Opioids in postoperative pain treatment

Studies on analgesic efficacy and reduction of opioid-induced side effects

Thesis for the degree philosophiae doctor

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"One, remember to look up at the stars and not down at your feet. Two, never give up work. Work gives you meaning and purpose and life is empty without it. Three, if you are lucky enough to find love, remember it is there and don't throw it away."

Stephen Hawking

Sandvika, November 2020

2. Abbreviations and acronyms

AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASA: American Society of Anesthesiologists
ATP: adenosine triphosphate
BFI: Bowel Function Index
CGRP: calcitonin-gene-related peptide
CI: confidence interval
CPT: cold pressor test
DNIC: diffuse noxious inhibitory control
DOP: δ-opioid peptide receptor
DRG: dorsal root ganglion
ER: extended-release
GABA: gamma-aminobutyric acid
HPT: heat pain test
IASP: The International Association for the Study of Pain
IR: immediate-release
KOP: κ-opioid peptide receptor
LTP: long-term potentiation
MOP: μ-opioid peptide receptor
MOR-NRI: μ-opioid receptor agonist/noradrenaline reuptake inhibition
NMDA: N-methyl-D-aspartate
NOP: nociceptin/orphanin FQ receptor or nociceptin peptide receptor
NRS: numerical rating scale
NSAID: non-steroidal anti-inflammatory drugs
OIC: opioid-induced constipation
OIH: opioid-induced hyperalgesia
OR: odds ratio
PAG: periaqueductal grey area
PCA: patient-controlled analgesia
PID: pain intensity difference
PONV: postoperative nausea and vomiting
PR: prolonged-release
RVM: rostral ventromedial medulla
SD: standard deviation
SPID: summed pain intensity difference
TOTPAR: total pain relief
VAS: visual analog scale

3. List of papers

Paper I

Comelon M, Wisloeff-Aase K, Raeder J, Draegni T, Undersrud H, Qvigstad E, Bjerkelund CE, Lenz H. A comparison of oxycodone prolonged-release vs. oxycodone + naloxone prolonged-release after laparoscopic hysterectomy. Acta Anaesthesiol Scand 2013; 57(4): 509-17. DOI: 10.1111/aas.12051.

Paper II

Comelon M, Raeder J, Drægni T, Lieng M, Lenz H. Tapentadol versus oxycodone analgesia and side effects after laparoscopic hysterectomy: a randomised controlled trial. (Under revision)

Paper III

Comelon M, Raeder J, Stubhaug A, Nielsen CS, Draegni T, Lenz H. Gradual withdrawal of remifentanil infusion may prevent opioid-induced hyperalgesia. Br J Anaesth 2016; 116(4): 524-30. DOI: 10.1093/bja/aev547.

4. Synopsis

Opioids have an important role in the treatment of moderate to severe postoperative pain, making them essential drugs in the field of anesthesiology. However, opioids are encumbered with side effects which affect patient comfort, recovery and may even cause lethal complications. In the postoperative setting, the most common and well-known side effects are nausea, vomiting, pruritus, constipation, ileus, dizziness, urinary retention, tolerance, sedation and respiratory depression. In recent years there has also been increased focus on a less known side effect, opioid-induced hyperalgesia. The dramatic increase in physical dependence and opioid addiction, especially in North America during the last decades, has drawn attention to the consequences of opioid treatment and side effects in a wider perspective. There is emerging evidence that the different opioids may have unique side effect profiles, and research efforts are now turning to new mixed and biased opioids with less side effects.

We have conducted three studies with research questions focusing on three different opioids with analgesic effect and/or side effects of relevance in the postoperative setting. The studies, two clinical and one experimental, were all randomized controlled trials done with blinding. In the first clinical study, we found no effect on constipation from an opioid drug mixture of peripherally acting naloxone added to oxycodone prolonged-release tablets administered the first three days after hysterectomy. The addition of naloxone did not antagonize the analgesic effect of oxycodone. In the second clinical study on hysterectomy patients, we found similar analgesic effects from tapentadol, a mixed molecule with both μ-opioid receptor and noradrenaline reuptake inhibition effects, and oxycodone during the first 24 h postoperatively. Significantly less nausea and less need for antiemetics also suggest clinical usefulness of tapentadol over a pure μ-opioid drug postoperatively. The third and final study was an experimental crossover study on healthy volunteers. We demonstrated that gradual withdrawal from remifentanil infusion, as opposed to abrupt withdrawal, could prevent opioid-induced hyperalgesia in a heat pain model. We were, however, not able to replicate this in a cold pressor pain model. In both modalities, we found that

hyperalgesia from a short-term, low-dose remifentanil administration persisted for less than 105 min after end of infusion.

In general, the use of new medications should be restricted, both due to initial lack of evidence of their benefits over standard treatment and extra costs of patented drugs. The clinical studies in this thesis contribute to the build-up of evidence on which patient groups may have benefits from these drugs, and the studies have had direct implications on the clinical practice at our department. We limit the use of oxycodone-naloxone prolonged-release drugs to long-term immobilized patients with a high risk of constipation postoperatively. Tapentadol is increasingly used as an alternative for patients who have a history of postoperative nausea and vomiting, previous negative experiences with oxycodone side effects, or when there is a need for opioid rotation. Furthermore, the study on opioid-induced hyperalgesia has put a focus on this less known effect of opioids and increased the awareness of adverse postoperative effects from perioperative opioids among nurse anesthetists and anesthesiologists. Lastly, tapering off the remifentanil infusion at the end of surgery to prevent opioid-induced hyperalgesia has gained some international attention after publication of the data, as reflected in referencing in other papers.

5. Norwegian summary

Opioider er blant de viktigste medikamentene for postoperative smertebehandling og derfor essensielle innen faget anestesi. Dessverre har opioider mange velkjente bivirkninger som påvirker pasientens postoperative velvære i tillegg til mer sjeldne, men alvorlige komplikasjoner. I postoperativ sammenheng er de vanligste bivirkningene kvalme, oppkast, kløe, obstipasjon, ileus, svimmelhet, urinretensjon, toleranseutvikling og sedasjon, mens alvorlig respirasjonsdepresjon er den mest fryktede bivirkningen. De siste tiårene har det også blitt mer fokus på en mindre kjent bivirkning, opioidindusert hyperalgesi. I et samfunnsmessig perspektiv er også bivirkninger som fysisk opioidavhengighet og rusmisbruk av økende betydning. Den mye omtalte opioidkrisen i Nord-Amerika, med dramatiske konsekvenser for hele samfunnet, kan spores tilbake til opioidbruk initiert som medisinsk behandling. Mye tyder på at de ulike opioidene har unike bivirkningsprofiler og senere tids forskning har derfor blitt rettet mot nye opioider med kombinerte eller differensierte virkningsmekanismer.

Doktorgraden omfatter tre studier som fokuserer på tre ulike opioiders analgetiske effekter og bivirkninger i den postoperative settingen. De tre studiene, to kliniske og en eksperimentell, er randomiserte, kontrollerte studier gjort med blinding. I den første studien fant vi ingen effekt på obstipasjon av oksykodon depottablett tilsatt opioidantagonisten nalokson gitt i tre dager etter hysterektomi. Nalokson virket ikke antagonistisk på den analgetiske effekten fra oksykodon. I den andre kliniske studien på hysterektomipasienter undersøkte vi tapentadol, et opioid med tosidig virkningsmekanisme i form av μ-reseptor agonisme i kombinasjon med noradrenalin-reopptakshemming. Vi fant lik analgetisk effekt av tapentadol versus oksykodon de første 24 timene postoperativt. Signifikant mindre kvalme og mindre behov for antiemetika kan indikere at tapentadol er klinisk fordelaktig fremfor et opioid som hovedsakelig virker på μ-reseptorer. Den tredje og siste studien var en eksperimentell studie med crossover design på friske frivillige. Vi viste med en modell basert på smerte utløst av en varmeprobe, at gradvis nedtrapping av remifentanilinfusjon i motsetning til brå avslutning av infusjon kan forhindre utvikling av opioidindusert hyperalgesi. Dette ble ikke replikert i en

modell basert på kuldesmerte. I begge smertemodeller fant vi at hyperalgesi fra en kortvarig remifentanilinfusjon med lav dose vedvarte mindre enn 105 minutter etter endt infusjon.

Generelt bør nye medikamenter på markedet brukes restriktivt på grunn av manglende evidens for fordeler fremfor standard behandling initialt og ofte høyere kostnader på patenterte medikamenter. De kliniske studiene i denne doktorgraden bidrar til økt kunnskap om hvilke pasientgrupper som kan dra nytte av disse medikamentene og de har således hatt direkte implikasjoner for klinisk bruk ved vår avdeling. Vi begrenser i dag bruk av oksykodon-nalokson depotpreparater til pasienter som har høy risiko for obstipasjon på grunn av langvarig immobilisering postoperativt. Tapentadol brukes i økende grad som et alternativ for pasienter som tidligere har hatt uttalt kvalme og oppkast etter operasjon, dårlige erfaringer med oksykodon på grunn av bivirkninger eller hvis det er behov for opioidrotasjon. Studien på opioidindusert hyperalgesi har rettet fokus mot denne lite kjente bivirkningen av opioider og økt bevisstheten om at perioperativ opioidbruk kan ha negative konsekvenser postoperativt blant anestesipersonell. Denne studien har også fått en del internasjonal oppmerksomhet i forbindelse med publikasjon og har i etterkant blitt referert i en rekke artikler.

6. Introduction

6.1 Pain physiology

6.1.1 General considerations

The International Association for the Study of Pain (IASP) defines pain as “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”.(1) Fong and Schug and Olesen et al. (2, 3) explain pain physiology well in their papers, and the following paragraph summarizes some of their considerations on the topic. In the peripheral body tissues, free nerve endings are stimulated or modified by noxious thermal, chemical or mechanical stimuli. Such nociceptors are widely distributed in the skin, musculoskeletal system and visceral organs. There are at least two types of nociceptors: thermomechanoreceptors which respond to stimuli like pinprick and sudden heat via Aδ fibers, and polymodal receptors which respond to thermal and chemical stimuli through C fibers. The thermal, mechanical or chemical stimuli activate the peripheral terminals of the nociceptive fibers and induce an action potential mainly via transient receptor potential-generating, sodium, potassium and calcium channels, and transduction ensues. But upon tissue injury, histamine and inflammatory mediators such as peptides, neurotransmitters, lipids, and neurotrophins may contribute to the activation of the nociceptors as well. The action potentials travel through fast conducting, myelinated Aδ and slow conducting, unmyelinated C fibers to the dorsal root ganglion (DRG) and the dorsal horn. These primary afferent neurons mainly end in lamina I, II and V in the dorsal horn, where they release glutamate and substance P which act on several receptors (most importantly neurokinin-1, AMPA and NMDA receptors) involved in pain transmission. Aβ fibers which conduct low-intensity mechanical stimuli like touch to laminae III-IV may be involved in the transmission of chronic pain. Second order neurons cross over to the contralateral side and carry the signals from the dorsal horn into the anterolateral system of the spinal cord in several tracts. The spinothalamic tract ending in the thalamus is the most prominent pain pathway, but the spinoreticular, spinomesencephalic and spinohypothalamic tracts are relevant to other aspects of pain, such as the emotional, neuroendocrine and cardiovascular responses. From the thalamus, third

order neurons carry action potentials the last leg to the primary somatosensory cortex, where the anterior cingulate cortex and insula appear to be the most specific for pain. The projections to the insula probably modulate the autonomic responses to pain, and there are also projections to the limbic system which trigger emotional responses to pain.

Pain input may be modulated in several ways. The gate control theory of pain suggested a “gate” in the dorsal horn which can be opened or closed by different neural pathways resulting in activation or inhibition of pain pathways.(2) In other words, pain transmission from the peripheral nerve through the spinal cord is subjected to modulation by both intrinsic neurons and controls originating from the brain. Large afferent fibers could, for instance, exert an inhibitory action on more slowly conducting fibers, and the site of action was believed to be in the substantia gelatinosa cells of the dorsal horn. The “modulation of pain” principle of the gate control theory remains, but it is now generally accepted that pain modulation is much more complex. In the brainstem, the periaqueductal grey area (PAG) and the rostral ventromedial medulla (RVM) play essential roles in descending modulation of pain.(2) In the RVM there are three types of neurons: ON, OFF and neutral cells. The ON cells are excited by noxious stimuli and inhibited by opioids, so it is proposed that these cells facilitate nociceptive transmission. The OFF cells seem to decrease their ongoing activity during noxious stimulation and are excited by opioids, so these cells are proposed to inhibit nociception. The fibers descending from PAG and RVM to the dorsal horn have both inhibitory and facilitating effects on pain pathways through serotonergic, enkephalinergic, glycinergic, GABAergic and noradrenergic mechanisms. In a state of normal, resting physiology the descending inhibitory effects are dominant, but this may be modulated in either direction upon pain stimulation. With chronic pain the facilitating actions are shown to be dominating.

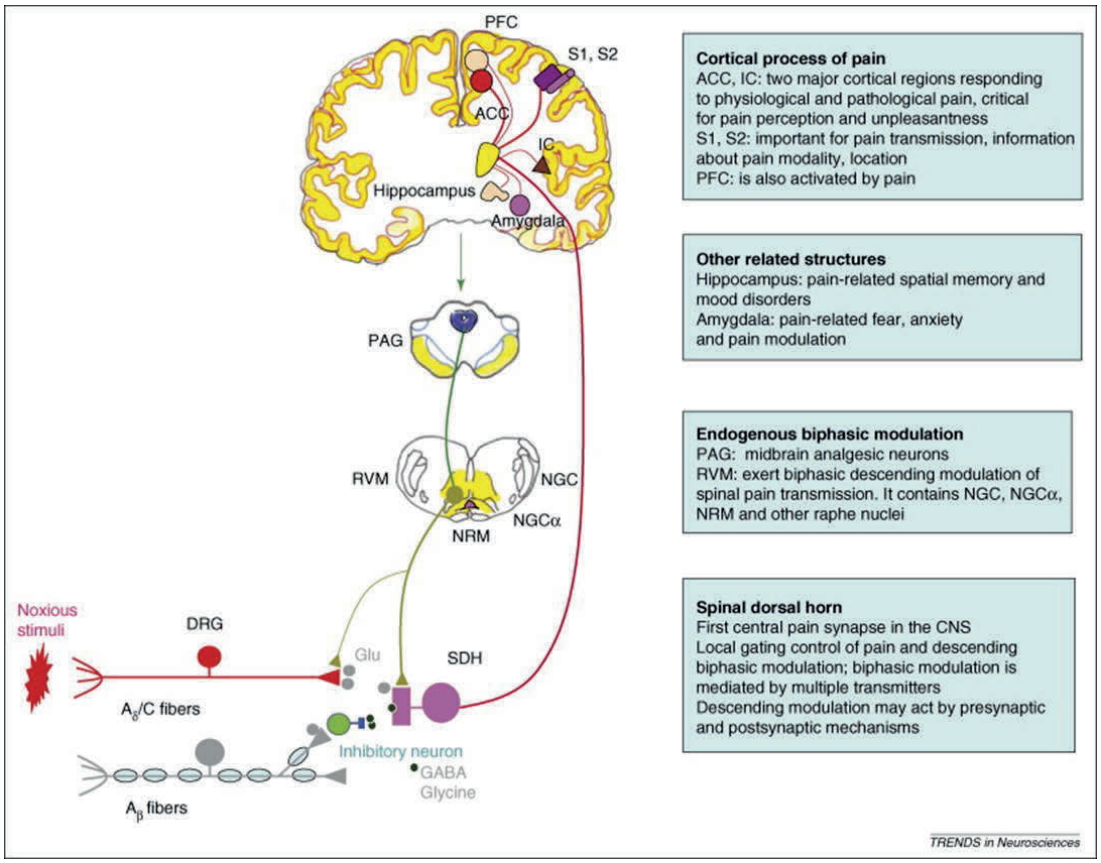

Figure 1. Overview of pain pathways. Nociceptive afferent fibers (Aδ and C) are activated in the periphery, inducing action potentials that trigger release of excitatory transmitters (glutamate, substance P) in the spinal dorsal horn. Second order neurons carry signals further in the anterolateral system of the spinal cord through the brainstem to the thalamus. From the thalamus third order neurons transmit the pain signals to the cortex and the limbic system. The periaqueductal grey area and the rostral ventromedial medulla in the brainstem play important roles in descending modulation of pain. Fibers descending from these areas to the dorsal horn have both inhibitory and facilitating effects on pain pathways. ACC anterior cingulate cortex; IC insular cortex; NGC nucleus reticularis gigantocellularis; NRM nucleus raphe magnus; SDH spinal dorsal horn; S1 primary somatosensory cortex; S2 secondary somatosensory cortex; PFC prefrontal cortex. Figure from Zhou M, "Cortical excitation and chronic pain", Trends Neurosci 2008;31:199-207. Reprinted with permission from RightsLink®.

The diffuse noxious inhibitory control (DNIC) phenomenon, often termed conditioned pain modulation in humans, should also be mentioned. DNIC involves the dorsal reticular nucleus, spinoparabrachial and spinoreticular pathways, and it is often referred to as "pain inhibits pain" since this modulation of pain happens when a distant noxious stimuli suppresses the firing of convergent second order sensory neurons.(4) DNIC analgesia is probably mediated by opioid receptors in the dorsal horn, along with catecholaminergic and serotonergic

systems. Finally, it should not be forgotten that the brain has a key role in the affective manifestation and cognitive control of pain. The somatosensory cortex, prefrontal cortex, insula and anterior cingulate cortex communicate with the forebrain and limbic structures to exert top-down control of sensory transmission and affective pain expression.(5) The ascending and descending pain pathways are illustrated in Figure 1.

There is also growing evidence of the role of non-neuronal cells in pain signaling, especially in long-lasting or chronic pain. Peptides, nucleotides and neurotransmitters (e.g., substance P, calcitonin-gene-related peptide (CGRP), adenosine triphosphate (ATP)) are released in the periphery upon noxious stimulation and activate immune cells such as mast cells and neutrophilic granulocytes. The neutrophilic granulocytes produce endogenous opioids and cytokines, which probably affect pain sensation. Microglia may even turn into macrophages after pain stimulation and release proteins that can intensify pain responses. It is shown that these glial cells in the DRG can release cytokines and inflammatory mediators which generate hypersensitivity.(6)

Pain has traditionally been classified into physiological pain (previous definitions have distinguished between nociceptive or inflammatory pain) and pathological pain (neuropathic or central nervous system dysfunctional pain). Nociceptive pain occurs when the peripheral nociceptors are stimulated and initiate a pain signal transmitted through the spinothalamic system to the higher brain centers where pain is perceived. Neuropathic pain can be caused by a peripheral or central lesion or disease of the somatosensory nervous system, and it is often spontaneous or usually triggered by a stimulus that would not trigger pain sensation. Previous classifications have considered inflammatory pain to be a combination of nociceptive and neuropathic pain.(7) Recently, a new class has been added by the IASP: nociplastic pain, which is a state of pain pathways being upregulated so that pain is perceived despite no clear evidence of tissue damage, disease or lesion causing the pain.(8) The dysfunctional nociplastic pain may occur in combination with any other type of pain.

6.1.2 Pathophysiology of hyperalgesia

Hyperalgesia is defined as increased pain from a stimulus that normally provokes pain. It is a clinical term that does not imply a mechanism.(9) Traditionally it has been divided into primary and secondary hyperalgesia, which are suggested to be consequences of peripheral or central sensitization, respectively. Primary hyperalgesia occurs at the point of injury as a result of the release of inflammatory mediators in an acidotic environment that increases neuronal excitability through altered functioning of the nociceptors. This is referred to as an "inflammatory soup" and includes neurotransmitters, peptides (substance P, CGRP, bradykinin), eicosanoids (prostaglandins, thromboxanes, leukotrienes, endocannabinoids), neurothropins, cytokines, nucleotides, nerve growth factor, as well as extracellular proteases and protons.(10, 11) Some of the inflammatory mediators can directly activate nociceptors, while other sensitize the pain system through modulation of the receptors.(3) Molecules in the peripheral receptors may phosphorylate and change their activation threshold or localization, thus leading to increased stimuli response at the site of injury. The process of primary hyperalgesia is viewed as reversible. In secondary hyperalgesia, the increased sensitivity spreads beyond the site of injury, possibly due to increased excitability of the dorsal horn by humoral signals from inflamed tissue, enhanced descending facilitation from higher central nervous system (CNS) centers, altered spinal dynorphin expression, enhanced neurokinin-1 receptor mediated transmission or even altered gene transcription. This central sensitization is probably a more prolonged process which is more difficult to reverse, and chronification of postoperative pain is proposed linked to some of these mechanisms. If the peripheral nociceptive input persists and/or spinal inhibitory systems are reduced in efficacy, the increasing central sensitization may be part of the chronification of pain.(12)

There is, however, some controversy to this explanation of the pathophysiology of hyperalgesia. Some believe that all hyperalgesia states after surgery are reflections of sensitization of the central nervous system. For instance, postoperative hyperalgesia may be caused by nociception-induced hyperalgesia as tissue and nerve are injured, but also by opioid-induced hyperalgesia (OIH) from the exposure during anesthesia.(13) With opioid-induced hyperalgesia, hyperalgesia

is induced by opioid molecular action per se. While opioids are effective analgesics by binding to the μ-receptor, they can induce a simultaneous, paradoxical lowering of the pain threshold. As long as the opioid has agonistic activity at the μ-receptor the hyperalgesia will not be evident, but with declining analgesic properties the hyperalgesia may be demasked, leaving the patient more pain sensitive than before opioid administration. OIH will be discussed more extensively in section 6.6.4.

6.1.3 Effects of pain on different organ systems

Acute pain has effects on most of the organ systems in the body, as Breivik has summarized in an article on postoperative pain management.(14) The respiratory system may suffer from alveolar collapse, hypoxemia and decreased oxygen delivery due to decreased tidal volumes, alveolar ventilation, functional residual and vital capacity. Inhibited coughing potentially leads to atelectasis or infection. In the cardiovascular system, pain induces sympathetic activity leading to tachycardia, hypertension and increased peripheral resistance. In vulnerable patients, the increased cardiac work and myocardial oxygen demand can cause myocardial ischemia, infarction or cardiac failure. This increased sympathetic activity even increases tonus in the intestinal muscles and sphincters so that peristalsis is inhibited, and ileus may follow. Urinary retention due to sphincter contraction is also a result of this autonomic imbalance. Furthermore, pain can trigger catabolic hormonal responses, leading to hyperglycemia and sodium and water retention from changes in antidiuretic hormone, aldosterone, cortisol and adrenaline. The immune system is also impaired from this stress response, potentially rendering the patient more susceptible to infection. These effects from pain may cause significant clinical harm and complications in the postoperative period.

6.2 Experimental pain

Pain is inherently difficult to measure objectively in a clinical environment due to its subjective nature and the many confounders that influence the patient's experience of pain. To control for such confounders, studies on analgesics are

often conducted with experimental pain models on patients or healthy volunteers. This is advantageous as the experimentally induced pain can be controlled (the nature, localization, intensity, frequency and duration of the stimulus), and quantitative measures of psychophysical, behavioral or neurophysiologic responses be obtained.(15)

Subject	Stimulus	Measure
• Gender • Age • Health status • Genetics • Epigenetics • Social factors • Testing conditions • Body tissue - Cutaneous - Muscle/bone - Visceral	• Etiology - Electrical - Thermal (heat, cold, laser) - Mechanical (touch, pressure, pinprick) - Chemical (capsaicin, nerve growth factor, glutamate, burn, freeze, menthol, ischemia etc.) • Time point - Single/repetitive - Short-/long-lasting	• Psychophysics - Visual analog scale - Numerical rating scale - Questionnaires - Pain threshold - Pain tolerance • Non-verbal - Behavior (mimics, vocalization) - Autonomic parameters (heart rate, skin temperature, electrical skin resistance, perspiration) - Reflexes (RIII) - Functional MRI - PET scan - Cortical event related potentials - Microneurography - Peripheral nociceptive responses

Table 1. Experimental pain models have three separate main components: the subject, the stimulus method and the measurement tool. The table is based Box 1 "Structure and function of experimental human pain models" from Lötsch et al. (copyright for original table obtained from RightsLink®) and modified with information from articles by Staahl et al. and Olesen et al.(3, 15, 16)

As shown in Table 1, the pain stimulus in experimental pain models can be electrical, thermal, mechanical, chemical or combinations in order to mimic clinical situations. Furthermore, the modalities can be applied to the different tissues: skin, visceral, or muscle and bone. The assessment of the evoked pain can be done by subjective measures (scales, questionnaires or thresholds) or objective

measures (physiological parameters or neurophysiological methods). This allows for the detection of discrete changes in pain intensity so that the analgesic effect can be evaluated, which may not be possible in clinical studies.(15) Experimental pain models in healthy volunteers and animals are also well suited to study basic pain mechanisms.(3, 6) Other advantages to standardized experimental test models are the possibility to: reproduce results with test-retest experiments, perform detailed studies of concentration-effect relationships of analgesics, and explore inter- and intraindividual variability.

Experimental pain models are often divided into 1) acute models and 2) models inducing hyperalgesia. In acute models, the normal physiological mechanisms are usually activated by peripheral nociceptors with thermal heat stimuli, but electrical stimuli which bypass the nociceptors and activate the nerve directly are also used. Other modalities used in acute models are pressure algometry and the cold pressor test (CPT), which both are probably more related to mechanisms in the sympathetic nervous system innervating muscle and nerve fascicles. It is debated if such acute models are relevant in mimicking pathological pain. On the other hand, pain models that invoke central phenomena like hyperalgesia, allodynia, temporal summation and referred pain are believed to better reflect the more chronic pain processes. These phenomena can be evoked by stimulation of all tissues, but skin has been most frequently investigated with intradermal capsaicin, repeated thermal or electrical stimuli.(15)

Experimental pain versus clinical pain

Pain is a subjective experience which is influenced by many factors such as psychological factors (anxiety, depression, personality traits, capacity, stress), gender, age, baseline pain sensitivity, cultural expectations, mood, sleep, testing environment (temperature, lighting, color, sound, research personnel behavior), and concurrent or chronic illness.(17) Experimental pain can only activate parts of the complex mechanisms involved in pathological pain, limiting the translation of experimental analgesic effects to clinical effects. Experimental models with acute stimuli may certainly activate the nervous system in other ways than pain in patients with, e.g., ongoing inflammation. Moreover, the nature of the stimuli are

different; experimental pain stimuli are often induced once or in repeated sequences, while postoperative pain is a more or less continuous stimulus over time. Another significant difference between experimental and clinical studies is the possibility for withdrawal from the painful stimulus at any time point, whereas pain might be inescapable under clinical conditions. To make a correct prediction of clinical analgesia in experimental studies, it is crucial that the correct pain model is chosen for the relevant clinical pain target.(16) So, when testing for analgesic efficacy of a drug used for postoperative pain relief, it is essential that the chosen experimental model activates several tissues to mimic a postoperative setting, and the tested drug must be administered in adequate doses. Experimental pain models may not be perfect, but they help obtain reproducible results and predict how the analgesic will behave in the clinic.(6, 15) Studies conducted with experimental models can also be cost-effective compared to larger clinical trials when trying to evaluate a drug's analgesic efficacy.(16)

6.2.1 Experimental pain models

As there is an extensive battery of experimental pain models to choose from, only the two models, cold pressor test (CPT) and heat pain test (HPT), used during my research for this doctoral thesis will be presented in detail.

Cold pressor test

In the cold pressor test, the test subject submerges the hand and wrist in circulating cold water. A temperature between 0-4ºC is commonly used. This acute and tonic cold pain stimulates peripheral nociceptors and central pain systems, especially the sympathetic nervous system innervating muscle and nerve fascicles, resulting in an immediate, intense pain followed by a radiating, deep and dull aching pain.(15, 18) The neuronal activation in cold pain is not clear, but it probably involves both Aδ- and C-fibers.(15) The CPT is a potent activator of the diffuse noxious inhibitory system as well. Outcome measures are typically: time to onset of pain, pain tolerance measured as time to hand withdrawal, and pain intensity measured by the visual analog scale (VAS) or numerical rating scale (NRS). As the pain response often is reproducible, the model is frequently used for measuring reduction of pain in response to analgesics. However, there are

inconsistencies in the response to different analgesics. No, modest or conflicting results are found in studies of NSAID, antidepressants and paracetamol, whereas for opioids the CPT seems reliable for demonstrating pain reduction.(3, 15, 19) It is necessary to be aware of the limitations of the CPT when examining the literature or when conducting a study. Large variability in the measurement of pain thresholds, withdrawal threshold, and subjective pain have been reported for the CPT. Furthermore, there is a lack of standardization with respect to duration of extremity cooling and how the response is rated.(3) It is important to adhere to a narrow temperature span of the cold water in order to replicate studies, and the possibility of gender variability must also be kept in mind, with men tolerating cold pressor stimulus longer than women.(20)

Heat pain test

Heat pain can be evoked by a gradually heating thermode applied to the skin. The rate the heating is done with is crucial for activation of the Aδ- and C-fibers.(3) Rapid heating of the skin (faster than 1ºC/s) activates the Aδ-fibers first, leading to an initial pain felt within 0.4 s after the heat stimulus is applied. Slow heating (<1ºC/s) gives preferential activation of C-fibers and is felt as second pain. This activation is thought to be more important for the peripheral opioid receptors.(15) Multiple radiation devices and thermodes for heat stimulation with different wavelengths and types of contact are available, so standardized testing is decisive for replicating studies. E.g., the rate of thermal transfer depends on the pressure the thermode is applied with to achieve thermode-skin contact; therefore, it is essential that the thermode is applied to the skin in a standardized way. Stimuli applied with different methods are not necessarily comparable, making comparisons between studies difficult.(3) Another restriction to this modality is the potential tissue damage when repetitive heat stimuli are delivered to the skin. The heat stimulus must also be restricted upwards to about 51ºC to avoid skin burn injuries. The heat pain test has been found both sensitive and insensitive to opioid analgesia, but it is possible that the inconsistencies between studies may partially be explained by differences in the rate heat has been applied or insufficient opioid doses.(3)

6.3 Pathophysiology of pain in the postoperative setting

The following four paragraphs are summarized from the papers “Postoperative pain – from mechanisms to treatment” by Pogatzki-Zahn et al.,(21) and “Molecular mechanisms of nociception” by Julius et al.(10) Elements of the pathophysiology of pain in general, such as inflammation and neural tissue damage are evident in postoperative pain, but the pathophysiology of pain after surgery is also unique with specific consequences. Animal models have shown that incisional pain is different from inflammatory, antigen-induced or neuropathic pain.

There are indications that both peripheral and central sensitization develop after surgical incisions as primary hyperalgesia will occur next to the incision, while there is secondary hyperalgesia in an extended area around the incision and even in the central nervous system. (This is further discussed in section 6.1.2.) In the periphery, C-fibers may be spontaneously activated after incision, leading to sensitization. The decreased tissue pH, oxygen tension and increased lactate concentration at the surgical site, e.g. after using retractor instruments, can contribute to peripheral sensitization as well. After surgery, the nociceptors may be affected by the release of chemical mediators from the sensory terminal of the nerve and from non-neural cells. Some components of the resulting “inflammatory soup” (protons, ATP, serotonin, lipids, bradykinin, nerve growth factor and more) can alter neuronal excitability to increase sensitization. The neuropeptides CGRP and substance P released from stimulated nociceptors are part of a neurogenic inflammation inducing pain with their increased functioning, but they also have tissue-protective effects by clearing the injury site from damage-induced metabolites. The role of inflammatory cell responses in pain has gained more attention in recent years. Neutrophilic granulocytes which release proinflammatory mediators (interleukins and more) and contain endogenous opioid peptides invade the injury site shortly after surgery, reaching a maximum at 24 h before declining to baseline within 3 days, and this is suggested to be instrumental to postoperative pain. Other non-neural cells, such as mast cells, glial cells and macrophages, are involved in the process too.

There is a multitude of molecules involved in central sensitization after surgical incision: phosphorylated extracellular signal-regulated kinases 1/2, brain-derived neurotrophic factor, tumor necrosis factor, inducible nitric oxide synthase, mitogen-activated protein kinase phosphatase 3, monoamine oxidase B, toll-like receptor 4 receptor and cyclooxygenase 2 among others. The details of their significance and interactions are still not fully known. On a higher level, we have little insight into how the brain activity and neuroplasticity react to incisional stimuli, but functional MRI studies indicate at least some involvement of GABA activity in the thalamus when it comes to hyperalgesia. Functional MRI has further been able to visualize a lack of descending inhibition in patients with chronic postoperative pain. It is also possible that changes in phenotype that lead to new gene expressions or activity play a role as well. The consequences of such epigenetic modulation (e.g., DNA methylation and histone acetylation) after incisional pain are investigated, and studies indicate that both peripheral and spinal epigenetic modulation are involved in increased nociceptive sensitization.

Moreover, it is important to bear in mind that postoperative pain depends on the body part involved and the type of surgery. Visceral pain results from distention and ischemia rather than direct trauma and has somewhat different mechanisms from cutaneous pain. Visceral pain is less localized and may have sites of referred pain. It is often associated with autonomic symptoms, which is less observed with cutaneous, nociceptive pain. Typically, gastrointestinal or gynecological surgery will encompass both types of pain, arising from the abdominal wall structures and the viscera. Lastly, small nerve fibers, and sometimes even major nerve trunks, are injured by the incisional trauma and account for a true neuropathic component to the postoperative pain. This neuropathic pain may manifest itself in the immediate postoperative period. In summary, somatic surgical pain is complex and cannot be viewed as a result of an inflammatory process alone or as the result of an isolated injury to the tissue or nerves.

Lastly, it should be stressed that pain is a subjective discomfort of the patient, and postoperative pain in particular can be strongly modulated by many different non-somatic factors such as: demographics (age, gender), psychological aspects (psychological distress, especially anxiety and depression; personality traits,

especially neuroticism and hostility; coping strategies such as catastrophizing and avoidance; available emotional or religious support; preoperative pain levels; pain experience; perception of pain) and surgical factors (type of surgery, duration, cancer diagnosis).(22, 23)

6.4 Postoperative pain epidemiology

Postoperative pain ranges from mild to severe intensity, but in the immediate period after surgery there is often need for strong analgesic medication. A Norwegian study indicated that 38% of in-hospital surgical patients experienced moderate pain and 11% severe pain during the first 24 h after surgery.(24) International studies have reported even higher prevalence of postoperative pain, 55% of patients suffered from moderate to severe pain the first day of surgery in a Dutch study and 76% in a US survey.(22, 25) A Danish study showed that more than 75% of patients received an opioid during the first 3 days postoperatively.(26) Poorly controlled postoperative pain may cause patient discomfort, complications such as thromboembolic events, impaired wound healing, increased heart and lung morbidity, infections, gastroparesis, ileus, prolonged in-hospital stays and higher health care costs.(22) One study has shown that the higher intensity of pain on the first postoperative day, the higher the risk of postoperative complications within 30 days.(25) It has been suggested that poorly managed acute pain after surgery can result in the development of chronic postoperative pain,(22) but the topic is debated and needs further research.

6.5 Principles of pain management and opioids in postoperative care

Over 200 years ago the German pharmacist Friedrich Sertürner made a ground-breaking discovery when he isolated morphine as the first known alkaloid from the opium sap. This discovery is possibly one of the greatest discoveries in modern medicine, not only for morphine’s analgesic properties, but it also led to an avalanche of other alkaloids being discovered, boosting medical progress in many fields. Initially, the opioids were not used during surgery since it was believed that pain was crucial for surviving surgery. It was not until the demonstration of ether anesthesia by William Morton in 1846 the recognition of

pain-free surgery was established. Then followed an era when opioids alone were regarded by many as sufficient pain treatment for surgical patients. Opioids are particularly well suited for peri- and postoperative pain treatment due to the nature of surgical pain, characterized by high intensity, rapid onset, and relatively speaking, short duration. To treat such pain, drugs with rapid onset and high potency are crucial, and there is also need for a diversity of administration forms as well as formulations that provide extended pain relief. Oxycodone, for instance, may be administrated orally, intravenously, intramuscularly, intranasally, subcutaneously, rectally, epidurally and transdermally in either immediate (IR)- or prolonged-release (PR) forms. Opioids remain the sole analgesic medication with these properties and are therefore still essential in current clinical practice. Nonetheless, despite many efforts at the refinement of treatment and prophylaxis over several decades, there has been little success in reducing the prevalence of postoperative pain. Furthermore, the increasing recognition of the far-reaching consequences of opioid side effects with medical and societal problems such as possible chronification of pain and the opioid crisis has turned our attention to a multimodal and opioid-restrictive pain management.

6.5.1 Opioid pharmacology

Some opioids occur in nature (codeine, morphine), but most are semi-/synthetic (alfentanil, buprenorphine, fentanyl, heroin, hydrocodone, hydromorphone, ketobemidone, methadone, oxycodone, pethidine, remifentanil, sufentanil, tapentadol, tramadol). The body itself produces endogenous opioids: dynorphin A, dynorphin B, β-endorphin, endomorphin 1, endomorphin 2, met-enkephalin and leu-enkephalin. There are opioids with pure agonistic effects on opioid receptors, but there are also drugs (buprenorphine and nalbuphine) with partial agonist or mixed agonist-antagonist features. Naloxone and methylnaltrexone are antagonists to opioid receptors. An attempt at summarization based on a PubChem search and articles by Pathan, James and Williams is shown in Table 2.(27-29)

The opioids are further classified by their receptors, and there are three well-recognized receptors in the opioid receptor gene family, μ, δ and κ. A fourth receptor, the nociceptin/orphanin opioid peptide receptor, has a high sequence

identity with the other opioid receptors but little affinity for opioid peptides, which has left it somewhat overlooked among the opioid receptors. Interestingly, recent research has showed promising results for evoking analgesia with reduced side effects when stimulating this receptor.(30)

The receptors are termed MOP, DOP, KOP and NOP in the current classification by the International Union of Basic and Clinical Pharmacology. It is highly debated which opioid receptors the different opioids mainly act upon, but all opioids in clinical practice today exert their action at least in part at the μ-receptor with varying activity at the other receptors (Table 2). After agonist binding the different receptors have different effects. MOP receptor activation results in analgesia, but also side effects such as sedation, respiratory depression, reduced gastric motility, nausea and vomiting. Activation of DOP receptors may cause

Agonists	Partial agonist	Mixed agonist-antagonist	Antagonists
Alfentanil (**μ**) Codeine (**μ**, κ, δ) Fentanyl (**μ**) Hydrocodone (μ) Hydromorphone (μ) Ketobemidone (μ) Methadone (**μ**, κ, δ) Morphine (**μ**, κ, δ) Oxycodone (**μ**, **κ**, δ) Pethidine (μ, κ, δ) Remifentanil (**μ**, κ, δ) Sufentanil (μ) Tapentadol (**μ**) Tramadol (**μ**)	Buprenorphine (**μ**-agonist, κ-antagonist)	Nalbuphine (μ-antagonist, κ-agonist)	Methylnaltrexone (**μ**, κ, δ) Naloxone (μ, κ, δ)

Table 2. Drugs classified by mode of action on opioid receptors and which group of opioid receptors they act upon. Receptor highlighted in bold caption is believed to be the main receptor activated.

analgesia and reduced gastric motility, while KOP receptor stimulation can produce analgesia, diuresis and dysphoria (see also 6.6.1).(29)

The opioid receptors are part of the superfamily of G protein-coupled receptors which are linked to Go/Gi inhibitory proteins. The cellular responses following receptor activation are similar for all of the receptors. Upon agonist binding, subunits of the G-protein are freed to interact with target proteins and this results in adenylate cyclase inhibition, which in turn reduces the intracellular cyclic adenosine monophosphate (cAMP) levels that affect membrane repolarization. The G-protein subunits further inactivate calcium channels and activate potassium channels, leading to decreased neuronal excitability. A G protein-independent signaling pathway via β-arrestin is also involved in opioid signaling, leading to internalization or desensitization of opioid receptors and activation of mitogen-activated protein kinase cascades. Overall, opioid receptor activation leads to inhibited neuronal activation.(29, 31, 32)

It has recently been shown that G protein-coupled receptors exist in multiple confirmations and that the binding of different agonists can result in distinct receptor-effector complexes that produce varying levels of activated or inhibited signaling cascades. This biased agonism (towards G-protein and away from β-arrestin intracellular signaling) is the basis for the emerging class of biased μ-receptor ligands which aim to produce analgesia with less side effects.(31) Studies have shown that activation of the G-protein pathway distal to the μ-receptor results in analgesia, while activation of the β-arrestin pathway is associated with opioid-related side effects as well as inhibition of G-protein-mediated analgesia.(22) There are also some indications that opioid receptors can be affected by the cellular environment they exist in so that the receptors may transform themselves to heterodimeric structures given certain changes in the environment, and this potentially leads to alterations in opioid signaling.(33, 34)

The opioids' analgesic effects mainly emanate from spinal and supraspinal opioid mechanisms, but opioid receptors are found outside the CNS in the peripheral tissue, immune system, vas deference, heart, eye and gastrointestinal tract as well. In the spinal cord, the μ-receptors are located mainly in the substantia gelatinosa

of the dorsal horn and the majority (70%) of the receptors are located presynaptically.(3) Hence, the opioids exert their effect by presynaptic inhibition, decreasing the release of neurotransmitters in C and Aδ fibers, but some postsynaptic mechanisms contribute to opioid effects too. In sum, the output from the spinal cord is attenuated by opioids.(3)

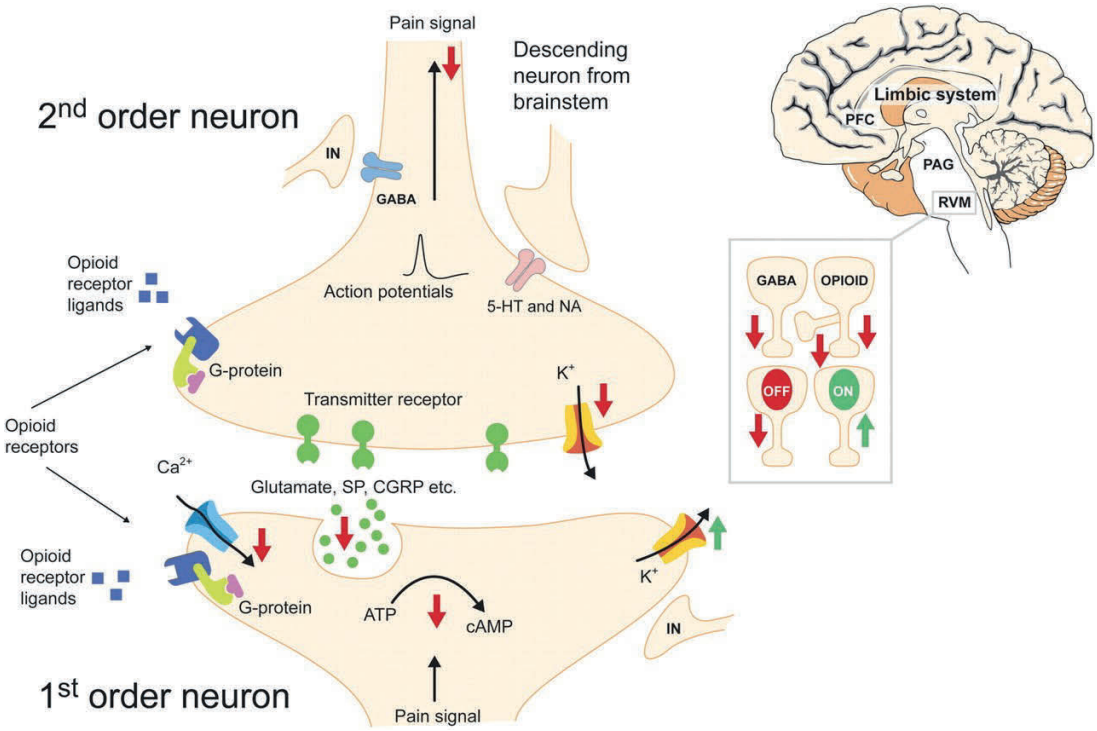

Figure 2. Molecular mechanisms for opioid actions in the CNS. Red arrows represent decrease, green arrows represent increase. Left, the presynaptic action of opioid receptor activation involves inhibition of calcium influx by enhancing outward movement of potassium or by inhibiting adenylate cyclase (the enzyme that converts ATP to cAMP). The release of neurotransmitters such as SP and CGRP is inhibited. The majority of opioid receptors are located presynaptically (70%). Postsynaptic action of opioid receptor activation involves inhibition of potassium ion efflux, which decreases neuron excitability. Right, the general organization of the supraspinal opioid control mechanisms. Opioids excite neurons in brain areas mainly in the limbic system, such as prefrontal cortex (PFC), hypothalamus, amygdala, and cingulate gyrus and thereby indirectly excite neurons in periaqueductal gray (PAG). Opioids also directly excite neurons in PAG, which project to the RVM. Opioids affect ON and OFF cells in RVM by inhibiting opioid receptor-bearing ON cells. They also inhibit GABAergic inputs to OFF cells, which are then disinhibited, again leading to inhibition of nociceptive transmission. RVM neurons project to substantia gelatinosa of the dorsal horn and exert inhibitory or excitatory influence on transmission via interneurons (IN) (left). Because GABA is a major inhibitory neurotransmitter and will inhibit the facilitatory pathways, GABAergic neurons also play a role in descending control to spinal cord level. SP substance P. Figure from Olesen et al., "Human experimental pain models for assessing the therapeutic efficacy of analgesic drugs", Pharmacol Rev 2010;64:722-9. Reprinted with permission from ASPET.

The prefrontal cortex, hypothalamus, amygdala, cingulate gyrus, PAG and RVM in the brain stem are the main supraspinal sites for opioid action. In these areas, opioid agonists bind to receptors that activate descending inhibitory neurons. There is also stimulation of serotonin- and enkephalin-containing neurons that communicate with the dorsal horn, blocking nociceptive transmission from the periphery. Figure 2 illustrates opioid mechanisms in the CNS.

In the periphery, opioid receptors are synthesized in the DRG and transported to both peripheral and central terminals of the primary afferent neuron. The antinociceptive effects upon opioid agonist activation of a peripheral receptor may be produced by many of the same mechanisms described for opioid receptor activation in the CNS. There are changes in calcium and potassium currents leading to hyperpolarization of the neuronal membrane, inhibition of cAMP production and decreased release of excitatory transmitters such as substance P, which reduce the excitability. Upon injury and inflammation of peripheral tissue, increased synthesis, axonal transport, membrane-directed trafficking and G-protein coupling of opioid receptors in the DRG ensue. Thus, in inflammatory pain states, there is increased receptor expression in the peripheral tissue causing enhanced potency of opioids. This opens up to opioid therapy outside the CNS, potentially with less side effects.(35, 36)

Furthermore, there are significant associations between an individual's genetic profile and drug response. This paragraph on genetics and opioids is summarized from two articles by Klepstad et al. and Stamer and Stüber.(37, 38) Genetic variables can modify both the pharmacokinetics and pharmacodynamics of drugs. Polymorphisms, i.e., genetic variations where individuals differ in their DNA sequence at a certain point of the genome, can cause alterations in drug effects that influence an individual's sensitivity to a drug and the regulation of metabolic pathways. The polymorphisms may occur within systems related to drug uptake, transport, metabolism or at the effector site, such as a receptor or an ion channel. For instance, the gene coding for the μ-receptor has many polymorphisms which can result in altered receptor functioning, while proteins important to transport of opioids over the blood-brain barrier also has genetic variation. The CYP450 gene

family is vital for drug metabolism, and the polymorphic CYP450 enzymes have considerable interindividual variability in catalytic activity. Genetic polymorphism of these enzymes leads to many different combinations of alleles, resulting in phenotypes of poor, intermediate, extensive and ultrarapid metabolizers of drugs. Especially the isoenzyme CYP2D6 is relevant for the metabolism of some opioids (codeine, tramadol, oxycodone, methadone, hydrocodone) into active metabolites with analgesic effect.

Considering all the steps where opioid signaling can be influenced: which agonist is used, different receptor bindings, intracellular protein actions, the receptors' environment and genetic variation to opioid metabolism, there is no wonder a plethora of pharmacological responses to opioids is seen. This partially explains the longstanding, but disputed, clinical observations of high variability in opioid effects seen between patients, and it also gives support to the notion of opioid rotation.

6.5.2 Specific opioids

The focus of this thesis has been the analgesic effects and the side effects constipation, nausea/vomiting and OIH occurring in the postoperative period from the three different opioids: oxycodone-naloxone, tapentadol and remifentanil.

Oxycodone-naloxone

Oxycodone (6-deoxy-7,8-dehydro-14hydroxy-3-O-methyl-6-oxomorphine) is a semi-synthetic derivative of thebaine. It has a relatively high oral bioavailability (>60%), and the metabolites have some clinical effect. It is metabolized by the CYP450 system in the liver to active metabolites, while clearance is done by the kidneys. The T1/2 is 2-3 h after intravenous (i.v.) administration, about 3 h for IR formulation and about 8 h for ER formulation, while maximum plasma concentrations are reached after 0.4, 1.3 and 2.6 h, respectively.(39) The oral oxycodone:morphine dose ratio is about 1:1-1:1.5. Oxycodone has agonist effects on the κ-receptor as well as the μ-receptor, which may in part, explain why it has been shown better efficacy for visceral pain in several studies.(40) It comes in a

wide range of oral and parenteral preparations and has surpassed morphine as the most used opioid worldwide.

Targiniq® is a molecule mixture with a fixed combination of prolonged-release (PR) oxycodone and PR naloxone designed to address opioid-induced constipation. The opioid receptor antagonist, naloxone, has negligible systemic availability when administered orally because of extensive first-pass hepatic metabolism. It acts by blocking enteric μ-receptors so that peristalsis and gastric emptying can be preserved, while analgesia is maintained by the oxycodone that enters the CNS.(31, 41, 42) Several studies on chronic non-malignant, cancer and postoperative pain patients have shown less constipation due to the naloxone effect on the μ-receptors in the gut wall without impairment of the general analgesic efficacy of oxycodone.(42-46) Metabolism of this combination drug is done by both gut and liver, and excretion occurs in feces and urine.

Tapentadol

Recently, a class of mixed ligand opioids with effects on non-opioid sites, often termed bifunctional ligands or MOR-NRI drugs, has been developed. Tapentadol hydrochloride (3-[(2*R*,3*R*)-1-(dimethylamino)-2-methylpentan-3-yl]phenol) acts as a partial agonist on μ-opioid receptors in combination with inhibition of noradrenaline reuptake in the CNS. The increased noradrenaline levels at the spinal synapses activate postsynaptic alfa-2 adrenoreceptors and result in an analgesic effect by potentiating descending inhibitory control (Figure 3).(12, 31) This dual mode of action is supposed to give synergistic analgesic effects.

Tapentadol has a "μ-load" of ≤ 40% compared to classic opioids which have a "μ-load" of 100% by definition. The concept of "μ-load" is an attempt to look at the relative contribution of tapentadol's opioid component to analgesia and adverse effects relative to pure μ-opioid receptor agonists at equianalgesic doses.(48) Since there is less stimulation of the μ-opioid receptors less side effects are expected, making tapentadol beneficial over the pure opioid agonists.(12, 48-50) Another advantage is a low drug interaction potential as tapentadol is an active compound without metabolites and not reliant on enzyme systems.(49, 51) It is

metabolized mainly by UGT glucuronidation in the liver but also by the CYP450 system. Almost all of the excretion of the drug and metabolites is in the urine.

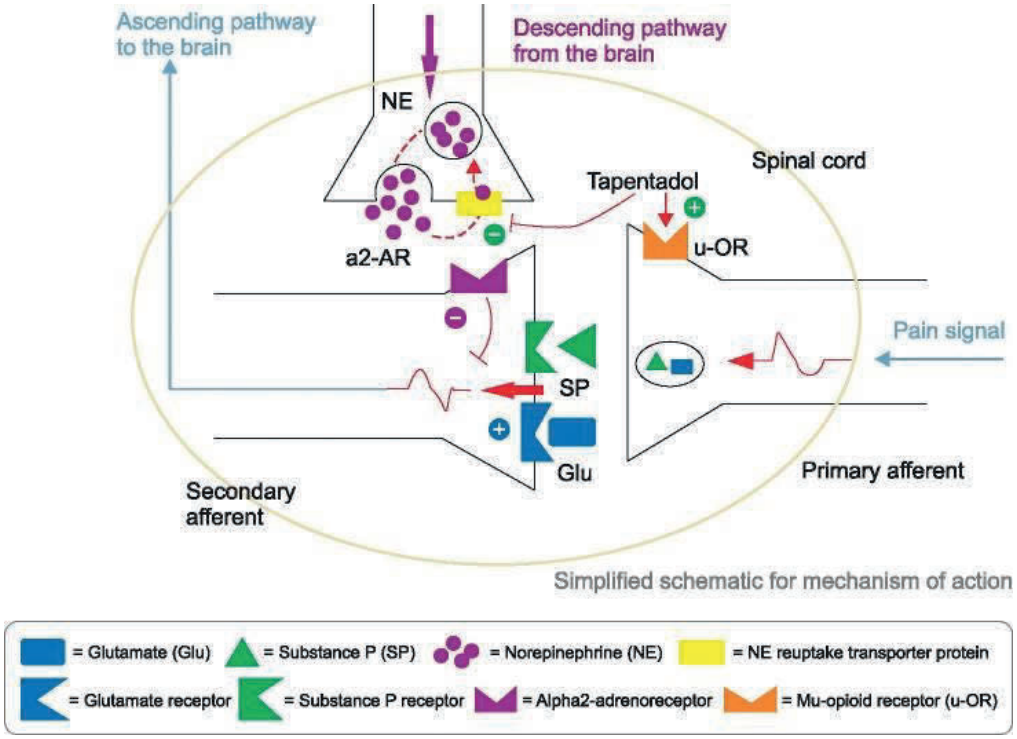

Figure 3. The dual action of tapentadol. Figure from Chang et al., "Tapentadol: Can it kill two birds with one stone without breaking windows?", Korean J Pain 2016;29:153-7.(47) The article is open-access with permission for unrestricted non-commercial use, distribution, and reproduction in any medium.

Tapentadol is available as IR (Palexia®) and ER (Palexia depot®) formulations, but the i.v. formulation is not yet marketed in Europe. T1/2 is about 4 h for the IR formulation and about 5-6 h for the ER formulation, while plasma concentrations are at their maximum after 1.25 and 3-6 h, respectively. An approximately 1:5-1:7 ratio in analgesic potency between oxycodone and tapentadol is assumed for both IR and PR formulations.(52, 53)

There are relatively few clinical studies published on the analgesic effect and side effects of tapentadol since it is a new drug. Tramadol, however, has been on the market for decades and has similar properties to tapentadol. They are both monoaminergic drugs, but tramadol additionally has a serotonergic function. It is

believed that serotonergic mechanisms partially cause nausea and vomiting, and since tapentadol is devoid of these mechanisms it may potentially be a better drug than tramadol, side effect wise. Tapentadol has been shown to be an effective analgesic with less gastrointestinal side effects in studies on acute or chronic nociceptive, neuropathic or cancer-related pain.(52, 54-57)

Remifentanil

The synthetic opioid remifentanil hydrochloride (3-(4-methoxycarbonyl-4-[(1-oxopropyl)-phenylamino]-L-piperidine) propanoic acid, methyl ester) is a piperidine derivate. It is unique among the opioids for several reasons. It is about 100-200 times more potent than morphine, has a strong affinity for the μ-receptor, is lipid-soluble and ultra-short acting with a context-sensitive half-life of minutes (± 4-8 min), allowing for rapid onset of analgesia (± 1 min) and fast, predictable recoveries. It is metabolized by plasma and tissue esterases and can safely be used in patients with liver or renal impairment. Its metabolite is 800-2000 times less potent than the mother compound.(58, 59) Among the clinically available opioids, remifentanil is the only one that does not accumulate with prolonged infusion, making it very beneficial in long-term use.(59, 60) It is commonly used as i.v. infusion for general anesthesia and intensive care sedation, but it can also be administered as pain relief for parturients and postoperative patients.(60, 61) It is the most studied opioid in regard to OIH, and a meta-analysis found that high intraoperative doses of remifentanil are associated with a significant increase in postoperative pain and more need for rescue opioids the first postoperative day.(62) Remifentanil is only available for infusion and marketed as Ultiva® in Norway.

6.6 Opioid-induced side effects

6.6.1 General considerations

The focus of this thesis has been three opioids commonly used peri- or postoperatively. The opioids are all important to analgesia but may also result in side effects that influence patient comfort or even induce severe complications in the postoperative period. Agonism of the μ-receptor is mainly responsible for the

analgesic properties of opioids, but as the side effects are linked to stimulation of the μ-receptors too, the good and the bad are intertwined. It is becoming more and more evident that the opioids in clinical use today also have significant functional interaction with the other opioid receptors resulting in both analgesia and other effects (Table 3).(27)

MOP	DOP	KOP	NOP
Analgesia Sedation Respiratory depression Bradycardia Nausea/vomiting Reduced gastric motility	Spinal/supraspinal analgesia Reduced gastric motility	Spinal analgesia Diuresis Dysphoria	Analgesia Less respiratory depression?

Table 3. Effects by agonist binding to the MOP, DOP, KOP and NOP receptors. Based on information in article by Pathan and Williams.(27)

There are many well-known side effects of opioids differing in frequency between the opioids, dose, setting, route and speed of administration, as well as inter- and intraindividual differences.(63-65) Besides patient- and drug-related factors, the occurrence of side effects is influenced by disease-related and social factors.(30) Some of the side effects will, for these reasons, occur more frequently in some settings than others and may accordingly be reported differently outside the postoperative setting (Table 4). In a review on adverse events associated with postoperative opioid analgesia, the most frequently reported side effects were nausea, vomiting, pruritus, somnolence, dizziness, psychoses and urinary retention.(64) Mechanisms behind gastrointestinal side effects and opioid-induced hyperalgesia will be explored further as they have been the focus of my thesis, while other opioid-induced side effects will only be touched upon briefly.

A common misconception is that increased tolerance to the analgesic effects of opioids is associated with increased tolerance to side effects; thus, gradually increasing the dose for analgesia would not entail any greater risk of harm to the

patient. It is, however, shown that opioid analgesic tolerance can develop within a short time frame after exposure to high doses (a phenomenon termed tachyphylaxis). It also appears that tolerance to all opioid effects do not coincide; opioid tolerance development is fastest for analgesic actions, less for respiratory depressant effects, and even less for the peripheral gastrointestinal effects. The concept of differential tolerance development has been introduced to explain that different effects of opioid drugs do not develop tolerance at the same speed and to the same degree.(68)

Very common	Common	Less common	Rare/unknown
Nausea Vomiting Constipation Pruritus Dizziness Sedation Cognitive impairment Miosis Negative chronotropy Respiratory depression	Dry mouth Insomnia or reduced quality of sleep Reduced appetite Urinary retention Myoclonus, tremor Rigidity (“stiff chest”) Cough suppression Hyperalgesia Headache Dyspepsia Hyperhidrosis Tolerance	Ileus Hallucinations Delirium Mood changes (anxiety, depression) Seizures Bronchoconstriction Allodynia Biliary spasm Non-cardiogenic pulmonary edema Physical dependence Psychological addiction	Urticaria Hypotension (severe) Negative inotropy Cancer Infection Endocrine changes Immunosuppression

Table 4. Opioid side effects and frequency in the peri- and postoperative period. The table is a summary based on information in chapter 31 of Wall & Melzack’s Textbook of Pain, information on opioid side effects in Felleskatalogen and clinical experience. (66, 67)

6.6.2 Opioid-induced constipation and postoperative ileus

Opioid-induced constipation (OIC) has no generally accepted definition,(69) but has been proposed to be a change from baseline bowel habits (reduced bowel movement, reduced frequency, straining to pass bowel movements, sense of incomplete rectal evacuation or harder stool consistency) after initiating opioid therapy.(70) It is the most common side effect in long-term opioid therapy, but it may also occur in the initial postoperative period.(41, 70, 71) Development of

tolerance is rarely seen in this side effect, so constipation often persists and requires treatment.(41, 72)

Three of the opioid receptors have been identified in the human intestinal tract. Although δ- and κ-receptors are involved in colonic motility,(30, 73) it seems like the stimulation of μ-opioid receptors located in the myenteric plexus and submucosal plexus are mainly responsible for OIC.(41, 74) Opioids increase the tonus of the smooth musculature in the gut, resulting in reduced peristalsis. Opioids additionally inhibit the neurotransmitters acetylcholine, nitric oxide and vasoactive intestinal peptide, which are important to coordination of gut motility. Together with decreased secretion in the gut and increased contraction of sphincters, these factors result in OIC.(41, 70) Constipation can further lead to complications such as colonic distention, ileus and perforation, and the economic burden of OIC is viewed as substantial.(70) For these reasons, it has been essential to develop pharmacological treatments such as the systemic opioids with peripherally acting opioid receptor antagonists, to relieve pain without concomitant constipation.

Postoperative ileus also lacks consensual definition but may be defined as cessation of bowel mobility after surgical intervention. This is a common occurrence after gastrointestinal, pelvic and even non-abdominal procedures. Due to the lack of definition the estimates are broad, but some state incidences between 10-30% in patients undergoing abdominal surgery.(74) The pathophysiology of postoperative ileus is complex, involving intestinal paralysis due to pain and surgical stress responses, as well as inflammatory, fluid, electrolyte, pharmacological and neurogenic factors that interact.(74) As opioids independently impair gastrointestinal motility, it is difficult to distinguish the impact of opioids on postoperative ileus from surgical reasons in clinical studies.

6.6.3 Nausea and vomiting

Postoperative nausea and vomiting (PONV) occurrence is hard to estimate due to variation between patient populations, but incidences between 22-52% are commonly stated in surgical populations.(75) Many patients find these side effects

quite bothersome and rate them high among outcomes they would like to avoid after anesthesia.(76-78) Nausea, and especially retching or vomiting, can lead to complications due to aspiration, wound rupture, esophageal rupture, bleeding, and raised arterial, intracranial or intraocular pressure.(74, 76) PONV may result from the surgery itself, pain or the volatile anesthetic and opioid components used for general anesthesia.

The mechanisms for opioid-induced nausea and vomiting are not fully elucidated. Opioids in circulating blood or cerebrospinal fluid can directly activate μ-receptors in the chemoreceptor trigger zone. This is an area in the medulla important to vomiting. The chemoreceptor trigger zone and the nucleus tractus solitarius in the brain stem both receive vagal afferent input from the gastrointestinal tract, which can induce vomiting. Furthermore, the vestibular sensitivity may be enhanced by direct stimulation of μ-receptors in the vestibular epithelium, and also gastric emptying is delayed by opioids.(65, 74, 76, 79)

The surgery in itself can elicit stress responses with gastrointestinal symptoms overlapping opioid side effects. For instance, the sympathetic hyperactivity from pain after surgery cause reflex inhibition of gastrointestinal function leading to paralytic ileus, nausea and vomiting. This can be a significant confounder in studies on opioid-induced side effects.

Use of opioids peri- and/or postoperatively is one of the risk factors for PONV along with female gender, non-smoking status, and previous PONV or motion sickness. Surgical factors such as type of surgery and duration, and choice of anesthetic agents are also associated with PONV.(80) Nausea and vomiting are more common during the initiation of opioid therapy, it is dose-related, and tolerance usually develops rapidly.(65) PONV may occur despite use of pre-emptive antiemetics, which pose additional problems with increased risk of side effects from the adjuvant drugs, drug interactions and increased total cost.

6.6.4 Opioid-induced hyperalgesia

An opioid side effect that has received increasing attention in the last decades is opioid-induced hyperalgesia (OIH). In OIH, a lowered pain threshold occurs after opioid exposure. So, paradoxically, patients may experience more pain after

opioids being administered than they would without exposure to opioids. With OIH, an increase in opioid dose would only aggravate pain due to further lowering of the pain threshold, thus increasing sensitivity to a stimulus. It is debated whether this stimulus could be of both nociceptive and non-nociceptive nature. This contrasts with opioid tolerance (also termed acute opioid tolerance or opioid-induced tolerance) where there is a gradual decrease in analgesic efficacy of the opioid, and an increased dose would resolve the pain. Various definitions of OIH and opioid tolerance have been stated in several reviews.(68, 81, 82) The difference between OIH and opioid tolerance is conceptually easy to understand, but it is difficult to separate the two in a clinical situation as both present as increased pain.(68) Table 5 provides an attempt at a summary of mechanisms and how to differentiate the two states.

	Opioid tolerance	Opioid-induced hyperalgesia
Mechanisms	Desensitization of pain signaling pathways to opioids (loss of potency) Induced by higher doses of opioids rather than low	Opioid-mediated sensitization of pain signaling pathways Induced by higher doses of opioids rather than low
Differentia-tion between states	Increased opioid dose can resolve the pain No sign of reduced pain threshold or hyperalgesia outside the immediate site of injury Development of tolerance to some opioid side effects may be observed over time	Increased opioid dose will aggravate the pain Lowered pain threshold in general which increases sensitivity to non-/painful stimuli Spread of pain to other locations than site of surgery May be stimulus-specific (e.g. heat stimuli)

Table 5. Features characteristic of opioid tolerance and OIH.

Mechanisms behind OIH are thoroughly described in many articles and reviews.(82-88) A compilation of these articles is done in the following six paragraphs. The detailed mechanisms behind OIH are not yet fully elucidated, but several pathways have been explored. OIH has been described in terms of an "opponent process theory", whereby the exogenous central effect of the drug (antinociceptive activity) is counter-balanced by an endogenous response (pronociceptive activity).(68) At a neuronal level, the mechanisms can be divided into (i) sensitization of primary afferents (ii) sensitization of second order neurons to excitatory neurotransmitters and (iii) adaption of descending pain control which causes upregulation of nociceptive neuromodulators and increased glutamate release by primary afferents.

The peripheral μ-opioid receptors on primary nociceptors are seen as crucial in the development and maintenance of OIH by many researchers, although this has been debated.(85) Opioids may sensitize the primary afferents since they act conjointly as NMDA receptor agonists. Stimulation of the NMDA system leads to suppressed reuptake or increased release of the excitatory neurotransmitters glutamate, aspartate and substance P. Central sensitization may result from NMDA receptor activation in the dorsal horn and the RVM. Furthermore, the NMDA receptor is believed to be important in long-term potentiation (LTP), which is a sensitization of homosynapses causing increased strength of the synapse and its signal transduction. LTP is shown to occur at synapses between C fibers and neurons in the dorsal horn after opioid administration. This will lead to hypersensitivity and thereby contribute to hyperalgesia. Since LTP and OIH share many common signaling pathways, it is believed that LTP is of importance in OIH development.

It is also likely that descending pain systems are involved in OIH. In the RVM, the subsets of neurons, ON and OFF cells, mediate pain transmission. The ON cells can be paradoxically stimulated by opioids to increase pain signal transmission, acting via cholecystokinin and upregulation of spinal dynorphin. Dynorphin probably sensitizes NMDA receptors, which cause a release of cytokines and excitatory neurotransmitters. It is shown that opioid infusion increases dynorphin leading to a release of CGRP from primary afferents, which

in turn enhances the pro-nociceptive input at the spinal level. As dynorphin is an endogenous opioid, this attests to opioids not being entirely antinociceptive in nature.

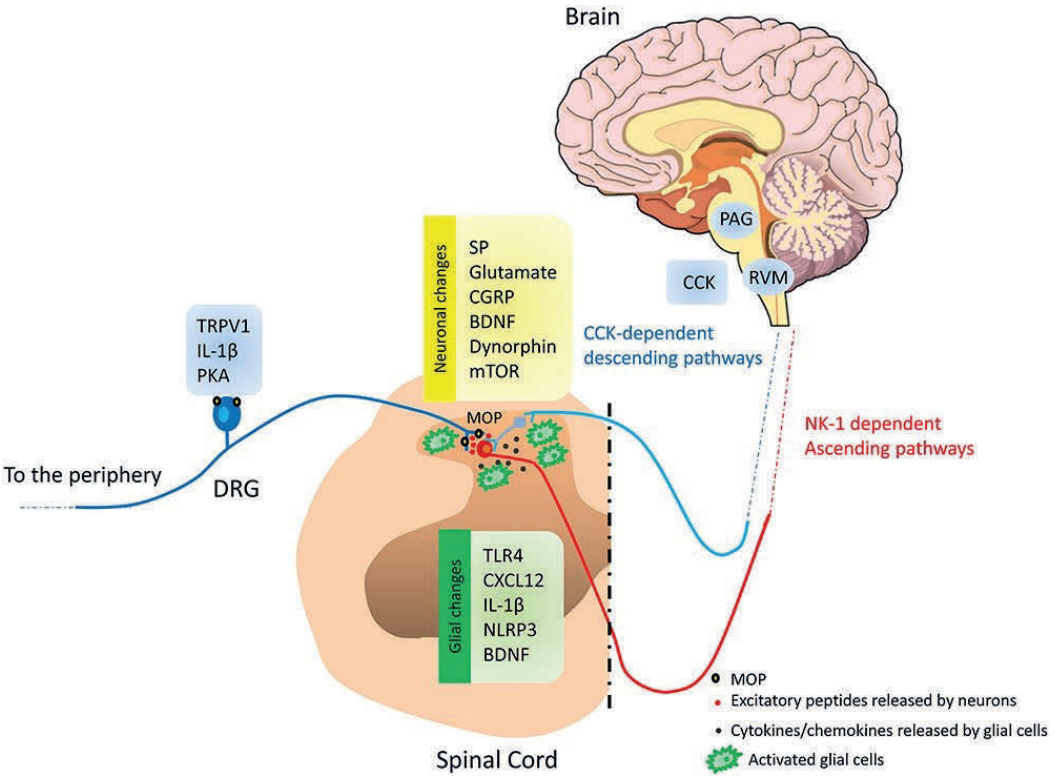

Figure 4. Opioid-induced pain sensitization may occur in the periphery, centrally and in ascending and descending pathways. In the periphery changes in TRPV1, IL and PKA are examples of changes that increase transmission and lead to release of excitatory substance P, glutamate and CGRP in the dorsal horn. In the spinal cord glial cells sensitize neurons through mechanisms such as mammalian target of rapamycin (mTOR) or they lead to overactivity of ascending pathways through chemokines, cytokines and brain-derived neurotrophic factor (BDNF). An increase in CCK in RVM after opioid administration may activate descending facilitatory pathways to increase excitatory peptides in the spinal cord. CCK cholecystokinin; CXCL12 stromal derived factor 1; MOP μ-opioid receptor; PKA protein kinase-A; SP substance P; further abbreviations see text. Figure from Rivat and Ballantyne, "The dark side of opioids in pain management: basic science explains clinical observation", Pain Rep 2016;1:e570.(84) Permission to reprint figure is obtained from RightsLink®.

Sensitization of afferent pathways by other neurotransmitters and receptors has also been suggested. For instance, after noxious stimulation, substance P is synthesized in primary afferent nociceptors and released in the dorsal horn where it binds to neurokinin-1 receptors. This leads to an upregulation of the neurokinin-1 receptor activity which has been implicated in OIH. Several other molecular targets have been suggested as well; antagonists to the transient receptor potential cation channel subfamily V (TRPV1) and 5-hydroxytryptamine receptors have been found to block OIH, indicating an involvement of these mechanisms too.

Recent research has shown that even neuroinflammatory mechanisms participate in the development of OIH. Opioids trigger astrocytes and activate microglia, which results in the release of excitatory substances such as cytokines (TNF-α, IL-6, IL-1β) and other chemokines. The cytokines probably act by increasing AMPA and NMDA receptor activity while down-regulating GABA receptors, all contributing to neuronal hyperexcitability which establishes and maintains OIH. Figure 4 is a simplified illustration of some of the mechanisms involved in opioid-induced pain sensitization.

OIH is also under the influence of gender, species and genetics, and depends on the dose of opioid used. For instance, females are suggested to be more prone to OIH than males in animal studies. Genes may play a role via different genotypes for the enzyme catechol-O-methyltransferase which breaks down catecholamines; this is of significance since varying levels of catecholamines in synapses affect pain sensitivity. The genetic variability of μ-opioid receptors partially explains why there are observed differences in studies on OIH. Epigenetic adaptions are now studied to see if environmental impact on DNA leading to modulation of gene transcription can be part of the mechanisms behind OIH.

The differentiation between OIH and acute opioid tolerance is difficult, both in studies and in the clinical setting. It is debated whether these two phenomena are two different entities or overlapping from the same mechanisms.(81) In acute opioid tolerance, desensitization may occur after opioid receptor down-regulation or uncoupling of the receptor from G-protein leading to internalization of the receptor.(82) Heterodimerization with other receptors such as chemokine

receptors has been implied as a mechanism behind opioid tolerance too.(81) Alterations of the NMDA receptor and its intracellular messenger systems seem just as important to the development of acute tolerance as for OIH. To sum up, one might say that tolerance results from desensitization of antinociceptive pathways to opioids, while OIH results from opioid-mediated sensitization of pronociceptive pathways.(89)

The knowledge on the clinical relevance of OIH so far is well described in a systematic review and meta-analysis by Fletcher and Martinez.(62) They found a small but significant increase in acute pain after surgery in patients who received remifentanil. It should also be noted that analgesic and hyperalgesic effects can coincide as studies on fentanyl and remifentanil have shown development of hyperalgesic areas while lowering or not affecting pain scores.(90, 91) It may be that the opioid's analgesic effect, to some degree, conceals parallel ongoing hyperalgesia. Many studies have been conducted on adjuvants such as ketamine, NSAID, clonidine, gabapentin, magnesium, propofol and nitrous oxide to prevent OIH after opioid administration.(91-97) The drawback to the adjuvant approach is the potential of adding new side effects from other groups of drugs and drug interactions. Modulation of dose, infusion rate, infusion length and withdrawal of administration are therefore of interest when studying OIH prevention.

6.6.5 Other side effects

We have also registered other opioid side effects in the studies in this thesis for exploratory and safety reasons. Respiratory depression, pruritus, sedation, headache and dizziness are important when determining whether new opioids have more beneficial effect versus side effect profiles. These side effects were included as secondary aims and were not powered for in the clinical studies, but they were analyzed for tendencies to make suggestions for further research.

Respiratory depression needs special attention as it is the most feared side effect due to its potentially lethal outcome. Opioid receptors are present in the solitary tract of the brain stem, and this is probably the main area responsible for the respiratory effects of opioids. Opioid receptors involved in respiration are additionally found in higher centers such as the thalamus, insula and anterior

cingulate cortex, but they are also located in the carotid bodies and the nervus vagus in the periphery. When opioids stimulate these receptors, the respiratory rhythm generation is affected and the respiratory centers become less sensitive to pCO_2, thus increasing the risk of respiratory depression and arrest.(98) The effect is dose-dependent, and patients who are opioid-naïve, at the extremes of age or have pre-existing respiratory disorders are more at risk.(99, 100) A common conception is that tolerance develops after continuous opioid therapy and that patients on high doses may not be respiratory affected at all. This is debated in the newer theories on differential tolerance, which was discussed in section 6.6.1. It is now a more common view that while tolerance for the analgesic effect develops rather quickly, tolerance for respiratory depression does not, and the risk of fatal complications increase as higher doses of opioid are administered to achieve pain relief even in the opioid tolerant patient.

It is shown that the respiratory center responds to nociceptive input; hence, pain can counteract respiratory depression.(65, 98) It is worth noting that respiratory depression often is accompanied by sedation, which can be used as an indicator of imminent respiratory problems in the clinical setting.(101) The incidence of opioid-induced respiratory depression in the perioperative setting has been claimed to be as low as <1%,(30, 100) while others find that it occurs in as much as 46% of postoperative patients.(99) Since opioid-induced respiratory depression has no clear definition, it is difficult to find reliable and feasible measures and coherent outcomes in studies on the topic.(65, 100, 101) Any low occurrence of respiratory depression is probably partly due to close monitoring of opioid-induced respiratory depression, and extensive resources are often used to monitor respiration in the postoperative care unit and other wards when opioids are administered.

It is beyond the scope of this thesis to elaborate on the side effects of physical dependence and psychological addiction, but in the light of the opioid crisis the Western world is facing, it seems crucial to mention that these side effects may be initiated by therapeutic opioid use in postoperative care. Physical dependence can develop acutely depending on the dose and dosing intervals even after short-term use, and the withdrawal symptoms are characteristic with diaphoresis, yawning,

lacrimation, tachycardia, generalized pain, nausea and vomiting. The psychological dependence, also termed addiction, is characterized by a behavioral pattern of compulsive drug use resulting in physical, psychological and social harm. It does not usually occur after short-term therapeutic use in patients with acute postoperative pain. Anesthesiologists should not ignore their responsibility in the task of limiting opioid use and misuse after surgery.(102)

7. Aim and research questions

The main aim of this thesis was to study analgesic effects and important side effects of different opioids in the postoperative setting.

Specific research questions and study interventions:

1) Can the addition of peripherally acting naloxone to the centrally acting opioid oxycodone prevent opioid-induced constipation postoperatively?
   In a clinical study on hysterectomy patients, the molecule mixture of prolonged-release oxycodone and naloxone was compared with prolonged-release oxycodone administered orally for 3 days postoperatively (Paper I "Targiniq study").

2) Does a μ-opioid receptor agonist/noradrenaline reuptake inhibition (MOR-NRI) drug have similar analgesic effect to a pure opioid agonist?
   In this clinical study, the analgesic effect of oral tapentadol was compared with oral oxycodone during the first 24 h after hysterectomy (Paper II "Tapentadol study").

3) Can the mode of remifentanil withdrawal influence opioid-induced hyperalgesia?
   In an experimental study on healthy volunteers, we studied the effect of gradual versus abrupt withdrawal from remifentanil infusion on opioid-induced hyperalgesia (Paper III "OIH study").

8. Material and methods

8.1 Study populations

The studies for paper I and II were done on women, ASA classification I-III, scheduled for elective, laparoscopic supra-cervical or total hysterectomy for non-malignant reasons at Oslo University Hospital, Ullevål. The patients were asked to participate during the preoperative anesthesia consultation on the day of surgery and enrolled after written consent was obtained. The patient population in paper II also received information about the study by mail before hospital admission, with a few exceptions due to surgery scheduled on short notice.

In paper I, the age criterion was 18-70 years, while in paper II the criterion was 18-64 years. We had no weight criterion in paper I, but in paper II weight for inclusion was set to >55 kg and <85 kg, taking into consideration a BMI <31 kg m^{-2}. In paper I, the exclusion criteria were chronic pain syndromes, severe psychiatric disorders, contraindications to medication administered during the study and regular use of pain medication, antiemetics or steroids. In paper II, the exclusion criteria also included: severe heart, kidney or liver failure, untreated medical illness predisposing for respiratory depression, infection affecting clinical status, malignancy during the past five years, breastfeeding, and regular use of benzodiazepines, barbiturates, phenytoin, tricyclic antidepressants, gabapentinoids, clonidine, cimetidine, rifampicin, protease inhibitors, St John's wort, macrolides, antimycotics or serotonin-noradrenaline reuptake inhibitors. Patients enrolled in clinical trials during the last six months or not fluent in Norwegian were excluded.

The participants in the experimental study in paper III were recruited through an open invitation to students at the University of Oslo and colleagues at Oslo University Hospital, Ullevål, by posters or direct attendance at lectures. The inclusion criteria were healthy male volunteers, aged 18-60 years with BMI 17-30 kg m^{-2}. Other exclusion criteria were alcohol or drug abuse, allergies or intolerance to study medications, regular use of pain medication (including steroids) or herbal medicines, and participation in another clinical trial during the last six months. Any intermittent use of paracetamol, NSAID or codeine had to be

stopped a minimum of 24 h before a session. The participants had to be fluent in Norwegian.

8.2 Approvals and consent

All three studies (paper I, II and III) were approved by the Regional Committee for Medical and Health Research Ethics in South Eastern Norway and the Norwegian Medicines Agency, and conducted in adherence to the guidelines for Good Clinical Practice.(103) The study for paper II was also independently monitored by the Clinical Trial Unit at Oslo University Hospital.

The studies were registered in ClinicalTrials.gov (paper I NCT 01109511; paper II NCT 03314792; paper III NCT 01702389) and the European Union Drug Regulating Authorities Clinical Trials database (paper I 2009-017140-14; paper II 2017-001285-23; paper III 2011-002734-39).

Written, informed consent was obtained from all participants in the studies.

8.3 Study design and interventions

Both paper I and II were randomized, blinded, parallel-group, single-center clinical studies. Randomization for both studies was done with computer-generated codes using block randomization by blocks of ten. In paper I, all patients received oral paracetamol 2 g, diclofenac 100 mg and the first dose of study medication 1-2 h before surgery. The patients were randomly allocated to either group O which received oxycodone 10 mg prolonged-release (PR), or group ON which received oxycodone 10 mg + naloxone 5 mg PR. The surgery was conducted under general anesthesia with propofol and remifentanil. As part of a standardized multimodal pain and antiemesis regimen the patients also received perioperative dexamethasone, droperidol and ondansetron. By the end of the surgery, the incision sites were infiltrated with bupivacaine and oxycodone 0.1 mg kg^{-1} i.v. was administered to all patients. According to randomization, oxycodone 10 mg PR or oxycodone + naloxone 10 mg/5 mg PR was repeated every 12 h for 3 days, the last day at the patient's discretion. All patients had access to a patient-controlled analgesia (PCA) pump with oxycodone 0.03 mg kg^{-1} i.v. bolus as

rescue medication during the first 24 h. The PCA pump could be activated maximum 6 times per hour while in the PACU and 4 times per hour in the gynecological ward. Oxycodone 5 mg IR was used as per oral (p.o.) rescue medication after the PCA pump was discontinued. The initial 3 postoperative days, the patients received p.o. paracetamol 1 g x 4 and diclofenac 50 mg x 3 daily. The patients received 4 capsules of oxycodone IR to administer at their own discretion upon discharge from the hospital.

In paper II, the patients were randomized to either group T receiving 50 mg tapentadol extended-release (ER) or group O receiving 10 mg oxycodone ER, along with paracetamol (1.5 g <60 kg, 2.0 g ≥60 kg) and etoricoxib (90 mg <60 kg, 120 mg ≥60 kg) as oral premedication 1 h before surgery. The patients underwent surgery in general anesthesia with propofol and remifentanil. All patients had bupivacaine infiltrated at the incision sites and received i.v. dexamethasone, ondansetron and 2 μg kg^{-1} fentanyl 10 min before the end of surgery. In the PACU, 1 μg kg^{-1} fentanyl i.v. was allowed for urgent relief of severe pain or until the patient could ingest oral medication, but IR tapentadol 50 mg or oxycodone 10 mg were used as the main rescue medication throughout the study period. Twelve hours after the premedication, all patients received an additional dose of ER study medication. The patients also received p.o. paracetamol every 6 h during the 24 h study period.

The experimental study (paper III) was a randomized, double-blinded, placebo-controlled, crossover study with three different treatment sessions: A) abrupt withdrawal of remifentanil infusion, B) gradual withdrawal of remifentanil infusion, and C) placebo infusion with saline. Computer-generated codes stored in sequentially numbered envelopes secured randomization of the sessions. The participants received each of the treatments with a minimum wash-out period of 4 days in between. The whole study could be conducted over a minimum of 11 days in total. They were familiarized with the numerical rating scale for pain, the heat pain test and the cold pressor test prior to the first session.

In all three sessions, two infusion pumps were running simultaneously to ensure blinding of both investigators and subjects. Session A: pump 1 administered

remifentanil 2.5 ng ml^{-1} until it was stopped abruptly after 30 min, while pump 2 with saline was gradually reduced over an additional 15 min (see further details explained under session B). Session B: pump 2 was the active pump administering remifentanil 2.5 ng ml^{-1} for 30 min, before gradual withdrawal was done by 0.6 ng ml^{-1} every 5 min for the final 15 min of the infusion. Accordingly, pump 1 contained saline and the infusion was abruptly stopped after 30 min. Session C: both pumps contained saline and administration of infusion was abruptly stopped for pump 1 and gradually reduced for pump 2 as described in sessions A and B. In each session the two pain tests were performed 5 min before the infusion, 20 min into the infusion, and 45 and 105 min after the end of infusion (Figure 5).

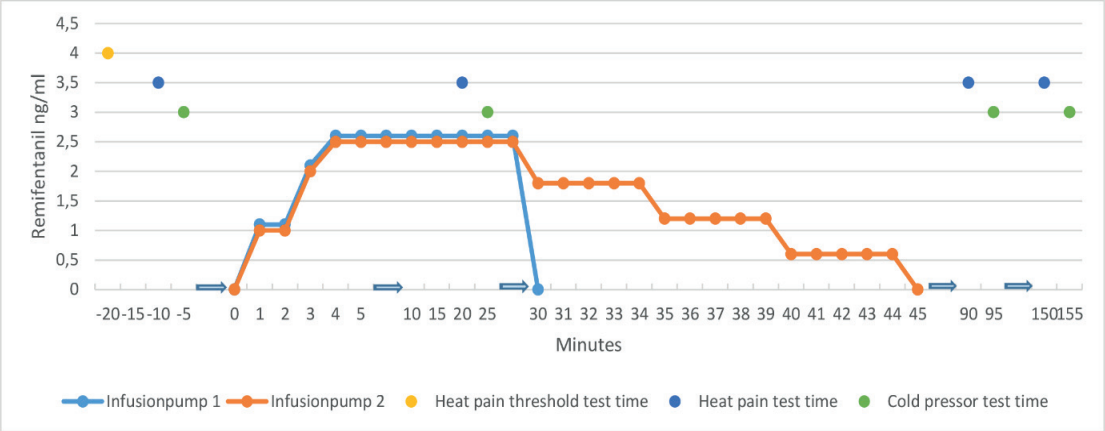

Figure 5. Schematic illustration of the experimental model in the "OIH study".(104) (Original material, permission to reprint not required.)

8.4 Study medicine and blinding

In study I, Targiniq® was used for PR oxycodone-naloxone and OxyContin® for PR oxycodone. In study II, Palexia depot® was used for ER tapentadol and OxyContin® for ER oxycodone. IR oxycodone, OxyNorm®, was used as oral rescue medicine for all groups studied. In both studies, the study medicines were distributed in a dosing box prepacked in identical, sequentially numbered, opaque envelopes by a researcher not involved in patient handling. These envelopes with instructions for self-administration of the study medication were given to the patients at the time of premedication by a ward nurse not involved in the studies. In paper I, patients judged to be able to recognize the study medicines by the

tablet design were excluded. Moreover, the ward nurses were instructed not to discuss the type of study medicine with the patients to ensure blinding. In paper II, patients with previous use of the study medicines were not excluded and could potentially recognize them by the tablet design.

In the third, experimental study, a nurse anesthetist not participating in the subjects' handling or evaluation prepared remifentanil and saline in syringes for infusion according to the randomization. In all three sessions, the two infusion pumps were running simultaneously to ensure the blinding of both investigators and subjects.

In paper II and III, the statisticians were blinded for the group allocations when they analyzed the outcome measures.

8.5 Main outcome measures

8.5.1 Outcome measure - Pain

Because pain is a subjective experience, it is in the nature of pain that an objective measurement is impossible. As there exist no objective measures as of yet, surrogate measures such as pain intensity, pain relief, rescue opioid consumption, time to perceptible or meaningful pain relief, and patient global assessment of study medication are used to evaluate the effects of pain treatment.

Pain intensity has been viewed as the most favorable patient-reported outcome measure in studies on postoperative pain.(105) The visual analog scale (VAS) and the numeric rating scale (NRS) are commonly used to measure pain intensity, and they show equal sensitivity in assessing acute postoperative pain.(106-108) It is important that the scales are used correctly to obtain high-quality research data. The VAS scale must be 100 mm in length with scale descriptors to the left and right of the scale anchors, and marking of pain intensity should be done by a single vertical line on the scale. Both research personnel and patients must be instructed in the use of scales before a study starts.(17) The NRS is a numerical rating scale with 0 = no pain and 10 = worst pain imaginable. It is essential that the question (e.g., " On a scale from 0 to 10, where 0 is no pain and 10 is the worst imaginable pain, how much pain are you in right now?") is posed in the

same way at each measurement.(17) Both scales can be used to evaluate pain intensity right now or as worst/least/average pain over a period.

Other scales used to measure pain intensity are Likert scales of varying types. Pain is then often categorized into none, mild, moderate or severe pain. But since NRS and VAS are more powerful in detecting pain intensity differences than verbal categorical rating scales (VRS),(107, 108) such scales should only be applied after careful consideration or used as a coarse screening tool in studies. The NRS was used in all three papers in this thesis.

Rescue opioid consumption, total opioid consumption or time to rescue medication are often reported as surrogate measures for pain. In paper I and II, we reported on cumulative doses of rescue medicine, and in paper II, we also included time to first request for rescue medicine.

8.5.2 Outcome measure - Constipation

In paper I, the primary outcome measure was opioid-induced constipation (OIC). As OIC lacks a generally accepted definition,(69, 70) there are no defined outcome measures. Many assessment tools have been developed for constipation, but they are mostly focused on patient groups with chronic constipation disorders and/or chronic opioid use.(109) We based our evaluation of constipation on previous experiences with the Bowel Function Index (BFI) and the Bristol Stool Form Scale and developed modified scores with several variables relating to constipation.(110, 111) The BFI score is originally calculated as a mean score of three variables: ease of defecation, feeling of incomplete bowel evacuation and personal judgment of constipation, using a numerical analog scale of 0-100. The Bristol Stool Form Scale was initially devised to see if stool form could be a predictor of intestinal transit time and an objective measure of abnormality in intestinal function.(111)

The variables included in our modified scores used in study I were objective data such as number of defecations and occurrence of flatus and defecation within 24 h, 72 h and 1 week postoperatively. Subjective measures were also included, such as feeling of bowel emptying, feeling of easy defecation, feeling of constipation

and stool consistency. The subjective measures were reported on a numerical rating scale from 0-10 (complete to no emptying; very easy to extremely difficult defecation; no to severe feeling of constipation). The stool consistency was evaluated using the following scale: 0 = looser consistency; 1 = normal consistency; 2 = harder consistency, corresponding to the Bristol Stool Form Scale types 6, 3 and 1.

8.5.3 Outcome measures - Nausea and vomiting

Postoperative nausea and vomiting (PONV) is defined as nausea and/or vomiting that occurs within the first 24 h after surgery.(112) Same as for pain and constipation, there is no consensus on outcome measures for PONV.(113) Vomiting or retching are objective measures that can be counted, or the amount of emesis can be recorded. For nausea, which is a subjective experience, the presence can be reported as yes/no, or it can be classified into categorical scales (mild, moderate or severe) or by using numerical rating scales for intensity. To my knowledge, there are only two assessment tools for nausea and vomiting which have been validated in the postoperative setting, the Ambulatory Surgery Index of Nausea, Vomiting, and Retching and the PONV Intensity Scale.(113-115) The Functional Living Index-Emesis has been used as well but not validated.(113) In papers I and II, we evaluated nausea and vomiting as separate measures with dichotomous answers (yes/no) at several time points. We additionally measured antiemetic consumption in paper II, which is frequently used as a surrogate measure for nausea and vomiting.

8.6 Statistical analyses

Papers I and II were both clinical studies in which two parallel treatment groups were compared. We obtained the mean with standard deviation (SD) for metric data, and percentages or counts were presented for categorical data. Confidence intervals (CI) for differences in means were obtained for relevant data in both papers and constructed using bootstrapping in paper II. The distribution of data was assessed with skewness, histograms and box plots.

In papers I and II, the independent samples t-test, a parametric test, was used to compare groups when the assumptions of normal distribution, independent observations and use of continuous scales were fulfilled. When these assumptions were not fulfilled, the non-parametric test Mann-Whitney U test was applied. The chi-square test for independence was used to compare relationships between categorical variables. Some of the data in paper II, such as nausea and vomiting, were also analyzed with the generalized mixed models for repeated measures and presented as odds ratios (OR) with CI. The third paper was an experimental study with a crossover design, thus examining the same individuals over three separate sessions. We used the independent samples t-test for the demographic data, but the main analyses were done with linear mixed models.

The level of statistical significance was set to 0.05 in all three papers. Bonferroni corrections were applied on repeated measures in paper I. As the secondary outcomes in paper II were considered exploratory, we decided not to correct for multiple testing for these measures.

In paper I, the power calculation was based on a previous study which had shown that 70% had no defecation the first 24 h after surgery when treated with opioids, while the incidence was only 32% for those treated with non-opioid analgesics.(71) A 50% reduction in the incidence of no defecation was considered of clinical interest. Thus, to demonstrate a difference between the groups, with a power of 90% and significance level 0.05, a minimum of 80 patients were needed. We decided to include a total of 90 patients in order to allow for dropouts. The power calculation of paper II was based on the study in paper I, where we found a mean NRS score for pain 1 h after hysterectomy to be 4 with a SD of 1.5.(116) Based on these data, a power of 80% and the significance level 0.05, 72 patients were needed to reveal a difference of 1 unit in pain scoring. We planned for 90 patients to allow for dropouts in the study. We also used a previous study done by our research group as the basis for power calculation in paper III.(92) To detect a difference of 0.5 in the NRS for pain with SD 0.5 and power 96%, we needed 16 volunteers but included 19 to allow for dropouts.

In paper I, the data were analyzed using the SPSS statistical software for Windows, version 16.0 (IBM Inc, Chicago, IL, USA), while in paper II, data were analyzed with SPSS version 25.0 (IBM, Armonk, NY, USA) and Stata version 16 (StataCorp LP, College Station, TX, USA) for some of the analyses. In paper III, the Levenberg-Marquardt nonlinear least-squares algorithm implemented in the minpack.lm package for R version 3.0 (R Core Team, 2015) was used for curve fitting and the statistical analyses were done with Stata version 13 (StataCorp LP, College Station, TX, USA). The sample size calculations were done using nQuery Advisor version 7.0 (Statistical Solutions, Boston MA 02110, USA).

9. Results

9.1 Paper I (Targiniq study)

In this study, we explored the effect of adding peripherally acting naloxone to systemic acting oxycodone on postoperative constipation and analgesia after hysterectomy. There were no significant differences in any variables related to the primary outcome constipation. During the first 24 h postoperatively 0% had defecation in group ON (oxycodone + naloxone) and 7% in group O (oxycodone; P = 0.10). Between 24-72 h, 75% vs 80% had had defecation in group ON and O, respectively (mean (SD) 1.2 (1.1) vs 2.1 (2.4); P = 0.03 (ns with Bonferroni correction)). There were no significant differences found for the other variables related to constipation: feeling of bowel emptying, feeling of easy defection, stool consistency or feeling of constipation.

As for analgesic effect, the groups were similar in pain scores at rest or while coughing at all time points during the study period (data reported only for 0-24 h in paper I). The use of i.v. rescue medication was also similar for the groups during the first 24 h with mean (SD) oxycodone 17.0 mg (13.4) in group ON and 20.0 mg (15.9) in group O, P = 0.35. The mean (SD) number of rescue oxycodone tablets used in the 24-72 h postoperative period was 0.78 (1.3) in group ON and 1.09 (1.4) in group O, P = 0.29. Rescue oxycodone tablets were used by 42% of all patients (both groups pooled) in the 24-72 h period (no significant difference between the groups).

There were no significant differences in the opioid-induced effects of nausea, vomiting, dizziness or pruritus between the groups and no cases of respiratory depression or severe sedation during the study.

9.2 Paper II (Tapentadol study)

In this paper, we examined the analgesic effect and opioid-induced side effects of the bifunctional opioid ligand tapentadol in hysterectomy patients. There was no significant difference between group T (tapentadol) and group O (oxycodone) for the primary outcome pain at rest 1 h postoperatively (mean NRS 4.4 (95% CI 3.8-5.0) vs mean NRS 4.6 (95% CI 3.8-5.3), respectively). The groups also had

similar scores for NRS at rest and while coughing during the rest of the 24 h study period (P = 0.857 and P = 0.973, respectively). Furthermore, there were no significant differences in i.v. rescue analgesics (mean (SD) fentanyl 279 µg (175) in group T and 238 µg (138) in group O; P = 0.619) and oral rescue analgesics (mean (SD) number of tablets 3.8 (1.7) in group T and 3.0 (1.6) in group O; P = 0.914).

At 24 h, more patients in group O (44%) reported nausea than group T (22%) (P = 0.038, not Bonferroni corrected). There were increased odds for nausea in both groups over time compared to baseline (OR 3.3 (95% CI 1.2-9.5); P = 0.026), but when taking into consideration an interaction between groups and time there were significantly lower odds for nausea at 2 and 3 h postoperatively in group T (P = 0.040 and P = 0.020, respectively). There was also a trend towards significance for less nausea at 24 h in group T (P = 0.060). Statistically significant higher need for antiemetics and repeated administrations of antiemetics were registered for group O (P = 0.040 and P = 0.038, respectively). The odds for vomiting were numerically higher for group O, but the ratio did not reach the level of statistically significant difference (OR = 1.7 (95% CI 0.6-4.9); P = 0.371).

We did not find any statistically significant differences between the groups for the opioid-induced side effects of respiratory depression, dizziness, pruritus, headache or sedation.

9.3 Paper III (OIH study)

In this paper, we studied if gradual withdrawal of remifentanil infusion versus abrupt withdrawal could prevent development of opioid-induced hyperalgesia (OIH) after infusion in healthy volunteers. The subjects were exposed to three sessions in randomized order: remifentanil infusion with gradual withdrawal, remifentanil infusion with abrupt withdrawal and placebo infusion with saline.

During infusion, the remifentanil sessions were significantly lower in NRS scores compared to the placebo session, indicating analgesic effect of remifentanil, both when testing with heat pain test (HPT) and cold pressor test (CPT) (both P < 0.01). When testing with the HPT 45 min after end of infusion, there was a

statistically significant higher NRS score in the abrupt withdrawal session compared to both the gradual withdrawal and the placebo session (both $P < 0.01$), indicating development of OIH from abrupt withdrawal. There was no indication of OIH development in the gradual withdrawal session as the NRS score was similar to the placebo session ($P = 0.93$) testing with the HPT at this time point. In the CPT, however, we saw evidence of OIH in both remifentanil sessions as there were statistically significant higher NRS scores 50 min after end of infusion compared to placebo (gradual vs placebo $P = 0.01$; abrupt vs placebo $P < 0.01$), and there was no significant difference in the OIH between the remifentanil sessions ($P = 0.27$). In the final assessment with HPT and CPT at 105 and 110 min after end of infusion there were no significant differences in the NRS scores for the remifentanil sessions compared to the placebo session, indicating no presence of OIH (HPT: gradual vs placebo $P = 0.94$; abrupt vs placebo $P = 0.29$; gradual vs abrupt $P = 0.26$. CPT: gradual vs placebo $P = 0.83$; abrupt vs placebo $P = 0.47$; gradual vs abrupt $P = 0.61$).

10. Discussion

10.1 Main results

10.1.1 Paper I

Research question: Can the addition of peripherally acting naloxone to the centrally acting opioid oxycodone prevent opioid-induced constipation postoperatively?

In this paper, we found no difference in constipation between the group receiving oxycodone and the group receiving oxycodone with peripherally acting naloxone after hysterectomy. Of particular interest were also the secondary endpoints relating to pain scores since naloxone potentially could reverse the analgesic effect of oxycodone. No differences in pain scores between the groups were found in the study. Previous studies on oxycodone-naloxone in postoperative pain treatment have been summarized in two review articles by Morlion et al. and Gkegkes et al.(42, 46) They report on the same eight studies, but Gkegkes et al. have included two additional studies. The ten studies included in total were a mixture of non-/randomized, retrospective and prospective trials on orthopedic, colorectal, gynecological, cardiac and thoracic patients.

Only one of the studies in the reviews reported statistically significant results relating to constipation. In a study on laparoscopic colorectal patients, there was shorter time to first bowel movement in the oxycodone-naloxone group compared to the oxycodone group, but no differences were found for other constipation measures.(117) A recently published study not included in the reviews compared oxycodone, oxycodone-naloxone and placebo treatment in cystectomy patients who had epidural analgesia.(118) The study showed prolonged time to first defecation and delayed return of bowel function in the oxycodone group, but the oxycodone-naloxone group did not significantly differ in constipation measures from the placebo group. Even though they concluded with no benefit from adding naloxone in this regimen with epidural, it seems like this study could help substantiate an effect of naloxone on OIC; after all, the oxycodone-naloxone group was similar to the placebo group in terms of constipation measures.

Another recent study done by Iorno et al. showed positive outcomes in all measures of a modified BFI for p.o. oxycodone-naloxone compared with i.v. morphine in a 7-day follow-up of hysterectomy patients.(119) However, the study is not completely comparable to our study as laparotomy patients were included, and NSAID was administered to the morphine group but not the oxycodone-naloxone group postoperatively. It should be noted that when calculating oral morphine equivalent doses for the groups in the study, the morphine group received much higher opioid doses than the oxycodone-naloxone group. These differences in analgesic treatment could have impacted constipation and possibly lead to less constipation in the oxycodone-naloxone group.

A reason why no differences in constipation were found in our study could be that postoperative ileus from other factors than opioids overshadowed any effect from naloxone. Postoperative ileus is a rather common occurrence the first 0-72 h, especially after abdominal surgery.(74, 120) It is difficult to distinguish the impact of OIC from postoperative ileus of non-opioid reasons in studies. In our study, there were low incidences of constipation in both groups throughout the study, indicating that there was little impact of postoperative ileus in general.

In the studies included in the reviews by Morlion et al. and Gkegkes et al., there were only found differences in analgesic effect between groups in one study. In a study on patients undergoing video-assisted thoracic surgery or thoracoscopy, higher pain scores were found in the oxycodone-naloxone group than the oxycodone group on day 2, but no difference on day 5 or 6.(121) In contrast, the study by Iorno et al. on hysterectomy patients comparing p.o. oxycodone-naloxone with i.v. morphine found statistically significant differences in static pain on day 2 to 3 and dynamic pain on day 3 in favor of the oxycodone-naloxone group.(119) As already mentioned, this study is not entirely comparable to our study as both laparoscopy and laparotomy patients were included, and it is not distinguished between the surgery types when analyzing pain measures. Our study group has also previously shown that i.v. oxycodone is superior to i.v. morphine for visceral pain, which could be of relevance when interpreting the results in the Iorno study.(40) The nine other studies in the reviews did not find any differences in pain measures when comparing oxycodone-naloxone to other opioids, which

are in accordance with the results in our study. This supports the notion that peripherally acting naloxone does not impede the analgesic effect of the co-administered opioid. Overall, reversal of analgesic effect from naloxone has only been observed in one small study on nine patients where oral naloxone 2-4 mg was administered three times daily, and the study has been subjected to criticism for methodological issues.(122)

The patients in our study received a mean of 19 mg i.v. oxycodone as rescue medicine on top of the 20 mg p.o. oxycodone/oxycodone-naloxone administered as study medicine the first 24 h postoperatively. It could be argued that the additional oxycodone overruled the effect of naloxone in the oxycodone-naloxone group, but the 1:4 naloxone:oxycodone ratio in our study should be well within range according to a study that has shown an effect of 1:6 on OIC.(123)

One could speculate if the evaluation period of 72 h in our study was too short to reveal any differences in pain and constipation, as previous studies on oxycodone-naloxone in acute, chronic and cancer patients have shown less constipation and comparable analgesic efficacy to oxycodone and other analgesics.(42, 43, 45, 119, 124) In chronic pain patients the differences in constipation measures often do not appear before several weeks into long-term studies.(43, 125, 126) The postoperative patient is certainly different from the chronic pain patient in type of pain, mobilization, nutrition and baseline bowel function, and opioid medication is rarely required over longer periods for surgical pain. In the hysterectomy study by Iorno et al., the most convincing improvements in BFI measures appeared from day 2-7.(119) Of the studies on postoperative patients included in the aforementioned reviews, only two studies evaluated constipation beyond 21 postoperative days. One study, which did evaluations on days 3 and 6, week 3 and 5, and 6 months postoperatively, found numerical differences in median scores for BFI but no statistically significant difference between an oxycodone-naloxone group versus a control group with other opioids.(127) In this study, the mean (SD) days of oxycodone-naloxone use was 25.6 (20) days, making oxycodone-naloxone less likely to be of importance to the later evaluations. In our study in paper I, the patients could administer IR opioid study medication at their own discretion after day 3. While 42% (both groups pooled) used IR opioid in the 24-

74 h period, this dropped to 14% in the 72 h-7-day period indicating decreasing need for opioids beyond day 3. This implies that 72 h of observation were sufficient in this patient population. In our study, the patients were also mobilized and started per oral nutrition on the day of surgery, both factors promoting fast recovery of intestinal motility. It would be reasonable to focus any future studies on oxycodone-naloxone in postoperative pain management on patient groups with long-term opioid-demanding pain and a longer immobilization period that affects bowel functioning. It seems less likely that oxycodone-naloxone will be of any difference to patients with short-lasting pain trajectories and who quickly resumes per oral nutrition and mobilization after surgery.

The review by Gkegkes et al. also touch upon the problems of measuring pain and constipation as there are no gold standards or core outcome sets for these variables.(46) A diversity of outcome measures were used in the oxycodone-naloxone studies included in the two reviews: the NRS, the Brief Pain Inventory Short Form, registration of spontaneous bowel movement, time to first defecation, the BFI, and modified BFI for constipation. This makes it difficult to directly compare our findings with previous studies and even more so to conduct systematic reviews and meta-analysis when so many different pain and constipation scales are used. This is more thoroughly discussed along with the problems of surrogate measures in section 10.2.4 “Outcome measures” under “Methodological considerations”.

Summed up, the conflicting findings on constipation in our and other oxycodone-naloxone studies in the postoperative setting are most likely due to short treatment periods, low opioid doses and other factors that disturb bowel function after surgery, as already stated in an expert opinion on the role of oxycodone-naloxone in the management of patients with pain and OIC.(128)

10.1.2 Paper II

Research question: Does a μ-opioid receptor agonist/noradrenaline reuptake inhibition (MOR-NRI) drug have similar analgesic effect to a pure opioid agonist?

In paper II, we showed that patients who received tapentadol have similar analgesic effect compared with oxycodone the first postoperative day after hysterectomy. When exploring secondary endpoints, we also found lower odds for nausea at 2 and 3 h postoperatively in the tapentadol group and a higher need for antiemetics in the oxycodone group. The findings in our study are supported by previous studies done on orthopedic and dental surgery patients, showing comparable analgesic effects between tapentadol IR and oxycodone IR, but with less nausea.(129-131) Several summaries and reviews have also been done on analgesic and side effects from tapentadol in acute pain patients, including both postoperative patients and patients with acute musculoskeletal pain.(52, 56, 57, 132) Overall, they conclude with similar analgesic efficacy and less nausea and/or vomiting for tapentadol IR compared with other opioids (oxycodone, tramadol and morphine). A recently published study on total knee arthroplasty patients compared tapentadol ER with oxycodone ER and placebo for 7 days after surgery.(133) They found no significant difference between groups on the primary outcome measure area under the curve for pain on mobilization the first week. Nevertheless, they did note a trend of better pain relief, less adverse effects and higher activity level in the tapentadol group compared with both oxycodone and placebo when looking at multiple secondary and exploratory measures of pain and opioid-induced side effects. Constipation was significantly lower in the tapentadol group, and there was also a trend towards less nausea in this group. A limitation to the study was the use of oxycodone IR as rescue medication in all three groups as this may have obscured the results of the tapentadol group which received two different opioids. We have only found one previous study on postoperative pain management that includes both IR and ER tapentadol.(134) This study on women 24-48 h after caesarean section failed to prove analgesic superiority of tapentadol over oxycodone and showed no differences in side effects. Still, the above-mentioned studies on tapentadol IR in acute pain and the many studies on

tapentadol ER in chronic pain and cancer patients that have found similar analgesic effects between tapentadol and other opioids with a more beneficial gastrointestinal profile seem convincing in this matter.(54, 55, 135-137)

Our primary endpoint in the study was pain at rest 1 h postoperatively. One could argue that this time point was not optimally chosen as the patients' pain perception could be affected by residual anesthesia and/or fentanyl rescue medicine. This illustrates the problem of evaluating pain in the postoperative period, one time point is as valid as the next, and no one objective measure can capture the whole picture in pain research. We rely our conclusion of analgesic effects also on the additional findings throughout the study period, showing similar pain scores both at rest and while coughing, even though the study was not powered for these endpoints. Furthermore, the surrogate measures of rescue opioid doses were not significantly different between groups, indicating that no group had inferior pain treatment than the other. We could have done more evaluations of pain measures at later time points, analyses of pain intensity differences (PID/SPID) or areas under the curve measures to obtain more information, but this is still rarely done in clinical studies outside the industry. On the other hand, restraint in the number of measurements done in a study is important as more endpoints increase the risk of reporting a false-positive finding.(138)

A limitation to the study is the use of fentanyl as rescue medication. This opioid might have obscured effects from tapentadol or oxycodone. Fentanyl was chosen as tapentadol i.v. is not licensed in Europe, and it was therefore not possible to carry out the study with "clean" groups (one which only got tapentadol and one which only got oxycodone). Fentanyl was used as the analgesic bridge from general anesthesia into postoperative pain relief and was also allowed for urgent pain relief or if the patient could not swallow IR study medicine initially. Fentanyl was only used, if any, during the first hours of the postoperative period, and the doses were low and similar between the groups, so we believe it had a limited impact on our endpoints.

In our study, there were significantly lower odds for nausea at 2 and 3 h postoperatively in the tapentadol group, while there was no difference at 1 h and only a trend towards significance at 24 h. It could be that pain, residual anesthesia, perioperative ondansetron or fentanyl administered to all patients at the end of surgery influenced the measurement at 1 h but had decreasing effect at later evaluation points. At 24 h, the groups should not have been influenced by other opioids than the study medicines, but antiemetics administered upon request could have influenced the results. In the oxycodone group 44% reported nausea at 24 h, while only 22% did so in the tapentadol group, which was not of statistical significance when corrected for repeated measures with Bonferroni. However, a statistically significant higher need for antiemetics and repeated doses of antiemetics in the oxycodone group throughout the study period supports a true difference between groups. The low incidence of vomiting is probably a result of the prophylactic antiemetic regimen and liberal administration of antiemetics at symptom debut. In the only similar study found on tapentadol IR and ER with women post caesarean section no differences in nausea and vomiting were found. However, the study had no protocol for administration of antiemetics leading to higher doses of perioperative antiemetics in the oxycodone group, which could have affected the results.(134) Lastly, we cannot truly know if the patients in our study were nauseous due to other reasons than the opioids, such as pain or postoperative ileus. Nevertheless, the groups should have been similarly affected by surgery and general anesthesia, and they were similar in the Apfel score for prediction of PONV. As our study was not powered for evaluation of nausea and vomiting, we cannot draw final conclusions upon the matter, but it appears to be in line with previous research as already discussed.(52, 56, 57, 132) The growing literature on tapentadol seems to underline that this drug's forte is less stimulation of μ-receptors leading to less nausea and/or vomiting, while retaining analgesic effect through noradrenaline reuptake inhibition. Further studies with i.v. tapentadol and oxycodone as rescue medication so that the groups are only exposed to the opioid of allocation would be of interest.

There is increasing awareness of the predisposing factors for poor postoperative pain control. A recent systematic review and meta-analysis has shed light on

which predictors to focus on.(139) Younger age, female sex, smoking, depressive symptoms, anxiety symptoms, sleep difficulties, higher BMI, preoperative pain and use of preoperative analgesics were identified as statistically significant preoperative predictors of increased postoperative pain and should be considered included in future studies. A strength to our study was the consideration of the factors: anxiety, depression, catastrophizing, preoperative pain and use of analgesics before surgery. The factors came out equally distributed between the groups, so we believe they were not confounders to the pain results in the study.

10.1.3 Paper III

Research question: Can the mode of remifentanil withdrawal influence opioid-induced hyperalgesia?

In paper III, we found development of OIH after abrupt withdrawal of remifentanil infusion, but not after gradual withdrawal of infusion, when applying the heat pain test (HPT). The results were not reproduced with the cold pressor test (CPT). To the best of my knowledge, there are no other human, experimental studies replicating these findings, but one experimental study has been conducted in rodents and two clinical studies are done on gradual withdrawal from remifentanil after thyroid surgery.(140-142) In the rodent study, tapering of the remifentanil infusion prevented opioid withdrawal long-term potentiation (LTP).(142) LTP is believed to share signal transduction pathways with OIH (see section 6.6.4 “Opioid-induced hyperalgesia”). After thyroidectomy, Han et al. showed less need for rescue analgesics and lower NRS scores with gradual withdrawal than abrupt withdrawal, but no difference in time to administration of first rescue analgesic dose.(140) The results were interpreted as a prevention of OIH by gradual withdrawal. Another clinical study by Saxena et al. found delayed initial demand for rescue medication in the gradual withdrawal group, but no other significant differences for pain scores or overall morphine consumption between the groups.(141) A relevant question to this study is whether such a conclusion can be drawn when remifentanil infusion was ongoing for 120 min postoperatively in the gradual withdrawal group. Although low doses were administered towards the end, remifentanil might have given some pain relief in

this group, delaying the need for rescue medication. Both clinical studies lack testing for sensitization at other sites than the surgery site or testing of pain thresholds. This could have helped confirm OIH over acute development of tolerance or direct analgesic effect of ongoing remifentanil infusion. It is difficult to draw firm conclusions on the validity of our own results in paper III since so few studies are done in this area, but some strong support comes from another human experimental study. In a study using functional MRI, reduced heat pain thresholds and increased neuronal responses in the brain, brain stem and spinal cord to heat pain were demonstrated after abrupt remifentanil withdrawal.(143) This study indicates that signaling in the descending pain pathways may be altered after short-term opioid infusion, is worsened by abrupt withdrawal, and leads to hyperalgesia more than tolerance.

One important question to the results in our study is the lack of replication of the HPT results in the CPT. Remifentanil has demonstrated its analgesic effect against heat stimulation, and it is shown that hyperalgesia appears after withdrawal of remifentanil infusion with models using electrical, capsaicin or heat stimulation.(15) The previously mentioned study with functional MRI by Sprenger et al. adds further support to heat pain as a valid model for testing hyperalgesia.(143) Remifentanil is one of the most extensively investigated opioids with various pain models, but the cold pressor test has not been frequently used with remifentanil and hyperalgesia. Our research group has previously demonstrated remifentanil-induced hyperalgesia with both electrical pain and the cold pressor test, but effect from pretreatment with COX-inhibitors on hyperalgesia were only detectable with the electrical pain test, not the CPT.(92) Another study on eye surgery patients also failed to prove hyperalgesia with the CPT, while they did find decreased pressure pain tolerance thresholds after remifentanil infusion.(144) On the other hand, the CPT has previously been used for testing many other opioids, and the model is deemed sensitive to opioid analgesia.(15) Krishnan et al. even concluded that the CPT is the most effective model in detecting OIH in a study on methadone and buprenorphine maintained patients.(145)

There are many possible explanations for these conflicting findings, such as the differential activation of Aδ and C fibers by heat and cold stimulation (see section 6.2.1 “Experimental pain models”). Different receptors channels in the nociceptors probably operate the detection of hot (e.g., TRPV1) and cold (e.g., TRPM8) noxious stimuli.(11) Thus, the different responses to different experimental pain modalities may be representations of different pathways in the pain system.(146) The inconsistencies in findings could also be an indication that opioids modulate the different nociceptive (i.e., heat, cold, pressure) systems in different ways; in other words, OIH is modality-sensitive.(145, 147)

We considered the possibility that conditioned pain modulation (also termed DNIC) by endogenous descending inhibitory pathways could have interfered with the pain responses in the CPT as the HPT was conducted 5 min before the CPT. From the nature of these pain stimuli, we believe this was the correct order in which to conduct these two models since pain after CPT prevails for minutes while pain after HPT is short-lasting. It is not known exactly how long DNIC effects prevail, studies vary from rapid disappearance to 30 min, but one study reported complete inhibition of the RIII-reflex up to 9 min after heat conditioning.(148) In another study designed to evaluate the effect of DNIC on repeated HPT and CPT, it was not found any evidence of the first HPT inducing inhibitory responses on the latter tests.(149) In our study, the pain during the CPT followed the expected trajectory, indicating no interference from the previous heat pain stimulus involving descending inhibitory mechanisms. Furthermore, since the CPT affects larger skin surface areas than the HPT, the CPT may have engaged endogenous pain modulation mechanisms such as spatial summation and vasomotor reactions stronger than the HPT,(150) leading to higher pain ratings in the CPT.

It has to be pointed out that experimental pain models in many studies have produced contradictive findings even when using the same opioid and pain stimulus.(15) There can be many methodological explanations for this: different pain assessment methods, different study populations, different dosing regimens or slight differences in conduction of the studies. For instance, in our study, we could have used a lower temperature in the CPT. There is no consensus on which

temperature should be applied during the CPT, but studies are often conducted using 0 to 4ºC. To achieve comparable results, a narrow temperature span of the water should be used and has to be monitored closely when replicating studies.(20) We could further have controlled for skin temperature of the hand before the experiment by immersing the extremity in a warm bath at 35ºC for 2 min before conducting the CPT.(18, 20) This way, we could have controlled better for the variability in baseline extremity temperature. There is, however, no doubt that pain was induced in our volunteers by the CPT as mean NRS scores were close to 5 in the study. In comparison, the mean NRS scores with the HPT were about 3. It could be that the intensity of cold pressor pain overshadows any subtle changes in hyperalgesia.

To sum up the question of why the results in the HPT were not replicated in the CPT, it is necessary to bear in mind when studying the literature of OIH and experimental pain models that opioid effects in one modality cannot be extrapolated to another modality, and neither should lack of findings in one modality lead to negative conclusions all over.(145) Moreover, it is suggested that a combination of experimental pain modalities should be included in studies as they represent different pathways.(146) From our experience in this study it seems like the HPT is an adequate candidate for assessing the effect of remifentanil and hyperalgesia, but future studies should consider models with, e.g., electrical pain or pressure pain as well.

Even though several studies have indicated that remifentanil and other opioids induce hyperalgesia and/or tolerance after administration,(81) the existence and clinical relevance of OIH and it's delimitation from acute tolerance have been extensively debated.(81, 151-153) The last word is certainly not said, any future studies on OIH should do measurements of sensitization outside the surgical area and testing for pain thresholds, and not just rely on pain scorings and cumulative opioid use to distinguish OIH from acute opioid tolerance.(151) Even more extensive psychophysical measurements like quantitative sensory testing should be considered if feasible.(81, 152, 154) Our study has a limitation as we did not do pain threshold testing, peripheral sensitivity testing or quantitative sensory testing to delimit OIH from tolerance.

Noteworthy questions remaining after this study is done are the speed and dose intervals gradual withdrawal of remifentanil infusion should be done with to prevent OIH in the clinic. This is discussed in section 10.4 “Clinical implications” and 10.5 “Future research and perspectives”.

Lastly, the secondary endpoint of hyperalgesia duration should be mentioned. In both modalities, we found that hyperalgesia from remifentanil persisted for less than 105 min after end of administration. The duration of remifentanil-induced hyperalgesia has been discussed in a meta-analysis and systematic review on OIH in surgical patients by Fletcher and Martinez.(62) They concluded with a significant increase in postoperative pain lasting 24 h postoperatively after high-dose remifentanil infusion. The pain was markedly increased 1 h after surgery with a gradual decrease over 24 h. Another review by Kim et al. mentions studies with aggravation of pain after remifentanil exposure from 30 min to 4 h.(153) The conclusions in these reviews are in line with our findings in paper III. It is believed that infusion rate, cumulative dose and duration of administration influence remifentanil-induced hyperalgesia and, most likely, also the extent of the hyperalgesia in time. The short duration of hyperalgesia observed in our study may therefore be related to all three factors being limited (short exposure with a low target effect site concentration resulting in a low total dose).

10.2 Methodological considerations

10.2.1 Bias, validity and reliability

Validity and reliability of measurements are important to the quality of data, and they demonstrate whether the results are trustworthy. If the same scores are achieved upon repeated tests, the reliability is high. This is of limited interest if what is measured is not what we intended to measure, i.e., low validity. Pain, constipation, nausea and vomiting are symptoms that are difficult to evaluate with one single question or even a questionnaire, thus the validity of the measurements may be low. Therefore, a questionnaire should be evaluated on the constructs of content, construct and criterion validity. Content validity expresses to what extent the questionnaire covers all aspects of the phenomenon in question, while construct validity expresses if it measures what it was intended to measure. The

criterion validity says something about how well the questionnaire correlates with or can predict another variable. The results of a study also have internal validity, an expression of how correct the measurements are for the population studied (a reflection of the causal relationship between treatment and outcome), and external validity, an expression of how valid the measurements are in other conditions and different populations.(155) Aspects of the internal validity of the studies in this thesis have been discussed in 10.1 “Main results”, and the external validity of the studies is further discussed under 10.2.2 “Study populations”.

The collection of data which we base our analysis of causal effects between exposure and different outcomes on are affected by bias, confounders and interactions. Random errors can be due to human variability or happen by chance, and any distortion of measurements can be in either a positive or negative direction. Systematic errors are innate flaws in the data collection due to techniques or instruments which distorts the measurements in one direction. Such non-random variations lower the internal validity of the study. Several types of bias can occur, but most common in pain medicine research are recall, observational, attrition, misclassification and selection bias.(156) Of relevance to the studies in my thesis are possibly observational bias in paper III and selection bias in paper I and II. In an experimental setting as the one in paper III, the subjects are under continuous observation and these conditions can alter the way a person behaves; this is known as the Hawthorne effect. However, the subjects in paper III were observed in a crossover study, so one could expect this effect to be of equal significance in all three sessions. In paper I and II there was an impression that the patients who declined to participate in the studies were more anxious. This could mean that we ended up with a population that did not include patients with anxiety, which is an important factor to postoperative pain. In paper II, the patients received information about the study one week before surgery in an attempt to lower stress and anxiety on the day of surgery when study inclusion was done.

10.2.2 Study populations

A high proportion of patients did not fulfill the inclusion criteria or had exclusion criteria in paper I and II. In paper I, 141 of 250 patients were not found eligible during pre-screening. One hundred and nine patients were enrolled in the study and data for 85 patients were studied. The main reasons for exclusion after randomization were administration of opioids out of protocol, change of surgical or anesthetic procedure and no contact upon follow-up. In paper II, 325 of 518 patients were excluded during pre-screening, mainly due to weight, malignancy, chronic pain syndromes or chronic opioid therapy. Of the remaining 193 eligible patients, several were missed out on because research personnel were not available on the days of surgery. Other reasons for exclusion were allergy to medication in the protocol, lack of indication for surgery, language barrier, or unwillingness to participate. Of the 86 included patients, data for 13 patients were excluded because of administration of analgesics outside the protocol, missed premedication, change of surgical or anesthetic procedure, or need for postoperative epidural. By chance, no patients in ASA class III were included in either study. This limits our results in paper I to healthy women without regular use of pain medication, while in paper II, the study population is limited to healthy, normal-weight women not using opioids. This lessens the generalizability of our findings in the studies to the broader group of women undergoing hysterectomy. Many patients are scheduled for this procedure because of chronic pain and chronic use of pain medication. As preoperative pain and especially chronic use of analgesics are risk factors for increased postoperative pain, one could expect other findings if these patients were studied.(23, 139, 157) In paper II, we further limited the population to women with a normal BMI as more recent studies have shown that higher BMI is a predictor of increased postoperative pain.(139) It is a tendency in randomized controlled trials that key groups such as elderly, obese, chronic pain patients and chronic opioid users are excluded. As the clinical cohorts' change in the direction of older patients with higher weight and more chronic pain study results become less relevant. This discrepancy can restrict the generalizability of research results, and pragmatic studies that resemble real-world conditions should be more emphasized.(158)

When compiling this thesis, an interesting observation was done between paper I and II. Building on the same study population, healthy women for hysterectomy without regular use of opioid analgesics, the patients in paper II (Tapentadol study) scored approximately 2 units higher on the NRS for rest and mobilization the first 3 postoperative hours than the patients in paper I (Targiniq study). The total opioid consumption in this period was also higher in paper II. A difference between the studies was the administration of different NSAID (diclofenac versus etoricoxib), but there had been a change in the surgical technique over the years as well, with progressively more total hysterectomies done than supracervical hysterectomies. This had led to shorter surgery time and time under general anesthesia. All these factors could influence measures on pain and opioid-induced side effects. None of the factors have been subjected to statistical analyses, but it illustrates the precautions one should have when comparing apparently similar studies in research. As pointed out in the article by Pedersen et al., external validity is a time-dependent concept since clinical populations change over time.(158)

The findings in the third paper are limited to healthy men without regular use of pain medication. Nineteen volunteers were included, but only 16 completed the study according to protocol and were studied. One volunteer was excluded because of side effects, one because of problems with compliance with study protocol and one because of technical problems during a session. Only males were included because variations in pain sensitivity during menstrual cycle in the minimum 11-day study period could potentially confound findings.(159) Although gender is a known predictor for pain in a clinical setting,(139) the importance of gender is questioned in the experimental setting and especially for the CPT.(160) The generalizability of our results in paper III is most likely limited by gender, and there is still the question of significance in a clinical setting.

10.2.3 Study design

All three studies in the thesis are randomized controlled trials, which is the study design considered to yield the most reliable form of scientific evidence as it

reduces bias and examines cause-effect relationships between intervention and outcomes.(161, 162)

The clinical studies in paper I and II were parallel design with randomization to one of two treatment groups. The challenge with this design is that it often requires a large sample size, which requires time and resources. The crossover design used in paper III draws advantage of the fact that variation within an individual is less than between individuals. The crossover design allows the individual to be his own control, this reduces between-subject variability and allows for a smaller sample size and smaller differences to be detected. A disadvantage to crossover studies is the potential for carryover effects influencing successive sessions.(163) This was not considered a problem in our study since analgesic effect from remifentanil has rapid off-set and the wash-out period was set to a minimum of 3 days.

It was essential that the study on OIH was conducted as an experimental study since in a clinical setting other opioids administered at the end of surgery for analgesic bridging into the postoperative period would obscure any findings. Evidently, this limits the study's external validity as healthy volunteers differ from a hospital population. (See "Experimental versus clinical pain" in Section 6.2. "Experimental pain".)

Furthermore, the multimodal prophylactic pain and antiemetic regimens used in the clinical studies probably influenced the results to some degree. In paper I, all patients received diclofenac, which may induce diarrhea or constipation, and ondansetron, which may induce constipation. Diclofenac, along with paracetamol and dexamethasone, probably affected the pain scores in paper I. Likewise, in paper II, perioperative ondansetron and dexamethasone were administered to all patients. Postoperatively, metoclopramide, ondansetron and droperidol were administered according to protocol. All patients received etoricoxib and paracetamol during the study period, which could have contributed to less nausea due to less pain, but nausea is also a well-known side effect of coxibs. It was carefully considered that our clinical studies replicated modern analgesic and

antiemetic procedures so that the results could be of relevance to real-world, everyday practice.

Blinding

It has been shown that trials that are not double-blinded yield larger estimates of treatment effects than double-blinded trials.(162) Blinding in studies is essential to eliminate bias and other confounders, but it is not always appropriate or feasible. In clinical trials, the patients can, for instance, recognize the study medicines due to previous use, they have access to internet resources that can help identify the tablet design, or group allocation is revealed to them by health care professionals not involved in the study. In paper I, patients who had used any of the study medications previously were excluded to ensure blinding. This was not a relevant issue in paper II as tapentadol was a rather new drug on the market and less known. Re-encapsulation of study medicines to make identical units was considered for optimal blinding in paper II, but not found feasible as the units would be too large to swallow and the matrix construction for prolonged release of depot tablets would be compromised. Another measure to prevent unblinding is instructions to patients and ward personnel not to disclose or seek information related to study medicines. Moreover, blinding can be troublesome when opioids are the subject of investigation in experimental pain studies as the effects are not disguisable.(15) Correspondingly, in placebo-controlled trials, it is not always possible to conceal the placebo-arm as placebo medication often has no effects and this is noticed by the patients. The patients may then be skewed in their perception of the treatment. In paper III, blinding of both the volunteers and the researchers may have been compromised by observed opioid effects or no effect.

Blinding of investigators prevents them from influencing the patients' perceptions, use of supplemental care or treatment, or lets them make objective decisions if withdrawal from a study comes into question. Finally, and maybe most importantly, blinding may reduce differential assessment of outcomes by outcome assessors. There has, however, been a tendency towards overstating the significance of blinding in the prevention of bias. Even though a double-blinded study indicates a solid study design, it should not be the primary indicator of trial

quality. It has been shown that double-blinding prevents bias but it is less important in preventing bias than allocation concealment.(164)

10.2.4 Outcome measures

Outcome measure – pain

The overall problem of measuring pain is that it is a subjectively reported measurement with no objective gold standard. We lack the equivalent of the thermometer to measure pain. Instead we rely upon surrogate measures such as pain intensity and rescue opioid consumption. Consequently, it is critical that these measurements of pain are done as consistently and accurately as possible to obtain a somewhat reliable evaluation of pain treatment.

As previously discussed, the VAS and NRS are commonly used to measure pain intensity, and they show equal sensitivity in assessing acute postoperative pain (see section 8.5.1 "Outcome measure – Pain").(106, 108) In clinical studies, the NRS is more practical than the VAS since patients often are unable to use a visual scale due to sedation, blurry vision or reduced dexterity in the immediate postoperative period. It can be used in follow-up telephone interviews or with digital solutions. The NRS is convenient in the experimental setting because the volunteer does not have to focus on a computer or move their opposite hand to indicate pain with a marker on a visual scale. We chose NRS as the main outcome measure for pain intensity in all three papers for the above-mentioned reasons.

We measured pain both at rest and during movement with NRS due to differences in resting versus dynamic pain. Assessment of pain intensity at rest after surgery is important for patient comfort but assessing pain during mobilization or coughing has even further implications since it is associated with reduced risk of cardiopulmonary and thromboembolic complications in the postoperative period. Pain at rest may not reveal differences between potent pain interventions if pain intensity is low and treatment effects become too subtle.(108) Pertaining to paper III, it should be noted that pain ratings and hyperalgesia do not always correspond, as demonstrated in a study on healthy volunteers by Mauermann et al., where subjects receiving a high dose of fentanyl reported decreased pain intensity by NRS scores but an increased area of hyperalgesia.(90)

There is an ongoing discussion as to what is the least difference on the VAS or NRS that indicates relevant pain relief. In studies mainly done on the VAS, some propose a change of 1 unit as the minimal clinically important difference, while others have suggested between 0.8-4 units in change or a 30-50% decrease depending on initial pain intensity.(106, 107, 165-168) In the experimental study (paper III), we used a change of 0.5 unit on the NRS as a measure that would reveal difference, while in the clinical study (paper II) we used 1 unit.

A major disadvantage to one-dimensional pain assessment tools like the VAS and NRS is the limited evaluation of the pain experience. Many factors influence the patient's reporting of pain, such as psychological traits (mood, attitude or stoicism), cultural and social expectations (gender differences in acceptable reporting of pain), surrounding atmosphere (temperature, lighting, color and sounds in the examination room) and the behavior of study personnel. Moreover, the genetic and biological makeup (i.e., differences in pain thresholds, previous pain experience) of the patient influence how pain is reported. (17) All these factors need to be considered to standardize pain measures as best possible, but one-dimensional tools still cannot represent the multidimensional aspects of pain.(169) In conclusion, the VAS/NRS seems to have good reliability, but there is a fundamental question as to whether these measures have good validity.

Measurement of pain relief takes into consideration the baseline of pain and how much the pain has improved between measurements. Global assessment of study medication, quality of analgesia and patient global impression of change are other categorical evaluations of study medication. Many other derived measurements for pain such as pain intensity difference (PID), summed pain intensity difference (SPID), summed pain relief with PID (PRID), and total pain relief (TOTPAR) are also used,(170) illustrating the lack of a gold standard measurement for pain assessment in studies.

Some researchers view opioid consumption as a valid surrogate outcome measure for pain since there is a high degree of agreement between this measure and measures of change in pain intensity or pain relief.(170) Although multiple studies have shown an association between rescue opioid consumption and postoperative

pain, the strength of the correlation is not clear and a correlation alone is not sufficient for validation of a surrogate endpoint. For instance, other variables than pain intensity such as patient age, surgeon experience, and institutional variability in pain management (e.g., titration of opioids to reach NRS < 3) may impact opioid consumption.(171) Gilron et al. state: "Statistically significant decreases in opioid dose requirements per se are not sufficient to argue for superiority of test drug vs placebo or other drug (or nondrug intervention)".(157) Others have questioned whether the mean opioid consumption is a valid measure for comparing pain relief between groups as there tends to be a skewed distribution of such data.(172) "The Standardised Endpoints in Perioperative Medicine" initiative undertook an extensive Delphi process to identify important, valid and reliable measures of patient comfort after surgery. In this summary, neither opioid consumption nor the time to first dose of opioid after surgery were found important as measures in the postoperative period.(173) However, this study was focused on patient comfort and not postoperative pain per se. It may be debated whether measurement of rescue opioid consumption, total opioid consumption or time to first dose of opioid alone are valid and reliable measures for pain, but the measures still seem relevant in the total evaluation of a new analgesic treatment.(174) Rescue opioid consumption was therefore included in papers I and II, and time to first rescue analgesic was included in paper II.

When evaluating a new analgesic treatment, as we have done in paper I and II, it is not sufficient to only quantify pain intensity, but one has to consider many aspects including time to onset of analgesia, analgesic duration, consumption of rescue medication, side effects and patient global satisfaction with treatment.(169, 174) Secondary outcomes should be considered if they can be particularly helpful in lending supporting evidence for the primary endpoint even though it increases the risk for false-positive findings.(138) There have been several attempts at assessment tools for chronic pain, e.g., The Brief Pain Inventory and The McGill Pain Questionnaire.(108) But, so far, a core outcome set of critical patient-reported outcomes and corresponding measures for acute pain after surgery is lacking.(105) A standardization of the measurement of pain in trials will help reduce variability and increase statistical power.(17) A defined core outcome set

would also allow for better comparisons of pain studies in meta-analyses or systematic reviews. In the future, neurophysiological methods like functional MRI, PET scan, EEG, measurement of nociceptive withdrawal reflex or other devices and techniques (electric, pressure, dilators, ultrasound, thermal) which obtain objective assessments of nociception can be applied as well, but they are as of now viewed as too comprehensive for use in clinical studies.(3, 175)

Outcome measure - constipation

Many assessment tools for constipation have been developed, and the sheer number of rating scales suggests that none are sensitive enough to assess constipation across all patient groups.(70) There are no scales validated for constipation in the postoperative setting specifically.(109) The BFI is easy to use in a clinical setting but was developed for evaluation of OIC in patients with chronic pain.(109, 110, 176) In paper I, we used revised forms of the BFI and the Bristol Stool Form Scale (see 8.5.2 "Outcome measures – Constipation") to evaluate constipation, hence a limitation to the study is the use of a scales not validated for the population. The changes made to the measurement scales may have decreased the construct validity of the BFI and the Bristol Stool Form Scale. However, our modified scores included all the symptoms proposed essential to assessment of OIC in a recent consensus statement: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation and harder stool consistency.(70) A strength to our study is the collection of data on the patients' habitual frequency and consistency of defecation. As pointed out by Gaertner et al., the change from baseline bowel habits when starting opioid therapy should be investigated since patients may have functional constipation or other disorders influencing the results.(69) We decided to not include patient-reported global burden measures of OIC in our study, these are patient-reported outcome measures that quantify the impact of OIC on the patients' distress in daily activities or quality of life. Such measures seem less relevant in a postoperative period when many other issues limit activities and normal life.

Since other important factors like postoperative ileus and pain could influence the results in paper I and there are no validated outcome measures for OIC in the postoperative period, we chose to analyze several objective and subjective measures to better reflect different aspects of OIC. This is supported by a recent systematic review on outcome measures of clinical trials on OIC which suggests that a combination of objective measures, patient-reported outcome measures and patient-reported global burden measures of OIC should be used.(69) The review also points out that a defined core outcome set for measures of OIC would allow for easier comparisons of studies in meta-analyses or systematic reviews.(69)

Outcome measure – nausea and vomiting

In paper II, we evaluated nausea and vomiting with a dichotomous yes/no question. More extensive evaluation of nausea and vomiting can be done with assessment tools such as the Ambulatory Surgery Index of Nausea, Vomiting, and Retching or the PONV intensity scale. The Ambulatory Surgery Index of Nausea, Vomiting, and Retching includes questions on frequency, duration, distress from nausea, vomiting and retching, as well as the amount of emesis. It is a modified version of the Rhodes Index, which was developed for oncological patients, and has later been validated in the postsurgical setting.(114) The PONV intensity scale is less extensive, developed to suit surgical patients and has even been validated for gynecological patients.(115, 177) Applying other assessment tools in the study on tapentadol (paper II) could possibly have produced more valid results. However, just as for pain and opioid-induced constipation, because there is no consensus on how to measure nausea and vomiting, the consequence is several different assessment tools.(113) Association between PONV and need for antiemetics is also often seen reported in studies, (115) but it seems like antiemetic use as an outcome measure for PONV has never been evaluated. In paper II less need for antiemetics supported the finding of lower odds for nausea in the tapentadol group.

PONV is a complex question as there is no way to distinguish between nausea and vomiting from opioids and other surgical (e.g., type and length of surgery) or anesthetic (e.g., gastric distention, intubation, inhalation anesthetics, muscle

relaxants, use of anticholinesterase drugs) factors in the postoperative setting. This will always be a limitation to the evaluation of opioid-induced nausea and vomiting in this setting.

10.2.5 Statistical considerations

Sample size

The following two paragraphs are based on the article "Significance, errors, power, and sample size: the blocking and tackling of statistics." by Mascha and Vetter.(178) The determination of sample size is a key aspect to study design. An adequate sample size helps include enough observations, detect differences and reject the null hypothesis with sufficient power, hence avoiding chances of false-positive findings. An adequate sample size is crucial to avoid inclusion of more subjects than necessary in a study. It also ensures that a clinical trial is not underpowered, which would increase the risk of false-negative conclusions (beneficial treatments are missed). In both cases, subjects would be exposed to unnecessary harm. However, determining the sample size is always difficult because it involves unknown parameters that can only be estimated. To determine sample size, we have to decide which treatment effect should be detected for the primary outcome variable, the SD of the primary outcome variable, the α-level and the power.

A type I error occurs when rejecting the null hypothesis ("there is no difference") when it is actually true, i.e., it is falsely rejected (a false-positive study). A predetermined α-level is set to help assess at which level the null hypothesis can be rejected and the result is statistically significant. The α-level is typically set to 0.05 (5% significance level) in 2-tailed tests. In other words, we can be at least 95% confident that the difference we found is a true difference and not a chance finding. A type II error occurs when there is a true difference between groups (the alternative hypothesis is true), but no difference is found in the study (null hypothesis is not rejected), leading to a false-negative study. The β-level is a predetermined probability of failing to detect a true difference, and the level is often set at 0.10 and 0.20. This implies a probability of committing a type II error is less than 10 or 20%. The opposite of a type II error is correctly rejecting the

null hypothesis when the alternative hypothesis is true. This ability to detect a true difference so that the null hypothesis may be rejected is referred to as power (1 – β). Power is often set to 80 or 90%. The goal when planning a study has to be minimization of both error rates. The α-level was set to 0.05 in all three papers. Power was set to 90% in paper I, 80% in paper II and 96% in paper III.

The variability, SD, of the primary outcome variable can be adapted from other studies with similar patient populations enrolled and a control group. In paper I, we used the SD from a previous clinical study that found constipation in ambulatory day surgery patients.(71) It could be discussed if this was the correct population for estimation of SD in a study of hysterectomy patients and if choice of another population with a different variability could have affected the results. In paper II, we used the SD from pain measures in the similar population from paper I, and in paper III, we used the SD from a previous experimental study on hyperalgesia in volunteers. (92, 116) The treatment effects for the primary outcome variables are discussed in section 10.2.4 “Outcome measures”.

The sample sizes in the clinical studies (paper I 80 patients and paper II 72 patients) and the experimental study (paper III 16 patients) are in line with comparable studies. Especially in paper III, it was crucial to have an appropriate sample size since it would be unethical to include more volunteers than necessary, exposing them to an opioid with potentially harmful side effects.

P-values and confidence intervals

We presented P-values and confidence intervals (CI) for several of our comparisons in paper I, II and III. Both are ways of presenting the same information and are seen as measures of how trustworthy the results in a study are. P-values are calculated when testing for the null hypothesis and are often used to decide if the null hypothesis should be accepted or rejected. The previously mentioned α-level and the P-value are not the same as the α-level is a predetermined value while the P-value is generated by the application of a statistical test on the collected data in a study. When the observed P-value is less than α, the null hypothesis can be rejected. The P-value lacks some important pieces of information like the magnitude of the effect of interest and the precision

of the estimated magnitude of that effect. It tells us nothing about the clinical importance of an effect, such as the direction of an observed difference or the relative risk between the compared groups. The CI provides a range of plausible values of the effect size estimate and may add more information on the results' clinical significance than the P-value. The CI is an interval that contains the true population parameter in a fixed percentage of samples (confidence level, often set to 95%) with repeated sampling. In other words, the CI covers the true value in 95 of 100 studies performed. The CI is closely related to significance testing, so if the 95% CI of the effects size contains the value that indicates "no effect" (e.g., the null value of 0 for a difference, or 1 for an odds ratio) this means that the data are compatible with no effect, corresponding to a non-significant result with a 0.05 significance level. This paragraph is based on the articles by Schober et al. and du Prel et al.(179, 180) It must be pointed out that many researchers oppose the use of P-values and CI as dichotomous values to decide whether a result refutes or supports a hypothesis.(181) Many instead advocate a focus on describing how big the difference in effectiveness found is and how precise this estimate is.

Odds ratio

Effect size measures are used to quantify treatment effects between variables and differences in means are the most commonly cited. Other effect size measures that can be used are correlations, risk differences, risk ratios and odds ratios.(179) Odds ratios (OR) are used to compare the relative odds of the occurrence of the outcome of interest given exposure to the variable of interest. Odds is defined as the ratio of two probabilities: the probability of an event happening over the probability of the event not happening. The OR is the ratio between odds of exposure and the odds of non-exposure, i.e., it represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. It is a measure of the strength of association between an exposure (risk factor) and an outcome. If the OR is 1 there is no association between the exposure and the outcome. So, if the 95% CI for an OR includes 1, it means the result is not statistically significant. If the OR < 1, the odds are decreased for an outcome, while if the OR > 1 the odds are increased for

an outcome. OR were used in paper II on the secondary endpoints of opioid-induced side effects. For nausea and vomiting, the OR supported related findings in incidence, some of which had not yielded statistically significant differences (see also previous paragraph on P-values).

Multiple testing

Multiple testing is unavoidable in pain research. As previously discussed, no single measure can reflect all aspects of pain. Moreover, the overall success of opioid pain treatment is not only about analgesia but the occurrence of different opioid-induced side effects. Consequently, we do multiple testing, both in terms of testing at multiple time points and with multiple endpoints. When comparing groups multiple times and/or for multiple endpoints the chance of finding a difference purely by chance increases, i.e., there is an increased probability of false-positive findings (type I error). Methods to adjust for multiple testing are Bonferroni, Tukey, Hochberg and Holm's step-down methods.(182) There is a risk of increasing type II error when doing such statistical adjustments, failing to detect a difference that truly exists. No gold standard exists for correction of multiple testing, but Bonferroni is often applied even though it has been criticized for being too conservative.(183) We used Bonferroni adjustment in paper I but refrained from it on secondary endpoints in paper II. Paper II is a good example of looking at all the existing data and not correcting with Bonferroni so that valuable information would not be lost. In this study, we initially found a significant result for nausea at 24 h in favor of tapentadol, but we could not be sure if this was just a result of multiple testing. The significantly higher use of antiemetics in the oxycodone group indicated that there was something to the data concerning nausea. Further statistical analysis of this exploratory endpoint revealed an increase in odds for nausea at 2 and 3 h postoperatively. Of course, the results have to be interpreted with caution, especially since power was calculated for a different endpoint, but this illustrates why some researchers advocate caution against the use of Bonferroni.

Linear mixed models

The assumption of independence between observations is crucial to some statistical models. That is, the observations have to be truly randomly sampled from a population with one measurement not affecting the other. In studies that require several observations from the same individual at many time points (repeated measures), the data cannot be viewed as independent. The scoring at one time point may be influenced by the scoring at another time point. Linear mixed models are developed to handle repeated measurements, subject clustering and data sets with missing observations. In linear mixed models both fixed and random effects are integrated. The fixed effects are often the central variables of interest, which we expect to have an effect on the dependent variable. These variables are explanatory variables that do not vary and typically affect population means. Random effects are categorical variables independent of the explanatory variables, and they give information about the variability between measurement units. The research subjects may be such a unit themselves, and the differences between them can be viewed as random variation. In the crossover study in paper III, the volunteers were exposed to repeated sessions and experiences from previous sessions could influence later sessions. In this study, we took into account fully crossed random factors as all individuals experienced all levels of an effect.(184) One-way repeated-measures ANOVA could be applied to this type of data, but linear mixed models are generally more accurate and flexible. Linear mixed models are also advantageous if the data set has a lot of missing data as this model makes use of all available observations.(185)

Further strengths and limitations

A strength in all three studies is a rather uniform study implementation and data collection as we are a small research group. The investigators planned the study protocols together with research personnel doing the study interventions and collecting the data, this secured uniformity and quality of data. It is possible that this even led to the low incidence of missing data in our studies, hence increasing the statistical strength. Especially in the experimental study (paper III), it was easy to conduct and secure the collection of all the required data. The data in this study

were also analyzed with the linear mixed models, which deals with missing data as a statistical method (see previous paragraph). In paper II, generalized mixed models for repeated measures was used for some of the measures, and this model is quite robust for dealing with missing data too.(186) The limitation for mixed model regression analyses is, however, that the missing data have to be missing at random, which we expect in our studies.

In retrospect, some parts of the statistics could have been done or reported differently. In paper III, the mean should have been reported with SD and not range. In paper II, the median was evaluated in case of skewed data, but after evaluation by a statistician who found the differences between means and medians insignificant, only means were reported. In paper II, ordinal scales were used for several measures and should have been reported with medians and interquartile ranges. For repeated measures of categorical variables in the two clinical studies non-parametric statistical methods exist, e.g., McNemar's test and Cochran's test, and could have been applied to our data.

10.3 Ethical considerations

Research on volunteers is rightly debated. Healthy persons are inflicted upon disease or symptoms which put them at risk of harm. In paper III, volunteers were exposed to painful tests and an opioid. Several ethical issues were addressed before the study was conducted. Could the heat pain tests induce burn injuries? Could remifentanil evoke dangerous side effects like respiratory depression? Could brief opioid exposure elicit opioid liking and introduce the volunteers to recreational use of illicit drugs? There are guidelines for research on healthy people such as the Nürnberg codex, and from counseling bodies such as the World Health Organization and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. In general, there is agreement that research on volunteers can be performed if the risk of harm is kept as low as possible and the research gain is high.(187) In the experimental study, we took all measures to ensure the safety of the participants during sessions and two or more anesthesia personnel were available at all times. In terms of skin burn injuries, the maximum temperature was limited below harmful temperature.

Before inclusion in the study, the volunteers were asked about previous use of drugs and alcohol, and all volunteers were offered follow-up after the study (not exclusive for issues pertaining to drug use). There has been a conception in medical research that opioids do not readily elicit addition when used in medical settings.(65) Still, there is little literature on what brief opioid exposure in an experimental study can result in, and in view of the opioid crisis we must emphasize that caution should be used in any exposure to opioids.

The volunteers in paper III received compensation for travel expenses and a small monetary reward after participation. While patients in clinical studies potentially have personal gain from participation, such as therapeutic benefits or better understanding of their disease, volunteers may be motivated for financial reasons. Even though financial reward often is the primary motivation, there is evidence that reasons for participation are more complex involving curiosity, healthcare benefits, scientific interest in the specific study or a wish to contribute to science and health of others.(188) Although financial reward could have been the primary motivation for some of our subjects in paper III, the value was kept low so it would not be a large incentive for participation.

The major benefit for patients participating in clinical studies is extended information about their disease and what they can expect in terms of pain during the study. The patients in paper I and II received multimodal pain regimens standardized for our hospital in addition to the new experimental opioid or the standard opioid according to randomization. The new opioids in paper I and II, oxycodone-naloxone and tapentadol, were opioids already in use in other patient populations, so the effects and side effects were well-known. Thus, the patients received pain treatment similar to what they could expect if they did not participate in the studies and with a low risk of harm.

A Cochrane review concluded that industry-sponsored studies more often had favorable efficacy results and conclusions than non-industry sponsored studies.(189) This is worrisome as bindings to the industry could result in skewed impressions of drug effects and side effects affecting medical practice. Ahead of conducting the study in paper I, our research group had received a small non-

restricted grant from the company distributing oxycodone and oxycodone-naloxone. The findings in this paper were positive in terms of similar analgesia between the drugs, but the expected main benefit, less constipation, was not found. In my opinion, it is important to keep the emphasis on non-sponsored medical trials. However, non-sponsored medical trials are significantly decreasing in Western Europe (Johan Ræder, personal communication, 2020), which may be due to the increasing bureaucracy when conducting medical trials.

10.4 Clinical implications

Besides evaluating the effects and side effects of the drugs in paper I and II, the studies may have interest in terms of cost-benefit. New drugs are much too often introduced in the clinic, sometimes for off-label use, without proper examination of consequences such as the potential for drug interactions or cost-effect benefits in the specific setting. Since both oxycodone-naloxone and tapentadol were found to have similar analgesic effects as oxycodone, and tapentadol also showed a potential for reduced gastrointestinal side effects, they should be considered as options in postoperative pain treatment. However, new patented drugs tend to be more expensive, and the benefit from side effect reduction must be evaluated against cost. The first study led to oxycodone-naloxone being limited for patients with a high risk of constipation from long-term opioid treatment and significant immobilization in our department. Furthermore, patients with a preoperative disposition for constipation are treated with oxycodone-naloxone. The study on tapentadol introduced us to a new strong-acting analgesic, not previously used for postoperative pain treatment at our hospital. It is now used as an option if the patient has a previous history of extensive PONV, treatment-refractory constipation or negative gastrointestinal experiences with oxycodone. It is also considered as an alternative for opioid rotation in selected patients. Hence, these two studies were of importance in order to evaluate the use of new and more expensive analgesics before introduction to the clinic in our department.

As for the study on OIH (paper III), gradual withdrawal from remifentanil infusion at the end of surgery was already done by many nurse anesthetists and anesthesiologists, and this study put even more focus on this practice. In the

clinical setting, the gradual withdrawal of remifentanil infusion is an easy, low-cost intervention that only requires education of personnel. A standardized protocol for timing of withdrawal is, however, not implemented as there is still limited support for this in the literature.(62) More importantly, this study has brought attention to OIH in general among my colleagues. When published, the study was accompanied by an editorial in the British Journal of Anaesthesia,(190) and it has later been cited in several papers and at international conferences in anesthesia. Hopefully, our study will be a foundation for further studies on gradual withdrawal of remifentanil infusion and its relevance in the clinical setting.

10.5 Future research and perspectives

The opioids mainly used in the clinic today are high-affinity, highly selective MOP agonists causing side effects primarily via the β-arrestin pathway. Since the MOP, KOP, DOP and NOP receptors have significant functional interactions between them, this can be exploited to develop opioids with less side effects. The mixed MOP/NOP ligand cebranopadol has shown analgesic effect with less respiratory depression in human studies,(191) and more MOP/NOP and MOP/DOP drugs are under investigation.(30) There are also interesting developments with biased MOP ligands, which aim to produce analgesia without side effects by favoring G-protein signaling over β-arrestin signaling.(30, 31, 192)

Another intriguing concept is the activation of opioid receptors in peripheral inflamed tissue, thereby avoiding central side effects. At a site of injury, the tissue is acidotic from inflammation and in this environment G-protein coupled receptors may have augmented functioning. The hypothesis is that MOP ligands can selectively activate under low pH and will not elicit the same side effects as MOP ligands under physiological conditions. The central effects of opioids are eliminated since activation is only in the peripheral injured tissue. The concept is already shown to have effect in animal studies.(34, 193) A different approach is nanocarriers designed to selectively release opioids to upregulated opioid receptors in injured tissue. Because the nanocarriers have no blood-brain barrier permeation, the side effects are avoided.(194) There is also ongoing research on

endomorphins selective for MOP in the brain, which seems to elicit analgesic responses without side effects,(195) and enkephalinase inhibitors which prevent the degradation of endogenous opioid peptides.(193)

The road ahead for treatment of OIC may be other μ-receptor antagonists than naloxone. It can be advantageous to have an antagonist not integrated in a compound as this allows for titration of dose to effect and independence of the opioid administered. Methylnaltrexone, alvimopan, naloxegol and naldemedine are all peripherally acting μ-receptor antagonists which have shown efficacy for OIC.(73, 196-198) There are currently no ongoing studies on oxycodone-naloxone or tapentadol in the postoperative setting registered in clinicaltrials.gov.(199) As for potential studies with tapentadol, it would be interesting to look at patient groups where avoidance of PONV is particularly important in the postoperative period to avoid complications, such as neurosurgery or upper gastrointestinal surgery. Furthermore, as noradrenaline reuptake inhibitor drugs are known to be useful in chronic neuropathic pain,(200) it would be interesting to study if surgery which induces neuropathic pain (e.g., limb amputation, mastectomy, thoracotomy and hernia repair) might be better treated with tapentadol than pure μ-opioids.

In the last decade, the practice of opioid free anesthesia has gained attention.(201, 202) This ground shattering idea (to anesthesiologists at least) of not using any opioids before, during or after general anesthesia for surgery could obliviate the problem of opioid-induced side effects. By combining drugs with different modes of action, it is possible to induce hypnosis, analgesia and immobilization. Opioid free anesthesia further provides exciting new opportunities for research on opioids and side effects as it offers a comparator group of surgical patients free of opioid effects. For instance, the clinical impact of OIH on postoperative pain would be possible to explore in randomized controlled trials. An intriguing idea for a next study is to implement opioid free anesthesia and compare arms with different modes of remifentanil infusion in patients. This would help differentiate nociception-induced hyperalgesia (from the surgery) from OIH, if remifentanil-induced hyperalgesia is relevant in the clinical setting and if gradual withdrawal is beneficial to prevent it. More detailed studies on the speed and dose intervals

gradual withdrawal should be done as this could lead to standardized protocols for administration of remifentanil.

Finally, a word must be said about the larger perspective on opioids in light of the current opioid crisis. Patients exposed to opioids during hospitalization and who receive a prescription upon discharge are more likely to develop opioid addiction. A large Canadian study on opioid use after major surgery showed that 49% of opioid-naïve patients were discharged with an opioid prescription and 3.1% continued to use opioids after 3 months.(203) In Norway, the prescription of oxycodone is 8-doubled during the last 15 years.(204) It seems fitting to end these reflections on future perspectives with a reminder that we should not underestimate the role of the anesthesiologist in reducing opioid use and that we should aim to be a part of the solution together with other physicians.(205)

11. Conclusions

In paper I, we found no difference in constipation between the group receiving oxycodone PR and the group receiving oxycodone PR with peripherally acting naloxone during the first 3 days after hysterectomy. The analgesic effect of oxycodone was not compromised by the naloxone as pain scores were similar for both groups.

In paper II, we found that tapentadol, a μ-opioid receptor agonist/noradrenaline reuptake inhibitor, had similar analgesic effect to the pure μ-opioid receptor agonist oxycodone the first postoperative day after hysterectomy. There were lower odds for nausea over time in the tapentadol group and a higher need for antiemetics in the oxycodone group, indicating a beneficial effect on postoperative nausea from tapentadol.

In paper III, we found development of opioid-induced hyperalgesia after abrupt withdrawal of remifentanil infusion but not after gradual withdrawal of infusion with a heat pain test in healthy volunteers. There were statistically significant higher pain scores 45 min after abrupt withdrawal of infusion compared to both gradual withdrawal and placebo infusion. There was no indication of hyperalgesia in the gradual withdrawal session as the pain scores were similar to the placebo session. This indicated that gradual withdrawal from remifentanil infusion may prevent opioid-induced hyperalgesia. The results were not replicated with the cold pressor test. The hyperalgesia persisted for less than 105 min after end of remifentanil infusion when testing with both experimental modalities.

12. References

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13. Reprints of Paper I - III

II

Tapentadol versus oxycodone analgesia and side effects after laparoscopic hysterectomy: a randomised controlled trial

Short title (running head): tapentadol analgesia after hysterectomy

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Abstract

Background: Tapentadol is an opioid which acts as a μ-opioid receptor agonist and inhibits noradrenaline reuptake in the central nervous system. This dual mechanism of action results in synergistic analgesic effects and potentially less side effects. This has been shown in treatment of chronic pain, but postoperative studies are sparse.

Objective: The main aim was to compare the analgesic effect of tapentadol with oxycodone after hysterectomy. Opioid side effects were registered for secondary outcomes.

Design: Randomised, blinded trial.

Setting: Single-centre. Oslo University Hospital, Norway. December 2017 to February 2019.

Patients: Eighty-six opioid-naïve, American Society of Anesthesiologists class I-III, women undergoing laparoscopic hysterectomy for non-malignant conditions.

Intervention: The patients received either p.o. tapentadol (group T) or oxycodone (group O) as part of multimodal pain treatment. Extended-release study medicine was administered 1 h pre-operatively and after 12 h. Immediate-release study medicine was used as rescue analgesia.

Main outcome measures: Pain scores, opioid consumption and opioid-induced side effects were evaluated during the first 24 h after surgery.

Results: The groups scored similarly for pain at rest with the numerical rating scale (NRS) 1 h postoperatively (group T: 4.4, 95% CI 3.8 to 5.0, group O: 4.6, 95% CI 3.8 to 5.3). No statistically significant differences were found between the groups for NRS at rest or while coughing during the 24 h follow-up period (P=0.857 and P=0.973). Mean dose of oral rescue medicine was similar for the groups (P=0.914). Group T had significantly lower odds for nausea at 2 and 3 h postoperatively (P=0.040, P=0.020) and less need for anti-emetics than group O. No differences were found for respiratory depression, vomiting, dizziness, pruritus, headache or sedation.

Conclusion: We found tapentadol to be similar in analgesic efficacy to oxycodone during the first 24 h after hysterectomy, but with significantly less nausea.

Trial registration: ClinicalTrials.gov, NCT03314792.

Introduction

Opioids remain first-line drugs as part of multimodal postoperative pain treatment, but the use of opioids is limited by well-known side effects. Most feared in the postoperative setting is respiratory depression, but nausea, vomiting, constipation, pruritus, sedation, dizziness and headache may also cause patient discomfort or complications.[1,2] Given these limitations from pure opioid agonists, the search for strong analgesics with a better side effect profile in postoperative pain treatment is highly relevant.[3]

Tapentadol is a new mixed ligand opioid which acts as a μ-opioid receptor (MOR) agonist and also inhibits noradrenaline reuptake in the central nervous system.[4] This dual mechanism of action is believed to result in synergistic analgesic effects.[5,6] Since opioid side effects are strongly related to MOR stimulation, tapentadol is expected to have less side effects than the pure opioid agonists.[6,7]

Tapentadol has been shown effective for acute and chronic nociceptive, neuropathic or cancer related pain,[7,8] but there is lack of broad-based evidence for tapentadol in the postsurgical setting.[9] To our knowledge, the published studies on analgesic effects from tapentadol are mainly industry funded studies on orthopaedic and dental patients,[10-12] and few are related to procedures with major components of visceral pain, such as laparoscopy.[13,14] A review of tapentadol studies in the postoperative setting indicated less nausea, vomiting, constipation and pruritus compared with oxycodone, but no difference in somnolence, headache or dizziness.[10] Studies on respiratory depression from tapentadol in any setting are sparse.[9,12]

The aim of this study was to compare the analgesic effect of tapentadol with oxycodone during the initial 24 h period after laparoscopic hysterectomy. The primary outcome was pain at rest 1 h postoperatively, but pain at rest and while coughing were also recorded at several time points during the first 24 h postoperatively. Further secondary outcomes were nausea, vomiting, respiratory depression, sedation, pruritus, dizziness, headache, need for rescue medication and overall satisfaction with pain treatment.

Methods

The protocol of this randomised, parallel group, blinded, single-centre study on women undergoing elective, laparoscopic supracervical or total hysterectomy for non-malignant conditions, was approved by the Regional Committee for Medical and Health Research Ethics in Eastern Norway (Chairperson Prof B-I Nesheim; 31 May 2017; protocol number 2017-001285-23) and the Norwegian Medicines Agency. The study was registered in clinicaltrials.gov (NCT03314792) and EudraCT (2017-001285-23). The study was independently monitored by the Clinical Trial Unit at Oslo University Hospital, and data analysis was performed after the final monitor report was done to ensure that requirements for Good Clinical Practice and the Declaration of Helsinki were met.

Women aged 18-65 yr classified as American Society of Anesthesiologists class I to III were included after written informed consent was obtained. Patients with weight <55 kg, >85 kg or BMI >31 were excluded. Other exclusion criteria were chronic pain syndromes in organ systems other than the female reproductive system, severe heart, lung, liver or kidney failure, severe psychiatric disorders, malignancy previous five yr, chronic medication with opioids, steroids, benzodiazepines, gabapentanoids, tramadol, clonidine or serotonin-noradrenaline reuptake inhibitors, alcohol or drug abuse and allergy or intolerance to any medication in the study.

The patients' demographic data and pre-operative risk factors of postoperative pain, such as pain from any organ system, analgesics used during the last four weeks, disposition for catastrophizing and episodes of anxiety or depression were registered. Previous postoperative nausea and vomiting (PONV), disposition for motion sickness and smoking status were registered and used to calculate the Apfel score for prediction of PONV.[15] The patients were instructed in the use of the numerical rating scale (NRS) to verbally rate pain on a scale from 0 to 10 (0 = no pain, 10 = worst pain imaginable).

Dosing was based on previous studies on surgical patients, showing approximately 1:5 equipotency in analgesic effect between oral oxycodone and tapentadol.[9,16] Tapentadol depot 50 mg p.o. (Grünenthal GmbH, Aachen, Germany) was chosen as the equivalent extended-release (ER) medicine to oxycodone depot 10 mg p.o. (Mundipharma Pharmaceuticals, Cambridge, UK), and immediate-release (IR) tapentadol 50 mg p.o. as the equivalent to oxycodone 10 mg p.o. for rescue medicine.

Intervention

According to a computer-generated code, using block randomisation by blocks of ten, patients were allocated to receive either tapentadol (group T) or oxycodone (group O) during the study period. Group T received ER tapentadol 50 mg p.o. and group O received ER oxycodone 10 mg p.o. as part of premedication. After 12 h all patients received an additional dose of ER study medication. IR tapentadol 50 mg or oxycodone 10 mg were available as rescue medication. Study medication was distributed in opaque, identical looking dosing boxes prepacked by a physician not participating in the treatment or evaluation of the patients. A dummy dosing box was demonstrated to the patients at the time of inclusion in order to prepare them for self-administration of rescue medicine. The researchers involved in inclusion, treatment and evaluation of the patients were blinded to which study medication the patients received.

All patients also received paracetamol (1.5 g <60 kg, 2.0 g ≥60 kg), etoricoxib (90 mg <60 kg, 120 mg ≥60 kg) as oral premedication. Metronidazole 1.5 g and cefuroxime 1.5 g i.v. were administered as prophylactic antibiotics. The patients underwent surgery in general anaesthesia with propofol and remifentanil. Rocuronium 0.6 mg kg^{-1} i.v. was administered only when required for surgical access. All patients received dexamethasone 8 mg i.v., ondansetron 4 mg i.v., 20 ml of bupivacaine 0.25% infiltrated at the incision sites

and fentanyl 2 μg kg^{-1} i.v. 10 min before end of surgery. Monitoring was done with ECG, pulse oximetry, non-invasive blood pressure and end-tidal carbon dioxide ($ETCO_2$).

IR study medication was available for breakthrough pain both in the postanaesthesia care unit (PACU) and in the gynaecological ward. In the PACU fentanyl 1 μg kg^{-1} i.v. was allowed as rescue medicine for initial urgent pain relief. Rescue analgesic medication was titrated until effect in patients who rated pain as 4 or more on the NRS and requested additional analgesia. The patients also received oral paracetamol every 6 h during the study period. Metoclopramide 10 mg i.v. was drug of choice in case of PONV, followed secondly by ondansetron 4 mg and thirdly droperidol 0.625 mg.

Outcomes

The primary outcome, pain at rest 1 h postoperatively, was evaluated with the NRS. Pain at rest and while coughing were recorded at 15 min, 30 min, 1, 2, 3 and 24 h postoperatively as secondary outcomes. Furthermore, nausea, vomiting, pruritus, dizziness, headache, sedation, respiratory rate (RR) and use of rescue medication were recorded at 30 min, 1, 2, 3 and 24 h postoperatively. Nausea, vomiting, pruritus, dizziness and headache were yes/no questions, while sedation was scored using the Pasero opioid-induced sedation scale (S = sleep; 1 = awake; 2 = slightly drowsy; 3 = frequently drowsy; 4 = somnolent).[17] The cumulative doses of rescue analgesics were recorded in μg for fentanyl and number of IR study medication taken. Time to first requirement of i.v. or oral rescue medicine was registered. Oxygen saturation (SpO_2) and nasal $ETCO_2$ were continuously monitored [Smart CapnoLine® Plus O_2 (Oridion Medical 1987 Ltd., Jerusalem 9777407, Israel), IntelliVue MX500® and X2® (Philips Healthcare, Böblingen, Germany)] and data collected at 30 min, 1, 2, 3 and 24 h (SpO_2 only) postoperatively. At the end of the study patient overall satisfaction with pain treatment, taking into consideration both analgesic effect and side effects, was evaluated using a five-point scale (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent).

Statistical analysis

In a previous study on oxycodone after hysterectomy we found that patients at rest had a mean NRS pain score of 4 with a standard deviation (SD) of 1.5, 1 h postoperatively.[18] Using these data, the statistical power of 80% and a significance level alpha of 5% , we would need 36 patients in each group to reveal a clinically relevant difference of 1 unit on the NRS.

The continuous data are presented as means and SD, and categorical data as counts and percentages. Confidence intervals (CI) for the means were constructed using bootstrapping. Data were analysed using the independent samples t-test for parametric data, the Mann-Whitney U-test for non-parametric data and the X^2-squared test for categorical data. Some of the secondary outcomes were also analysed using generalized mixed models for repeated measures with identity link for continuous data or logit link for categorical data when appropriate. These results are expressed as odds ratios (OR) with 95% CI and the

baseline defined as 30 min postoperatively. All models were fitted with type of treatment, time and an interaction term time*type of treatment to assess if the development over time differed between the two treatments.

The significance level was set at 0.05. As the study was considered exploratory for the secondary outcomes, no correction for multiple testing was performed for these measures. All tests were two-sided and statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA) and Stata version 16 (StataCorp LP, College Station, TX, USA).

Results

Recruitment was done from December 16, 2017 to February 28, 2019 at Oslo University Hospital. Of 518 potentially eligible patients, 193 patients were approached for participation and 86 were enrolled and randomised into the study (Fig. 1). The final evaluation included 37 patients allocated to the tapentadol group and 36 patients to the oxycodone group. Demographic and baseline subject characteristics, including pre-operative risk factors of postoperative pain and nausea, as well as intra-operative variables, were similar between the two groups (Table 1).

Primary outcome

The mean level of pain was similar in both groups when assessed with the NRS at rest 1 h postoperatively, group T 4.4 (95% CI 3.8 to 5.0) vs group O 4.6 (95% CI 3.8 to 5.3) (Fig. 2).

Secondary outcomes

The groups were also similar for pain while coughing at 1 h postoperatively, the mean NRS for group T was 5.1 (95% CI 4.4 to 5.8) and 5.3 (95% CI 4.6 to 6.0) in group O (Fig. 3). There were no statistically significant differences between the groups for NRS at rest or NRS while coughing over time when considering the whole 24 h follow-up period (*P*=0.857 and *P*=0.973; Fig. 2 and 3). Mean ± SD dose of i.v. rescue fentanyl was 279 ± 175 μg in group T and 238 ± 138 μg in group O, while mean ± SD numbers for oral rescue medicine were 3.8 ± 1.7 and 3.0 ± 1.6 in group T and group O, respectively. Furthermore, no statistically significant differences were found between the groups for rescue medication doses of fentanyl or oral IR study medication over time (*P*=0.619 and *P*=0.914). The groups were also similar (ns) in mean ± SD time to first dose of i.v. rescue medicine (group T 15 ± 15 min vs group O 19 ± 15 min) and oral rescue medication (group T 28 ± 26 min vs group O 27 ± 20 min).

At 24 h, 44% in group O reported nausea vs 22% in group T (*P*=0.038; Table 2). Both groups had significantly increased odds for nausea over time compared to baseline (OR 3.3, 95% CI 1.2 to 9.5; *P*=0.026). When estimating the interaction between groups and time, we found that group T had significantly lower odds for nausea than group O at 2 and 3 h postoperatively compared to baseline (*P*=0.040 and *P*=0.020), with a

trend towards significance at 24 h (*P*=0.060). There was also statistically significant higher need for anti-emetics and repeated administrations of anti-emetics in group O as shown in Table 2. Relatively few patients vomited during the observation period (Table 2), and while the odds for vomiting were numerically higher for group O, the ratio did not reach the level of statistical significance difference (OR 1.7, 95% CI 0.6 to 4.9; *P*=0.371).

There were no statistically significant differences in mean values for respiratory variables between the groups (Table 3). When analysing $ETCO_2$, SpO_2 and RR over time compared to baseline and in-between groups, no significant differences between odds were observed (*P*=0.771, *P*=0.441, and *P*=0.220 respectively). Furthermore, we did not find any statistically significant differences between the groups when examining presence (i.e. %) of dizziness, pruritus, headache or sedation (Table 3) or when estimating the odds for these outcomes (data not shown). The proportions of patients who scored their satisfaction with pain treatment as high (scores good, very good and excellent satisfaction pooled) were similar (group T 89% and group O 97%; *P*=0.364). No relevant serious adverse events were reported during the study.

Discussion

We have shown that tapentadol was not significantly different from oxycodone for treatment of acute postoperative pain after hysterectomy. The pain intensity at rest was similar not only at 1 h postoperatively, which was the primary outcome, but throughout the 24 h study period for both pain at rest and while coughing. Tapentadol was favourable in terms of less nausea and need for anti-emetics, but there were no differences between the groups for respiratory depression, vomiting, dizziness, sedation, pruritus or headache.

Our results are in agreement with previous findings on tapentadol after dental or orthopaedic surgery, indicating comparable analgesic effects with oxycodone, but less nausea.[9,10,19-21] Two systematic reviews on tapentadol vs oxycodone, morphine, tramadol or placebo included both postoperative and musculoskeletal pain.[11,12] The reviews concluded with similar analgesic effects from tapentadol compared with other opioids, but less gastrointestinal side effects and dizziness from tapentadol. Although our findings are partially in accordance with these systematic reviews, the patient data are not fully comparable. Most of the studies in the reviews were on orthopaedic patients, and the results from a sole hysterectomy study are so far not published in a peer-review journal. Also, the inclusion of patients with musculoskeletal pain in the reviews may result in findings that are not relevant to postoperative pain. All studies in the reviews were on IR tapentadol, but we have found one study comparing ER tapentadol with oxycodone.[13] The study was done on parturients 24-48 h post caesarean section and failed to prove superiority of tapentadol over oxycodone. They found no differences in side effects, however, there was uneven administration of anti-

emetics between the groups as this was not standardised in protocol, which could have affected reported gastrointestinal side effects. As PONV affect recovery, complications, discharge and overall satisfaction after surgery,[22,23] tapentadol may be a favourable drug in the postoperative setting. Moreover, the resulting need for less anti-emetics with potential side effects would be beneficial.

The most feared opioid side effect is respiratory depression because of potential fatal outcome.[2,24] An experimental study found significantly larger respiratory depressant effect from oxycodone 20 mg than tapentadol 100 mg when measuring the ventilatory response to hypercapnia and ventilation at an extrapolated $ETCO_2$ of 7.3 kPa.[25] We have only found one clinical study evaluating respiratory depression from tapentadol as part of safety assessments.[19] The authors claim that all incidents of low SpO_2 in the study could have been due to technical failure of the pulse oximetry device and conclude with no effect from tapentadol on respiratory depression. However, opioid-induced respiratory depression is difficult to measure and has no clear definition in the literature with arbitrary thresholds for desaturation, bradypnea and hypercapnia.[2] In our study we chose to monitor RR, $ETCO_2$ and SpO_2 based on previous studies,[24,26] and we found no differences between the groups in any of these respiratory parameters. Continuous measurement of $ETCO_2$ has been shown to be a more sensitive measure than SpO_2 for respiratory depression.[27] Even though $ETCO_2$ was only recorded at set time points for study purposes in our study, there were no reports of $ETCO_2$ out of range during continuous monitoring in the PACU. While there were some incidents of RR <10 in both groups, they were resolved by verbal stimulation of the patient, leaving no clinical impact on oxygenation.

Reduction of opioid side effects is important in postoperative pain treatment to reduce complications and shortening in-hospital admissions.[23] In terms of patient comfort, a previous study have shown that patients will accept some level of pain if opioid side effects are reduced.[28] The side effects from tapentadol in surgical patients need further exploration in clinical studies.

Our study has some limitations. Due to the matrix construction of depot tablets and capsule format of IR oxycodone it was not possible to re-encapsulate the study medication into identical units for optimal blinding of the groups. Another limitation is our choice of i.v. opioid for urgent pain relief during the initial period in the PACU. Since i.v. tapentadol is not licensed in Europe, i.v. fentanyl was chosen as rescue medication. Fentanyl predominantly effects MORs, but the fentanyl doses were low and similar between the groups, so we cautiously contend our findings to be associated with tapentadol. Opioid-induced hyperalgesia may be a problem with our study design of pre-operative opioids in combination with peri-operative remifentanil infusion. However, any potential hyperalgesia induced by opioids could have been limited by the cox-II inhibitor etoricoxib, total i.v. anaesthesia with propofol and low-dose remifentanil administered to all patients

in the study.[29-31] As the remifentanil dose was identical in both study groups it should not have interfered with the interpretation of the main study results. Since tapentadol scarcely has been studied in the postoperative setting, the design of combined pre- and postoperative study medication was chosen in order to tease out potential differences between the study medications in the immediate postoperative period, not necessarily reflecting an ideal setup in clinical practice. It may also be a limitation that data from three patients who received epidural analgesia due to severe pain were not included. These patients received an epidural early in the study period, and further analgesic effects of the study drugs were overruled by the effective epidural analgesia. Lastly, the study was limited to healthy, adult women, so we cannot extrapolate our findings to men as there may be differences in opioid analgesic potency and side effects between gender.[32] Also, the study is limited to patients without pre-operative chronic pain syndromes or chronic opioid therapy, which can be important confounders for postoperative pain.

The patients were only studied for 24 h after surgery since a previous study on the same patient population done by our research group had shown no need for ER opioids at regular intervals beyond 24 h when treated with IR opioids p.r.n., paracetamol and nonsteroidal anti-inflammatory drugs.[18] A strength to our study is the consideration of predisposing factors for increased postoperative pain: anxiety, depression, catastrophizing, pain and use of analgesics before surgery. As these factors came out equally distributed between the groups, they are not expected to be confounders to the pain results in the study. We also believe that this study is one of the first independently funded studies to explore the effects of ER and IR tapentadol vs oxycodone on visceral pain, as the majority of previous studies have been industry sponsored studies on tapentadol IR after orthopaedic or dental surgery.[11] The overall evaluation of pain treatment was positive in more than 93% of the patients, indicating that both tapentadol and oxycodone work well as part of a multimodal treatment with paracetamol, nonsteroidal anti-inflammatory drugs and steroids for postoperative pain.

In conclusion, we found tapentadol to be similar in analgesic efficacy to oxycodone the first 24 h after hysterectomy. Tapentadol resulted in less nausea than oxycodone, but no differences were found for respiratory depression, vomiting, dizziness, pruritus, headache, sedation or patient satisfaction.

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Conflict of interest: Marit Lieng has received an honorarium for chairing a Gedeon Richter seminar in 2018 and she is principle investigator at Oslo University Hospital for a multi-centre study ("In-bag morcellation during laparoscopic hysterectomy") sponsored by Olympus, Europe.

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Captions

Table 1 Patient characteristics and intra-operative variables. Unless otherwise stated values are presented as mean ± SD. No significant P-values were found.

Table 2 Comparison of secondary outcomes related to nausea and vomiting. P-values reported are based the X^2-square test. * statistically significant P-value <0.05. § No correction for multiple testing.

Table 3 Comparison of secondary outcomes related to respiration, dizziness, pruritus, headache, sedation and overall satisfaction with pain treatment. Unless otherwise stated values are presented as mean ± SD. P-values reported are based on X^2-square test for categorical data and independent samples t-test or Mann-Whitney U test according to normality of continuous data.

Fig. 1 CONSORT flow chart.

Fig. 2 Pain measured with numerical rating scale (NRS) at rest. Data are plotted as means with 95% CI.

Fig. 3 Pain measured with numerical rating scale (NRS) while coughing. Data are plotted as means with 95% CI.

Table 1 Patient characteristics and intra-operative variables. Unless otherwise stated values are presented as mean ± SD. No significant P-values found.

	Tapentadol (*n*=37)	**Oxycodone (*n*=36)**
Age (yr)	43.1 ± 5.9	44.6 ± 7.4
ASA class I/II/III (%)	73/27/0	72/28/0
Height (cm)	168 ± 5	167 ± 5
Weight (kg)	68 ± 9	67 ± 9
BMI (kg m^{-2})	24.0 ± 3.3	24.1 ± 2.6
Apfel score	2.6 ± 0.6	2.7 ± 0.5
Pain related to surgical area last week before surgery (NRS)	2.8 ± 2.8	2.9 ± 3.2
Pain in other organ systems last week before surgery (NRS)	1.9 ± 2.3	1.1 ± 2.1
Any type of analgesic last four weeks before surgery (%)	65	63
Anxiety (%)	17	21
Depression (%)	31	24
Catastrophizers (%)	11	6
SpO_2 before surgery (%)	99.3 ± 0.9	99.6 ± 0.8
Anaesthesia duration (min)	130 ± 28	133 ± 33
Surgery duration (min)	83 ± 30	86 ± 31
Type of surgery (LH/LSH, %)	84/16	81/19
Total propofol (mg)	1046 ± 238	1078 ± 286
Total remifentanil (µg)	1636 ± 538	1739 ± 635
Intra-operative fentanyl dose (µg)	136 ± 18	133 ± 17
Intra-operative muscle relaxant (%)	8	6

ASA, American Society of Anesthesiologists; BMI, body mass index; SpO_2, peripheral capillary oxygen saturation; LH, laparoscopic hysterectomy; LSH, laparoscopic supracervical hysterectomy.

Table 2 Comparison of secondary outcomes related to nausea and vomiting. P-values reported are based the X^2-square test. * statistically significant P-value <0.05. [§] No correction for multiple testing.

	Tapentadol (*n*=37)	**Oxycodone (*n*=36)**	***P*-value**
Nausea 30 min, baseline (%)	13.5	11.1	1.000
Nausea 1 h (%)	16.2	8.3	0.479
Nausea 2 h (%)	10.8	8.3	1.000
Nausea 3 h (%)	8.1	19.4	0.190
Nausea 24 h (%)	21.6	44.4	0.038[§]
Vomiting 30 min, baseline (%)	2.7	0	1.000
Vomiting 1 h (%)	2.7	0	1.000
Vomiting 2 h (%)	0	5.6	0.240
Vomiting 3 h (%)	0	5.6	0.240
Vomiting 24 h (%)	18.9	27.8	0.417
Any anti-emetic (%)	48.6	72.2	0.040*
Anti-emetic several administrations (%)	21.6	44.4	0.038*

Table 3 Comparison of secondary outcomes related to respiration, dizziness, pruritus, headache, sedation and overall satisfaction with pain treatment. Unless otherwise stated values are presented as mean ± SD. P-values reported are based on X^2-square test for categorical data and independent samples t-test or Mann-Whitney U test according to normality of continuous data.

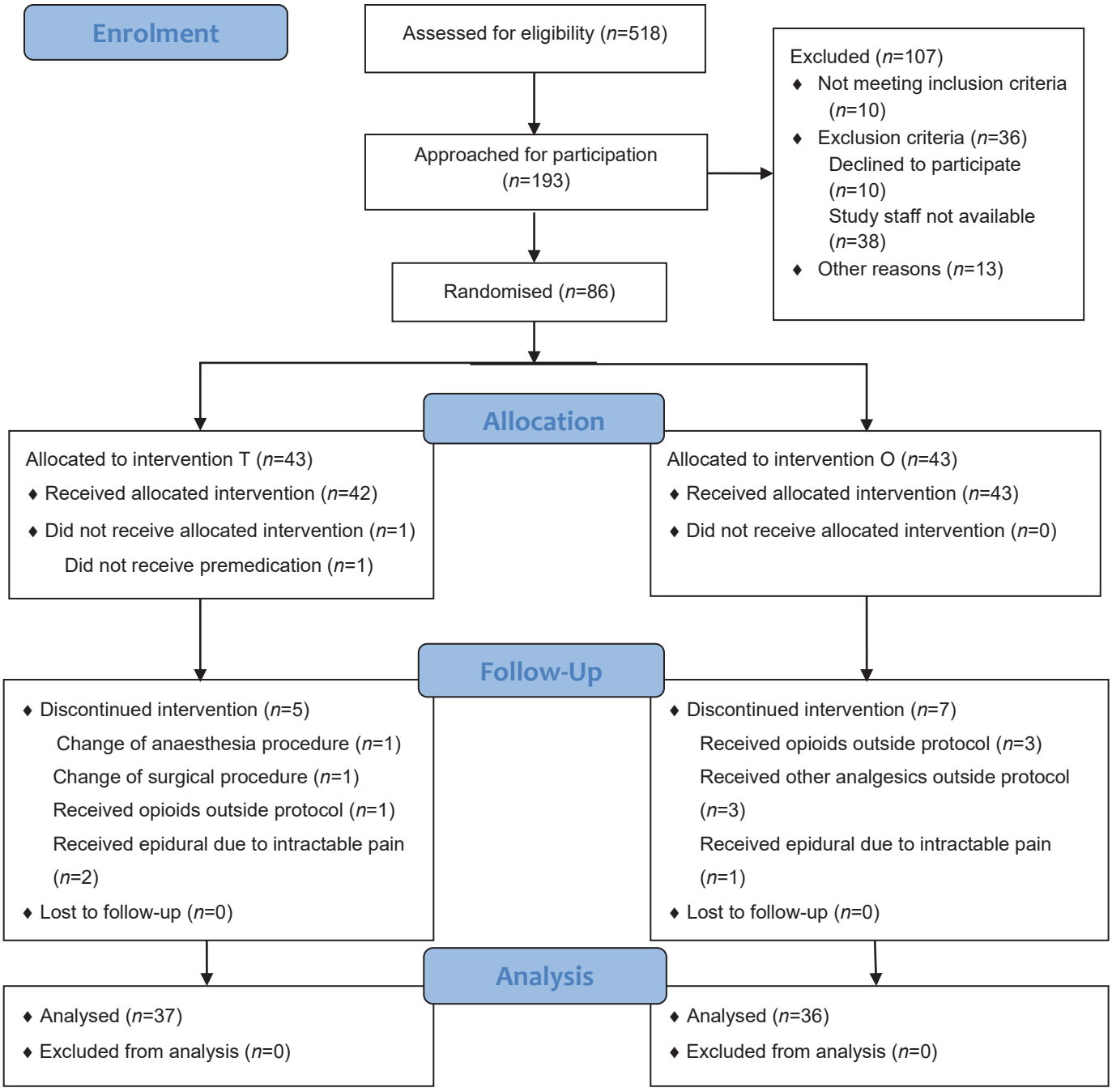
	Tapentadol (*n*=37)	**Oxycodone (*n*=36)**	***P*-value**
Incidents of $ETCO_2$ >7 kPa first 3 h (%)	0	0	
Incidents of respiratory rate <10/min first 3 h (%)	16	22	0.512
Respiratory rate 30 min (breaths/min)	12.8 ± 2.7	13.8 ± 2.9	0.070
Respiratory rate 1 h (breaths/min)	13.7 ± 2.9	13.2 ± 2.8	0.472
Respiratory rate 2 h (breaths/min)	14.5 ± 2.9	13.5 ± 2.8	0.150
Respiratory rate 3 h (breaths/min)	14.7 ± 2.8	13.8 ± 2.7	0.159
Respiratory rate 24 h (breaths/min)	16.0 ± 2.4	15.0 ± 2.2	0.155
$ETCO_2$ 30 min (kPa)	4.8 ± 0.6	4.8 ± 0.6	0.853
$ETCO_2$ 1 h (kPa)	4.8 ± 0,6	4.8 ± 0.6	0.834
$ETCO_2$ 2 h (kPa)	4.9 ± 0.5	4.8 ± 0.4	0.320
$ETCO_2$ 3 h (kPa)	4.8 ± 0.5	4.9 ± 0.4	0.868
SpO_2 30 min (%)	98.2 ± 2.2	98.4 ± 1.8	0.949
SpO_2 1 h (%)	98.5 ± 1.9	99.1 ± 1.1	0.293
SpO_2 2 h (%)	97.7 ± 1.9	97.8 ± 2.1	0.827
SpO_2 3 h (%)	97.1 ± 1.7	97.5 ± 1.6	0.214
SpO_2 24 h (%)	97.3 ± 1.3	97.6 ± 1.4	0.300
Dizziness 30 min (%)	24	20	0.659
Dizziness 1 h (%)	32	19	0.206
Dizziness 2 h (%)	30	17	0.187
Dizziness 3 h (%)	24	22	0.832
Dizziness 24 h (%)	32	53	0.079
Pruritus 30 min (%)	0	3	0.486
Pruritus 1 h (%)	5	14	0.261
Pruritus 2 h (%)	19	14	0.562
Pruritus 3 h (%)	16	22	0.515
Pruritus 24 h (%)	16	26	0.321
Headache 30 min (%)	5	0	0.493

$ETCO_2$, end-tidal carbon dioxide; SpO_2, peripheral capillary oxygen saturation.

Headache 1 h (%)	0	0	
Headache 2 h (%)	0	0	
Headache 3 h (%)	3	0	1.000
Headache 24 h (%)	22	8	0.113
Sedation 30 min (Pasero scale S/1/2/3/4) (%)	9/50/32/9/0	9/26/57/9/0	0.167
Sedation 1 h (Pasero scale S/1/2/3/4) (%)	16/54/24/5/0	17/47/33/3/0	0.803
Sedation 2 h (Pasero scale S/1/2/3/4) (%)	20/60/20/0/0	17/47/36/0/0	0.319
Sedation 3 h (Pasero scale S/1/2/3/4) (%)	17/66/17/0/0	25/64/8/3/0	0.460
Sedation 24 h (Pasero scale S/1/2/3/4) (%)	6/94/0/0/0	12/88/0/0/0	0.334
Overall satisfaction 24 h (0/1/2/3/4) (%)	0/11/16/35/38	0/3/22/47/28	0.364

$ETCO_2$, end-tidal carbon dioxide; SpO_2, peripheral capillary oxygen saturation.

Fig. 1 CONSORT flow chart



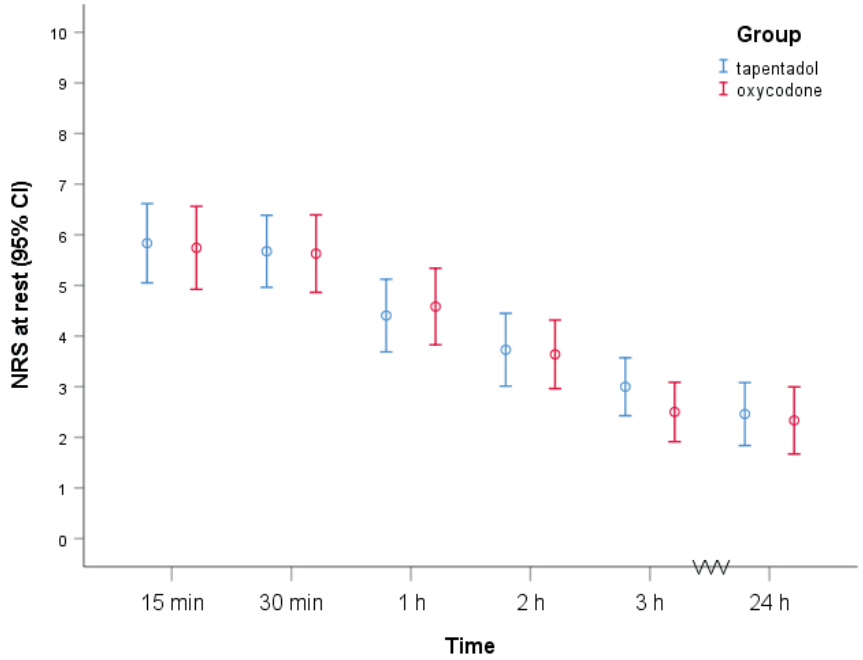


Fig. 2 Pain measured with numerical rating scale (NRS) at rest. Data are plotted as means with 95% CI.

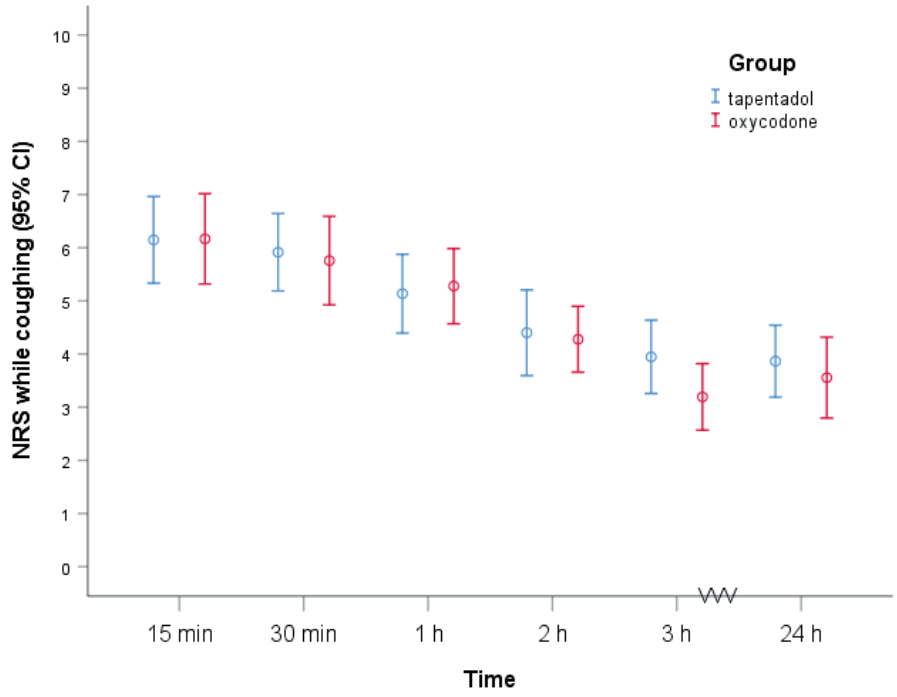


Fig. 3 Pain measured with numerical rating scale (NRS) while coughing. Data are plotted as means with 95% CI.