyl group compared to 50.0% in the methadone group). In the methadone group seven patients were not opioid naïve (3 tramadol, 2 codeine, 2 fentanyl for breakthrough) versus two (tramadol) in the fentanyl group. All patients were included in the analysis. There was no statistical difference within the methadone group due to the non-availability of 2.5 mg methadone.

There was a considerable loss to follow up during the course of the study. Data of the 1st visit at 1 week after randomization are complete for all but 6 patients (7.3%). The loss to follow up increased for the 2nd visit at three weeks (20 patients, 24.4%), and the 3rd visit at 5 weeks after randomization (30 patients, 36.5%). Most patients stopped their medication because it was no longer necessary (fentanyl group 4, methadone group 8), 7 patients stopped using their medication due to side effects (fentanyl 3, methadone 4), 1 patient stopped because no effect of the medication was noticed (fentanyl), 2 patients deceased during the study (fentanyl 1, methadone 1), 2 patients suffered from intercurrent disease (methadone), and 6 patients were lost to follow up due to other reasons (Figure 1). Because of the per-protocol analysis, these patients were not included in the analysis of that specific follow-up measurement.


Enrolment
Assessed for eligibility n= 111
Excluded n= 29
• Not meeting inclusion criteria n= 4
• Declined to participate n= 15
• Other reasons n= 10
Randomised n= 82
Allocation
Allocated to fentanyl n= 40
• Received allocated intervention n= 40
Allocated to methadone n= 42
• Received allocated intervention n= 42
Follow-Up
1 week
Lost to follow-up n= 3
Did not start medication 1
Side effects 1
Unclear 1
1 week
Lost to follow-up n= 3
Deceased 1
Side effects 1
Prescription error 1
3 weeks
Lost to follow-up n= 4
Side effects 1
Deceased 1
No effect med 1
Discontinued intervention n= 1
No pain anymore 1
3 weeks
Lost to follow-up n= 10
Side effects 2
Intercurrent disease 2
Out of medication 1
Too much trouble 1
Discontinued intervention n= 1
No pain anymore 1
5 weeks
Lost to follow-up n= 5
Side effects 1
Stop radipotherapy 1
Discontinued intervention n= 3
No pain anymore 3
5 weeks
Lost to follow-up n= 5
Side effects 1
Discontinued intervention n= 4
No pain anymore 4

	Fentanyl (n= 40)		Methadone (n= 42)	
	Mean/N	SD or %	Mean/N	SD or %
Age, years	63.6	10.5	64.4	9.6
Mean pain (BPI)	5.5	1.8	5.3	1.9
Quality of life (Eqol5)	.52	.32	.40	.33
Male sex	29	72.5%	21	50%
Education				
Primary school	28	70%	22	52.4%
Secondary school	5	12.5%	9	21.4%
College/university	7	17.5%	11	26.2%
Employment status				
Working	7	17.5%	7	17.1%
Housewife / man	6	15%	7	17.1%
Old-age pension	19	47.5%	18	43.9%
Disability pension	3	7.5%	4	9.8%
Sick leave	3	7.5%	5	12.2%
Volunteer work	2	5%	0	0%
Living arrangements				
At home alone	12	30%	11	26.2%
At home with partner	27	67.5%	29	69%
Different	1	2.5%	2	4.8%
Depression (HADS)				
No	12	30%	10	23.8%
Borderline	18	45%	25	59.5%
yes	10	25%	7	16.7%
Anxiety (HADS)				
No	13	32.5%	8	19%
Borderline	10	25%	8	19%
yes	17	42.5%	26	62%
Prior chemotherapy	14	35%	14	33%
Prior surgery	5	12.5%	2	4.8
Prior weak opioid exposure	2	5%	7	16.7%

Table 1. Baseline characteristics

3.2 Pain and clinical success

Analysis of the primary outcome, the difference in change in NRS score of mean pain at 3 weeks, showed that methadone was not inferior to fentanyl. The lower bound of the 95% confidence interval (CI) did not exceed the pre-specified noninferiority limit of 1 point on the NRS score. Even more so, the point estimate indicated that methadone decreased average pain more than fentanyl (the difference was 0.75 points on the NRS scale, 95% confidence interval: -0.21, 1.71, in favor of methadone). Figure 2a shows the point estimates and 95% CI of the difference in change scores between fentanyl and methadone for all three follow-up measurements. Positive values indicate that on average methadone decreased NRS scores more than fentanyl. The estimate at the 3rd follow-up visit at 5 weeks indicated non-inferiority, just as both other measurements,

but should be regarded as inconclusive because the lower bound of the 95% CI crossed the non-inferiority limit.

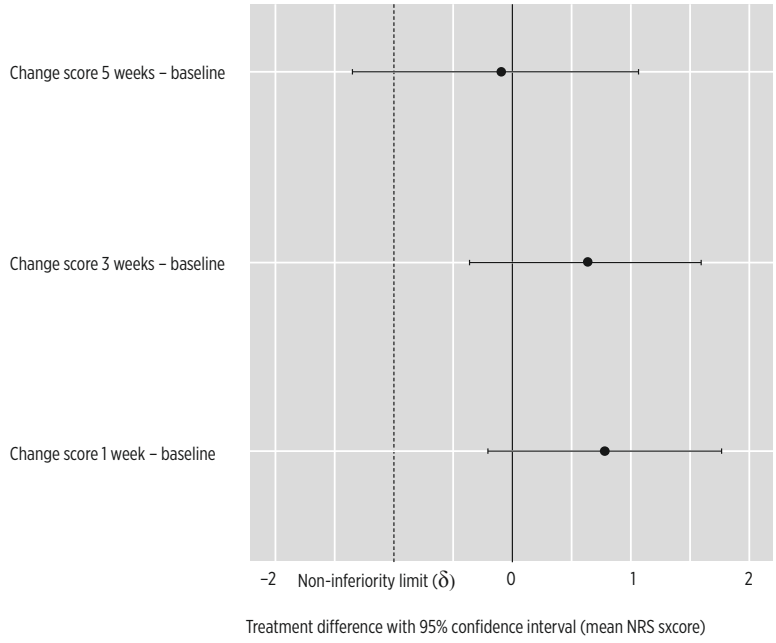


Figure 2A. Point estimates and 95% confidence intervals of the difference in change-from-baseline of mean NRS scores between fentanyl and methadone.

Similar conclusions held when analyzing the difference in decrease of the maximum NRS score between the fentanyl and methadone group. Again, methadone is non-inferior for all measurements up to 5 weeks, but remained inconclusive at 5 weeks (Figure 2B). At 3 weeks, methadone seemed clearly superior to fentanyl, as the lower bound of the 95% CI did not cross the null.

In addition, methadone was noninferior with respect to clinical success, as defined as a reduction in average NRS score of 50% or more (Figure 2C). All point estimates indicated that methadone performed better, yet the 95% CI's at 3 and 5 weeks cross the noninferiority limit. Therefore, at these follow-up measurements the result are inconclusive.

The intention-to-treat analyses, based on all randomized individuals, yielded similar conclusions.

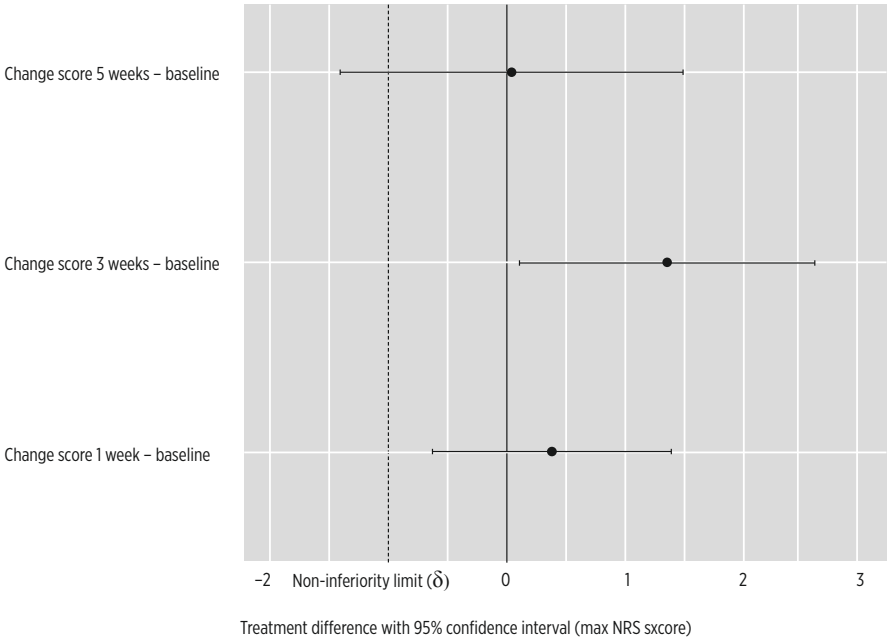
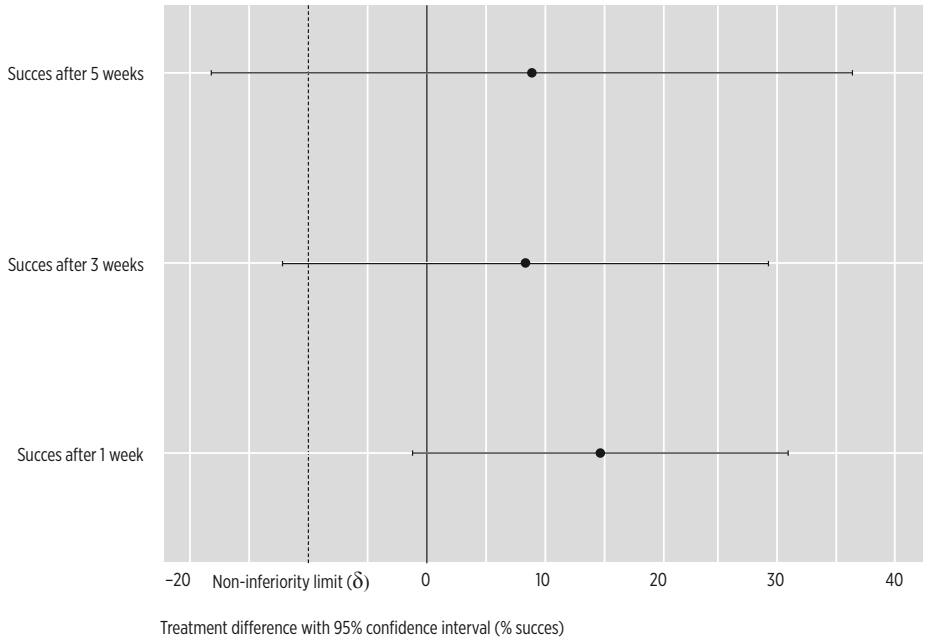


Figure 2B. Point estimates and 95% confidence intervals of the difference in change-from-baseline of maximum NRS scores between fentanyl and methadone.

Figure 2C. Point estimates and 95% confidence intervals of the difference between fentanyl and methadone in clinical success as defined as a change in NRS score from baseline of 50% or more.



3.3 Secondary outcomes:

3.3.1 Interference

The pain interference decreased in both groups. Interference in the methadone group started
51 at 27.16 (SEM 2.56) and decreased to 19.61 (SEM 2.472) at week 1, 17.58 (SEM 1.59) at week 3 and 14.53 (SEM 1.64) at week 5. In the fentanyl group interference decreased from 25.3 (SEM 2.51) at baseline to 22.0 (SEM 2.91) at 1 week, 24.3 (SEM 2.40) at 3 weeks, and 18.3 (SEM 1.85) at 5 weeks. The decrease in interference was higher in the methadone group at all time points. This difference was statistically significant at 3 weeks (p=0.023). At 1 and 5 weeks the difference was not statistically significant. *(Figure 3*).

Further testing of the interference subscores at 3 weeks showed a significant difference in the score for general activity, walking ability and working ability. For general activity, walking ability and working ability the fentanyl group scored 4.5, 1.85 and 4.12 (SEM 0.57, 0.43, 0.58), as compared to the methadone group scores of 2.78, 0.74 and 2.48 (SEM 0.49, 0.30, 0.50) (p=0.03, 0.048 and 0.042).

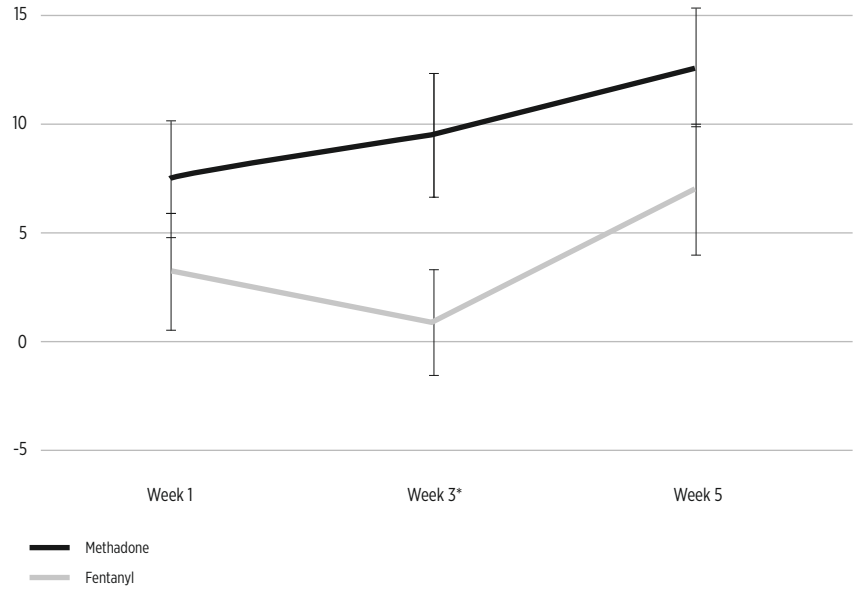


Figure 3. Decrease in Pain Interference. This figure shows the difference in pain interference at one, 3 and 5 weeks. A high number means a larger decrease in pain interference. The difference between the groups is significant (*P = 0.023) at 3 weeks.

3.3.2 Opioid escalation index

The opioid escalation indices (dose/starting dose) were 1.10 (SEM 0.065), 1.44 (SEM 0.13) and 1.50 (SEM 0.19) in the methadone group. These indices were 1.10 (SEM 0.056), 1.99 (SEM 0.14) and 2.32 (SEM 0.28) in the fentanyl group. The difference in opioid increase ratio was statistically significant at 3 weeks and at 5 weeks (p=0.004 and 0.013, respectively; Figure 4).

There was no significant difference in amount (measured as total dosage per day, and as number of doses per day) of breakthrough medication used between the groups.

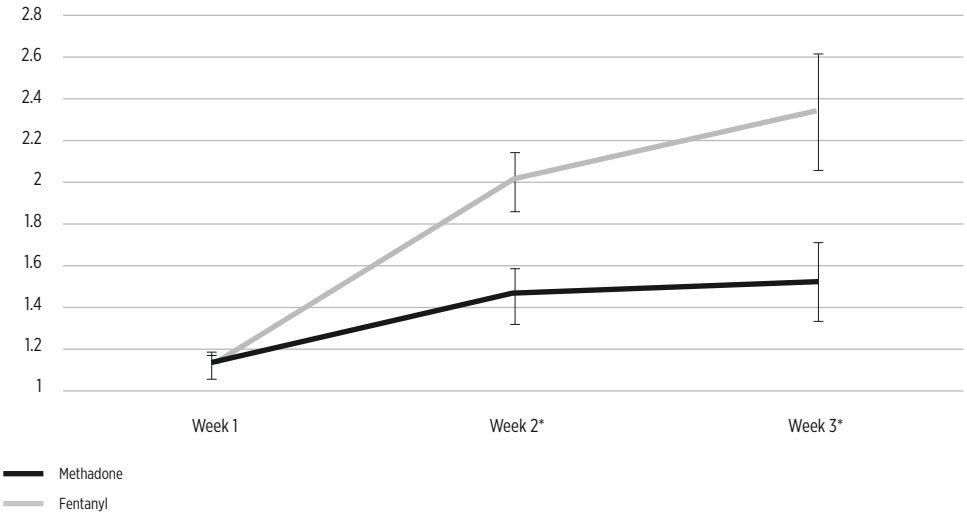


Figure 4. Opioid escalation index. This figure shows the difference in opioid escalation index. The difference is statistical significant at 3 and 5 weeks (*P < 0.05).

3.3.3 Global Perceived Effect

The GPE did not show significant differences between the groups at any time point. Up to 18.25% of the patients reported worse pain (little and severe deterioration) at week 3 in the fentanyl group vs 15.7% in the methadone group. At 1 week 67.25% of the patients reported improvement in the fentanyl group (little, much or complete pain relief) vs. 88% of the patients at 1 week in the methadone group.

3.3.4 Side effects

There was no significant difference in reported serious side effects, measured as a score of 3 or 4 on the side effects questionnaire. The most common side effect was a dry mouth, which was reported by 72% of the patients during the complete study (81% in the fentanyl group vs 64% in the methadone group, difference not statistically significant). In the methadone group five patients stopped their medication due to side effects whereas two patients stopped due to side effects in the fentanyl group. This difference was not statistically significant.

4. Discussion

This is the first non-inferiority trial performed comparing methadone to fentanyl. We showed that methadone is not inferior to fentanyl in the treatment of severe nociceptive pain caused by radiation-induced mucositis in patients with head-and-neck cancer at 1 and 3 weeks after pharmaceutical pain therapy. When success was measured noninferiority was only shown after one week of pain therapy. There was a significant decrease in pain interference in the methadone group at three weeks of pharmaceutical pain therapy. The opioid escalation index was lower in the methadone group as compared to the fentanyl group. There were no differences in side effect profile or in GPE.

Our findings seem to be in accordance with those published in previous studies, which were unable to show a difference in effect between methadone and other strong opioids as measured by pain scores and side effects in patients with nociceptive pain.[4, 19, 20] However, these studies were designed to show superiority of one drug over the other, whereas our study intended to show noninferiority. A recent study reported better pain relief in patients with neuropathic pain in head-and-neck cancer when treated with methadone as compared to fentanyl.[11] The results from the trial comparing methadone to fentanyl in neuropathic pain caused by head-and-neck cancer could result in an increase in treatment with methadone in cancer patients in general, and possibly in cancer patients with nociceptive pain. Our study shows that treatment with methadone will not result in inferior pain relief in patients with nociceptive pain caused by head-and-neck cancer.

The lower increase in opioid consumption in the methadone group can be interpreted as better pain relief by methadone as compared to fentanyl, as a similar increase with methadone could result in lower pain scores. The lower pain scores could result in clear noninferiority at all time points, and possibly in superiority. Many studies comparing effectivity of pain medication in acute pain management settings fail to show superiority of one drug on pain NRS scores, but show a difference in opioid consumption.[21] It must be stressed that this case cannot be made for methadone, as there is a high inter-individual variability, and conversion of methadone into a morphine equivalent dose is not straightforward.[22]

This study showed significant lower pain interference with methadone as compared to

fentanyl at 3 weeks. This difference was not significant at 1 week and is no longer significant at 5 weeks. The fact that the subscore analysis showed difference for walking and working ability and for general activity, is difficult to explain. As this study was not powered to show a difference in pain interference, and the difference in pain interference is not statistically different at one week and at five weeks we expect this difference to have little clinical significance.

The effect of methadone in cancer related pain was evaluated in two systematic reviews. The 2007 Cochrane review concluded that the efficacy of methadone is similar to morphine and this conclusion was based on 9 RCT's.[4] When no difference between nociceptive and neuropathic pain was made, no difference in pain relief between morphine and methadone could be observed. A more recent systematic review[23], based on 4 RCT's published after the 2007 Cochrane review, showed no difference in effectiveness between methadone compared to other strong opioids in 2 RCT's.[20, 24] Two other RCT's used in this systematic review evaluated the effect of opioid rotation to methadone: in one study no conclusion on the efficacy of methadone in treatment of cancer related pain could be presented due to the number of dropouts[25], the other reported a decrease in pain intensity switching from morphine to methadone and a patient preference for methadone.[26] It is important to realize that these studies were performed to show superiority instead of noninferiority of one drug over another.

The unique pharmacological properties make methadone a difficult drug in inexperienced hands. There is great inter-individual variability in bioavailability (41 to 90%), possibly due to gene polymorphisms.[27] Furthermore, methadone is known to have a long and variable half-life (7 to 65 hours) influenced by urine pH, high protein binding (85 to 90%), and a distribution volume of 3.6 l/kg.28 The metabolism of methadone by CYP 3A4 and 2B6 implies numerous drug-drug interactions and methadone can prolong the QTc-time resulting in risk for torsades de points.[29] Due to the complicated dosing, and possible side effects, we advocate this drug to be used only by physicians who have clinical experience with methadone, especially in patients with a higher chance of malnutrition, which can cause increased bio-availability of methadone due to decreased protein binding.

This study has some limitations. The original sample size calculation was performed for statistical testing of the difference between methadone and fentanyl in pain patients with head-and-neck cancer, and not for testing noninferiority in patients suffering from only nociceptive pain. Furthermore, the sample size calculation was based on the combination of neuropathic and nociceptive pain. As a result, the sample size calculation that was performed yielded a sample too small to obtain a conventional power for determining noninferiority. Post-hoc power analysis yielded a power of about 45% to reject a noninferiority limit of 1 point on the NRS pain scale. Despite the low statistical power, our analysis showed that the design and used sample size allowed to detect significant evidence that methadone is not inferior to fentanyl.

Although most participants were available for the analysis of short-term pain relief, we observed a significant loss to follow-up over the course of five weeks, which was mostly due to treatment success. Due to this relative high loss to follow-up the confidence interval widens causing inconclusiveness at 5 weeks when we focus at the decrease in NRS, and at 3 and 5 weeks when we look at treatment success. To compute unbiased estimates of treatment effects, to obtain the statistical precision that we needed to detect a clinically relevant difference, and to make the intention-to-treat sample (i.e. for all results except the non-inferiority analysis) available for analysis we used multiple imputation. As compared to many other frequently used methods

of handling missing data, multiple imputation yields correct standard errors and unbiased estimates when data are missing at random.[30]

The interpretation of radiotherapy induced pain as being nociceptive was not tested with a DN4 score. The diagnosis of the pain being nociceptive was made by the clinician without standardized use of the DN4-score. Despite this limitation we feel comfortable and think the clinical diagnosis is correct.

Another limitation of this study is the difficulty to differentiate the pain caused by radiation mucositis from pain caused by the disease. Pain before radiotherapy was not an exclusion criteria, however, pain due to radiation induced mucositis was the scope of this article. Therefore patients suffering from pain before radiotherapy were not included. There is a still a chance that tumor progression or regression of mucositis interfered with the pain outcomes in this study.

5. Conclusion

Methadone is not inferior to fentanyl in the treatment of radiation-induced nociceptive pain in patients with head-and-neck cancer at 1 to 3 weeks of pharmaceutical pain treatment.

1. **Te Boveldt N**, **Vernooij-Dassen M**, **Burger N**, **Ijsseldijk M**, **Vissers K**, **Engels Y**. Pain and its interference with daily activities in medical oncology outpatients. *Pain physician*. 2013;**16**:379-389.

2. **van den Beuken-van Everdingen MH**, **Hochstenbach LM**, **Joosten EA**, **Tjan-Heijnen VC**, **Janssen DJ**. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage*. 2016;**51**:1070-1090 e1079.

3. **Meuser T**, **Pietruck C**, **Radbruch L**, **Stute P**, **Lehmann KA**, **Grond S**. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain*. 2001;**93**:247-257.

4. **Nicholson AB**. Methadone for cancer pain. *Cochrane Database Syst Rev*. 2007:CD003971.

5. **Hadley G**, **Derry S**, **Moore RA**, **Wiffen PJ**. Transdermal fentanyl for cancer pain. *The Cochrane database of systematic reviews*. 2013;**10**:CD010270.

6. **Schmidt-Hansen M**, **Bromham N**, **Taubert M**, **Arnold S**, **Hilgart JS**. Buprenorphine for treating cancer pain. *The Cochrane database of systematic reviews*. 2015;**3**:CD009596.

7. **Schmidt-Hansen M**, **Bennett MI**, **Arnold S**, **Bromham N**, **Hilgart JS**. Oxycodone for cancer-related pain. *The Cochrane database of systematic reviews*. 2015;**2**:CD003870.

8. **Clark AJ**, **Ahmedzai SH**, **Allan LG**, **Camacho F**, **Horbay GL**, **Richarz U**, et al. Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. *Current medical research and opinion*. 2004;**20**:1419-1428.

9. **Yang Q**, **Xie DR**, **Jiang ZM**, **Ma W**, **Zhang YD**, **Bi ZF**, et al. Efficacy and adverse effects of transdermal fentanyl and sustained-release oral morphine in treating moderate-severe cancer pain in Chinese population: a systematic review and meta-analysis. *Journal of experimental & clinical cancer research: CR*. 2010;**29**:67.

10. **Tassinari D**, **Sartori S**, **Tamburini E**, **Scarpi E**, **Raffaeli W**, **Tombesi P**, et al. Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: a meta-analysis and systematic review of the literature. *Journal of palliative medicine*. 2008;**11**:492-501.

11. **Haumann J**, **Geurts JW**, **van Kuijk SM**, **Kremer B**, **Joosten EA**, **van den Beuken-van Everdingen MH**. Methadone is superior to fentanyl in treating neuropathic pain in patients with head-and-neck cancer. *European journal of cancer*. 2016;**65**:121-129.

12. **Radbruch L**, **Loick G**, **Kiencke P**, **Lindena G**, **Sabatowski R**, **Grond S**, et al. Validation of the German version of the Brief Pain Inventory. *Journal of pain and symptom management*. 1999;**18**:180-187.

13. **Wang XS**, **Mendoza TR**, **Gao SZ**, **Cleeland CS**. The Chinese version of the Brief Pain Inventory (BPI-C): its development and use in a study of cancer pain. *Pain*. 1996;**67**:407-416.

14. **Caraceni A**, **Mendoza TR**, **Mencaglia E**, **Baratella C**, **Edwards K**, **Forjaz MJ**, et al. A validation study of an Italian version of the Brief Pain Inventory (Breve Questionario per la Valutazione del Dolore). *Pain*. 1996;**65**:87-92.

15. **Farrar JT**, **Young JP** Jr., **LaMoreaux L**, **Werth JL**, **Poole RM**. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;**94**:149-158.

16. **Spinhoven P**, **Ormel J**, **Sloekers PP**, **Kempen GI**, **Speckens AE**, **Van Hemert AM**. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychological medicine*. 1997;**27**:363-370.

17. **Zigmond AS**, **Snaith RP**. The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica*. 1983;**67**:361-370.

18. **EuroQol G**. EuroQol--a new facility for the measurement of health-related quality of life. *Health policy*. 1990;**16**:199-208.

19. **Haroutiunian S**, **McNicol ED**, **Lipman AG**. Methadone for chronic non-cancer pain in adults. *The Cochrane database of systematic reviews*. 2012;**11**:CD008025.

20. **Mercadante S**, **Porzio G**, **Ferrera P**, **Fulfaro F**, **Aielli F**, **Verna L**, et al. Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. *European journal of pain*. 2008;**12**:1040-1046.

21. **Wang L**, **Johnston B**, **Kaushal A**, **Cheng D**, **Zhu F**, **Martin J**. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials. *Can J Anaesth.* 2016;**63**:311-325.

22. **Mercadante S**. Switching methadone: a 10-year experience of 345 patients in an acute palliative care unit. *Pain medicine.* 2012;**13**:399-404.

23. **Good P**, **Afsharimani B**, **Movva R**, **Haywood A**, **Khan S**, **Hardy J**. Therapeutic challenges in cancer pain management: a systematic review of methadone. *Journal of pain & palliative care pharmacotherapy.* 2014;**28**:197-205.

24. **Lauretti GR**, **Rizzo CC**, **Mattos AL**, **Rodrigues SW**. Epidural methadone results in dose-dependent analgesia in cancer pain, further enhanced by epidural dexamethasone. *British journal of cancer.* 2013;**108**:259-264.

25. **Moksnes K**, **Dale O**, **Rosland JH**, **Paulsen O**, **Klepstad P**, **Kaasa S**. How to switch from morphine or oxycodone to methadone in cancer patients? a randomised clinical phase II trial. *European journal of cancer.* 2011;**47**:2463-2470.

26. **Cubero DI**, **del Giglio A**. Early switching from morphine to methadone is not improved by acetaminophen in the analgesia of oncologic patients: a prospective, randomized, double-blind, placebo-controlled study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2010;**18**:235-242.

27. **Kharasch ED**, **Regina KJ**, **Blood J**, **Friedel C**. Methadone Pharmacogenetics: CYP2B6 Polymorphisms Determine Plasma Concentrations, Clearance, and Metabolism. *Anesthesiology.* 2015;**123**:1142-1153.

28. **Fredheim OM**, **Moksnes K**, **Borchgrevink PC**, **Kaasa S**, **Dale O**. Clinical pharmacology of methadone for pain. *Acta Anaesthesiol Scand.* 2008;**52**:879-889.

29. **Beuken-van Everdingen van den MHJ**, **Geurts JW**, **Patijn J**. Prolonged QT interval by methadone: Relevance for daily practice? A prospective study in patients with cancer and noncancer pain. *J Opioid Manag.* 2013;**38**:263-269.

30. Buuren Sv. Flexible imputation of missing data. Boca Raton, FL: CRC Press; 2012.

V

The Association between patient characteristics and opioid treatment response in neuropathic and nociceptive pain due to cancer

J. Haumann; S.M.J. van Kuijk; E. A. Joosten;
M.H.J. van den Beuken-van Everdingen

Journal of Palliative Medicine
2019 Feb;22(2):157-163.

Abstract

Background: Cancer pain remains a difficult problem, for which opioids are often necessary. Currently it is difficult to predict the effectiveness of opioid therapy.

Objectives: we aim to assess the association between patient characteristics and opioid treatment response in cancer patients, and develop a model to predict probability of response.

Subjects: We used data from two previously published randomized clinical trials,[1, 2] in which patients with head and neck cancer were treated with fentanyl or methadone (total n=134).

Measurements: Treatment success was defined as ≥ 50% pain reduction at one and at five weeks. We analyzed patient characteristics (age, sex, depression and anxiety), treatment characteristics (having had chemotherapy, radiotherapy, surgery, methadone or fentanyl) and pain characteristics (neuropathic, nociceptive).

Design: Based on univariable and multivariable regression analyses determinants of therapy success were assessed. Based on these analyses a prediction model was developed.

Results: Our analyses shows that one week therapy success was associated with methadone (OR 5.21), duration of pain in months (OR 1.12) and neuropathic pain (OR 3.36), and with the age of the patient in years (OR 0.95). Inclusion of these four characteristics into our prediction model resulted in an area under the curve of 81,6%.

Conclusions: Careful analyses of patient attributes, treatment and pain type of patients with head and neck cancer resulted in a prediction model which allowed to predict short term pain relief and the opioid treatment response in neuropathic and nociceptive pain due to cancer.

1. Introduction

Pain continues to be a major cause of distress in cancer patients.[3] Despite an increased awareness of pain in cancer patients the prevalence of cancer pain has not changed significantly when comparing the period 2005-2014 to the period 1966-2005.[4] An important algorithm used to treat cancer pain is the World Health Organization pain ladder,[5] which has proven to provide significant pain relief in most patients.[6, 7] This algorithm suggests treatment of cancer pain using strong opioids at a relative early stage. Therefore we can say that opioids are the cornerstone of cancer pain management.

Although opioids are highly effective at providing pain relief, some patients do not experience this pain reduction.[8] Despite centuries of experience with opioids[9] it remains difficult to predict which patient will show a good response, and which patient will show a poor response or needs an incremental dose of opioids. A recent study revealed an association between the presence of liver metastases, breakthrough pain and non-responsiveness to opioids.[10] Other studies showed associations between genetic markers such as the mu-opioid receptor (OPRM1) allele and postoperative opioid consumption and pain relief.[11] Interestingly an association between genetic sensitivity to opioid analgesics and opioid effect in postoperative pain patients was only noted for the first 24 hours. Moreover, the inability to predict an opioid's clinical effectiveness can be a problem when a patient wants to know how effective the pain relief will be.

To address this problem it is important to identify factors that are associated with effectiveness of pain therapy. This could result in more effective treatment of cancer pain using opioid therapy tailored to a patient's profile. Furthermore, a clinician can use these predictors to provide patients with reasonable expectations of pharmacological pain therapy. A retrospective study in patients with neuropathic pain showed that those patients with realistic expectations had lower levels

of disability and psychological distress as compared to patients with unrealistic expectations. Patients with optimistic expectations showed lower levels of disability as compared to those patients with realistic assumptions. Patients with pessimistic expectations were characterized by higher levels of catastrophizing and psychological distress.[12]

In order to provide the patient and clinician with the most accurate information about the chance of opioid therapy success we performed this analysis. We assessed the associations between patient- and cancer treatment characteristics and the probability of achieving pain relief with either methadone or fentanyl. Also, we combined these predictors of pain relief into one model to be able to predict short term pain relief within one week.

2. Methods

2.1 Source of data

Patient data from two randomized clinical trials were used for this study.[1, 2] In short, strong opioid naïve patients (i.e. patients had only been prescribed weak opioids such as codeine and tramadol, or no opioids at all) with head-and-neck cancer and pain (Numeric Rating Scale (NRS) > 4) were stratified in two groups. One with a neuropathic pain component, defined as a Douleur Neuropathique 4 (DN4) score of ≥4, and the other with nociceptive pain after radiotherapy induced mucositis (shortly after the start of radiotherapy). After informed consent was obtained patients were randomly assigned to either the fentanyl or the methadone group. The randomization was stratified by surgery, chemotherapy and radiotherapy, and performed using the web based program TENALEA (Trans European Network for Clinical Trials Services).

The total duration of follow up was 5 weeks, and patients were seen 4 times after informed consent was obtained. At baseline patients provided demographic data, and completed the Brief Pain Inventory (BPI), side effect questionnaires, Hospital Anxiety Depression Scale (HADS) and Quality of life (EUROQoL 5D). Methadone 2,5 mg twice daily or fentanyl-patch 12 μg/hr was prescribed as well as fentanyl nose-spray 50 μg or fentanyl sublingual 100 μg as necessary up to 6x/day for breakthrough pain. Due to delivery problems with the methadone 2.5 mg tablets the starting dose was altered to 2 mg twice daily later in the study.

At 1 week, 3 weeks and 5 weeks patients completed the Brief Pain Inventory, side effect questionnaires and global perceived effect (Patient Global Impression of Change (PGIC)). If necessary the strong opioid dose was increased by 50%. As the fentanyl-patch has 12 μg/hr as the lowest dose this could only be doubled the first time. If deemed possible the strong opioid dose was decreased by 30% (or stopped if medication was at starting dose). Therapy discontinuation due to side effects was assessed at every visit.

2.2 Outcome

The primary outcome parameter used was treatment success, defined as a change in pain score from baseline pain of at least 50%. Pain was measured using an 11-point Numeric Rating Scale. For this study, pain measures of one and five weeks after treatment were used to quantify short- and long-term treatment success respectively.

2.3 Determinants of treatment success

In our analyses we measured associations between treatment success and several patient characteristics such as; sex, age, HADS depression score, HADS anxiety score and HADS total

score. Treatment characteristics and pain characteristics were analysed as well; using methadone or fentanyl, having had chemotherapy, having had radiotherapy, having had surgery, pain duration, and pain type (nociceptive (radiation induced mucositis) or neuropathic (pain with a neuropathic pain component as measured with the DN4)).

2.4 Statistical analyses

Before univariable and multivariable analysis, we imputed missing characteristics using multiple imputation. The number of imputations was set to 10, and the imputed values were drawn using predictive mean matching. Compared to the use of completed cases only for the analysis, the use of imputation provides more precision as all subjects will be included for the analysis. Also, multiple imputation is less prone to yield biased coefficients when compared to complete case analysis.[13]

We used logistic regression analyses to compute the univariable, or unadjusted, associations between determinants of treatment success and actual treatment success at one and five weeks after opioid treatment initiation. In a subsequent analysis, all parameters were included in a multivariable logistic regression model to correct for other determinants.

To develop a model to predict short term treatment success, we entered all determinants in a logistic regression model and used backward stepwise elimination to arrive at a more parsimonious model. As suggested by prediction modelling guidelines, we used a less stringent alpha for statistical testing of 0.30. Variables that were selected in over half of the 10 imputed datasets were selected for the prediction model.[14-16]

The performance of the prediction model was quantified by measures of discriminative ability and calibration. The discriminative ability of the model pertains to the models ability to distinguish between patients who will experience treatment success, and those who will not. It is quantified as the area under the receiver operating characteristic curve (AUC). The AUC ranges between 50% (no discriminative ability at all, like flipping a coin) and 100% (perfect separation between success and no success). Calibration of the model compares predicted probabilities of treatment success to actual probabilities. We visually assessed the calibration plot to assess calibration over the whole range of predicted probabilities. The prediction model was internally validated using bootstrapping techniques.

All analyses were performed using R version 3.3.3.

3. Results

In total, 134 patients were included in both randomized clinical trials. Because of the imputation step, all patients were included in the analysis. Of all patients, 30 (22.2%) reported short term pain decrease of 50% or more. Baseline characteristics of all patients are shown in table 1.

3.1 Determinants of treatment effect

Univariable analysis for short (one week) and long term (five weeks) treatment success revealed that only at one week a significant (positive or negative) association with treatment success was noted for: 1. having had surgery, 2. baseline pain, 3. neuropathic pain and 4. treatment with methadone. In the univariable analysis having had surgery was associated with a decreased chance of treatment success. Baseline pain, neuropathic pain and treatment with methadone

were associated with an increased chance of therapy success. Univariable analysis did not show a correlation between age and treatment success. (Table 2)

At five weeks 55 patients were lost to follow up (7 side effects, 4 deceased, 17 pain free, 8 patients stopped due to other reasons, 16 inter-current disease, 3 medication stopped by other physician). This loss to follow up was corrected for by using imputation methods. At five weeks 47% of patients experienced pain reduction of 50% or more, no factors were significantly associated with treatment success.

	n= 134	
	No[1]	**%[1]**
Age, years		
Median	64	
SD	9.7	
Mean pain[2] (BPI)	5.7	1.8
Quality of life[#] (Eqol5)	.42	.33
Male sex	86	64%
Education		
Primary school	56	42%
Secondary school	32	24%
College/university	46	34%
Employment status		
Working	17	12.7%
Housewife / man	21	16%
Old-age pension	60	45%
Disability pension	17	13%
Sick leave	13	10%
Volunteer work	4	3%
Living arrangements		
At home alone	37	28%
At home with partner	94	70%
Different	3	2%
Depression (HADS)		
No	70	52%
Borderline	12	21%
yes	36	27%
Anxiety (HADS)		
No	78	58%
Borderline	27	20%
yes	29	22%
Prior radiotherapy	106	79%
Prior chemotherapy	39	29%
Prior surgery	21	16%
Methadone	68	51%
Fentanyl	66	49%
Anti-neurotic co-medication[3]	19	14%
Prior weak opioid exposure*	32	24%

Table 1. Baseline characteristics

Abbrevations:
BPI: brief Pain Inventory;
Eqol5: Euroqual 5;
HADS: Hospital Anxiety and Depression Scale, depression/anxiety
no 0 – 7 points, *borderline* 8 – 10, *yes* 11 – 21;

[1]Unless otherwise specified
[2]Median and SD
[3]gabapentin, pregabalin or amitriptyline

	Short term		Long term	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age (years)	0.97 (0.93 - 1.01)	0.151	0.97 (0.93 - 1.02)	0.238
Female	1.18 (0.50 - 2.80)	0.707	1.33 (0.53 - 3.29)	0.535
Pain duration (months)	1.07 (0.93 - 1.24)	0.308	1.03 (0.97 - 1.11)	0.256
Radiotherapy	1.38 (0.51 - 3.73)	0.526	0.93 (0.27 - 3.18)	0.907
Chemotherapy	0.76 (0.31 - 1.85)	0.548	0.67 (0.26 - 1.74)	0.400
Surgery	0.33 (0.12 - 0.88)	0.028	0.46 (0.15 - 1.39)	0.165
Baseline pain (NRS)	1.28 (1.00 - 1.63)	0.045	1.07 (0.85 - 1.34)	0.560
HADS total score	1.03 (0.98 – 1.09)	0.210	0.97 (0.93 – 1.02	0.244
HADS depression score	1.08 (0.98 - 1.20)	0.106	0.96 (0.87 – 1.06)	0.446
HADS anxiety scale	1.05 (0.95 - 1.16)	0.292	0.94 (0.86 - 1.04)	0.232
Neuropathic vs nociceptive	2.06 (1.12 - 6.18)	0.027	1.01 (0.37 - 2.78)	0.986
Methadone vs fentanyl	4.25 (1.65 - 10.95)	0.003	1.42 (0.64 - 3.14)	0.381

Table 2. Univariable associations between patient characteristics and short (1 week) and long-term (5 weeks) treatment success

3.2 Predicting short-term treatment effect

The backward stepwise elimination procedure in each of the 10 imputed datasets yielded 4 predictors for the prediction model for short term treatment success: age, methadone (compared to fentanyl), duration of pain (in months), and neuropathic pain (compared to nociceptive pain). Age was negatively associated with the probability of short term treatment success, all other predictors were positively associated. Table 3 is comprised of all regression coefficients and odds ratios after penalization of the prediction model due to overfitting. The shrinkage factor that was used for penalization was based on our data, and was 0.85.

The prediction model discriminated well between patients with and without short term pain treatment success. The AUC of the prediction model was 81.6% (95% confidence interval [CI]: 73.8 – 81.6). The calibration plot revealed that the model was well calibrated. All subgroups of patients based on similar predicted risk clustered around the 45-degree line of perfect calibration (*Figure 1*).

	Regression coefficient	OR (95% CI)
Intercept	-0.18	
Age (years)	-0.05	0.95 (0.90 - 1.00)
Methadone (yes)	1.65	5.21 (1.56 - 17.5)
Duration of pain (months)	0.12	1.12 (0.98 - 1.29)
Neuropathic pain (yes)	1.30	3.36 (1.21 - 11.1)

Table 3. Prediction model for the probability of short-term pain treatment success after opioid intake

An individual's probability of short-term pain treatment success can be calculated as:
1 / (1 + e-LP), in which LP (ie linear predictor) = -0.18 − 0.05*age + 1.65*methadone + 0.12*duration of pain + 1.30*neuropathic pain. For example, a 65-year old patient who reports experiencing pain for 5 months, classified as neuropathic pain, who will be treated with methadone has a probability of treatment success of:
LP = -0.18 − 0.05*65 + 1.65*1 + 0.12*5 + 1.30*1 = 0.12
probability = $1 / (1 + e^{0.12}) = 0.47 = 47\%$

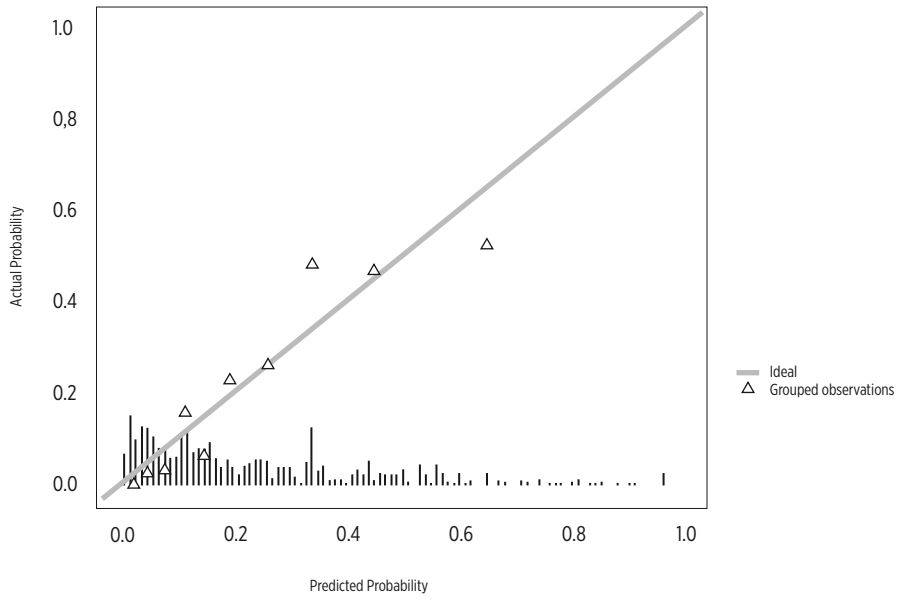


Figure 1. Calibration plot of the prediction model for short term pain treatment success.

4. Discussion

In this study we identified multiple predictors of opioid therapy success in head and neck cancer related pain, and used these to create a prediction model. This results in an effective model, that may be used to predict the chance of therapy success. Although this prediction model needs to be validated, our results suggest it will be of help for doctors and patients with cancer related pain to improve the informed, shared decision making around pain medication (i.e. to start opioid therapy, or to try alternative pain medications such as NSAID's, antidepressants and gabapentinoids before).

4.1 Predictors

The possible predictors as used in this study were chosen based on clinical reasoning and available evidence, as prescribed by current guidelines on reporting about prognostic modelling.[14-16] Each possible predictor will be discussed separately:

4.1.1 Age

Based on various studies it is suggested that elderly respond as well as or even better than younger age groups to opioid therapy, in chronic and in acute postoperative pain.[17-19] Hence we expected that age might have a beneficial effect on therapy success (i.e. higher age could result in higher percentage of clinical success). However, in our population we noticed the opposite. Possible reasons for this difference could be related to the fact that there was a limited spread in our population's age (64 mean, SD 9,6 year, 25-86), and we did not dichotomise the patient population into a group under and a group over 65 years old, as compared to the above mentioned studies.

An aged population is likely to be at a higher risk for side effects of opioids. This is caused by the increased frailty of this population, as well as the higher likeliness of co-morbidity and co-medication which can result in different interactions.[20] Methadone elimination depends on several cytochrome reduction pathways, as well as on renal filtration.[21] Different pharmaceuticals can interact with the CYP2D6 or CYP 3A4 pathway and cause a decrease or increase of the methadone plasma levels.[22] Fentanyl elimination depends on CYP 3A4, and medication influencing CYP 3A4 activity can influence plasma levels of fentanyl.[23] The transdermal fentanyl patch reduces the first pass effect, and increases bioavailability to around 90%. However, large variations in plasma level have been measured in different patients, and it has been shown that patients at a higher age absorb less fentanyl when compared to patients at a lower age.[24]

The possible unpredictable opioid plasma levels could be a reason to be more careful with opioid therapy in an aged population. Our model shows that an aged population is less likely to benefit from opioids in general.

4.1.2 Anxiety and Depression

Anxiety and depression, as measured with the HADS questionnaire have previously been associated with chronic pain. In chronic pain a higher HADS score has been reported to decrease effectiveness of non-pharmacological pain therapy.[25,26] Despite previously reported association between HADS and pain therapy success in chronic pain patients we were not able to confirm this with our data.

4.1.3 Surgery, chemotherapy and radiotherapy

We included previous surgery, chemotherapy and radiotherapy treatment in our analyses as this might affect pain in several ways. It can be argued that surgery, chemotherapy and radiotherapy might be beneficial to pain treatment, as these therapies might help to reduce or remove the cancer and thus the accompanying pain. However, as these treatments can also cause pain they might also worsen the pain. In our patient population we noted no association between surgery, radiotherapy or chemotherapy and opioid treatment response. Although surgery seems to be associated to opioid treatment success (with a RR of 0.33 it seems to be associated with a lower success rate), this association was not noticed in the multivariate analysis.

4.1.4 Pain type

The European Federation of Neurological Societies (EFNS) guidelines mention opioids as a second or third line therapy for neuropathic pain. [27] Also guidelines for cancer related pain do advice the use of gabapentinoids, tricyclic antidepressants or Selective Serotonin and Noradrenalin Reuptake Inhibitors (SNRI) for neuropathic pain.[28] An important reason for being prudent with opioids in a population with neuropathic pain is the side effect profile and the dependence-producing nature of opioids. Finnerup has shown that opioids do provide good pain relief in a patient population with neuropathic pain, with a number needed to treat (NNT) of 4.3 to provide 1 patient with 50% pain relief. The maximum effectiveness was noticed at doses of 180 mg morphine or equivalent.[29] This dose and number needed to treat is higher compared to opioids given for acute postoperative pain, which can be classified as nociceptive pain. In the latter patient population Moore calculated that oxycodone 10 mg has a NNT of 1.8 or 2.7, depending on the accompanying dose of paracetamol (650mg and 1000 mg respectively). There is no reliable NNT for oxycodone alone.[30] Because the NNT is lower in the nociceptive patient population, combined with a much lower dose we expected that neuropathic pain would have a negative impact on pain therapy success. We were surprised to notice that in our patient population neuropathic pain was associated with a higher chance of opioid therapy success. A possible explanation is the fact that we used methadone, which could have effect on neuropathic pain through the NMDA receptor antagonist qualities of methadone.[31] A recent study evaluating factors associated with effectiveness of tapentadol showed more effectiveness of tapentadol in a population with a description of a neuropathic pain component. It was hypothesized that this could be due to the noradrenaline reuptake inhibitor capabilities of tapentadol.[32] It could also be hypothesized that neuropathic pain responds better to opioids than we always assumed.

4.1.5 Baseline pain

The univariate analysis showed that a high baseline pain is associated with a higher treatment success, but this was not noticed in the multivariate analysis. We did not expect that the initial pain score would be correlated with opioid treatment success, because we scored success as 50% pain reduction. Patients were not treated differently if they had higher pain scores as compared to patients with lower pain scores. Therefore it would be unlikely that baseline pain would be associated with opioid therapy success.

4.1.6 Pain duration

Longer duration of pain is associated with reduced treatment success in pain syndromes such

as shoulder and neck pain, radicular pain and coccygodynia,[33-35] but was not associated with therapy success in other pain syndromes.[36, 37] As there might be an association between opioid therapy success and duration of pain we included this in our study. Our results show that with pain caused by cancer in the pharyngeal region no association between pain duration and opioid therapy success is noted. A possible explanation is the completely different pain mechanism involved in our population as compared to the studies mentioned above. Furthermore, it is important to note that the average duration of pain in our patient population is much shorter as compared to those studies showing an association between duration of pain and lack of treatment success.[33-35]

4.1.7 Methadone or Fentanyl

As the original studies [1,2] compared methadone to fentanyl in neuropathic and nociceptive pain in patients with head and neck cancer, we included these medications in our analyses. In the neuropathic pain population methadone proved to be superior to fentanyl on short term pain treatment.[1] In the nociceptive pain population methadone was not inferior to fentanyl.[2] Because these results showed that over-all methadone seems to have a higher success rate we included these predictors in our analyses. Overall methadone is associated with a better short term treatment success. Therefore, methadone is a good treatment for cancer pain, as long as the clinician is familiar with methadone and has knowledge of its complex pharmacokinetics.

The additional effect of methadone on the N-methyl-D-Aspartate (NMDA) receptor [31, 38] is most likely the underlying mechanism which explains the better response of cancer pain patients with a neuropathic pain component to methadone. The NMDA receptor is involved in different pain conditions such as neuropathic pain, pain due to inflammation, ischemic pain and allodynia.[39-42] Additional blockade of the NMDA receptor by methadone, combined with its opioid qualities can therefore result in further pain reduction and in particular in those pain states associated with central sensitization and NMDA receptor opening such as neuropathic pain and massive nociception.

4.2 Long term

The results led us to conclude that the association between patient characteristics and opioid treatment response only exists in the first week (short-term), and not at five weeks (long-term). In this context it is important to note that our patient population decreased due to loss to follow up. Although the loss to follow up is well accounted for it does reduce the strength of the data. This reduction cannot be compensated completely with imputation methods and might explain the loss of an association at five weeks.

4.3 Limitations

This study produced a robust prediction model. However, it should, be taken into account that the data are from two specific patient populations: the nociceptive and the neuropathic pain group. This makes it difficult to extrapolate if the prediction model will adequately predict treatment success in other populations. It is important to note that the nociceptive pain population suffered from radiotherapy induced mucositis. This might affect the effect of radiation-therapy and success of pain relief.

Another limitation of this study is that no data were available on how long before study

inclusion the patients underwent surgery, chemotherapy or radiotherapy (except for the patients suffering from radiation induced mucositis). A further specification of current ongoing therapy might then provide better insights into the possibility of (effective) treatment of the underlying disease or not.

4.4 Evaluating factors associated with pain therapy success

Recent data suggest that the presence of liver metastases and breakthrough pain in a mixed patient population were determinants of opioid therapy failure.[10] Differences in patient population and in treatment protocol as used in this study[10] as compared to our study might be important reasons for the contrasting results. Our study focused on therapy success, whereas the aforementioned study[10] evaluated therapy failure. The determinants of both therapy success and therapy failure need to be studied in more detail in order to provide clinicians with relevant data to determine the best possible treatment for the cancer pain patient. Other characteristics, such as genetic variations in the patient population have shown to be associated with opioid therapy success in postoperative pain. However, the OPRM1 gene is only associated with pain therapy success at 24 hours, and this association is no longer significant after 48 hours.[11] The use of a prediction model can be of great help for the clinician. Different prediction models are in use, and help doctors predict the likelihood of correct diagnosis or chance of successful therapy. It is important to note that an area under the curve of 0.82 is a good prediction model for the chance of therapy success. A diagnostic model should have a higher AUC, such as the model predicting the chance of appendicitis in children with an AUC of 0.91.[43] However, in a predictive model for achieving pathologic complete response in patients with breast cancer an AUC of 0.77 is considered good.[44] Although we do have a good prediction model for therapy success, it is necessary to validate this model in another patient population. This model still needs external validation, therefore we did no add a specific normogram. We hope that more studies will focus on characteristics associated with pain therapy success in order to improve our model. Possible characteristics to include in an improved model could be genetics and proteomics.

5. Conclusion

This study shows that age, type of pain (neuropathic pain component vs nociceptive pain), pain treatment (methadone vs fentanyl), and pain duration are important determinants of opioid therapy success in patients with pain due to head-and-neck cancer. Using these determinants in a prediction model results in an effective model, that may be used predict the chance of therapy success, but only after external validation. This model can help the clinician to provide accurate information to the patient, and improve shared decision making in a vulnerable patient population.

1. **Haumann J**, **Geurts JW**, **van Kuijk SM**, et al.: Methadone is superior to fentanyl in treating neuropathic pain in patients with head-and-neck cancer. *Eur J Cancer*. 2016;**65**:121-129.

2. **Haumann J**, **Geurts JW**, **van Kuijk SM**, et al.: Methadone versus Fentanyl in Patients with Radiation-Induced Nociceptive Pain with Head and Neck Cancer: A Randomized Controlled Noninferiority Trial. *Pain Pract.* 2017.

3. **van den Beuken-van Everdingen MH**, **Hochstenbach LM**, **Joosten EA**, et al.: Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage*. 2016;**51**(6):1070-1090 e1079.

4. **Haumann J**, **Joosten EBA**, **Everdingen M**: Pain prevalence in cancer patients: status quo or opportunities for improvement? *Curr Opin Support Palliat Care*. 2017;**11**(2):99-104.

5. **Ventafridda V**, **Saita L**, **Ripamonti C**, et al.: WHO guidelines for the use of analgesics in cancer pain. *Int J Tissue React*. 1985;**7**(1):93-96.

6. **Carlson CL**: Effectiveness of the World Health Organization cancer pain relief guidelines: an integrative review. *J Pain Res.* 2016;**9**:515-534.

7. **Ventafridda V**, **Tamburini M**, **Caraceni A**, et al.: A validation study of the WHO method for cancer pain relief. *Cancer.* 1987;**59**(4):850-856.

8. **Corli O**, **Floriani I**, **Roberto A**, et al.: Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV 'real life' trial on the variability of response to opioids. *Ann Oncol.* 2016;**27**(6):1107-1115.

9. **Brownstein MJ**: A brief history of opiates, opioid peptides, and opioid receptors. *Proc Natl Acad Sci U S A.* 1993;**90**(12):5391-5393.

10. **Corli O**, **Roberto A**, **Bennett MI**, et al.: Non-responsiveness and susceptibility of opioids side effects related to cancer patients' clinical characteristics: a post-hoc analysis. *Pain Pract.* 2017.

11. **Ren ZY**, **Xu XQ**, **Bao YP**, et al.: The impact of genetic variation on sensitivity to opioid analgesics in patients with postoperative pain: a systematic review and meta-analysis. *Pain Physician.* 2015;18(2):131-152.

12. **Bostick GP**, **Kamper SJ**, **Haanstra TM**, et al.: Pain expectations in neuropathic pain: Is it best to be optimistic? *Eur J Pain.* 2017;**21**(4):605-613.

13. **Buuren Sv**: Flexible imputation of missing data. Boca Raton, FL: CRC Press; 2012.

14. **Harrell FE**: *Regression modeling strategies : with applications to linear models, logistic regression, and survival analysis.* New York: Springer; 2001.

15. **Steyerberg EW**, **Moons KG**, **van der Windt DA**, et al.: Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med.* 2013;**10**(2):e1001381.

16. **Steyerberg EW**: *Clinical prediction models : a practical approach to development, validation, and updating.* New York, NY: Springer; 2009.

17. **Likar R**, **Vadlau EM**, **Breschan C**, et al.: Comparable analgesic efficacy of transdermal buprenorphine in patients over and under 65 years of age. *Clin J Pain.* 2008;**24**(6):536-543.

18. **Kaiko RF**: Age and morphine analgesia in cancer patients with postoperative pain. *Clin Pharmacol Ther.* 1980;**28**(6):823-826.

19. **Nasar MA**, **McLeavy MA**, **Knox J**: An open study of sub-lingual buprenorphine in the treatment of chronic pain in the elderly. *Curr Med Res Opin*. 1986;**10**(4):251-255.

20. **Pergolizzi J**, **Boger RH**, **Budd K**, et al.: Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract.* 2008;**8**(4):287-313.

21. **Eap CB**, **Buclin T**, **Baumann P**: Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet.* 2002;**41**(14):1153-1193.

22. **Fredheim OM**, **Moksnes K**, **Borchgrevink PC**, et al.: Clinical pharmacology of methadone for pain. Acta Anaesthesiol Scand. 2008;52(7):879-889.

23. **Feierman DE**, **Lasker JM**: Metabolism of fentanyl, a synthetic opioid analgesic, by human liver microsomes. Role of CYP3A4. *Drug Metab Dispos.* 1996;**24**(9):932-939.

24. **Solassol I**, **Caumette L**, **Bressolle F**, et al.: Inter- and intra-individual variability in transdermal fentanyl absorption in cancer pain patients. *Oncol Rep.* 2005;**14**(4):1029-1036.

25. **Wasan AD**, **Jamison RN**, **Pham L**, et al.: Psychopathology predicts the outcome of medial branch blocks with corticosteroid for chronic axial low back or cervical pain: a prospective cohort study. BMC *Musculoskelet Disord.* 2009;**10**:22.

26. **Bendinger T**, **Plunkett N**, **Poole D**, et al.: Psychological Factors as Outcome Predictors for Spinal Cord Stimulation. *Neuromodulation.* 2015;**18**(6):465-471; discussion 471.

27. **Attal N**, **Cruccu G**, **Baron R**, et al.: EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol.* 2010;**17**(9):1113-e1188.

28. **Piano V**, **Verhagen S**, **Schalkwijk A**, et al.: Treatment for neuropathic pain in patients with cancer: comparative analysis of recommendations in national clinical practice guidelines from European countries. *Pain Pract.* 2014;**14**(1):1-7.

29. **Finnerup NB**, **Attal N**, **Haroutounian S**, et al.: Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015;**14**(2):162-173.

30. **Moore RA**, **Derry S**, **Aldington D**, et al.: Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. *Cochrane Database Syst Rev.* 2015(9):CD008659.

31. **Gorman AL**, **Elliott KJ**, **Inturrisi CE**: The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett.* 1997;**223**(1):5-8.

32. **Reimer M**, **Hullemann P**, **Hukauf M**, et al.: Prediction of response to tapentadol in chronic low back pain. *Eur J Pain.* 2017;21(2):322-333.

33. **Taskaynatan MA**, **Tezel K**, **Yavuz F**, et al.: The effectiveness of transforaminal epidural steroid injection in patients with radicular low back pain due to lumbar disc herniation two years after treatment. *J Back Musculoskelet Rehabil.* 2015;**28**(3):447-451.

34. **Kooijman MK**, **Barten DJ**, **Swinkels IC**, et al.: Pain intensity, neck pain and longer duration of complaints predict poorer outcome in patients with shoulder pain–a systematic review. *BMC Musculoskelet Disord.* 2015;**16**:288.

35. **Puentedura EJ**, **Cleland JA**, **Landers MR**, et al.: Development of a clinical prediction rule to identify patients with neck pain likely to benefit from thrust joint manipulation to the cervical spine. *J Orthop Sports Phys Ther.* 2012;**42**(7):577-592.

36. **De Ridder D**, **Vancamp T**, **Lenders MW**, et al.: Is preoperative pain duration important in spinal cord stimulation? A comparison between tonic and burst stimulation. *Neuromodulation.* 2015;**18**(1):13-17; discussion 17.

37. **Pitsika M**, **Thomas E**, **Shaheen S**, et al.: Does the duration of symptoms influence outcome in patients with sciatica undergoing micro-discectomy and decompressions? *Spine J.* 2016;**16**(4 Suppl):S21-25.

38. **Ebert B**, **Andersen S**, **Krogsgaard-Larsen P**: Ketobemidone, methadone and pethidine are non-competitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. *Neurosci Lett.* 1995;**187**(3):165-168.

39. **Yaksh TL**: Behavioral and autonomic correlates of the tactile evoked allodynia produced by spinal glycine inhibition: effects of modulatory receptor systems and excitatory amino acid antagonists. *Pain.* 1989;**37**(1):111-123.

40. **Sher GD**, **Cartmell SM**, **Gelgor L**, et al.: Role of N-methyl-D-aspartate and opiate receptors in nociception during and after ischaemia in rats. *Pain.* 1992;**49**(2):241-248.

41. **Mao J**, **Price DD**, **Hayes RL**, et al.: Intrathecal treatment with dextrorphan or ketamine potently reduces pain-related behaviors in a rat model of peripheral mononeuropathy. *Brain Res.* 1993;**605**(1):164-168.

42. **Coderre TJ**, **Melzack R**: The contribution of excitatory amino acids to central sensitization and persistent nociception after formalin-induced tissue injury. *J Neurosci.* 1992;**12**(9):3665-3670.

43. **van den Bogaard VA**, **Euser SM**, **van der Ploeg T**, et al.: Diagnosing perforated appendicitis in pediatric patients: a new model. *J Pediatr Surg.* 2016;**51**(3):444-448.

44. **Schipper RJ**, **Moossdorff M**, **Nelemans PJ**, et al.: A model to predict pathologic complete response of axillary lymph nodes to neoadjuvant chemo(immuno)therapy in patients with clinically node-positive breast cancer. *Clin Breast Cancer.* 2014;**14**(5):315-322.

VI

Methadone vs oxycodone for cancer induced bone pain: a double-blind randomized controlled trial

J. Haumann, S.M.J. van Kuijk, J.M. Meerum Terwogt, E.A. Joosten, M.H.J. Van den Beuken – Van Everdingen

Trials (submitted)

Abstract

Background: Over half of the patients with advanced cancer suffer from moderate to severe pain. Cancer Induced Bone Pain is an important cause for pain in patients with advanced disease states. Although CIBP is often referred to as being nociceptive, there is evidence suggesting a neuropathic pain component. In an earlier RCT it was shown that patients with head-and-neck cancer with a neuropathic pain component respond better to methadone as compared to fentanyl. Since neuropathic pain might respond better to methadone we describe a study protocol to study the effect of methadone as compared to oxycodone in patients with CIBP.

Methods: Patients with cancer induced bone pain due to various primary tumors will be assessed. Once they present themselves with pain due to a metastasis and need to start with strong opioids they will be informed about the study and written consent will be obtained. After randomization either oxycodone 2dd 5 mg or methadone 2dd 2.5 mg will be given (double blinded). After 1 and 3 weeks pain will be assessed. The primary outcome will be clinical success defined as 50% pain reduction on the numeric rating scale. Secondary outcome measures will be the change in NRS, side effects, global perceived effect, pain interference, opioid increase ratio and quality of life.

Sample size: We aim to include a total of 266 patients. The patients will be included in the MUMC+, a university hospital in Maastricht, and in the OLVG, a large teaching hospital in Amsterdam.

1. Introduction

Pain remains a major problem in patients with cancer. Over 50% of patients with an advanced disease state suffer from moderate to severe pain.[1] An important cause for pain in cancer patients is cancer induced bone pain (CIBP).[2,3] The most common solid tumors metastasizing to bone originate in the prostate, followed by the lung, kidney and breast.[4] Of patients with breast cancer and bone metastases one third does not suffer from pain. Most patients have multiple metastases, and about one third of the bone metastasis are painful.[5] A study comparing prostate and breast cancer patients revealed ossal metastases in 12% of patients without pain in prostate cancer, and in 71% of patients with breast cancer without pain.[6] From this study it can be concluded that prostate carcinoma metastases are more often painful when compared to breast cancer metastases. Pain caused by intraosseous tumour growth is complex: Ischemic, inflammatory, neuropathic and cancer specific mechanisms play a role in the aetiology of CIBP.

Multiple animal models of CIBP show a neuropathic pain component; anti-neural growth factor significantly reduces pain in a mouse model of osseous prostate carcinoma metastases;[7] changes in the dorsal root comparable to neuropathic pain states have been shown in a rat model of CIBP;[8] gabapentin, known to have effect on neuropathic pain, reduces pain-related behavior in a rat model of CIBP.[9] In humans a recent Randomized Controlled Trial (RCT) including 233 patients did not show additional effect of pregabalin (compared to radiotherapy alone) on CIBP in a population with ossal metastasized cancer (prostate 38%, breast 33%, lung 18%) receiving radiotherapy.[10] Another RCT studying the effects of pregabaline on CIBP was terminated after the interim analysis. A higher sample size was needed to show statistical significant differences. This study favored pregabaline use for CIBP, but no statistical significant differences were found.[11] Nishihara showed that the addition of an antidepressant (imipramine or mirtazapine) to pregabaline resulted in an increased pain reduction in CIBP as compared to treatment with pregabaline alone.[12]

Because there is limited evidence on the effectiveness of neuropathic pain medication in the pharmacological treatment of CIBP in humans, guidelines state that the WHO pain ladder should be used. The WHO pain ladder is an easy to follow and effective algorithm, however pharmacological interventions directed to neuropathic pain are not included.[13] In view of the possibility that a neuropathic component is involved in CIBP the outcome of a recent study could prove important. This study demonstrates superiority of the pain relieving effect of methadone over fentanyl in head-and-neck cancer patients with neuropathic pain.[14] Methadone is a strong opioid but at the same time a significant non-competitive NMDA-receptor, a receptor known to be specifically involved in neuropathic pain.[15,16] The theoretical neuropathic pain component in CIBP and the dual mode of action of methadone makes this drug a good candidate to treat CIBP.

1.1 Hypothesis

We hypothesize that methadone will result in better pain reduction compared to the strong opioid oxycodone in patients with CIBP. This hypothesis is based on the presence of neuropathic pain component in CIBP. Cancer induced pain with a neuropathic pain component has been shown to respond better to methadone as compared to fentanyl. Therefore, the aim of the study is to assess the efficacy of methadone compared to an opioid without NMDA-receptor antagonist qualities on pain intensity reduction in patients with CIBP.

2. Methods

This trial protocol is reported according to the SPIRIT guidelines.[17] It is a double-blind randomized controlled multicenter trial to compare oral methadone to oral oxycodone, and will be performed at the Maastricht University Medical Center+ (MUMC+) in Maastricht, the Netherlands and OLVG in Amsterdam, the Netherlands. Patients will be included if they have CIBP and 1. a pain score of over 4 measured using the 11-point numeric rating scale (NRS), 2. are naïve to strong opioids, and 3. are able to understand and follow the treatment protocol. Patients will be excluded from participation if they: 1. have a contra-indication for oxycodone or methadone (allergy or prolonged QT syndrome with a QTc >460 ms), 2. experience pain caused by pathologic fracture or nerve root compression, 3. have had surgery within the last week, 4. have an indication for surgery to prevent pathological fractures, 5. have had radiotherapy in the last 6 weeks, 6. are unable to comply with the treatment protocol, 7. use irreversible MAO inhibitors, 8. have bronchial asthma, or 9. have myasthenia gravis.

The study will be briefly explained to the patients by the treating physician and the information sheet will be handed out. That same day the patients will be consulted by the clinician-researcher and study design will be explained in more detail. After written informed consent is given the patient will be randomized to receive one of the two treatments. The patient and the treating physician will be blinded to treatment allocation. After randomization, patients will be asked to complete a questionnaire booklet to obtain various baseline patient characteristics. An Electrocardiogram (ECG) will be performed to measure the QTc. Outcome measurements will be collected by questionnaires 1 and 3 weeks after treatment starts. Deviations from the protocol will be documented. In case of patient drop-out due to side effects the treatment protocol will be made available to allow for opioid rotation. The duration of the study is limited to three weeks in order to prevent overlap with a decrease or increase in pain due to (treatment of) the underlying disease.

2.1 Randomization

After signing the informed consent the patients will be randomly allocated to either oxycodone or methadone. Block randomization with random permuted block sizes stratified by center will be used. Randomization will be performed with the web based randomization program TENALEA CTCM.

2.2 Definition of end points and outcome measures

2.2.1 Primary endpoint

The primary endpoint is the percentage of patients experiencing a pain reduction of 50% or more on the average NRS score measured with the Brief Pain Inventory at three weeks after start of treatment.

2.2.2 Secondary endpoints

Secondary endpoints are 1. the change in NRS at one and at three weeks compared to baseline; 2.the differences in occurrence of side effects between the groups; 3. GPE on a seven-point Likert scale; 4. Pain interference; 5. opioid increase ratio (ie dose at three weeks/starting dose); 6. Quality of life.

2.3 Treatment protocol

After inclusion, treatment for pain will be started according to the allocated treatment. In the methadone group treatment will be started with methadone 2.5 mg twice daily. The oxycodone group will start with oxycodone slow release (SR) 5 mg twice daily. According to the guidelines we start at a low dose.[18] Breakthrough pain will be treated with oxycodone immediate release (IR) 5 mg in both groups. Both groups will be treated with movicolon to prevent constipation.[18] After one week pain will be assessed again (earlier if necessary), and opioid treatment can be increased or decreased by 50% if necessary.

2.4 Outcomes and measurements

2.4.1 Baseline Characteristics

At the start of the study baseline characteristics will be collected from the patient's file, or the questionnaire booklet. These will include demographic variables (age, gender, education level, WHO performance status) and disease specific variables (primary tumor site, date of diagnosis, treatment history (operation, chemotherapy, immunotherapy, radiotherapy), current medication and possible opioid side effect symptoms (xerostomia, nausea, vomiting, constipation, somnolence, drowsiness).

2.4.2 Pain intensity and pain interference (Brief Pain Inventory - short form)

The Brief Pain Inventory (BPI)[19, 20] is a patient completed numeric rating scale that assesses the severity of pain and its impact on daily functioning. The BPI includes the four item severity scale (worst pain, least pain, average pain and pain now) and the seven item pain Interference Scale (general activity, mood, walking, relationships, sleep, normal work and enjoyment of life). Each item is scored on a Numeric Rating Scale (NRS) ranging from 0 to 10 anchored at zero for "no pain'" and 10 for "pain as bad as you can imagine" for severity, and "does not interfere" to "completely interferes" for interference. The items of the severity of pain and the seven interference items

will be averaged to form two composite scores, the Pain Severity Index and the Pain Interference Index.

The BPI has a high internal consistency with coefficient alphas that ranged from .78 to .97 in various cancer population samples in different countries.[21-28]

2.4.3 Global perceived effect (Patient Global Impression of Change)

Patient Global Impression of Change (PGIC) reflects a patient's belief about the efficacy of treatment. PGIC is a 7 point scale depicting a patient's rating of overall improvement. Patients rate their change as "very much improved", "much improved", minimally improved", "no change", "minimally worse", "much worse" or "very much worse". Categories of "much improved" and "very much improved" were used as determinants of a clinically important difference.[29]

2.4.4 Depression and anxiety (Hospital Anxiety and Depression Scale)

Depression and anxiety were measured using the Dutch version of the Hospital Anxiety and Depression Scale (HADS).[30] The HADS showed good performance to assess symptom severity of anxiety disorders and depression in somatic, psychiatric and primary care patients, with a sensitivity and specificity of approximately 0.80.[31] Patients are grouped according to their depression and anxiety subscale scores 0-7 non-cases, 8-10 borderline and 11-21 definite.[30]

2.4.5 Quality of Life (EuroQol-5D)

The EuroQol 5D is a standardized measure of health status developed by the EuroQol-5D Group in order to provide a generic measure of health for clinical and economic appraisal.[32] It provides a descriptive profile and a single index value for health status. EQ-5D is designed for self-completion by respondents and is cognitively undemanding, taking only a few minutes to complete. The EuroQol-5D consists of 2 pages- the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The decision of the level results in a 1 digit number expressing the level selected for that dimension. The 5 different digits can be combined in a 5 digit number describing the respondent's health state. The EQ-VAS records the respondent's self-rated health on a vertical, VAS were the endpoint are labelled. This information can be used as a quantitative measure of health outcome as judges by the individual respondents.

2.4.6 Daily Pain and Breakthrough Medication

Patients will be asked to document their "average pain" and all breakthrough medication needed once a day in a pain sheet.

2.4.7 Opioid side effects

Opioid side effects (xerostomia, nausea, vomiting, constipation, somnolence, drowsiness) will be scored on a 11-point NRS.

		T= -1	T=0	T=1	T=2
Demographic variables	(7 items)	X			
ECG		X			
EuroQol-5D	(5 items)		X		X
HADS	(14 items)		X		X
BPI	(7 items)		X	X	X
Side effects	(6 items)		X	X	X
Breakthrough medication	(1 item)			X	X
Global perceived effect	(1 item)			X	X

2.5 Statistics

To facilitate intention-to-treat analysis, missing values will be imputed using an imputation method that is appropriate for the proportion of missing values and the assumptions that can be made for the mechanism of incompleteness.[33] This will be determined after data collection.

In order to compare differences in the primary outcome between the oxycodone and the methadone group the Pearson's Chi square test will be performed. Testing group-differences with secondary outcomes is based on independent samples t-test for pain (NRS and interference), the opioid increase ratio, and the Mann Whitney U test for the GPE.

In case of subjectively determined differences in baseline characteristics, we will use multivariable regression analyses to correct for these differences. Linear and logistic regression will be used depending on the measurement level of the outcome variable.

All analyses will be performed using IBM SPSS or R. Type-I error rate is fixed to 5%.

2.5.1 Sample size calculation

The primary outcome is the proportion of patients reaching 50% pain reduction. In a previous study in patients with cancer-induced neuropathic pain,[14] 44% of patients experienced 50% pain reduction or more with methadone, and 27% of patients experienced 50% pain reduction with fentanyl 1 week after start of treatment. In order to reject the null hypothesis with a power of 0.8 and an alpha of 0.05 we need to include at least 121 patients in each group. In order to correct for a potential loss to follow-up of 10% we will need to include 266 patients (133 in each medication group).

2.5.2 Interim analyses

The assumptions we made to be able to compute the necessary sample size are based on a similar study but in patients with head-and-neck cancer. As a result, the assumptions we made could be too optimistic or too conservative. Therefore, an interim analysis will be performed after the inclusion of 40 patients to estimate the proportion of patients reaching 50% pain reduction or more in each group. These data are then used to evaluate whether the sample size calculation needs adjustment and to examine the feasibility of the study itself.

3. Discussion

This study will be the first to compare the pure opioid antagonist oxycodone with methadone, an opioid with NMDA receptor antagonist capabilities, in the treatment of CIBP. Previous studies have compared different opioids in less well-defined groups of patients with cancer and pain.[34-38] No differences in the effectiveness of different opioids in the treatment of pain in the patient with cancer have been reported, although the side effect profile seems to favor one opioid (transdermal fentanyl) over another opioid (oral morphine).

In a group of patients with cancer pain with a neuropathic pain component, superiority of methadone over fentanyl was documented.[14] Interestingly within the same head and neck cancer-induced pain population methadone was not inferior to fentanyl in patients with nociceptive pain caused by radiation induced mucositis.[39]

Clearly, neuropathic or nociceptive pain need different and specific treatment, and this could be the next step in optimizing pain treatment in patients with cancer. Cancer related pain can have different causes, and for each different cause a different treatment could be optimal. Therefore it is necessary to discriminate between pain types within cancer-induced pain patients and study those different pain types separately. This increases the specificity of the research question, and may therefore lead to more effective pain treatments.

3.1 Mechanisms of pain

Sensory and nociceptive information enters the spinal cord via the dorsal horn. Here starts a complex interplay between various inhibitory and excitatory neurotransmitters and receptors. The excitatory neurotransmitters glutamate and aspartate are involved in the transmission of nociception in the dorsal horn of the spinal cord. There are several receptors for glutamate in the spinal cord and in the brain; ionotropic: the N-methyl-D-aspartate (NMDA) and the alpha-amino-3-hydroxy-5-methyl-4isoxazole-propionic acid (AMPA) receptor, and metabotropic receptors. AMPA receptors are activated by acute stimuli, NMDA receptors can only be activated by continuous (neuropathic pain) and/or very intense stimuli (massive nociception). NMDA receptors show a “wind-up” phenomenon and, by lowering the threshold of the AMPA receptors, central sensitization occurs. The latter results in a more severe and chronic pain.[40]

Opioid receptors have been shown to play a major role in pain transmission and perception. Opioid receptors can be subdivided in four different groups, μ, δ, κ and opiod-receptor-like-1. The most important opioid receptor for pain management is the μ- opioid receptor. Opioid receptors belong to the G protein class receptors. Activation of the μ-opioid receptor results in hyperpolarization of the cell membrane through different mechanisms. This hyperpolarization results in a decreased glutamate release, and affects pain perception through this mechanism.[41]

Oxycodone is a strong opioid that has agonist capabilities on the μ-, δ-, κ-opioid receptors. Recent meta-analyses have shown that oxycodone induced effects on pain do not differ from other opioids like morphine. Furthermore, side effects have been shown to be similar as well.[34] Therefore oxycodone is considered to be an equally good opioid for treatment of cancer induced pain as morphine. With 31.5 % of patients using oxycodone this drug is currently the most prescribed strong opioid in The Netherlands.[42] The widespread use of oxycodone makes it the first line strong opioid of use for many clinicians.

Methadone is a strong opioid agonist which acts on μ-, δ-, κ-opioid receptors. Besides an opioid agonist, non-competitive NMDA-receptor antagonist qualities have been described.[15, 16]

It is likely that methadone modulates the glutamate transmission at the pain gate in the spinal cord where nociceptive afferents pass their signal to the dorsal horn pain neurons via the AMPA and NMDA receptors. Hence methadone may also affect the increased synaptic plasticity at the glutamatergic synapse or central nervous system in the case of neuropathic pain. Because of the pharmacokinetic profile of methadone (described below) it is often not the opioid of first choice. Many small studies and case-reports in patients with cancer describe the successful rotation from different strong opioids to methadone.[43-48] A positive clinical response, better pain control and/or less side effects, is seen in more than 50% of patients after any opioid rotation.[49, 50] However, it seems that rotation to methadone could be more effective: Moryl et al. rotated 13 patients from methadone to another strong opioid (hydromorphone, morphine, fentanyl or levorphanol) for no other reason than study. Twelve of these patients had to be rotated back because of pain increase and dysphoric effects.[51] Cubero et al rotated 50 patients from morphine to methadone for study reasons. The rotation resulted in improvement of analgesia and reduction of side-effects. Most patients (70.8%) preferred methadone to morphine.[52] To our knowledge there are no studies that selected patients with CIBP to be treated with methadone. This group of patients could profit from the NMDA-receptor-antagonist properties of methadone.

3.2 Pharmacodynamics

Methadone is a pharmaceutical agent with a complex pharmacological profile. Due to gene-polymorphisms in the CYP2B6 gene there is a large inter-individual variability in bio-availability between patients (41-90%).[53] The half-life of methadone is relatively long and variable (7-65 hours). This half-life is affected by urine pH and protein binding.[54] The metabolism by CYP 3A4 and 2B6, both enzymes/monooxygenases known to be involved in drug metabolism and synthesis of cholesterol, steroids and other lipids results in numerous drug-drug interactions, which can result in an increased or decreased plasma level of methadone. Finally, methadone can prolong the cardiac QTc-time. This can result in torsades-de-points in patients with a pre-existent prolonged QTc-time, or when combined with other pharmaceuticals that prolong the QTc-time (see contra-indication).[55]

Oxycodone is metabolized by CYP3A4 as well, and to a lesser extent by CYP2D6. Genetic variations and drug-drug interactions resulting in variations in plasma levels are described with oxycodone as well. However, oxycodone half time is much less variable and the bioavailability is high (compared to morphine)[56] This results in a relative straightforward and predictable profile for oxycodone.

The more complex pharmacological profile of methadone makes it a drug that should be used by experienced clinicians only. Nevertheless, the additional pain relieving effect of methadone in neuropathic pain is hypothesized to result in an improved effect on pain scores in a population with CIBP as compared to oxycodone. With the present study design this hypothesis will be tested.

1. **van den Beuken-van Everdingen MH**, **Hochstenbach LM**, **Joosten EA**, **Tjan-Heijnen VC**, **Janssen DJ.** Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage* 2016; **51**(6): 1070-90 e9.

2. **Grond S**, **Zech D**, **Diefenbach C**, **Radbruch L**, **Lehmann KA**. Assessment of cancer pain: a prospective evaluation in 2266 cancer patients referred to a pain service. *Pain* 1996; **64**(1): 107-14.

3. **Banning A**, **Sjogren P**, **Henriksen H**. Pain causes in 200 patients referred to a multidisciplinary cancer pain clinic. *Pain* 1991; **45**(1): 45-8.

4. **Hernandez RK**, **Wade SW**, **Reich A**, **Pirolli M**, **Liede A**, **Lyman GH**. Incidence of bone metastases in patients with solid tumors: analysis of oncology electronic medical records in the United States. *BMC Cancer* 2018; **18**(1): 44.

5. **Front D**, **Schneck SO**, **Frankel A**, **Robinson E**. Bone metastases and bone pain in breast cancer. Are they closely associated? *JAMA* 1979; **242**(16): 1747-8.

6. **Levren G**, **Sadik M**, **Gjertsson P**, **Lomsky M**, **Michanek A**, **Edenbrandt L**. Relation between pain and skeletal metastasis in patients with prostate or breast cancer. *Clin Physiol Funct Imaging* 2011; **31**(3): 193-5.

7. **Halvorson KG**, **Kubota K**, **Sevcik MA**, **et al**. A blocking antibody to nerve growth factor attenuates skeletal pain induced by prostate tumor cells growing in bone. *Cancer Res* 2005; **65**(20): 9426-35.

8. **Schwei MJ**, **Honore P**, **Rogers SD**, **et al**. Neurochemical and cellular reorganization of the spinal cord in a murine model of bone cancer pain. *J Neurosci* 1999; **19**(24): 10886-97.

9. **Donovan-Rodriguez T**, **Dickenson AH**, **Urch CE**. Gabapentin normalizes spinal neuronal responses that correlate with behavior in a rat model of cancer-induced bone pain. *Anesthesiology* 2005; **102**(1): 132-40.

10. **Fallon M**, **Hoskin PJ**, **Colvin LA**, **et al**. Randomized Double-Blind Trial of Pregabalin Versus Placebo in Conjunction With Palliative Radiotherapy for Cancer-Induced Bone Pain. *J Clin Oncol* 2016; **34**(6): 550-6.

11. **Sjolund KF**, **Yang R**, **Lee KH**, **Resnick M**. Randomized study of pregabalin in patients with cancer-induced bone pain. *Pain Ther* 2013; **2**(1): 37-48.

12. **Nishihara M**, **Arai YC**, **Yamamoto Y**, **et al**. Combinations of low-dose antidepressants and low-dose pregabalin as useful adjuvants to opioids for intractable, painful bone metastases. *Pain Physician* 2013; **16**(5): E547-52.

13. **Carlson CL**. Effectiveness of the World Health Organization cancer pain relief guidelines: an integrative review. *J Pain Res* 2016; **9**: 515-34.

14. **Haumann J**, **Geurts JW**, **van Kuijk SM**, **Kremer B**, **Joosten EA**, **van den Beuken-van Everdingen MH**. Methadone is superior to fentanyl in treating neuropathic pain in patients with head-and-neck cancer. *Eur J Cancer* 2016; **65**: 121-9.

15. **Ebert B**, **Andersen S**, **Krogsgaard-Larsen P**. Ketobemidone, methadone and pethidine are non-competitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. *Neurosci Lett* 1995; 187(3): 165-8.

16. **Gorman AL**, **Elliott K**, **Inturrisi CE**. The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett* 1997; **223**(1): 5-8.

17. **Chan AW**, **Tetzlaff JM**, **Altman DG**, **et al**. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013; **158**(3): 200-7.

18. **Caraceni A**, **Hanks G**, **Kaasa S**, **et al**. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol* 2012; **13**(2): e58-68.

19. **Daut RL**, **Cleeland CS**, **Flanery RC**. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain* 1983; **17**(2): 197-210.

20. **Cleeland CS**, **Ryan KM**. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994; **23**(2): 129-38.

21. **Caraceni A**, **Mendoza TR**, **Mencaglia E**, **et al**. A validation study of an Italian version of the Brief Pain Inventory (Breve Questionario per la Valutazione del Dolore). *Pain* 1996; **65**(1): 87-92.

22. **Serlin RC**, **Mendoza TR**, **Nakamura Y**, **Edwards KR**, **Cleeland CS**. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain* 1995; **61**(2): 277-84.

23. **Ger LP**, **Ho ST**, **Sun WZ**, **Wang MS**, **Cleeland CS**. Validation of the Brief Pain Inventory in a Taiwanese population. *J Pain Symptom Manage* 1999; 18(5): 316-22.

24. **Wang XS**, **Mendoza TR**, **Gao SZ**, **Cleeland CS**. The Chinese version of the Brief Pain Inventory (BPI-C): its development and use in a study of cancer pain. *Pain* 1996; **67**(2-3): 407-16.

25. **Uki J**, **Mendoza T**, **Cleeland CS**, **Nakamura Y**, **Takeda F**. A brief cancer pain assessment tool in Japanese: the utility of the Japanese Brief Pain Inventory–BPI-J. *J Pain Symptom Manage* 1998; **16**(6): 364-73.

26. **Radbruch L**, **Loick G**, **Kiencke P**, **et al**. Validation of the German version of the Brief Pain Inventory. *J Pain Symptom Manage* 1999; **18**(3): 180-7.

27. **Saxena A**, **Mendoza T**, **Cleeland CS**. The assessment of cancer pain in north India: the validation of the Hindi Brief Pain Inventory–BPI-H. *J Pain Symptom Manage* 1999; **17**(1): 27-41.

28. **Mystakidou K**, **Mendoza T**, **Tsilika E**, **et al**. Greek brief pain inventory: validation and utility in cancer pain. Oncology 2001; **60**(1): 35-42.

29. **Farrar JT**, **Young JP**, Jr., **LaMoreaux L**, **Werth JL**, **Poole RM**. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; **94**(2): 149-58.

30. **Zigmond AS**, **Snaith RP**. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**(6): 361-70.

31. **Bjelland I**, **Dahl AA**, **Haug TT**, **Neckelmann D**. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; **52**(2): 69-77.

32. **EuroQol G**. EuroQol–a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**(3): 199-208.

33. **Buuren Sv**. Flexible imputation of missing data. Boca Raton, FL: CRC Press; 2012.

34. **Schmidt-Hansen M, Bennett MI, Arnold S, Bromham N, Hilgart JS**. Oxycodone for cancer-related pain. *Cochrane Database Syst Rev* 2017; **8**: CD003870.

35. **Schmidt-Hansen M, Bromham N, Taubert M, Arnold S, Hilgart JS**. Buprenorphine for treating cancer pain. *The Cochrane database of systematic reviews* 2015; 3: CD009596.

36. **Nicholson AB, Watson GR, Derry S, Wiffen PJ**. Methadone for cancer pain. *Cochrane Database Syst Rev* 2017; **2**: CD003971.

37. **Wang DD, Ma TT, Zhu HD, Peng CB**. Transdermal fentanyl for cancer pain: Trial sequential analysis of 3406 patients from 35 randomized controlled trials. *J Cancer Res Ther* 2018; **14**(Supplement): S14-S21.

38. **Bao YJ**, **Hou W**, **Kong XY, et al**. Hydromorphone for cancer pain. *Cochrane Database Syst Rev* 2016; **10**: CD011108.

39. **Haumann J**, **van Kuijk SMJ**, **Geurts JW**, **et al**. Methadone versus Fentanyl in Patients with Radiation-Induced Nociceptive Pain with Head and Neck Cancer: A Randomized Controlled Noninferiority Trial. *Pain Pract* 2017.

40. **Basbaum AI**, **Bautista DM**, **Scherrer G**, **Julius D**. Cellular and molecular mechanisms of pain. *Cell* 2009; **139**(2): 267-84.

41. **Al-Hasani R**, **Bruchas MR**. Molecular mechanisms of opioid receptor-dependent signaling and behavior. *Anesthesiology* 2011; **115**(6): 1363-81.

42. **Weesie Y**, **Dijk L. van**, **Nielen M**, **Flinterman L**, **Hek K**. Voorschrijven van opioïden in de huisartsenpraktijk. *NIVEL* 2016.

43. **Ripamonti C**, **Bianchi M**. The use of methadone for cancer pain. *Hematol Oncol Clin North Am* 2002; **16**(3): 543-55.

44. **Moryl N**, **Kogan M**, **Comfort C**, **Obbens E**. Methadone in the treatment of pain and terminal delirum in advanced cancer patients. *Palliat Support Care* 2005; **3**(4): 311-7.

45. **Mercadante S**. Opioid rotation for cancer pain: rationale and clinical aspects. *Cancer* 1999; **86**(9): 1856-66.

46. **Manfredi PL**, **Borsook D**, **Chandler SW**, **Payne R**. Intravenous methadone for cancer pain unrelieved by morphine and hydromorphone: clinical observations. *Pain* 1997; **70**(1): 99-101.

47. **Benitez-Rosario MA**, **Salinas-Martin A**, **Aguirre-Jaime A**, **Perez-Mendez L**, **Feria M**. Morphine-methadone opioid rotation in cancer patients: analysis of dose ratio predicting factors. *J Pain Symptom Manage* 2009; **37**(6): 1061-8.

48. **Lawlor PG**, **Turner KS**, **Hanson J**, **Bruera ED**. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. *Cancer* 1998; **82**(6): 1167-73.

49. **Quigley C**. Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev* 2004; (3): CD004847.

50. **Mercadante S**, **Bruera E**. Opioid switching: a systematic and critical review. *Cancer Treat Rev* 2006; **32**(4): 304-15.

51. **Moryl N**, **Santiago-Palma J**, **Kornick C**, **et al**. Pitfalls of opioid rotation: substituting another opioid for methadone in patients with cancer pain. *Pain* 2002; **96**(3): 325-8.

52. **Cubero DI**, **del Giglio A**. Early switching from morphine to methadone is not improved by acetaminophen in the analgesia of oncologic patients: a prospective, randomized, double-blind, placebo-controlled study. *Support Care Cancer* 2010; **18**(2): 235-42.

53. **Kharasch ED**, **Regina KJ**, **Blood J**, **Friedel C**. Methadone Pharmacogenetics: CYP2B6 Polymorphisms Determine Plasma Concentrations, Clearance, and Metabolism. *Anesthesiology* 2015; **123**(5): 1142-53.

54. **Fredheim OM**, **Moksnes K**, **Borchgrevink PC**, **Kaasa S**, **Dale O**. Clinical pharmacology of methadone for pain. *Acta Anaesthesiol Scand* 2008; **52**(7): 879-89.

55. **van den Beuken-van Everdingen MH**, **Geurts JW**, **Patijn J**. Prolonged QT interval by methadone: relevance for daily practice? A prospective study in patients with cancer and noncancer pain. *J Opioid Manag* 2013; **9**(4): 263-7.

56. **Soderberg Lofdal KC**, **Andersson ML**, **Gustafsson LL**. Cytochrome P450-mediated changes in oxycodone pharmacokinetics/pharmacodynamics and their clinical implications. *Drugs* 2013; **73**(6): 533-43.

VI

I

Summary

Cancer is currently the leading cause of morbidity and mortality worldwide, and the prevalence of cancer is expected to increase in the near future.[1] This increase is caused by the aging of the population, combined with better therapies for cancer and thus longer average survival. The prevalence of pain in cancer patients is high, and has not declined over the last decade as compared to the 4 decades before[2,3] (Chapter 2). In Chapter 2, mechanisms are explored that could help explain the lack of improvement in pain prevalence caused by cancer or cancer treatment.

Important barriers in the treatment of cancer related pain are both patient related (e.g. fear of substance abuse)[2] and physician related (e.g. lack of knowledge or monitoring).[3] Another factor for the lack of improvement could be an increase in comorbidity, due to advanced age of many of the patients. Physicians could reduce the prevalence of pain in patients with cancer by better monitoring the presence of pain, and keeping their knowledge up to date.

It has been shown that pain is an important cause of distress in patients suffering from cancer, and up to 33% of patients suffering from cancer express their pain as being intolerable.[4-6] The combination of high prevalence of pain and the impact it has on quality of life shows that pain is important to address when treating a patient with cancer. Furthermore, it shows that we should strive to optimally treat pain in patients with cancer. In order to optimally treat the patient suffering from pain and cancer it is important to understand the type of pain involved (Chapter 1, page 8). Because the term cancer pain itself does not discriminate between nociceptive or neuropathic pain an optimal treatment is not possible. Research has shown that these two types of pain need different pharmacological treatment algorithms,[7,8] and therefore discrimination in either nociceptive or neuropathic pain will likely result in a better pharmaceutical treatment of the cancer pain patient (Chapter 2, page 18). It needs no further comment that guided pharmaceutical treatment based on the type of pain provides optimal care for all patients with cancer and this will reduce the prevalence of pain in patients with cancer.

The pharmacological treatment of pure neuropathic pain is focused on pharmaceuticals such as tricyclic antidepressants, gabapentinoids and selective serotonin- or noradrenaline reuptake inhibitors (SSRI/SNRI). Another important mechanism in neuropathic pain is central sensitization where the NMDA receptor is involved (Chapter 1 page 8).[9,10] Methadone is an interesting drug as it has affinity with the mu-opioid receptor as well as the NMDA receptor.[11,12] The affinity for these two receptors makes methadone a potential pharmaceutical in the treatment of nociceptive and neuropathic pain. Methadone has proven to be effective in neuropathic pain states such as post-herpetic neuralgia.[13] Despite the theoretical advantages of an opioid with NMDA receptor affinity the advantage of methadone over other opioids has never been examined in cancer related pain with a neuropathic pain component. In view of guided pharmaceutical treatment based on the type of pain, nociceptive and neuropathic pain, and the dual binding capacity of methadone we studied the pain relieving effect of this drug as compared to an opioid in cancer patients in 2 randomized controlled trials (RCT's).

Chapter 3 presents the first RCT on the pain relieving effect of methadone versus fentanyl in patients with neuropathic pain caused by tumor growth in the head-neck region. A total of 52 patients were included in the study, of whom 26 were treated with fentanyl and 26 were treated with methadone. The reduction in the average score on an 11-point numeric rating scale for pain (NRS), clinical success (defined as at least 50% reduction in average pain), and reduction in pain interference were the primary outcome measures. The effect of methadone compared to fentanyl was evaluated at one, three and five weeks after treatment started. As hypothesized,

methadone was more effective compared to fentanyl in cancer patients with neuropathic pain at one and three weeks. Although a difference in pain relief was noted at five weeks, this was no longer statistically significant. An important limitation of the study in Chapter 3 was the loss to follow up, which was well accounted for (e.g. death due to natural progression of disease, patient being pain free, patient needs surgery for progression). This loss to follow up caused a decrease of statistical power which eventually may underlie the lack of a statistical significance in the difference between pain relieving effect of methadone and fentanyl in this population at five weeks.

The superior effect of methadone on pain in patients with a neuropathic pain component was expected due to the role of the NMDA receptor in neuropathic pain. Neuropathic pain is characterized by central sensitization in which the NMDA receptor plays a pivotal role. With nociceptive pain the role of the NMDA receptor is less pronounced and targeting these receptors is not expected to have a significant effect.[14] Because the type of pain is often not well described in cancer patients, the increased effectiveness of methadone in neuropathic pain states could lead to an increase in prescription of methadone in nociceptive pain states as well. Therefore it is of utmost importance to know if methadone will result in an inferior pain relieving effect in a population with nociceptive pain as described in Chapter 4.

A randomized controlled non-inferiority trial comparing methadone to fentanyl was performed as described in Chapter 4. In a sample of patients with nociceptive pain caused by radiation induced mucositis which was caused by radiation for head-and-neck cancer the effect of methadone versus fentanyl was tested (see also RQ4). A total of 82 (strong) opioid-naïve patients were included in the study. Forty patients were treated with fentanyl, and forty-two patients were treated with methadone. NRS, pain interference, global perceived effect, side effects and opioid escalation index were measured at one, three and five weeks after the start of medication. The results of this study demonstrate non-inferiority of methadone as compared to fentanyl in cancer patients with nociceptive pain at one and three weeks. At five weeks the results were inconclusive, again likely due to a high rate of loss to follow up and decreased statistical power .

The data from the two randomized controlled trials as reported in Chapter 3 and 4 showed that some patients responded very well to methadone and fentanyl, while other patients needed incremental doses of medication without reporting a beneficial effect on pain. The observation that the response to opioids differed between patients led us to address the question if we could identify patients that were more or less likely to experience pain reduction. We explored the association between patient, pain and treatment characteristics to develop a tool that could assist in predicting a patient's probability of pain reduction in Chapter 5.

Chapter 5 describes the development of a prediction model that can be used to estimate a patient's probability of clinical success as defined by a 50% reduction in NRS compared to baseline pain is described. The prediction model was developed on the data generated by the two RCT's combined (see Chapters 3 and 4). Predictors that were entered into our prediction model were:

1. Neuropathic pain (compared to nociceptive pain)
2. Age
3. The use of methadone (compared to fentanyl)
4. Duration of pain before opioid treatment started (in months)

Implementation of these predictors in our model allowed to discriminate between patients

with and without clinical success with an area under the curve of 81.6%. This indicated that the model has good ability to separate those patients with a high probability of pain relief after treatment from those patients with a low probability of pain relief. An important limitation of this prediction model is the fact that it is based on a relatively small sample on the one hand as well as the use of a specific patient population on the other. Further research should be aimed to (externally) validate our prediction model. For this validation it will be necessary to use data from other patient populations.

The RCT's described in chapter three and four were based on cancer induced pain patients with either neuropathic pain (Chapter 3) or with pain due to radiation induced mucositis (nociceptive pain) in head-and-neck cancer (Chapter 4). In order to further extend and investigate our findings based on the selection and subtyping of cancer pain patients we intend to study the effect of methadone in cancer patients often suffering from bone pain. Although this cancer induced bone pain (CIBP) seems nociceptive (it is pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors[15]), there is ample evidence implicating a neuropathic pain component.[16,17] Therefore, methadone could have an additional effect as compared to a pure opioid in the patient with CIBP .

Hence in Chapter 6 a study protocol is described to evaluate the effect of an opioid with additional NMDA receptor antagonist capacities (methadone) compared to a pure opioid (oxycodone). The CIBP patients recruited for this study will be opioid naïve and with painful osseous metastasis of different tumors. Besides the fact that this study is aimed to increase efficacy of pain treatment in CIPB patients the data can also be used for the external validation of our prediction model (Chapter 5).

1. World Cancer Report. Geneva, Switzerland: World Health Organization Press; 2014.

2. **Gunnarsdottir S**, **Sigurdardottir V**, **Kloke M**, **et al**. A multicenter study of attitudinal barriers to cancer pain management. *Support Care Cancer* 2017; **25**(11): 3595-602.

3. **Kwon JH**. Overcoming barriers in cancer pain management. *J Clin Oncol* 2014; **32**(16): 1727-33.

4. **Kroenke K**, **Theobald D**, **Wu J**, **Loza JK**, **Carpenter JS**, **Tu W**. The association of depression and pain with health-related quality of life, disability, and health care use in cancer patients. *J Pain Symptom Manage* 2010; **40**(3): 327-41.

5. **Breivik H**, **Cherny N**, **Collett B**, **et al**. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. *Ann Oncol* 2009; **20**(8): 1420-33.

6. **Porter LS**, **Keefe FJ**. Psychosocial issues in cancer pain. *Curr Pain Headache Rep* 2011; **15**(4): 263-70.

7. **Piano V**, **Verhagen S**, **Schalkwijk A**, **et al**. Treatment for neuropathic pain in patients with cancer: comparative analysis of recommendations in national clinical practice guidelines from European countries. *Pain Pract* 2014; **14**(1): 1-7.

8. **Attal N**, **Cruccu G**, **Baron R**, **et al**. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; **17**(9): 1113-e88.

9. **Schwartzman RJ**, **Alexander GM**, **Grothusen JR**, **Paylor T**, **Reichenberger E**, **Perreault M**. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain* 2009; **147**(1-3): 107-15.

10. **Eichenberger U**, **Neff F**, **Sveticic G**, **et al**. Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg* 2008; **106**(4): 1265-73, table of contents.

11. **Gorman AL**, **Elliott KJ**, **Inturrisi CE**. The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett* 1997; **223**(1): 5-8.

12. **Ebert B**, **Andersen S**, **Krogsgaard-Larsen P**. Ketobemidone, methadone and pethidine are non-competitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. *Neurosci Lett* 1995; **187**(3): 165-8.

13. **Teixeira MJ**, **Okada M**, **Moscoso AS**, **et al**. Methadone in post-herpetic neuralgia: A pilot proof-of-concept study. *Clinics (Sao Paulo)* 2013; **68**(7): 1057-60.

14. **Petrenko AB**, **Yamakura T**, **Baba H**, **Shimoji K**. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg* 2003; **97**(4): 1108-16.

15. definition pain iasp. https://www.iasp-pain.org/education/content.aspx?ItemNumber=1698#Pain.

16. **Sjolund KF**, **Yang R**, **Lee KH**, **Resnick M**. Randomized study of pregabalin in patients with cancer-induced bone pain. *Pain Ther* 2013; **2**(1): 37-48.

17. **Laird BJ**, **Walley J**, **Murray GD**, **Clausen E**, **Colvin LA**, **Fallon MT**. Characterization of cancer-induced bone pain: an exploratory study. *Support Care Cancer* 2011; **19**(9): 1393-401.

III

General discussion

1. Aims and Research Questions

The aims of this thesis are: 1. To understand why the prevalence of pain in cancer patients has not reduced over the last decade as compared to the decades before. 2. To examine if it is possible to improve the treatment of pain in patients with cancer by discriminating between neuropathic and nociceptive pain. Based on the involvement of central sensitization and the role of the NMDA receptor in neuropathic pain methadone, with its dual mechanism of action both directed at the mu-opioid receptor as well as at the NMDA receptor, is tested for effect on pain relief and compared to presently commonly used opioids. The following research questions were formulated (see Introduction Chapter 1 pages 10):

- RQ1 Why is the prevalence of pain in cancer patients not reduced in the decade 2005-2014 as compared to the decades 1966-2005?
- RQ2 Is methadone superior to fentanyl in head-and-neck-cancer patients with neuropathic pain?
- RQ3 Is methadone superior/inferior to fentanyl in head-and-neck-cancer patients with nociceptive pain?
- RQ4 Can we predict which patient will benefit from opioid therapy?

When addressing RQ 1 it is important to realize that under-treatment of pain remains a major problem in patients with cancer.[1] A cause for this under-treatment could be the fact that pain is not monitored accurately in patients with cancer.[2] Once pain is correctly monitored and diagnosed it is necessary to start the most appropriate therapy for the pain. It seems that often cancer pain is not sub-diagnosed based on types of pain: nociceptive or neuropathic pain, and thus cancer pain is not treated optimal.[3] Furthermore a patient with cancer might suffer from many complaints, pain only being one of them. Optimal care for a patient with cancer comprises correctly monitoring all the complaints a patient can suffer from, including pain. It is possible that pain is sometimes overlooked by the treating physician, but if the treating physician cannot make time for monitoring pain, help should be asked in order to correctly monitor and treat pain.

In order to improve and optimize pain treatment it is necessary to understand the mechanism of action of the pharmacological agents used. In this context methadone was chosen as it is known to have a dual mode of action; it has a combined affinity for both the opioid receptors and the NMDA receptor.[4,5] The NMDA receptor is one of the three families of glutamate receptors, next to the AMPA and kainate receptor. The NMDA receptors play an essential role in brain plasticity, and seem to be essential in the creation of long-term synaptic structures that are essential for higher cognitive functions, but also with synaptic plasticity of the nociceptive system in the spinal cord. This opening of the spinal pain gate includes the process of central sensitization in which the NMDA receptor is pivotal.[6] The NMDA receptors are formed by the combination of several subunits. To date a total of seven subunits have been identified, which are grouped in three subfamilies (GluN1, GluN2 and GluN3). The NMDA receptor is a hetero-tetramer, usually formed by the combination of GluN1 and GluN2 subunits or a combination of GluN2 and GluN3 subunits.[7] Slight differences in subunit composition allow for a variety of NMDA receptor subtypes with slightly different characteristics. Although there are slight differences within the NMDA receptor family they show properties that distinguish them from other ionotropic receptors. Activation of the NMDA receptors necessitate a co-agonist such as D-serine or glycine next to

glutamate.[8] Once activated the NMDA receptor shows relative slow kinetics due to slow glutamate unbinding.[9] Furthermore, NMDA receptors have many modulatory sites in the extracellular environment. This makes the receptors sensitive to the extracellular environment, and therefore it can be modified relatively easily for instance by the opioid methadone.[10]

The effectiveness of methadone on pain relief has previously been compared to other opioids in cancer related pain patients. The first study comparing methadone with morphine in patients with cancer induced pain was published in 1967 by Beaver.[11] Since then more studies have been published on the pain relieving effect of methadone as compared to other opioids in patients with cancer induced pain.[12-15] The most recent systematic review (published in 2017) included six studies with a total of 388 participants.[16] The conclusion from their meta-analysis was that there is no significant difference between effectiveness in pain relief between methadone and other opioids in patients with cancer. The fact that no difference between methadone and other opioids was observed, might be related to the fact that no discrimination was made between types of pain. As neuropathic pain is characterized by central sensitization and the involvement of the NMDA receptor, a drug like methadone might specifically target the pain in this subpopulation. This was then formulated in our hypothesis (see Introduction Chapter 1 pages 9-10).

The efficacy of modulating the NMDA receptor in the treatment of chronic pain has been shown extensively in different animal models of inflammatory pain, neuropathic pain, ischemic pain and allodynia.[17-22] The pain relieving effects of NMDA receptor antagonists, such as ketamine and memantine have been documented in human settings of neuropathic pain.[23-26] Aiyer et al. performed a systematic review on the effect of different effects of several NMDA-receptor antagonists and their effects on different neuropathic pain states.[27] This review shows that of the 58 studies performed with eight different NMDA-receptor antagonists 39 of them show clinical effect of NMDA-receptor antagonists on different neuropathic pain states. The superiority of an opioid with NMDA receptor antagonist abilities could be implied from many case reports and case series describing successful rotation from other opioids to methadone. At the same time Moryl has shown that rotation from methadone to another opioid is less likely to result in pain relief, in fact, 12 out of 13 patients required a switch back to methadone.[28]

Based on our hypothesis that methadone will result in superior pain relief in patients with pain in which the NMDA receptor is involved such as neuropathic pain, we formulated RQ2 and RQ3 and performed two RCT's as presented in Chapters 3 and 4.

These RCT's are the first to compare an opioid with NMDA receptor antagonist abilities (i.e. methadone) with a pure opioid in a cancer pain population subdivided by type of pain: neuropathic pain (Chapter 3) and nociceptive pain (Chapter 4). By specifying the pain type the RCT's showed that an opioid with NMDA receptor antagonist abilities (i.e. methadone) results in better pain relief as compared to a pure opioid (i.e. fentanyl) in patients with cancer and neuropathic pain. At the same time the data show that methadone is not inferior to fentanyl in a patient population experiencing nociceptive pain (Chapter 4).

2. Limitations

Despite the fact that superiority of methadone over fentanyl was observed in patients with neuropathic pain (Chapter 3) and no inferiority of methadone versus fentanyl in nociceptive pain patients (Chapter 4) some limitations of these RCT need to be discussed.

The most important limitation of the two RCT's (Chapters 3 and 4) was the loss to follow up

that increased considerably over the 5 week follow-up period. Although almost all of the loss to follow up can be explained by reasons such as inter-current disease or success of therapy, the loss to follow up introduced uncertainty in the analysis. The loss to follow up was corrected for using imputation methods. The use of imputation methods provides more precision as all subjects will be included in the analysis, and is less prone to yield biased coefficients when compared to complete case analysis.[29] Although the use of imputation methods increases the reliability of the data, it is not as good as having no missing data at all.[29] Further limitations of our RCT- studies in Chapters 3 and 4 are related to the specificity of the head-and neck cancer patient population. Nevertheless, despite these limitations the results based on these two RCT's are robust and will likely improve the pharmacological treatment of pain in patients with cancer.

Measurement of Pain

A general problem in studies addressing pain is that the measurement of pain remains difficult. In this thesis we used the Brief Pain Inventory for pain interference. For measuring pain intensity we used the 11-point Numeric Rating Scale, or NRS, which is the preferred measurement tool for pain.[30] Many studies measuring pain and pain relief only report NRS scores of patient groups, and do not report global perceived effect (GPE) or percentage of patients achieving a predefined clinical significant reduction of pain. In order to optimally study the difference between treatments it is important to not only measure the NRS in both groups, but to perform a responder analysis as well. Many studies only provide average NRS scores from both treatment groups. Pooling data from multiple studies that only use an NRS score, and not clinical success, ignores the percentage of patients achieving clinical meaningful pain relief. This could result in false conclusions. Dichotomizing the results based on clinical relevant pain reduction can show clinical important differences in odds ratios of achieving clinical relevant pain reduction.[31,32] Reporting pain reduction both based on a difference in NRS as well as the percentage of clinical relevant pain reduction may then assist in finding characteristics associated with clinical relevant pain reduction. The statement of the United States Food and Drug Administration (FDA) in their Guidance for Industry on patient reported outcomes states that group averages are not an appropriate measurement for expected individual change.[33] If studies fail to provide percentages of clinical significant effects a systematic review or meta-analyses can only pool the average results, leading to suboptimal conclusions. Therefore researchers should always try to provide data on clinical significant effects for the different study groups.

Another advantage of providing data on clinical significant effects in the study populations is that it can show which (sub)populations may have a higher or lower chance of achieving clinical significant effects. This then may answer our 4th RQ. The assessment of characteristics associated with clinically relevant pain reduction (or lack of pain reduction) can result in more efficient patient management. The ability to predict whether a patient will have better or worse results is very valuable for the patient and the physician as it helps manage expectations. The search for patient characteristics associated with pain intensity or opioid consumption is relatively common in patients with acute post-operative pain. This has resulted in, among other things, the discovery of an association between thermal pain and reduced subcutaneous lidocaine efficacy and red haired women.[34] It is important to realize that further evaluation of associations are important. For instance the before mentioned association between thermal pain and red haired woman could not be reproduced in follow up studies.

Characteristics associated with pain

More recently the association between genotype and opioid consumption has been tested widely. This has shown associations between several genotypes and post-operative opioid consumption. Many studies have focused on several genes coding for different proteins with important roles in opioid effectiveness, such as cytochromes important in opioid pharmacodynamics or the opioid receptor μ1 (OPRM1) gene.[35] Most of the post-operative studies show some association between genetic profile and postoperative morphine consumption up to the first 24 hours. Due to the relative heterogeneous results from the studies[44] this has not resulted into a specific gene focus, let alone patient genotyping to optimize pain treatment. Currently the cost of genetic profiling does not seem to outweigh the possible benefits of personalized pain therapy. The search for genetic profile and optimized personal therapy has started in the cancer population suffering from pain, however, at this date it is still not possible to accurately predict the effects of medication based on genetic profile.[36,37]

The first study to discuss patient characteristics associated with response to opioids in cancer related pain was performed by Corli et al. in 2017[38] This study reported that the presence of liver metastases and breakthrough pain were associated with less response to opioids. This study did not report on the treatment for breakthrough pain, and it remained unclear if the pain was caused by the liver metastasis in these patients.[47] The liver function was not assessed in these patients. It is difficult to find a good explanation why these patient characteristics (liver metastases and breakthrough pain) would be associated with a poor response to opioids. Nevertheless the principle to study if there are characteristics associated with better or poor response to opioids is important in the search for patient characteristics associated with a higher or lower chance of achieving clinical relevant pain relief. Characteristics do not need to be causally related to the outcome, as long as they provide accurate prediction of pain relief. When we are able to predict which pharmaceutical has a high a priori chance of providing clinical relevant pain relief in which patient, optimal treatment for each patient is within our reach. This then allows the patient to experience pain reduction faster and more pronounced, the patient will need less consultation from the physician, and is less likely to experience side effects.

In order to be able to predict the individual probability of achieving clinical significant pain relief a model needs to be developed. The development of a prediction model is complex, but when done correctly this prediction models can assist many physicians. This could potentially result in a significant increase in efficiency and therefore reduce health care cost. In the future other pharmaceuticals such as gabapentinoids and antidepressants can be added to the model. This could lead to a complete overhaul of the WHO pain ladder and possibly simplify the complicated choices for different pain pharmaceuticals. We have provided a first step by developing a model on data of both RCTs, but this model needs external validation before it can be used for decision making purposes.

Barriers

There are different barriers that are known to It has been shown that pain is described properly in only a minority of the patients, and only a fraction of patients with signs of neuropathic pain are treated with pharmaceuticals related to this type of pain.[2,3] After implementation of the guideline these numbers have improved, but are still low.[39] One possible cause of the lack of correct monitoring of pain in general, and neuropathic pain in particular could be due to the lack

of impact on pain therapy. If pharmacological treatment of neuropathic and nociceptive pain would be similar the differentiation between these two types would be of no use. Nevertheless, the RCT described in Chapter 3 demonstrates that patients with a neuropathic pain component benefit more from a pharmaceutical treatment that has effect on the NMDA receptor and the μ-opioid receptor as compared to an opioid alone. The correct monitoring and reporting of type of pain might thus result in a significant decrease in the prevalence of pain in cancer patients.

An important patient related barrier in the use of opioids is fear of opioid addiction. In a recently performed multicenter study evaluating attitudinal barriers in a European patient population suffering from cancer related pain fear of addiction was the most important barrier. It was also shown that patients with higher barrier scores as measured by the barriers questionnaire II were often older Caucasian males. Furthermore, longer opioid use was correlated with a lower barrier score.[40] Methadone is often associated with substance dependence. The use of methadone in other settings than substance abuse could assist in breaking another barrier. Nevertheless, in general it is necessary to correctly inform and educate the patient in order to break this barrier.

Opioid crisis

Closely related to the issue of substance abuse is the present opioid crisis in many western countries.[41] The widespread use of opioids in the general population is a considerable problem in many countries, and has increased in severity over time.[42] The use of the correct opioid in the correct setting is paramount to provide efficient pain relief and may therefore help prevent problematic opioid use. Substance abuse can develop in patients suffering from cancer-related pain as well as in other patients. Research shows that at least 20% of patients with cancer is at risk for opioid use disorder.[43] These patients at risk for opioid use disorder show greater health care utilization, higher morphine-equivalent use and higher symptom burden. Therefore it is important to monitor opioid use and aberrant behavior in these patients. In general it is stated that opioids with a rapid action tend to cause more misuse as compared to opioids with a slow action. In the United States novel synthetic opioids are often used illicitly, and are the cause for many opioid related deaths. These non-prescribed opioids are highly potent, and therefore cause overdose easily.[44] Based on case reports one could conclude that transmucosal fentanyl for breakthrough pain could cause substance abuse.[45] However, research has shown that aberrant behavior in opioid use is comparable in a group with transmucosal fentanyl as compared to short acting opioids.[46]

Substance abuse is associated with opioid dose escalation in chronic pain.[47] Furthermore, higher doses of opioids postoperatively are associated with a higher chance of prolonged opioid use after shoulder arthroscopies.[48] Both dose escalation and use of higher doses of opioids postoperatively may further increase opioid abuse and then add to the opioid crisis. In this light it is important to note that those patients using methadone for pain relief showed a lower opioid escalation index as compared to the patients using fentanyl (Chapter 4). This suggests that methadone is less likely to result in opioid abuse as compared to fentanyl. Nevertheless the latter aspect and relation to opioid abuse and opioid crisis was beyond the scope of the present thesis and the studies presented in Chapters 3 and 4 were not designed to study effects on opioid abuse.

3. Conclusions

Due to the observed increase in cancer prevalence over the last decennia, it is expected that the prevalence of cancer related pain will further increase in the (near) future. An important reason why the prevalence of pain in cancer patients has not been reduced over the last decennia is related to under-treatment, most likely due to a lack of correct monitoring of pain in patients with cancer leading to suboptimal treatment . In cancer related pain with a neuropathic pain component an opioid with NNMDA receptor antagonist qualities (i.e. methadone) provides superior pain relief as compared to an opioid without NMDA receptor antagonist qualities (i.e. fentanyl). At the same time methadone is not inferior to fentanyl in providing pain relief in cancer patients with nociceptive pain due to radiation induced mucositis.

In order to predict which patients have a high probability to benefit from using opioid therapy it is important to know the type of pain (neuropathic or nociceptive), to know the treatment (methadone or fentanyl), to know the age of the patient and the duration of the pain.

The correct monitoring of pain combined with the knowledge that methadone provides superior pain relief in patients with cancer and a neuropathic pain component can help decrease the prevalence of pain in the next decades.

1. **Greco MT**, **Roberto A**, **Corli O**, **et al**. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. *J Clin Oncol* 2014; **32**(36): 4149-54.

2. **te Boveldt ND**, **Vernooij-Dassen MJ**, **Jansen A**, **Vissers KC**, **Engels Y**. Pain is not systematically registered in Dutch medical oncology outpatients. *Pain Pract* 2015; **15**(4): 364-70.

3. **Oosterling A**, **te Boveldt N**, **Verhagen C**, **et al**. Neuropathic Pain Components in Patients with Cancer: Prevalence, Treatment, and Interference with Daily Activities. *Pain Pract* 2016; **16**(4): 413-21.

4. **Gorman AL**, **Elliott KJ**, **Inturrisi CE**. The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett* 1997; **223**(1): 5-8.

5. **Ebert B**, **Andersen S**, **Krogsgaard-Larsen P**. Ketobemidone, methadone and pethidine are non-competitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. *Neurosci Lett* 1995; **187**(3): 165-8.

6. **Paoletti P**, **Bellone C**, **Zhou Q**. NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat Rev Neurosci* 2013; **14**(6): 383-400.

7. **Cull-Candy SG**, **Leszkiewicz DN**. Role of distinct NMDA receptor subtypes at central synapses. Sci STKE 2004; **2004**(255): re16.

8. **Cummings KA**, **Popescu GK**. Glycine-dependent activation of NMDA receptors. *J Gen Physiol* 2015; **145**(6): 513-27.

9. **Tovar KR**, **Westbrook GL**. Modulating synaptic NMDA receptors. *Neuropharmacology* 2017; **112**(Pt A): 29-33.

10. **Paoletti P**. Molecular basis of NMDA receptor functional diversity. *Eur J Neurosci* 2011; **33**(8): 1351-65.

11. **Beaver WT**, **Wallenstein SL**, **Houde RW**, **Rogers A**. A clinical comparison of the analgesic effects of methadone and morphine administered intramuscularly, and of orally and parenterally administered methadone. *Clin Pharmacol Ther* 1967; **8**(3): 415-26.

12. **Mercadante S**, **Porzio G**, **Ferrera Pet al**. Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. *Eur J Pain* 2008; **12**(8): 1040-6.

13. **Mercadante S**, **Casuccio A**, **Agnello A**, **Serretta R**, **Calderone L**, **Barresi L**. Morphine versus methadone in the pain treatment of advanced-cancer patients followed up at home. *J Clin Oncol* 1998; **16**(11): 3656-61.

14. **Bruera E**, **Palmer JL**, **Bosnjak S**, **et al**. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *J Clin Oncol* 2004; **22**(1): 185-92.

15. **Ventafridda V**, **Ripamonti C**, **Bianchi M**, **Sbanotto A**, **De Conno F**. A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. *J Pain Symptom Manage* 1986; **1**(4): 203-7.

16. **Nicholson AB**, **Watson GR**, **Derry S**, **Wiffen PJ**. Methadone for cancer pain. *Cochrane Database Syst Rev* 2017; **2**: CD003971.

17. **Eisenberg E**, **LaCross S**, **Strassman AM**. The effects of the clinically tested NMDA receptor antagonist memantine on carrageenan-induced thermal hyperalgesia in rats. *Eur J Pharmacol* 1994; **255**(1-3): 123-9.

18. **Sher GD**, **Cartmell SM**, **Gelgor L**, **Mitchell D**. Role of N-methyl-D-aspartate and opiate receptors in nociception during and after ischaemia in rats. *Pain* 1992; **49**(2): 241-8.

19. **Ren K**, **Hylden JL**, **Williams GM**, **Ruda MA**, **Dubner R**. The effects of a non-competitive NMDA receptor antagonist, MK-801, on behavioral hyperalgesia and dorsal horn neuronal activity in rats with unilateral inflammation. *Pain* 1992; **50**(3): 331-44.

20. **Yaksh TL**. Behavioral and autonomic correlates of the tactile evoked allodynia produced by spinal glycine inhibition: effects of modulatory receptor systems and excitatory amino acid antagonists. *Pain* 1989; **37**(1): 111-23.

21. **Mao J**, **Price DD**, **Hayes RL**, **Lu J**, **Mayer DJ**, **Frenk H**. Intrathecal treatment with dextrorphan or ketamine potently reduces pain-related behaviors in a rat model of peripheral mononeuropathy. *Brain Res* 1993; **605**(1): 164-8.

22. **Coderre TJ**, **Melzack R**. The contribution of excitatory amino acids to central sensitization and persistent nociception after formalin-induced tissue injury. *J Neurosci* 1992; 12(9): 3665-70.

23. **Pud D**, **Eisenberg E**, **Spitzer A**, **Adler R**, **Fried G**, **Yarnitsky D**. The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: a double blind, randomized, placebo controlled trial. *Pain* 1998; **75**(2-3): 349-54.

24. **Niesters M**, **Aarts L**, **Sarton E**, **Dahan A**. Influence of ketamine and morphine on descending pain modulation in chronic pain patients: a randomized placebo-controlled cross-over proof-of-concept study. *Br J Anaesth* 2013; **110**(6): 1010-6.

25. **Schwartzman RJ**, **Alexander GM**, **Grothusen JR**, **Paylor T**, **Reichenberger E**, **Perreault M**. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain* 2009; **147**(1-3): 107-15.

26. **Maier C**, **Dertwinkel R**, **Mansourian N**, **et al**. Efficacy of the NMDA-receptor antagonist memantine in patients with chronic phantom limb pain–results of a randomized double-blinded, placebo-controlled trial. *Pain* 2003; **103**(3): 277-83.

27. **Aiyer R**, **Mehta N**, **Gungor S**, **Gulati A**. A Systematic Review of NMDA Receptor Antagonists for Treatment of Neuropathic Pain in Clinical Practice. *Clin J Pain* 2018; **34**(5): 450-67.

28. **Moryl N**, **Kogan M**, **Comfort C**, **Obbens E**. Methadone in the treatment of pain and terminal delirum in advanced cancer patients. *Palliat Support Care* 2005; **3**(4): 311-7.

29. **Buuren Sv.** Flexible imputation of missing data. Boca Raton, FL: CRC Press; 2012.

30. **Hjermstad MJ**, **Fayers PM**, **Haugen DF**, **et al**. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *J Pain Symptom Manage* 2011; **41**(6): 1073-93.

31. **Dworkin RH**, **Turk DC**, **Farrar JT**, **et al**. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005; **113**(1-2): 9-19.

32. **Shanthanna H**, **Busse JW**, **Thabane L**, **et al**. Local anesthetic injections with or without steroid for chronic non-cancer pain: a protocol for a systematic review and meta-analysis of randomized controlled trials. *Syst Rev* 2016; **5**: 18.

33. **McLeod LD**, **Coon CD**, **Martin SA**, **Fehnel SE**, **Hays RD**. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. *Expert Rev Pharmacoecon Outcomes Res* 2011; **11**(2): 163-9.

34. **Liem EB**, **Joiner TV**, **Tsueda K**, **Sessler DI**. Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. *Anesthesiology* 2005; **102**(3): 509-14.

35. **Choi SW**, **Lam DMH**, **Wong SSC**, **Shiu HHC**, **Wang AXM**, **Cheung CW**. Effects of Single Nucleotide Polymorphisms on Surgical and Postsurgical Opioid Requirements: A Systematic Review and Meta-Analysis. *Clin J Pain* 2017; **33**(12): 1117-30.

36. **Nielsen LM**, **Olesen AE**, **Branford R**, **Christrup LL**, **Sato H**, **Drewes AM**. Association Between Human Pain-Related Genotypes and Variability in Opioid Analgesia: An Updated Review. *Pain Pract* 2015; **15**(6): 580-94.

37. **Vieira CMP**, **Fragoso RM**, **Pereira D**, **Medeiros R**. Pain polymorphisms and opioids: An evidence based review. *Mol Med Rep* 2019; **19**(3): 1423-34.

38. **Corli O**, **Roberto A**, **Bennett MI**, **et al**. Nonresponsiveness and Susceptibility of Opioid Side Effects Related to Cancer Patients' Clinical Characteristics: A Post-Hoc Analysis. *Pain Pract* 2017.

39. **Besse K**, **Vernooij-Dassen M**, **Vissers K**, **Engels Y**. The Impact of a National Guideline on the Management of Cancer Pain on the Practice of Pain Assessment and Registration. *Pain Pract* 2016; **16**(2): 148-53.

40. **Gunnarsdottir S**, **Sigurdardottir V**, **Kloke M**, **et al**. A multicenter study of attitudinal barriers to cancer pain management. *Support Care Cancer* 2017; **25**(11): 3595-602.

41. **Manchikanti L**, **Helm S**, **2nd**, **Fellows B**, **et al**. Opioid epidemic in the United States. *Pain Physician* 2012; **15**(3 Suppl): ES9-38.

42. **Rummans TA**, **Burton MC**, **Dawson NL**. How Good Intentions Contributed to Bad Outcomes: The Opioid Crisis. *Mayo Clin Proc* 2018; **93**(3): 344-50.

43. **Carmichael AN**, **Morgan L**, **Del Fabbro E**. Identifying and assessing the risk of opioid abuse in patients with cancer: an integrative review. *Subst Abuse Rehabil* 2016; **7**: 71-9.

44. **Prekupec MP**, **Mansky PA**, **Baumann MH**. Misuse of Novel Synthetic Opioids: A Deadly New Trend. *J Addict Med* 2017; **11**(4): 256-65.

45. **Nunez-Olarte JM**, **Alvarez-Jimenez P**. Emerging opioid abuse in terminal cancer patients taking oral transmucosal fentanyl citrate for breakthrough pain. *J Pain Symptom Manage* 2011; **42**(6): e6-8.

46. **Passik SD**, **Narayana A**, **Yang R**. Aberrant drug-related behavior observed during a 12-week open-label extension period of a study involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet or traditional short-acting opioid for breakthrough pain. *Pain Med* 2014; **15**(8): 1365-72.

47. **Henry SG**, **Wilsey BL**, **Melnikow J**, **Iosif AM**. Dose escalation during the first year of long-term opioid therapy for chronic pain. *Pain Med* 2015; **16**(4): 733-44.

48. **Gil JA**, **Gunaseelan V**, **DeFroda SF**, **Brummett CM**, **Bedi A**, **Waljee JF**. Risk of Prolonged Opioid Use Among Opioid-Naive Patients After Common Shoulder Arthroscopy Procedures. *Am J Sports Med* 2019; **47**(5): 1043-50.

IX

X

Valorisation

Description of the Problem

In 2018 cancer was the cause of close to 47.000 deaths in the Netherlands, according to the Dutch Central Bureau of Statistics (CBS).[1] With this number cancer was the most prevalent cause of death in The Netherlands. The incidence of cancer has increased over the last years in The Netherlands, from 98.505 new cases in 2010 to 116.537 new cases in 2018 (based on preliminary numbers). Besides a raised incidence of cancer, survival after cancer has been diagnosed has increased over the last years, from 56% in the period 2001-2005 to 64% in the period 2011-2015.[2]

The combination of increased incidence and survival rates leads to an increased prevalence of patients suffering from cancer, and an enlarged population of patients that has been treated for cancer. It is known that a large proportion of patients that suffer from, or survived cancer experience pain. Even after successful curative treatment of cancer still 28% of the patients experience moderate to severe pain, and up to 66% of patients with advanced disease state suffer from moderate to severe pain.[2,3]

Pain in patients with cancer has a large impact on society. It negatively affects the patient's quality of life. In the case of advanced disease during long-term care of the patient, severe pain can impair the possibility of good closure of ones life. This can result in impaired mourning of the relatives. Furthermore, with long term care severe pain can lead to the development of chronic pain, complicating re-integration in normal daily life.

In Chapter 2 we describe several problems that can complicate the treatment of pain in the patient with cancer. One of these problems is the undertreatment of pain in the patient with cancer. The most important cause for this seems to be lack of knowledge. Raised awareness for pain in the patient with cancer combined with better guidelines to treat pain in the patient with cancer seems to increase the knowledge slowly. Another factor complicating the treatment of pain is the presence of comorbidities in cancer patients. Especially renal problems affect up to 20% of the patients with cancer and pain, and create difficulties in predicting plasma levels of many pharmaceuticals. Furthermore, neuropathic pain, which is prevalent in about one third of the patients with cancer and pain, remains difficult to treat. This is further complicated by the fact that often these patients suffer from combined neuropathic and nociceptive pain. The pharmacological approach to this combined nociceptive and neuropathic pain profile remains difficult, as guidelines advice to prescribe opioids for nociceptive pain, and pharmaceuticals such as SSRI's or gabapentinoids for neuropathic pain.[4,5]

Target group

The first goal of the research described in this thesis is to improve the treatment of pain in patients with cancer. Central sensitization, a process in which the NMDA receptor is pivotal, is a crucial step in the development of neuropathic pain. Due to this it is to be expected that patients with a neuropathic pain component respond better to a pharmaceutical agent that influences the NMDA receptor. Therefore we expected that methadone (which has both opioid receptor agonist and NMDA receptor antagonist characteristics) will have a better effect on pain with a neuropathic component as compared to pure opioid drugs like fentanyl or oxycodone which only bind to the opioid receptor. The studies described in Chapters 3 and 4 are the first investigations that focus on this specific patient population (cancer patients with and without a neuropathic pain component). The results published in this thesis can optimize pain treatment in a patient population with cancer-related pain. In a population with a neuropathic pain component the

choice for methadone leads to improved and faster pain reduction. In a population without a neuropathic pain component the choice for methadone is not inferior as compared to fentanyl. This can lead to an improved quality of life in patients with a neuropathic pain component. From a valorisation point of view our results indicate that the discrimination between neuropathic and nociceptive pain characteristics and the specific targeting can lead to a better pain treatment in cancer pain patients (see also paragraph on dissemination).

This thesis contributes to the acknowledged research agenda (kennisagenda) of the Dutch Society of Anesthesiology (NVA), as published on the website of the NVA.[6]

The second goal is to further use our study results on methadone and neuropathic pain in cancer patients to improve shared decision making by developing a prediction model. Based on this prediction model physicians can (after external validation of the model) discuss with the patient the probability of reaching a pain reduction of at least 50%. With this information the patient can make an informed decision on which pharmaceutical to start, and what to expect from this pharmaceutical.

Products and scientific yield

This research will improve the treatment of pain in patients with cancer, leading to an improved quality of life. In order to optimally treat the pain it is imperative that we differentiate between nociceptive and neuropathic pain. Based on the results as in this thesis patients with a neuropathic pain component respond better to methadone as compared to fentanyl. In the case of nociceptive pain there is no clear difference between the two pharmaceutical agents.

The predictive model described in Chapter 6 can be used (after external validation) to develop an app that helps clinicians to calculate the chance of pain relief. This then may assist in the choice of the most optimal opioid for this specific patient.

Dissemination

The findings presented in this thesis are of practical use for clinicians as they will result in a better treatment of pain in cancer patients. In order to present this data to clinicians we will need to share them with different committees to ensure that this data will be used to optimize the treatment of as many patients as possible. The most important way to reach the largest population will be to incorporate the data of this study in different guidelines. The original instigator of this study (Prof. M. Van den Beuken – Van Everdingen) is part of the National Guideline Committee for the treatment of cancer related pain in the Netherlands. Implementation and update of Guideline for treatment of pain in cancer patients with our findings should not only be at a national level, but also in Europe. In order to facilitate and speed up the latter we presented data on the European Association of Palliative Care (2018), the world congress of the International Association for the Study of Pain (2018) as well as at different national and international symposia and national palliative care courses.

As said before the development of an app for palliative care, including the modality of selecting the most optimal opioid, could potentially assist many clinicians. In order to robustly present this app we need external validation of the results as described in this thesis. This external validation can be performed using an alternative cancer patient population such as patients with cancer induced bone pain. The data that will be generated with this alternative CIPB patient population can then be used for external validation of our prediction model (see

Chapter 6). After this external validation the prediction model then can be implemented in the app. This subsequently will lead to dissemination of our findings in the clinical community not only in The Netherlands but also beyond.

Impact

The research presented in this thesis will lead to an improved treatment of cancer pain patients.

1. opendata.cbs.nl/statline/#/CBS/nl/dataset/7052_95/table?fromstatweb

2. www.cijfersoverkanker.nl. https://www.cijfersoverkanker.nl/selecties/incidentie_kanker_totaal/img5c597a7436f2d.

3. **van den Beuken-van Everdingen MH**, **Hochstenbach LM**, **Joosten EA**, **Tjan-Heijnen VC**, **Janssen DJ**. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage* 2016; **51**(6): 1070-90 e9.

4. **Piano V**, **Verhagen S**, **Schalkwijk A**, **et al**. Treatment for neuropathic pain in patients with cancer: comparative analysis of recommendations in national clinical practice guidelines from European countries. *Pain Pract* 2014; **14**(1): 1-7.

5. **Sloot S**, **Boland J**, **Snowden JA**, **et al**. Side effects of analgesia may significantly reduce quality of life in symptomatic multiple myeloma: a cross-sectional prevalence study. *Support Care Cancer* 2015; **23**(3): 671-8.

6. www.demedischspecialist.nl/sites/default/files/doelmatigheidsagendaNVAdef.pdf

Samenvatting

Introductie

Op dit moment is kanker de belangrijkste oorzaak van morbiditeit en mortaliteit ter wereld, en het vóórkomen van kanker zal naar verwachting toenemen in de nabije toekomst, vanwege toename van de gemiddelde leeftijd van de algehele populatie gecombineerd met betere behandelopties voor kanker waardoor de overlevingstermijn toeneemt.[1] De prevalentie van pijn is hoog bij patiënten met kanker, en het vóórkomen van pijn bij patiënten met kanker is niet afgenomen in het decennium 2005-2014 t.o.v. de vier voorgaande decennia (1966-2005). In hoofdstuk 2 beschrijven we de achterliggende oorzaken voor het gebrek aan afname van pijn bij patiënten met kanker.

Belangrijke barrières in de behandeling van pijn bij kankerpatiënten zijn of patiënt gerelateerd (zoals angst voor verslaving) danwel behandelaar gerelateerd (zoals gebrek aan kennis of onvoldoende meten van pijn).[2,3] Een andere belangrijke factor voor het gebrek aan afname van pijn bij patiënten met kanker is mogelijk een toename van bijkomende ziekten, veroorzaakt door de toegenomen leeftijd van patiënten met kanker. Behandelaars zijn in staat om het vóórkomen van pijn bij patiënten met kanker te verminderen, maar moeten er dan in ieder geval voor zorgen dat hun kennis op peil is en dat ze goed monitoren of hun patiënten pijn hebben.

Het is aangetoond dat het ervaren van pijn een belangrijke oorzaak is van stress en een verminderde kwaliteit van leven bij patiënten met kanker. Helaas geeft nog 33% van de patiënten met kanker aan dat hun pijn ondraaglijk is.[4-6] De standaard behandeling is in 1986 beschreven in de WHO kankerpijn ladder.[7] Deze ladder beschrijft een stapsgewijze benadering voor de behandeling van pijn, waarbij gestart wordt met een middel als paracetamol en eventueel een NSAID zoals naproxen. Bij onvoldoende effect wordt er gestart met een zwak opioïde zoals tramadol, en bij wederom onvoldoende effect wordt gestart met een sterk opioïde zoals bijvoorbeeld oxycodon. Dit relatief simpele behandel algoritme resulteert in goede pijnverlichting in 70-90% van de gevallen.[8]

Gezien de combinatie van het veel vóórkomen van pijn, en de impact van pijn op het leven van de patiënt met kanker is het noodzakelijk dat diegene die kanker behandelt ook een goede kennis heeft van de behandeling van pijn (of weet wanneer patiënt verwezen moet worden naar een pijnspecialist). Om pijn optimaal te behandelen is het noodzakelijk te weten waardoor de pijn veroorzaakt wordt (hoofdstuk 1). Een groot probleem hierbij is het gebruik van de term “kankerpijn”. Deze term zegt namelijk niets over de pijn zelf, maar suggereert dat we dit wel weten. Het gebruik van het woord “kankerpijn” doet ook automatisch grijpen naar de WHO kankerpijn ladder, waarin bijvoorbeeld minder goed beschreven staat dat er middelen gericht op bepaalde typen pijn, zoals neuropathische pijn, gegeven moeten worden. De term kankerpijn geeft niet aan of er wel of geen sprake is van neuropathische of nociceptieve pijn. Het is aangetoond dat verschillende types pijn beter en anders reageren op verschillende farmacologische behandelingen.[9,10] Het is daarom van belang dat er bij patienten met pijn als gevolg van kanker een onderscheid wordt gemaakt tussen nociceptieve en neuropathische pijn. Hierdoor kan de pijn beter behandeld worden en daarmee kan mogelijk een afname in het vóórkomen van pijn bij kanker gerealiseerd worden (hoofdstuk 2). Het spreekt dus voor zich dat gerichte farmacologische behandeling op basis van type pijn de pijnbehandeling optimaliseert voor alle patiënten met pijn bij kanker.

Neuropathische pijn

De farmacologische behandeling van pure neuropathische pijn bestaat met name uit tricyclische antidepressiva, gabapentinoïden en selectieve serotonine en/of noradrenaline heropname remmers (SSRI/SNRI). Een andere belangrijk mechanisme bij neuropathische pijn is centrale sensitisatie, een proces waarbij de NMDA receptor belangrijk is (hoofdstuk 1).[11-13] Hierbij is methadon een interessant middel, aangezien het aangrijpt op zowel de mu-opioïde receptor als op de NMDA receptor.[14,15] De affiniteit van methadon voor deze twee receptoren zorgt ervoor dat methadon aangrijpt op belangrijke processen die optreden bij zowel nociceptieve als neuropathische pijn. Methadon is aangetoond effectief bij bepaalde condities die gepaard gaan met neuropathische pijn zoals post-herpetische neuralgie.[16] Ondanks de theoretische voordelen van methadon ten opzichte van andere opioïden zonder NMDA receptor affiniteit is, tot aan het getoonde onderzoek in dit proefschrift, er nog nooit specifiek onderzoek gedaan naar de effectiviteit van methadon bij pijn bij kanker met een neuropathische pijncomponent. In het kader van optimaal gerichte farmacologische behandeling van pijn bij kanker hebben we het effect van methadon ten opzichte van een opioide zonder NMDA-receptor affiniteit (= fentanyl) onderzocht in een populatie van patiënten met pijn als gevolg van tumoren in de hoofd-hals regio waarbij onderscheid werd gemaakt tussen twee groepen: één groep leed aan neuropathische pijn en de andere groep leed aan nociceptieve pijn. Op basis van deze populatie en ondervedrdeling in twee groepen hebben we twee gerandomiseerde, gecontroleerde onderzoeken gedaan (RCT).

In hoofdstuk 3 onderzochten we met behulp van een RCT het pijnstillende effect van methadon ten opzichte van fentanyl in een populatie van patiënten met pijn met een neuropathische component veroorzaakt door tumorgroei in de hoofd-hals regio. In totaal werden 52 patiënten geïncludeerd in de studie, waarbij 26 behandeld werden met fentanyl en 26 met methadon. De afname in de gemiddelde score op een 11-punts schaal (0-10) voor pijn (Numeric Rating Scale (NRS)), klinisch succes (gedefinieerd als 50% pijnreductie op gemiddelde pijn), en afname van pijn interferentie (op een 70 punts schaal) waren de primaire uitkomst maten. Het effect van methadon danwel fentanyl werd geëvalueerd na één, drie en vijf weken na de start van behandeling. Methadon was effectiever in vergelijking met fentanyl bij de behandeling van pijn met een neuropathische pijncomponent na een en na drie weken. Alhoewel er verschil was in het pijnniveau na vijf weken tussen fentanyl en methadon was deze niet significant meer. Een belangrijke beperking aan de studie beschreven in hoofdstuk 3 is de relatief hoge uitval gedurende de studie. Van veel patiënten zijn na drie weken geen gegevens meer bekend, en hoewel deze uitval goed is uit te leggen (overlijden door natuurlijke oorzaak, patiënten die pijnvrij zijn, patiënten die geopereerd moeten worden etc.) zorgt deze voor een vermindering van statistische power welke verantwoordelijk kan zijn voor het gebrek aan statistische significantie in het verschil van pijnverlichting tussen methadon en fentanyl in deze patiëntenpopulatie na vijf weken.

Het superieure effect van methadon op pijn met een neuropathische component veroorzaakt door kanker was verwacht vanwege de betrokkenheid van de NMDA receptor bij neuropathische pijn. Bij nociceptieve pijn is de rol van de NMDA receptor minder uitgesproken, en daarom is de verwachting dat er weinig toegevoegde waarde is van het toedienen van methadon bij nociceptieve pijn.[14, 13] Aangezien er nog weinig diagnostiek wordt verricht naar het type pijn bij patiënten met kanker die pijn hebben is het mogelijk dat door de resultaten uit hoofdstuk 3 ook patiënten met nociceptieve pijn vaker methadon voorgeschreven zullen krijgen. Vanwege

een mogelijke toename in voorschrijven van methadon bij nociceptieve pijn willen we in ieder geval zeker weten dat dit niet zal resulteren in inferieure pijnstilling voor patiënten met pijn ten gevolge van kanker. Vandaar de studie gepresenteerd in hoofdstuk 4.

Nociceptieve pijn

Een gerandomiseerde, gecontroleerde non-inferioriteit studie waarin methadon met fentanyl werd vergeleken staat beschreven in hoofdstuk 4. In totaal werden 82 patiënten met nociceptieve pijn op basis van orale mucositis veroorzaakt door bestraling voor hoofd-halstumoren werden behandeld voor hun pijn. Uiteindelijk werden 40 patiënten behandeld met fentanyl, en 42 met methadon. Bij deze patiënten werden de pijnscore (NRS), pijn interferentie, globaal ervaren effect (op een 7 punts-schaal) , bijwerkingen en opioïde verhogingsratio gemeten na één, drie en vijf weken vanaf de start van de behandeling. Uit deze studie blijkt dat methadon niet inferieur is aan fentanyl bij de behandeling van nociceptieve pijn na één en na drie weken. Op basis van de uitkomsten na vijf weken kunnen we geen uitspraak doen over inferioriteit, waarbij er weer sprake was van een relatief hoog aantal patiënten dat uitgevallen was, waardoor de statistische power is afgenomen.

Voorspellend model

Uit de data van de twee studies gepresenteerd in hoofdstukken 3 en 4 blijkt dat er patiënten zijn die heel goed reageren op behandeling met methadon danwel fentanyl, terwijl andere patiënten minder resultaat ervaren van de behandeling. Deze observatie leidde ertoe dat we de vraag stelden of we op basis van patiëntengegevens konden voorspellen welke patiënten meer of minder kans hadden op pijnverlichting op basis van het starten van fentanyl danwel methadon. Door de associaties tussen patiëntengegevens en respons te onderzoeken is de bedoeling dat we een predictiemodel kunnen bouwen waarmee we de kans op succesvolle behandeling met opioïden kunnen voorspellen.

In hoofdstuk 5 beschrijven we hoe we dit predictiemodel hebben ontwikkeld. Dit model kan gebruikt worden om te voorspellen wat de kans is dat een bepaalde patiënt een pijnreductie van 50% (op de NRS) of meer zal ervaren. Het predictiemodel is ontwikkeld op basis van de data van de twee eerder beschreven RCT's (hoofdstukken 3 en 4). Voorspellers van klinisch succes die uiteindelijk in ons model terecht kwamen waren:

1. Neuropathische pijn (in vergelijking met nociceptieve pijn)
2. Leeftijd
3. Behandeling met methadon (in vergelijking met fentanyl)
4. Duur van de pijn voor start opioïden (in maanden)

Met deze voorspellers in ons predictiemodel lukt het om onderscheid te kunnen maken tussen welke patiënten wel en welke patiënten geen succesvolle pijnverlichting ervaren, en dat met hoge waarschijnlijkheid (gebied onder de curve van 81.6%). Op basis hiervan kunnen we zeggen dat ons model goed kan voorspellen welke patiënten een hoge kans hebben op pijnverlichting en welke patiënten een slechte kans hebben op pijnverlichting. Belangrijke beperkingen van dit predictiemodel zijn dat het gebaseerd is op een relatief kleine hoeveelheid patiënten en tegelijk op een vrij specifieke patiëntenpopulatie. Er moet nog verder onderzoek gedaan worden om dit model extern te valideren. Voor deze validatie is het nodig dat we data krijgen uit andere patiëntenpopulaties.

Toekomst

De beschreven RCT's in hoofdstukken 3 en 4 onderzoeken een patiëntenpopulatie met pijn met een neuropathische pijncomponent of nociceptieve pijn op basis van orale mucositis veroorzaakt door bestraling. Om de resultaten uit deze studies in een breder verband te trekken is het nodig om verder onderzoek te doen met andere patiëntenpopulaties met een mogelijke neuropathische pijncomponent. Alleen op deze manier kunnen we aantonen of voor deze specifieke patiëntenpopulaties methadon een toegevoegde waarde heeft ten opzichte van opioïden zonder NMDA receptor affiniteit. Een volgende studie die we voorstellen is een onderzoek naar de hypothese dat methadon een toegevoegde waarde heeft bij patiënten met pijn op basis van ossale metastasen. Deze kanker geïnduceerde bot pijn (KGBP) lijkt nociceptief (pijn op basis van beschadigd of bedreigd niet-neuraal weefsel, veroorzaakt door de activatie van nociceptoren[17]), maar er zijn ook aanwijzingen voor een neuropathische pijncomponent.[18,19] Vanwege deze mogelijke neuropathische component denken wij dat methadon een toegevoegde waarde zou kunnen hebben in de pijnbehandeling van deze patiënten.

De thesis wordt daarom afgesloten door hoofdstuk 6, waarin een onderzoeksprotocol waarmee we het effect van methadon (opioïde met NMDA receptor affiniteit) kunnen vergelijken met een puur opioïde zonder NMDA receptor affiniteit (oxycodon) in patënten met KGBP. Patiënten voor deze studie zullen opioïde naïef zijn, en zullen last hebben van pijn op basis van botmetastasen van verschillende primaire tumoren. Behalve dat deze studie de behandeling van KGBP kan verbeteren kunnen we de resultaten gebruiken voor externe validatie van ons predictie model (zie hoofdstuk 5).

De resultaten gepresenteerd in deze thesis zullen leiden tot een verbeterde behandeling van patiënten met pijn op basis van hoofd-hals tumoren.

1. World Cancer Report. Geneva, Switzerland: World Health Organization Press; 2014.

2. **Gunnarsdottir S**, **Sigurdardottir V**, **Kloke M**, **et al**. A multicenter study of attitudinal barriers to cancer pain management. *Support Care Cancer* 2017; **25**(11): 3595-602.

3. **Kwon JH**. Overcoming barriers in cancer pain management. *J Clin Oncol* 2014; **32**(16): 1727-33.

4. **Kroenke K**, **Theobald D**, **Wu J**, **Loza JK**, **Carpenter JS**, **Tu W**. The association of depression and pain with health-related quality of life, disability, and health care use in cancer patients. *J Pain Symptom Manage* 2010; **40**(3): 327-41.

5. **Breivik H**, **Cherny N**, **Collett B**, **et al**. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. *Ann Oncol* 2009; **20**(8): 1420-33.

6. **Porter LS**, **Keefe FJ**. Psychosocial issues in cancer pain. *Curr Pain Headache Rep* 2011; **15**(4): 263-70.

7. WHO's cancer pain ladder for adults. 1986. https://www.who.int/cancer/palliative/painladder/en/.

8. **Carlson CL**. Effectiveness of the World Health Organization cancer pain relief guidelines: an integrative review. *J Pain Res* 2016; **9**: 515-34.

9. **Piano V**, **Verhagen S**, **Schalkwijk A**, **et al**. Treatment for neuropathic pain in patients with cancer: comparative analysis of recommendations in national clinical practice guidelines from European countries. *Pain Pract* 2014; **14**(1): 1-7.

10. **Attal N**, **Cruccu G**, **Baron R**, **et al**. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; **17**(9): 1113-e88.

11. **Schwartzman RJ**, **Alexander GM**, **Grothusen JR**, **Paylor T**, **Reichenberger E**, **Perreault M**. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain* 2009; **147**(1-3): 107-15.

12. **Eichenberger U**, **Neff F**, **Sveticic G**, **et al**. Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg* 2008; **106**(4): 1265-73, table of contents.

13. **Petrenko AB**, **Yamakura T**, **Baba H**, **Shimoji K**. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg* 2003; **97**(4): 1108-16.

14. **Gorman AL**, **Elliott KJ**, **Inturrisi CE**. The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett* 1997; **223**(1): 5-8.

15. **Ebert B**, **Andersen S**, **Krogsgaard-Larsen P**. Ketobemidone, methadone and pethidine are non-competitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. *Neurosci Lett* 1995; **187**(3): 165-8.

16. **Teixeira MJ**, **Okada M**, **Moscoso AS**, et al. Methadone in post-herpetic neuralgia: A pilot proof-of-concept study. *Clinics (Sao Paulo)* 2013; **68**(7): 1057-60.

17. definition pain iasp. https://www.iasp-pain.org/education/content.aspx?ItemNumber=1698#Pain.

18. **Sjolund KF**, **Yang R**, **Lee KH**, **Resnick M**. Randomized study of pregabalin in patients with cancer-induced bone pain. *Pain Ther* 2013; **2**(1): 37-48.

19. **Laird BJ**, **Walley J**, **Murray GD**, **Clausen E**, **Colvin LA**, **Fallon MT**. Characterization of cancer-induced bone pain: an exploratory study. *Support Care Cancer* 2011; **19**(9): 1393-401.

Dankwoord

Het dankwoord is het gevaarlijkste onderdeel van het hele proefschrift. Het dankwoord is namelijk het deel dat door vrijwel iedereen uitgebreid zal worden nageplozen. Deze mening wordt vaak over het dankwoord gedeeld, maar ik ben het hier pertinent mee oneens. De inhoud van de rest van dit proefschrift is vele malen belangrijker. Uiteraard is het belangrijk om te kijken naar hoe dit proefschrift tot stand is gekomen, en hoe het mogelijk is dat ik dit publiekelijk mag verdedigen en zo de graad tot doctor kan behalen.

Een belangrijke wijsheid die bij ons thuis op een mok staat is: “Waarom moeilijk doen als het ook samen kan.” Het is enigszins cliché, maar daarom niet minder waar. Dit proefschrift was nooit tot stand gekomen als ik dit alleen had moeten doen. Het directe team om mij heen heeft enorm bijgedragen. Het scheelt enorm als een vraag direct beantwoord wordt, een manuscript snel van opmerkingen en verbeteringen wordt voorzien, en overleg op korte termijn gepland kan worden. Het is prettig om niet het gevoel te hebben dat er aan een dood paard getrokken moet worden, en dat er gezamenlijk een goed resultaat komt. Met name toen er in het privé leven wat life events gebeurde (verhuizen, andere baan (mede dankzij de publicaties), geboorte dochter, nogmaals verhuizen, baan wordt drukker en drukker) was er de mogelijkheid even ruimte te nemen, en kon later de draad weer opgepakt worden. Marieke, je hebt dit op een (in mijn ogen) perfecte manier gedaan! Sander, zonder je statistische hulp was ik waarschijnlijk nog steeds bezig om te checken of alles klopte qua statistiek voor mijn tweede artikel, en was ik zeker jammerlijk vastgelopen in de bouw van het model. Bert, fantastisch om te zien hoe je een zin die ik voor ogen had maar niet kon opschrijven uit mijn poging destilleert en deze kort maar krachtig als mogelijke wijziging in het manuscript aanbrengt! Marieke, Sander en Bert, zonder jullie had ik hier nooit gestaan!

Naast het bovengenoemde kernteam is er natuurlijk een belangrijk team dat van iets meer afstand heeft meegekeken en gewerkt met de publicaties. Zonder de medewerking van de afdelingen KNO en radiotherapie was de inclusie van de patiënten niet gelukt. Derhalve mijn dank voor de medewerking van deze afdelingen en Bernd Kramer en Frank Hoebers in het bijzonder. De afdeling interne en in het bijzonder Jetske Meerum-Terwogt wil ik danken voor het meedenken aan de opzet voor de studie bij Kanker Geïnduceerde Botpijn. Ook de leden van de beoordelingscommissie en de corona wil ik danken voor hun rol in het totstandkomen van dit proefschrift en de mogelijkheid deze te verdedigen.

Voor de hulp bij het schrijven van de artikelen wil ik ook mijn dank uiten aan Jose Geurts en Jaap Hol, jullie hebben belangrijke verbeteringen gesteund in verschillende hoofdstukken van dit proefschrift!

Een groep die vaak vergeten wordt in het dankwoord is de groep die de artikelen heeft gereviewed. Een enigszins anonieme groep, die ervoor zorgt dat de gepubliceerde artikelen ook daadwerkelijk verwacht nut zullen hebben voor artsen, verpleegkundigen of patiënten. Al was ik het uiteraard niet altijd eens met hun oordeel, ik wil hen zeker bedanken voor de kritische feedback waardoor de artikelen uiteindelijk beter zijn geworden.

Een belangrijk deel van dit proefschrift is geschreven in het OLVG locatie west. Met name tijdens de weekenddiensten van 24 uur, —die voor de traumalaterisatie soms rustig waren – kon ik nog wel eens “kilometers maken”. Maar ook later tijdens de wat drukkere diensten kon ik de tijd vinden om te schrijven, mede dankzij de hulp van de anesthesie- en OK-medewerkers. Uiteindelijk lukte het me niet om alles af te ronden zonder hiervoor wat extra tijd te krijgen van

mijn directe collega's, dus dank aan de vakgroep anesthesiologie voor het vrijroosteren.

Een oud Engels gezegde luidt: "All work and no play makes Jack a dull boy", waar door Maria
115 Edgeworth "all play and no work makes Jack a mere toy" aan is toegevoegd. De balans tussen werk en vrije tijd en hobby's is bij mij de afgelopen tijd wel doorgeslagen naar te veel werk. Desondanks ben ik blij dat er mensen zijn met wie ik af en toe dingen kan doen om uit de dagelijkse mallemolen te stappen, en een andere mallemolen in te gaan. Hiertoe horen natuurlijk vrienden, familie, oud-teamgenoten, (oud)collega's en (oud)buurtgenoten met wie ik af en toe lekker kan eten, stappen, kletsen, fietsen en koken. Belangrijke zaken om het hoofd weer leeg te maken en de energie weer te krijgen voor het starten aan een nieuw hoofdstuk.

Als laatste rest mij om mijn familie te danken voor alle steun die ik heb gekregen! Sorry Lotte, ik moest je toch even noemen.

Curriculum Vitae

Johan Haumann was born on August 27th 1980 in Senanga, Zambia. In 1983 he moved with his parents back to The Netherlands, and grew up in Nederhorst Den Berg. At the age of 9 he moved to Hilversum, where he attended secondary school. At age 17 he graduated secondary school (VWO), and started medical school at the Academic Medical Center in Amsterdam in 1998. In 2006 he graduated from medical school, and started working as a resident at the St Lucas Andreas Hospital. In 2007 he was accepted for the residency program of the Academic Medical Centre in Amsterdam. Before starting the residency programme he performed basic research in Milwaukee for two years. Although this resulted in several publications, it was not feasible to get a Ph. D. in this time frame. In 2009 the residency programme was started, and in 2014 he became a board certified anaesthesiologist. With this degree he started a fellowship programme at the Maastricht University Medical Centre (MUMC+) to become a pain specialist. During his fellowship programme at the MUMC+ research was started again, with Marieke van den Beuken – van Everdingen. This research was continued when Johan moved back to Amsterdam to work in the OLVG as an anaesthesiologist – pain specialist, and eventually resulted in this thesis. Currently Johan is still working at the OLVG.

Publications

The Association between Patient Characteristics and Opioid Treatment Response in Neuropathic and Nociceptive Pain due to Cancer. **Haumann J**, van Kuijk SMJ, Joosten EA, van den Beuken-van Everdingen MHJ. *J Palliat Med*. 2019 Feb;22(2):157-163.

Slow Ca2+ Efflux by Ca2+/H+ Exchange in Cardiac Mitochondria Is Modulated by Ca2+ Re-uptake via MCU, Extra-Mitochondrial pH, and H+ Pumping by FOF1-ATPase. **Haumann J**, Camara AKS, Gadicherla AK, Navarro CD, Boelens AD, Blomeyer CA, Dash RK, Boswell MR, Kwok WM, Stowe DF. *Front Physiol*. 2019 Feb 4;9:1914.

Haematoma and abscess after neuraxial anaesthesia: a review of 647 cases.
Bos EME, **Haumann J**, de Quelerij M, Vandertop WP, Kalkman CJ, Hollmann MW, Lirk P. *Br J Anaesth*. 2018 Apr;120(4):693-704.

Methadone versus Fentanyl in Patients with Radiation-Induced Nociceptive Pain with Head and Neck Cancer: A Randomized Controlled Noninferiority Trial. **Haumann J**, van Kuijk SMJ, Geurts JW, Hoebers FJP, Kremer B, Joosten EA, van den Beuken-van Everdingen MHJ. *Pain Pract*. 2018 Mar;18(3):331-340.

Pain prevalence in cancer patients: status quo or opportunities for improvement? **Haumann J**, Joosten EBA, Everdingen MHJVDB. *Curr Opin Support Palliat Care.* 2017 Jun;11(2):99-104.

Multidisciplinary treatment of orofacial pain. Geurts JW, **Haumann J**, van Kleef M. *Ned Tijdschr Tandheelkd.* 2016 Nov;123(11):547-551.

Letter response: Methadone is superior to fentanyl in treating neuropathic pain in patients with head-and-neck cancer. **Haumann J**, Geurts JW, van Kuijk SM, Kremer B, Joosten EA, van den Beuken-van Everdingen MH. *Eur J Cancer*. 2016 Nov;68:201-202.

Methadone is superior to fentanyl in treating neuropathic pain in patients with head and neck cancer. **Haumann J**, Geurts JW, van Kuijk SM, Kremer B, Joosten EA, van den Beuken-van Everdingen MH. *Eur J Cancer*. 2016 Aug 2;65:121-129

Mitochondrial free [Ca2+] increases during ATP/ADP antiport and ADP phosphorylation: exploration of mechanisms. **Haumann J**, Dash RK, Stowe DF, Boelens AD, Beard DA, Camara AK. *Biophysical Journal*. 2010 Aug 9;99(4):997-1006

Long-term neuroprotection with 2-iminobiotin, an inhibitor of neuronal and inducible nitric oxide synthase, after cerebral hypoxia-ischemia in neonatal rats. Van den Tweel ER, van Bel F, Kavelaars A, Peeters-Scholte CM, **Haumann J**, Nijboer CH, Heijnen CJ, Groenendaal F. *J Cereb Blood Flow Metab*. 2005 Jan;25(1):67-74