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**ANALGESIC, VENTILATORY, AND COGNITIVE
EFFECTS OF PREGABALIN AND OPIOIDS
STUDIES IN HEALTHY VOLUNTEERS AND KIDNEY
DONORS**

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NORSK POPULÆRVITENSKAPELIG SAMMENDRAG (NORWEGIAN SUMMARY)

Gabapentinoider har tradisjonelt vært brukt i behandlingen av kroniske nevropatiske smerter. I de senere årene har gabapentinoider også blitt tatt i bruk som en del av et multimodalt behandlingsregime for akutte postoperative smerter. Forskning har vist divergerende resultater i enkelt-analyser og meta-analyser vedrørende smertelindrende og opioid-sparende effekt.

I dette arbeidet har vi i en eksperimentell- og en klinisk studie undersøkt effekten av pregabalin alene og i kombinasjon med opioider. Vi fant at pregabalin alene har en moderat smertelindrende effekt, og en additiv smertelindrende effekt i kombinasjon med opioidet remifentanyl. Ved undersøkelse av pasienter 0–48 t etter gjennomgått kirurgi, fant vi ingen signifikant endring i smerte-skår mellom gruppen som ble behandlet med pregabalin versus placebo, men en signifikant reduksjon i forbruk av opioider. Kliniske undersøkelser av hyperalgesi, dvs. økt respons på smertefullt stimulus, viste at pregabalin kan ha anti-hyperalgesisk effekt 24 t etter kirurgi. Videre fant vi i tidlig postoperativ fase redusert kvalme og mindre søvnforstyrrelser forårsaket av smerte.

Opioid-sparende effekt i seg selv behøver ikke være fordelaktig hvis ikke den totale andelen av opioid-relaterte bivirkninger er redusert. Under eksperimentelle forhold fant vi at pregabalin potenserte den respirasjonshemmende effekten av opioider ved signifikant økning i mengden karbondioksyd i utåndingsluften målt ved kapnografi.

Tidligere studier har vist at pregabalin kan gi økt sentralnervøse bivirkninger som tretthet, ørhet og dobbeltsyn. I vår eksperimentelle studie fant vi at kombinasjonen pregabalin og opioider reduserte kognitiv funksjon i større grad enn ved hvert enkelt medikament alene. Pregabalins effekt på kognitiv funksjon har ikke tidligere vært undersøkt hos pasienter etter kirurgi. Ved hjelp av elektroniske nevropsykologiske tester undersøkte vi i en eksplorativ studie endringer i kognitiv funksjon før og etter kirurgi, og fant at pasienter behandlet med pregabalin hadde reduserte eksekutive funksjoner inkludert arbeidsminne, inhibisjon og oppmerksomhet.

Våre studier viser at pregabalin, som en del av et smerteregime med opioider, har moderat smertelindrende- og opioid-sparende effekt, mens andelen av potensielt alvorlige bivirkninger synes å være økt. Indikasjonen for pregabalin som en del av behandlingen av akutte postoperative smerter er usikker.

SUMMARY

Multimodal postoperative pain treatment has become the main standard for the treatment of postoperative pain emphasizing the importance of combining different drugs and techniques to alleviate and reduce pain. In the wake of this approach, pregabalin has gained popularity as an analgesic adjunct for acute postoperative pain. The evidence for acute analgesic efficacy of pregabalin has been inconsistent between clinical studies. As yet, pregabalin is approved for the treatment of neuropathic pain conditions, partial epilepsy disorders, and generalized anxiety and not for the use of acute postoperative pain. To prove the utility of pregabalin as add-on to a multimodal pain regime, the clinical benefit has to be demonstrated and total benefits must outweigh total harms. This can only be studied in drug combination trials.

In this thesis, we have investigated the analgesic- and opioid-sparing effects of pregabalin in an experimental and a clinical study. In the experimental cold pressor model, significant additive analgesic effects were demonstrated when pregabalin was combined with increasing remifentanyl doses (study I). In a randomized, parallel group, placebo-controlled study, we investigated patients undergoing laparoscopic donor nephrectomy, and found significant opioid-sparing, but no differences in pain intensity scores, 0–48 h after surgery, when pregabalin was added to a multimodal pain regime (study II). Hyperalgesia, pain-related sleep interference, and nausea were reduced in the early postoperative period.

The opioid-sparing effect may be of limited value if the side effects are not reduced accordingly. We found that pregabalin potentiates the ventilatory depressive effect of remifentanyl in healthy volunteers (Study I). Furthermore, the cognitive effects of pregabalin were explored, and the findings showed that pregabalin negatively affects executive functioning by impairing working memory and inhibition, measured as neuropsychological task performance (Study I and III). These potentially severe adverse effects warrant caution when administering pregabalin to vulnerable subgroups of patients.

LIST OF PAPERS

1. Myhre M, Diep LM, Stubhaug A. Pregabalin has analgesic, ventilatory, and cognitive effects in combination with remifentanyl. *Anesthesiology*.2016; 124:141-149. DOI: 10.1097/aln.0000000000000913
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NOMENCLATURE AND ABBREVIATIONS

ASA – American society of
anesthesiologists

AUC – area under the curve

CANTAB – Cambridge neuropsychological
test automated battery

CI – confidence interval

CNS – central nervous system

CPT – cold pressor test

CWIT – color-word interference test

EMA – European Medicines Agency

ETCO₂ – end-tidal carbon dioxide

FDA – Food and Drug Administration

IV – intravenously

kPa – pressure: Kilopascal. 1 kPa = 1000
Pascal

mmHg – pressure: Millimeter of mercury

MOT – motor screening task

mN – millinewton. 1 mN = 1/1000 Newton

MV – minute volume

NoNART – Norwegian national adult
reading test

NRS – numeric rating scale

Ng – weight: nanogram. 1 ng = 1e-9 gram

OR – odds ratio

PACU – post-anesthesia care unit

PAL – paired associates learning test

PCA – patient-controlled analgesia

POCD – postoperative cognitive decline

PPSP – persistent postsurgical pain

RF – respiratory frequency

RR – rate ratio

RVP – rapid visual processing

RTI – rapid time test

SD – standard deviation

SST – stop signal task

SWM – spatial working memory test

T_{1/2} – elimination half-life

TCI – target controlled infusion

TIVA – total intravenous anesthesia

VAS – visual analogue scale

1 INTRODUCTION

1.1 About the thesis

Postoperative pain management continues to be an important field in postoperative care. During the last few decades, research has led to ground-breaking advances in the understanding of pain physiology, and new analgesics and anesthetic techniques have been developed. Optimal postoperative pain management is now acknowledged as a prerequisite for reducing morbidity, shortening the length of hospital stay, and reducing the associated economic costs.¹ Accordingly, new standards for pain management have been established, including acute pain services² and pain guidelines from national and international medical societies. However, despite these promising developments, postoperative pain management continues to receive inadequate medical attention in everyday care in clinics and many patients experience moderate to severe pain after surgery.^{3,4} In a study conducted in Norwegian hospitals, two of every five patients experienced moderate pain on the first postoperative day and one of ten reported severe pain.⁵ In the past, postoperative pain management consisted of intramuscular opioids administered on request by health care providers.⁶ Nowadays, postoperative pain management is mostly based on non-opioid analgesics with addition of opioids as necessary and administration by the patients themselves. Furthermore, different regional anesthetic techniques, such as epidural anesthesia and peripheral nerve blocks, are increasingly used to attenuate postoperative pain and have proven advantageous when compared with opioids alone.⁷

The concept of combining different analgesic agents to improve analgesia has gained acceptance in postoperative care and has been the subject of extensive research. The overall aim of this multimodal treatment strategy is to improve analgesia by using agents with different modes of action, hence reducing the need for opioids and opioid-related adverse effects that have a negative impact on postoperative recovery.⁸

The gabapentinoids are a relatively new group of analgesic agents that are being used increasingly in the treatment of acute postoperative pain. Gabapentin was originally developed as an anti-epileptic agent⁹ but was subsequently approved for the treatment of neuropathic pain conditions, as was the second-generation agent, pregabalin. More recently, the gabapentinoids have become popular as “off-label” analgesic adjuncts for the treatment of acute postoperative pain. However, the analgesic efficacy of the gabapentinoids in patients with early postoperative pain is controversial because multiple studies have shown divergent

results.⁷ Nevertheless, the gabapentinoids are now included in many national postoperative pain guidelines and are widely prescribed for the treatment of acute postoperative pain.

Increasing attention has been paid to the adverse effects of perioperative administration of gabapentinoids. Therefore, to confirm the value of gabapentinoids in the management of acute postoperative pain, the beneficial effects must outweigh the unwanted effects, and the need for opioids should ideally be reduced.

In this thesis, the effects of pregabalin alone and in combination with opioids were investigated in experimental, clinical, and exploratory studies. In the first study, we investigated the analgesic, respiratory, and cognitive effects of pregabalin alone and in combination with remifentanyl in healthy volunteers. In the second study, the analgesic, opioid-sparing, and anti-hyperalgesic effects of standard postoperative analgesia in addition to pregabalin or placebo were investigated in patients undergoing laparoscopic donor nephrectomy. The patients were followed up at 6 weeks and at 6 and 12 months after surgery to assess the incidence of persistent postoperative pain. Furthermore, we performed a secondary explorative analysis of the cognitive effects of pregabalin in the early postoperative period in the same study population. The cognitive tests were performed using a computerized battery of tests specifically developed for this purpose.

Chapter 1 of this thesis presents and explains the central terms used in the field of postoperative pain and discusses the general aspects of postoperative pain management, including a short overview of the most widely used postoperative analgesics. Furthermore, the pharmacology of pregabalin and its assumed modes of action are described. Chapter 2 outlines the aims of the thesis and the accompanying research questions. The material and methods used in the studies are described in detail in chapter 3. Chapter 4 presents the main results of the three studies, which are discussed in chapter 5. Finally, the conclusions and implications of this research are discussed in chapter 6 and the clinical and research implications thereof are briefly addressed in chapter 7.

1.2 Physiological pain

According to the International Association for the Study of Pain, pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”¹⁰

Pain can be both useful and devastating. On one hand, physical pain is an important phenomenon that warns of imminent or actual tissue injury and protects the body from further damage;¹¹ on the other hand, uncontrolled pain and immobilization may increase morbidity.¹²

Furthermore, protracted postoperative pain may become chronic, causing suffering, nuisance, and diminished quality of life.¹³

In the very early days of pain research, pain was considered only as a one-dimensional sensory experience.¹⁴ However, pain was later recognized to be a complex subjective phenomenon not necessarily associated with physiological tissue damage. In 1968, Melzack and Casey suggested that pain is characterized by three psychological dimensions: the sensory-discriminative, the motivational-affective, and the cognitive-evaluative. According to their theory, all three categories provide information that contributes to how pain is perceived and the eventually subsequent motor response to the painful experience.¹⁵

Environmental changes, including thermal, chemical, and mechanical stimuli, are detected by the primary afferent nerve fibers and transduced into electrochemical activity and then transmitted through the nervous system. Free nerve-endings, that are transmitting pain, are called nociceptors, and are located in the skin, muscle, joint tissues, and viscera and respond to potentially damaging mechanical, thermal, or chemical stimuli by sending signals through the pain pathways. Activated nociceptors release inflammatory mediators such as substance P and calcitonin gene-related peptide (CGRP), causing neurogenic inflammation¹⁶ which includes sensitization of adjacent neurons. The cell bodies of the primary afferent fibers lie within the dorsal root ganglion for the body and in the trigeminal ganglion for the face and project to the dorsal horn of the spinal cord.¹⁷ At the spinal level, these excitatory neurotransmitters including e.g. substance P, glutamate, and calcitonin gene-related peptide activate receptors on second-order neurons sited mainly in lamina I and II in the dorsal horn. The most important receptors on second-order neurons are NMDA, GABA, AMPA, and opioid receptors.¹⁸ From the spinal cord, projection neurons form multiple ascending pathways that transmit pain information to the somatosensory cortex via the brain stem and thalamic loci.¹⁹

The primary afferent fibers can be divided according to their anatomy and functional properties into A fibers and C fibers. A β fibers are large-diameter, myelinated, rapidly conducting, and mainly detect innocuous stimuli, whereas A δ fibers are medium-diameter, myelinated, and mediate well-localized, fast, or first pain. C fibers are small-diameter, unmyelinated, slowly conducting fibers that transmit poorly localized second pain.²⁰ Most A δ and C nociceptors are polymodal and respond to thermal and mechanical stimuli. A δ nociceptors can be classified as type I or type II according to whether their thermal threshold is $>50^{\circ}\text{C}$ or $\sim 43^{\circ}\text{C}$, respectively.¹⁷ Equally, C nociceptors show a thermal threshold of $\sim 43^{\circ}\text{C}$. Both A δ and C nociceptors respond to cold stimuli.¹⁹

Nociceptors have various features in different end organs; therefore, pain that originates from the internal organs is different from pain that is somatic. The viscera are innervated by the autonomous nervous system and the sensory neurons are mainly dominated by C fibers terminating in larger regions of the spinal horns.²¹ In contrast with somatic pain, visceral pain is less distinct and may be hard to localize. At the spinal level, the afferent visceral fibers converge with other somatic afferent fibers on the same spinal neurons, giving rise to “referred pain”, which is perception of pain remote from the primary site of origin.²¹

Pain may be modulated at different levels in the nervous system, resulting in increased or decreased pain perception. In the periphery, the sympathetic nervous system may liberate norepinephrine, increasing the sensitivity of the nociceptors,²¹ and endogenous opioids, such as enkephalins and endorphins, exert inhibitory effects by activating various opioid receptors. At the spinal level, the excitatory inputs from the afferent A δ fibers and C fibers are converged and modulated. In 1965, Melzack and Wall launched the “gate control” hypothesis, suggesting that incoming excitatory impulses from the A δ fibers and C fibers were decreased via the A β fibers through inhibitory interneurons.²² Today, their hypothesis has been modified further to include the descending pathways that originate in higher brain structures, such as the periaqueductal gray and the rostral ventromedial medulla. By activating structures known as “on” and “off” cells, the descending pathways may increase or inhibit the incoming pain impulses at the spinal level.¹⁹ Moreover, nociceptive-specific neurons and wide dynamic range neurons modulate incoming signals at the spinal level. Wide dynamic range neurons may respond with a “wind-up” phenomenon, i.e., an increase in excitability of the dorsal horn neurons as a response to repeated stimuli (a process known as temporal summation).²³

The classification of pain is not easy and is continuously being discussed. Patients may also have mixed forms of pain. Underneath the main forms of pain are briefly described.

Nociceptive pain

Nociceptive pain is defined as “pain that arises from actual or threatened damage to non-neural tissue and is due to activation of nociceptors.”¹⁰

The nociceptors play a key role not only in acute pain transmission as described above, but also in prolonged and pathological pain conditions. Tissue damage, such as that caused by surgery, infection, or burns, initiates a local inflammatory response by activating multiple mediators and immune cells, resulting in the clinical symptoms characteristic of inflammation, i.e., redness, heat, pain, swelling, and loss of function (the quintet of rubor, calor, dolor, tumor, and functio laesa, recognized in ancient times).²⁴ Important signaling

mediators in these processes include bradykinin, serotonin, histamine, substance P, calcitonin gene-related peptide, prostaglandin E₂, and cytokines among others released from the primary afferent nerve endings and non-neuronal cells.²⁵ This “inflammatory soup” may modulate the receptive properties of nociceptors and cause peripheral sensitization, resulting in a reduced threshold for pain and an increase in its intensity, producing **hyperalgesia**. Hyperalgesia is a cardinal feature of tissue injury and inflammation and is defined as “increased pain from a stimulus that normally provokes pain.”¹⁰ **Primary hyperalgesia** is hyperalgesia localized at the immediate site of inflammation or tissue damage and **secondary hyperalgesia** refers to hyperalgesia outside the area of injury or inflammation. Secondary hyperalgesia is thought to result from changes in plasticity and modulation at the spinal level. The term **allodynia** is used to describe “pain due to a stimulus that does not normally provoke pain.”¹⁰ The current evidence suggests that allodynia and hyperalgesia are consequences of two conditions, i.e., **peripheral sensitization** and **central sensitization**. Peripheral sensitization is associated with environmental changes (the “inflammatory soup”) caused by tissue damage and neurogenic inflammation and is characterized by a decreased nociceptor threshold for incoming noxious stimuli, an augmented response to suprathreshold stimuli, and spontaneous firing in the peripheral nerves.²⁰ Equally, increased stimulation of second-order neurons by normal or subthreshold afferent inputs may alter pain transmission at the spinal level, causing central sensitization. Central sensitization may produce symptoms such as dynamic tactile allodynia, secondary hyperalgesia, aftersensations, and enhanced temporal summation.²⁶

Neuropathic pain

Neuropathic pain is defined as “pain caused by a lesion or disease of the somatosensory nervous system.”¹⁰ The somatosensory nervous system includes all the nerves in the body, including those supplying the visceral organs. Damage to this system could lie anywhere in the afferent nervous system, i.e., the peripheral nerve, the dorsal root ganglion, the dorsal root, or in the central nervous system. Neuropathic pain is often long-lasting and may become chronic without any obvious function. Importantly, neuropathic pain is a clinical description and not a diagnosis and may cause complex changes leading to abnormal functioning and sensory loss accompanied by spontaneous pain, hyperalgesia, and allodynia.

Nociplastic pain

According to the modern classification, pain is categorized as “nociceptive” or “neuropathic.” However, this terminology has been criticized for not including the considerable number of patients without evident activation of nociceptors or neuropathy.²⁷

There is growing evidence that this type of pain is evoked by pathophysiologic and psychologic triggers, resulting in various chronic pain syndromes labelled as fibromyalgia, complex regional pain syndrome, and irritable bowel syndrome.²⁸ Therefore, a third mechanistic descriptor, i.e., nociplastic pain, has been acknowledged. This term is intended to describe chronic pain characterized by “altered nociceptive function without no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.”²⁷

Pain of unknown origin

Pain not explained by any underlying organic pathology was traditionally referred to as idiopathic pain.²⁷ This term has often been met with skepticism and distrust in the health care system and implied that the pain was associated with psychopathology or an attempt to feign illness. Therefore, pain without an identifiable cause that cannot be classified as nociceptive, neuropathic, or nociplastic, may now be described as pain of unknown origin.

1.3 Experimental pain

Experimental pain models are used to investigate new analgesic agents and pain mechanisms in a controlled manner. Unlike pain encountered in the clinical setting, experimentally-induced pain can be standardized and controlled with respect to modality, localization, and intensity of the pain stimuli thereby allowing for reproducible results in test-retest experiments and allowing even small differences to be detected.²⁹ Experimental pain may be assessed using qualitative or quantitative methods depending on the nature of the trial, reflecting both the subjective and objective aspects of the experience of pain.

1.3.1 Pain modalities

Experimental pain models provide the opportunity to test nerve fibers in various tissues. The skin is the most investigated tissue, mainly because of ease of access, and robust experimental pain models are established for thermal, mechanical, ischemic, electrical, and chemical stimulation.³⁰

Thermal models use heat or cold stimuli to induce pain. Heat pain is induced by either direct contact between the heat source and the skin or by a radiant source whereas cold pain may be induced by iced water or a natural cooling agent, such as menthol or eucalyptol. The cold pressor test is a well-established cold model that is frequently used in pain research being primarily developed as a model of hypertension because of concurrent stimulation of sympathetic afferent nerve fibers that lead to an increase in blood pressure and heart rate.³¹

The cold pressor test is performed by immersing a limb in ice-cold water (0–4°C), which provokes an intense, radiating, deep, and dull aching pain that is most likely evoked by nociceptors in the deep veins.³² The immediate cold sensation provoked by this test is probably mediated by A δ fibers and the cold pain that follows is likely induced by slower conducting C fibers.³³

Mechanical stimuli as pressure (algometer), pinprick (needle) and dynamic stimuli such as brush are available methods for activating the sensory system. The skin may also be stimulated by von Frey hairs with variable stiffness according to the thickness of the hairs. While A β fibers evoke touch sensation, also thinner A δ and C fibers are involved in mediation of painful mechanical stimuli. Normally, the A β fibers are evoked by touch. However, thicker von Frey hairs cause pinprick sensation in inflamed or injured areas mediated by A δ fibers.³⁴

Ischemic, electrical, and chemical stimulation methods are also frequently used in experimental pain models. Ischemic pain may be investigated using pneumatic tourniquets around a limb³⁵ whereas in electrical pain models, various electrical devices are connected to electrodes applied to the skin and deliver stimuli with a variable duration, frequency, and current. For chemical stimulation, the irritant, e.g., capsaicin or mustard oil may be applied intradermally or topically to the skin, causing primary and secondary hyperalgesia.³³

1.3.2 Experimental versus clinical pain

Pain is a subjective experience and may be accompanied by elements such as fear, anxiety, depression, and cognition, in addition to symptoms of the underlying condition.³³ Consequently, multiple factors may affect the assessment of analgesic efficacy in a clinical setting, making pain research challenging. In an attempt to overcome these confounders, experimental trials may be advantageous when studying analgesics and pain mechanisms and may provide a bridge between basic research and clinical pain models. In an experimental pain trial, the stimulus can be controlled with exact intensity, duration, frequency, and localization, and various pain modalities can be tested.³⁰ However, experimental pain reflects only parts of the complex subjective multi-dimensional pain experience and cannot be compared directly with clinical pain models. An important difference between experimental and clinical pain studies is the ability to withdraw from a painful stimulus at any time point in an experimental trial whereas the pain may be unescapable under clinical conditions. Indeed, research has indicated that escapable and inescapable pain may even be distinguished via different central pain pathways.³⁶ Therefore, experimental and clinical pain studies cannot be

compared and used interchangeably, but may be used in a complementary manner in pain research, each of them eliciting different aspects of pain mechanisms and analgesic effect.

1.4 Acute postoperative pain

Acute postoperative pain is a unique type of pain³⁷ that includes nociceptive, inflammatory, and neuronal processes. Surgical incisions activate both thermal and mechanical nociceptors in the peripheral afferent nerve fibers. Experimental pain studies have demonstrated that incisional pain stimuli are transferred by A δ fibers and C fibers whereas the thin myelinated A δ fibers with high conduction velocities cause the first initial stinging pain and the unmyelinated C fibers mediate the slow aching pain that follows. Simultaneously, the tissue damage induces an inflammatory process, releasing various inflammatory mediators that increase the sensitivity of the nociceptors.²¹ There is also experimental evidence that silent non-nociceptive mechanical A β fibers are converted to activated nerve fibers that can contribute to hyperalgesia in the immediate vicinity of the injured area. If the surgical incisional pain is inadequately treated, central sensitization and neuroplastic modulation of the dorsal horn may develop, which increases the risk of persistent postsurgical pain.³⁸

1.4.1 Incidence

Several large national studies have shown that the incidence of postoperative pain is high and of great concern to patients. In a retrospective investigation from the US, 82% of surgical patients reported experiencing acute postoperative pain, and of those patients, 47% characterized their pain as moderate, and 39% reported the pain as severe or extreme.³⁹ In a French study that assessed pain in the 24 h after surgery, 4.2% and 26.9% of patients experienced severe pain (indicated by a Numeric Rating Scale [NRS] score ≥ 7) at rest and on movement, respectively, and 50.9% rated their maximal postoperative pain as severe (NRS ≥ 7).⁴⁰ In The Netherlands, a national survey of 1490 surgical patients reported that 41% of the patients experienced moderate or severe pain on the day of surgery, followed by 30%, 19%, 16%, and 14% on days 1, 2, 3, and 4, respectively.³ In a similar study in Norwegian hospitals, 38% of patients experienced moderate pain (an NRS score ≥ 4) and 11% reported an NRS pain score ≥ 6 on the first postoperative day.⁵ Overall, the evidence suggests that undertreated postoperative pain remains an unresolved clinical challenge in many countries.

1.4.2 Risk factors

The many negative consequences of postoperative pain have prompted research attempting to identify risk factors associated with moderate to severe postoperative pain.⁴¹ Better knowledge of these risk factors may facilitates early identification of susceptible patient groups and allow postoperative pain treatment and care on the ward to be tailored to the needs of these patients.⁴²

Surgery

The type of surgery is an important predictor of the severity of postoperative pain.⁴¹ Thoracic, open abdominal, and major orthopedic procedures are the most painful operations. In the above-mentioned study from The Netherlands,³ moderate to severe pain was reported by 30%–55% of patients on postoperative days 1 and 2 after abdominal surgery and by 20%–71% of patients on postoperative days 1–4 after orthopedic or back/spinal surgery. However, minor surgical procedures may also cause moderate to severe pain, so the severity of postoperative pain is not necessarily correlated with the size of the anatomic region involved or that of the surgical incision per se. For example, 66%, 33%, and 11% of patients reported moderate or severe pain on postoperative days 1, 6, and 28, respectively, after hernia repair.⁴³

Anesthesia

The choice of anesthesia and anesthetic technique depends on the type and duration of the surgical procedure, the underlying disease, and comorbidity. Ideally, the type of anesthesia selected should also provide analgesia during the postoperative period.⁴⁴ Although customized analgesia⁴⁵ and the newer anesthetic agents, such as short-acting volatile agents, e.g., desflurane,⁴⁶ intravenous anesthetic agents such as propofol, and remifentanyl, a short-acting opioid,⁴⁷ have reduced the time to recovery after surgery, studies comparing intravenous anesthesia with volatile anesthetics have produced inconsistent results with regard to the effect on postoperative pain.⁴⁸⁻⁵⁰ In contrast, regional anesthesia, such as epidural anesthesia, peripheral nerve block, and infiltration anesthesia, has been proven to reduce postoperative pain scores when compared with general anesthesia alone.⁴²

Age

It is widely believed that there is a negative correlation between age and postoperative pain, whereby younger patients are more likely to report moderate or severe postoperative pain than their older counterparts.⁵¹ Other studies indicate that also development of persistent postoperative pain is more likely in younger patients.⁵²

Sex

Many clinical and experimental pain studies indicate that female sex may be a predictor of postoperative pain⁵³ whereas other studies could not confirm this suggestion.^{42,54} Furthermore, some pain conditions, such as fibromyalgia, seem to have a predilection for female sex.⁵⁵ The sex-related difference in pain perception may be a confounding factor in pain research.⁵⁶

Intensity of preoperative pain

There is a strong association between the presence of preoperative pain and more severe postoperative pain.⁵⁴ Furthermore, preoperative use of analgesics, patient's perception of pain, and pain threshold may be essential factors influencing the perceived severity of postoperative pain.⁴¹

Psychological factors

Preoperative psychological factors, such as anxiety, psychological distress (e.g., hostility, depression) and coping strategies (e.g. catastrophizing) may influence postoperative pain.⁴¹ Expectation of pain and earlier pain experiences may also play a role in this regard.⁵⁷ In a study by Sommer et al, the expectation of a visual analog scale (VAS) pain score >40 was positively correlated with moderate to severe pain after surgery.⁵⁸

1.4.3 Pain assessment

Pain is a complex multimodal symptom that is not only a sensory experience but also influenced by subjective and emotional components. Unfortunately, there is no objective measurement of pain or a single test that can determine if pain is present or not. Moreover, there are wide inter-individual differences in pain perception, which may influence assessment of pain from person to person.

Pain may be measured in a psychophysiological, neurophysiological, or behavior manner. Pain rating scales are simple, useful, and valid tools to assess the intensity of acute pain. The use of graded pain scales has proven to be superior to dichotomous or categorical scales such as the Verbal Rating Scale.⁵⁹ A frequently used graded pain scale is the NRS, where "0" represents "no pain" and "10" represents "the worst pain imaginable." A similar pain scale is the VAS, on which a patient rates the pain on a line marked with "no pain" at one end and "the worst pain imaginable" at the other end. Both pain scales have been shown to be equally sensitive for the assessment of acute pain.⁵⁹ One advantage of the VAS is its ratio scale properties,⁶⁰ which allow for comparison of percent differences between measurements separated in time or between individuals.

Importantly, the NRS and VAS are one-dimensional tools that only assess self-reported pain intensity. Pain assessment using multi-dimensional questionnaires, e.g., the McGill Pain Questionnaire and the Brief Pain Inventory, may provide more detailed information about the patient's experience of pain.⁶¹ However, questionnaires may be time-consuming to administer and are used more often for chronic pain conditions.

More recently, newer neurophysiologic and imaging technologies, such as magnetic resonance imaging, electroencephalography, electromyography, and single photon emission computed tomography, have extended the ways in which pain can be assessed.³⁰ Together with subjective measurements, these techniques may be useful supplementary methods that increase the sensitivity of pain assessment. The limitations are the technical skills needed and the considerable expense incurred by the test procedures.

1.5 Postoperative pain management

The primary aim of postoperative pain management is to ensure optimal postoperative pain relief and patient comfort. However, postoperative analgesia is not only required for humanitarian reasons but also to reduce postoperative morbidity and enhance postoperative recovery. Postoperative pain may increase the surgical stress response, which primarily affects the cardiovascular system and the pulmonary system but may also increase the risk of morbidity, including serious complications such as postoperative acute myocardial infarction, hypotension/hypertension, kidney failure, and respiratory conditions such as pneumonia and atelectasis.⁴⁴ A number of postoperative recovery concepts have been introduced in an effort to attenuate these postoperative complications, such as ERAS (enhanced recovery after surgery) along with “fast-track” surgeries¹² and PROSPECT (procedure-specific pain treatment).⁶² These strategies, managed as a collaboration between surgeons and anesthesiologists, are built upon several simple principles, including thorough collection of preoperative patient information, provision of adequate pain relief with an emphasis on thoracic epidural analgesia when indicated, early mobilization, oral feeding, and avoidance of both fluid overload and hypovolemia, all of which may enhance postoperative recovery and shorten the hospital stay. However, recent focus has been on the growing number of patients with complex pain states, opioid-dependency, chronic neuropathic pain conditions, and psychiatric comorbidities, and the necessity to implement other specialists including psychiatrists and psychologists in the acute pain team.⁶³

Optimal postoperative pain management plays a key role in these postoperative recovery concepts. The debate on when to start treatment for postoperative pain has been

ongoing for many years. The term “pre-emptive analgesia” was coined by Wall in 1988⁶⁴ based on central sensitization studies in animals. The idea of pre-emptive analgesia was to block for the barrage of postoperative afferent traffic before starting the surgical procedure and thereby prevent central sensitization at the spinal level.⁶⁵ However, later reviews showed conflicting evidence for the efficacy of pre-emptive analgesia,⁶⁶ suggesting that the duration of analgesic treatment rather than the timing of its initiation was more important in terms of ensuring adequate analgesia and improving postoperative recovery. This observation led to the concept of “preventive analgesia”, i.e., administration of perioperative analgesia that provides reduction in pain for longer than the expected clinical duration of the drug.⁶⁷

1.5.1 Additive and synergistic effects

The idea of combining systemic analgesia with a neuraxial block was first introduced at least three decades ago. As observed by Kehlet and Dahl,⁶⁸ “...total or optimal pain relief cannot be achieved by a single agent or method without major expenditure on equipment or surveillance systems, or without significant side effects....” The aims of combined pain management are to increase analgesic efficacy and to decrease the risk of adverse effects from each agent by dose reduction.

The theoretical models developed to measure the drug-effect relationship in drug combination studies are somewhat complicated, and a detailed description of these models is beyond the scope of this thesis. Therefore, discussion of the theory of these models is limited to that necessary to understand the more important concepts. The term **additivity** is important in the framework of multimodal pain treatment. If drug A and drug B each have an analgesic effect and the effect of combination of these agents is additive, the effect of combination of drug A and drug B = effect of drug A + effect of drug B. However, the total effect is not simply the arithmetic sum of the two drugs. If each drug provides 70% pain relief when administered alone, combination of the two drugs cannot provide 140% relief.⁶⁹ Chou and Talalay introduced the term “fractional product method” based on the equation devised by Webb in 1963, i.e., $(1-0.7)(1-0.7) = 0.09$, $(1-0.09) = 0.91$. Therefore, the total pain relief provided by combination of drug A and drug B would be 91% if the combination was fully additive. However, according to Chou et al, this equation holds true only in the case of a hyperbolic dose-effect curve and not in the case of sigmoid-shaped curve, and the two agents need to have different mechanisms of action. Otherwise, more advanced models have to be used based on the mass-law equation.⁶⁹ Furthermore, the term **synergism** is frequently encountered in pharmacological studies, and is present when the effect of two agents is larger

than the calculated additive effect (agonism). In contrast, in subadditivity, the effect of the drug combination is smaller than the calculated additive effect of the combination (antagonism).⁷⁰ Finally, the term **potentiation** or **enhancement** is simply where drug A has an effect and drug B has no effect, but the effect of the combination of drug A and drug B is greater than that of drug A.⁶⁹

1.5.2 Multimodal pain management

Postoperative pain management has evolved over time from monotherapy with morphine to the multimodal pain management used today. The concept “balanced analgesia” or “multimodal approach” was introduced at the end of the 1980s.⁸ The idea behind multimodal analgesia is to achieve better analgesia by exploiting the additive or even synergistic effects of combinations of agents and at the same time reduce the analgesia-related adverse effects because of the lower doses required for each agent in the combination. Interestingly, the term “multimodal” pain treatment is not clearly defined⁷¹ However, it typically consists of at least two non-opioid analgesics, often in combination with regional analgesia, and top-up with opioids if required. Ideally, the improved pain relief achieved can facilitate early mobilization and enhanced postoperative recovery, leading to reduced morbidity and mortality.⁷¹ Since introduction of the multimodal pain treatment concept, many studies investigating a wide variety of analgesic combinations have been performed and some commonly used agents, which were also used in the studies underpinning this thesis, are briefly outlined here.

Paracetamol

Paracetamol (acetaminophen) is normally used as the basis for postoperative pain management because of its safety profile. The mechanism of analgesic action is not completely understood, but studies indicate that paracetamol inhibits production of prostaglandins by inhibiting the peroxidase activity of COX 1 and COX 2, thereby providing the analgesic and antipyretic effects indicated for mild pain conditions.⁷² It is somewhat controversial whether paracetamol is anti-inflammatory. According to recent literature, paracetamol is ineffective in severe inflammatory conditions,⁷³ whereas very elegant research in oral surgery demonstrated a marked effect on swelling.⁷⁴ Like nonsteroidal anti-inflammatory drugs, paracetamol has both central and peripheral analgesic effects. Recent literature suggests that the anti-nociceptive effect of paracetamol is attributable to interactions with neuronal systems, including the serotonergic system, endogenous opioids, endogenous cannabinoids, and the cholinergic system; therefore, inhibition of these systems may reduce

the analgesic effect of paracetamol.⁷³ However, paracetamol also exerts an anti-nociceptive effect by inhibiting certain neurotransmitters, including substance P and glutamate, and this interaction may be enhanced by other inhibitors of these neurotransmitters.⁷³ Although the adverse effects of paracetamol are considered to be mild, increased blood pressure, cardiovascular events, and asthma have been reported. Paracetamol is metabolized in the liver by cytochrome P450 enzymes and is excreted as glucuronide and sulfate. One of the metabolites of paracetamol, N-acetyl-p-benzochinonimine, is strongly hepatotoxic and may cause acute liver failure if the dose of paracetamol is too high or in patients with reduced metabolic capacity, such as those with chronic liver failure.⁷³

Glucocorticoids

Glucocorticoids exert anti-inflammatory and immunosuppressive effects through complex genomic and non-genomic interactions.⁷⁵ Central to their activity is the cortisol-glucocorticoid receptor, which inhibits inflammation by blocking the transcription of inflammatory proteins and inducing synthesis of anti-inflammatory proteins that inhibit phospholipase A2 and thereby the synthesis of prostaglandins and leukotrienes. Glucocorticoids has demonstrated significant analgesic effects 24 h after surgery when compared to placebo and reduced the need for opioids.⁷⁶ Stubhaug et al also showed that both methylprednisolone 125 mg and ketorolac 60 mg reduced secondary hyperalgesia in burns patients, indicating that glucocorticoids have central pain-modulating effects.⁷⁷ Furthermore, glucocorticoids have demonstrated anti-emetic properties when administered perioperatively⁷⁸ and is frequently used for prophylaxis against postoperative nausea and vomiting. Although glucocorticoids are associated with potentially serious adverse effects, such as impaired wound and bone healing, significant unwanted effects could not be demonstrated when single doses of glucocorticoids were administered perioperatively.⁷⁹

Local anesthetic agents

Local anesthetic techniques are commonly used in combination with other analgesics for postoperative pain management and can be administered by subcutaneous infiltration, continuous systemic infusion, or as a peripheral or regional nerve block.⁸⁰ Lidocaine, or the longer-acting agents, bupivacaine or ropivacaine, interact with voltage-gated sodium channels and inhibit formation of the action potential. Wound infiltration with local anesthetics are used in a wide range of surgeries,⁸¹ however, in combination with multimodal pain treatment the analgesic effect may be insignificant.⁸² Few adverse effects are encountered when a local anesthetic agent is used as infiltration anesthesia.⁸³ However, allergic reactions sometimes

occur, and accidental injection of a high dose of a local anesthetic in the subarachnoid space or intravenously may be lethal.

1.6 Opioids

Opiates are alkaloid compounds derived from the opium poppy (*Papaver somniferum*) and include natural (e.g. morphine, codeine, noscapine, thebain), semisynthetic (e.g. heroin, hydromorphone, hydrocodone, buprenorphine, and oxycodone), and fully synthetic (e.g. fentanyl, sufentanil, alfentanil, and remifentanil) compounds. The opioids bind to the mu, kappa, and delta opioid receptors in the periphery as well as centrally in the spine and brain, producing analgesia and anti-nociception.⁸⁴ More recently, opioid receptor-like (ORL) receptors, although structural different from the other opioid receptors, have been incorporated in the opioid receptor family. Some opioids are partial agonists that acting as agonists or antagonists depending on the type of opioid receptors they bind to. Other opioids, such as tramadol and tapentadol, have weak affinity for μ receptors and inhibit reuptake of noradrenaline and serotonin. The human body also produces its own endogenous opioid peptides, i.e., the endorphins, enkephalins, and dynorphins.

During inflammation, endogenous opioids are released from the axon terminals and from the immune cells in the injured tissue, thereby increasing the nociceptive threshold.⁸⁵ Presynaptic, the opioids interact with the opioid receptors on the A δ fibers and C fibers in the dorsal horn, inhibiting the influx of calcium ions and release of excitatory transmitters, and thus nociceptive transmission in the dorsal horn. Postsynaptically, the opioids increase the conductance of potassium ions, causing hyperpolarization of ascending neurons and depression of neuronal firing.⁸⁶ At the supraspinal level, the opioids activate the descending inhibitory pathways in the periaqueductal gray and rostral ventromedial medulla by inhibiting “on” cells and exciting “of” cells, causing decreased transmission of afferent input in the dorsal horn.²¹

The central adverse effects of the opioids, including respiratory depression, nausea, euphoria, and tolerance, are mainly caused by activation of μ receptors in the brain.⁸⁶ Opioid receptors outside the brain are also activated, leading to contraction of smooth muscle in the gut and the hepatobiliary and urinary tracts, which may cause disturbing and potentially serious adverse effects such as obstipation, biliary colic, and urinary retention.⁸⁶ More recently, studies have shown that opioids may lead to increased pain sensation, which is known as opioid-induced hyperalgesia.⁸⁷ The phenomenon is characterized by hyperalgesia and may be attenuated by several other agents, including S-ketamine and COX inhibitors.^{88,89}

Naloxone and naltrexone are competitive opioid receptor antagonists with higher affinity for the opioid receptors than the conventional opioids. Naloxone antagonizes both the analgesic and unwanted effects of opioids, and is mainly used as an antidote in opioid overdose causing respiratory depression.⁹⁰

Ketobemidone

Ketobemidone is a powerful synthetic opioid agonist that acts on the μ_1 and μ_2 opioid receptors.⁹¹ Its effectiveness is considered comparable with that of morphine, and an equipotent ratio of 1:1 is commonly used. When administered by intravenous injection, the maximum analgesic effect occurs in 10–30 min. Ketobemidone is metabolized in the liver, excreted 13%–24% unchanged in the urine after intravenous administration, and has an elimination half-life of 2–3 hours.⁹⁰

Remifentanil

Remifentanil is a selective synthetic μ -agonist, the analgesic effect of which is dose-dependent. This agent is considered to be slightly less potent than fentanyl but to be 40–70-fold more potent than alfentanil.⁹² Remifentanil has unique pharmacokinetic properties among the opioids in that it is metabolized by nonspecific esterases in plasma and in tissue. Consequently, remifentanil is metabolized more rapidly than other opioids, and must be administered as a continuous infusion to achieve adequate plasma levels. Remifentanil is present in plasma in a non-ionized form and equilibrates rapidly on either side of the blood-brain barrier. Hence, remifentanil is easy to titrate, has a rapid onset and offset of effects, and shows noncumulative effects even after a long infusion time. Thus, remifentanil is increasingly used for anesthesia and sedation in spontaneously breathing patients because of its favorable pharmacologic profile.⁹³

1.7 Gabapentinoids

The gabapentinoids were first developed as anticonvulsants and gained approval in 1993 as add-on antiepileptic treatment in patients with refractory partial epilepsy.⁹ However, animal studies and clinical case reports⁹⁴ suggested that gabapentin also has analgesic properties in neuropathic pain conditions. Together with the successor pregabalin, which was introduced in 2004, gabapentin received approval for the treatment of neuropathic pain conditions such as post-herpetic neuralgia and diabetic peripheral neuropathy. In 2005, pregabalin was approved as an adjunct treatment for partial epilepsy disorders, and approval for anxiety disorder and fibromyalgia was secured in 2006 and 2007, respectively (FDA).

More recently, pregabalin was also approved for the treatment of neuropathic pain conditions associated with spinal cord injury (2012) (FDA, EMA). In addition to the broadened indications for gabapentinoids in chronic neuropathic pain conditions, multiple clinical studies during the past two decades have investigated the analgesic efficacy of the gabapentinoids as adjuncts in the treatment of acute pain following tissue injury.

1.7.1 Pharmacology of gabapentinoids

Pharmacodynamics

The gabapentinoids are synthesized as lipophilic structural analogs of GABA (γ -amino-butyric acid) but do not act via the GABA receptors.⁹⁵ Both gabapentin and pregabalin bind to the α -2-delta site on the presynaptic voltage-gated calcium channels in the central nervous system, thereby inhibiting the influx of calcium ions and depolarization, leading to reduced release of excitatory neurotransmitters such as glutamate, substance P, noradrenaline, and calcitonin gene-related peptide, all of which are important neurotransmitters that are normally released in the central nervous system after nerve or tissue damage. The reduced release of these excitatory transmitters attenuates the central sensitization following nociception and inflammation, with minor or no effects on normal nociception. However, the mechanism of action of the gabapentinoids is not fully understood. Apart from inhibition of presynaptic calcium channels, preclinical studies demonstrating increased norepinephrine in the dorsal horn when gabapentinoids are applied suggest that gabapentinoids also activate the bulbospinal noradrenergic descending pathways.⁹⁶ Noradrenaline, which interacts with the α 2-adrenoceptors in the spinal cord, attenuates nociceptive firing neurons, thereby reducing the hypersensitivity response after tissue injury.⁹⁷

Pharmacokinetics

Gabapentin and pregabalin possess similarities, but also have several important differences in terms of their pharmacokinetic properties. Both these agents are absorbed via an amino acid transporter in the small intestine. However, while gabapentin has saturable and dose-limited absorption with a bioavailability of 33%–60% after oral administration, pregabalin shows dose-independent absorption with $\geq 90\%$ bioavailability, indicating that the absorption of pregabalin may be facilitated. Gabapentin reaches a maximum plasma level 3–4 h after administration whereas pregabalin reaches a peak plasma level within 1 h. Both these agents cross the blood-brain barrier. Neither gabapentin nor pregabalin are bound to proteins and have almost negligible hepatic metabolism (<2%), so it is very unlikely that the gabapentinoids have drug-drug interactions that involve inhibiting or inducing metabolism of

other agents.⁹⁸ Both gabapentin and pregabalin are excreted unchanged in the urine, i.e., their clearance is dependent on renal function.⁹⁹

1.7.2 Gabapentinoids for early postoperative pain

Encouraged by the analgesic effect seen in chronic neuropathic pain conditions and the increased knowledge gleaned from basic research, more formal preclinical animal investigations were performed to study the analgesic efficacy of gabapentinoids after tissue injury. In a rat model, Field et al showed that a single dose of gabapentin inhibited thermal hyperalgesia and tactile allodynia for 24 h and 49 h, respectively.¹⁰⁰ Interestingly, the authors showed that the contralateral hind paw was not affected, indicating that gabapentin did not influence physiological pain but only the hypersensitivity seen after tissue damage or in neuropathy. The same findings were also reported for pregabalin.¹⁰¹ In one of the first studies in healthy volunteers, Eckhardt et al found that the pain tolerance time in the cold pressor test was increased after administration of an oral combination of gabapentin and morphine compared with morphine administered alone.¹⁰² Two further studies demonstrated that gabapentin reduced mechanical allodynia following thermal injury and cutaneous hyperalgesia after heat-capsaicin sensitization in healthy volunteers.^{103,104}

In an early dental model in patients undergoing third molar extraction, 300 mg of pregabalin administered after surgery produced more favorable results in terms of pain relief and duration of analgesia than either placebo or the active comparator ibuprofen, whereas there was no difference in analgesic effect between pregabalin 50 mg and placebo.¹⁰⁵ In a randomized controlled trial in which 70 patients scheduled for mastectomy with axillary dissection received gabapentin 1200 mg or placebo 1 h before surgery, the patients who received gabapentin had significantly reduced VAS scores during movement but not at rest at 2 h and 4 h postoperatively. Moreover, total morphine consumption was 50% lower in the gabapentin group when compared with the placebo group and there was no significant between-group difference in adverse effects.¹⁰⁶ These positive findings introduced the idea that gabapentin could be used as a “broad-spectrum” analgesic.¹⁰⁷

During the following years, multiple clinical studies followed in a wide range of surgical fields including gynaecology, abdominal, orthopaedic and head-and neck surgery.^{36,108-113}

In a Danish study, 120 orthopedic patients scheduled for hip arthroplasty were allocated to placebo, pregabalin 300 mg, or pregabalin 300 mg + dexamethasone 8 mg. All patients received paracetamol 1 g four times daily. Pregabalin alone and in combination with steroids

significantly reduced morphine requirements compared to placebo 0–24 h after surgery, with no significant between-group differences in pain scores at rest or during movement or in the incidence of nausea.¹¹⁴ However, the reduced opioid consumption could not be replicated by the same researchers in another study in women scheduled for abdominal hysterectomy.¹¹⁵ Furthermore, in a well-known study by Jokela et al, the analgesic effects of pregabalin 75 mg and 150 mg were compared with those of diazepam 5 mg administered preoperatively in patients undergoing gynecologic laparoscopic surgery. All patients received ibuprofen 800 mg twice daily and fentanyl on demand in the recovery room. The group that received pregabalin 150 mg had less pain at rest and during movement in the 1–8 h after surgery than the group that received diazepam. There was no between-group difference in the amount of rescue opioids used.¹¹⁶ However, in another study that compared the analgesic effects of perioperative pregabalin 150 mg twice daily (total, 300 mg) or 300 mg twice daily (total, 600 mg) with those of diazepam 10 mg (total, 10 mg) in patients scheduled for laparoscopic hysterectomy, the total postoperative dose of PCA-oxycodone was lower in the pregabalin 600 mg group than in the diazepam 10 mg group 0–24 h after surgery. However, significantly more dizziness, blurred vision, and headache were observed with pregabalin.¹¹⁷ Finally, in a study by Gilron et al, the analgesic effects of meloxicam 15 mg and gabapentin 1200–1600 mg each used alone or in combination with the other, were investigated in patients scheduled for ambulatory laparoscopic cholecystectomy starting 1 h before surgery and continued until the second postoperative day. Pain was significantly less severe in the group that received gabapentin with meloxicam than in the group that received meloxicam alone. However, the combination of gabapentin and meloxicam did not provide better analgesia than that achieved by gabapentin alone. The authors of this study concluded that polypharmacy may not always be advantageous and called for further procedure-specific and combination-specific clinical studies.¹¹⁸

The many studies investigating the analgesic efficacy of gabapentinoids led to several systematic reviews and meta-analyses which concluded that the gabapentinoids significantly reduced pain intensity and opioid consumption in the 24 h after surgery¹¹⁹⁻¹²¹ but without a consistent reduction in unwanted effects.¹²⁰ In contrast with these reviews, two Cochrane reviews published in 2009 and 2010 concluded that there was no evidence to support the use of gabapentin or pregabalin in acute postoperative pain.^{122,123}

When work was started on this dissertation in 2010, most of the original studies had compared the analgesic-sparing and opioid-sparing effects of a single dose of a gabapentinoid with those of placebo. Although many of the human studies demonstrated opioid-sparing, the

evidence for analgesic efficacy was conflicting and that for a reduction in opioid-related effects was not convincing. Hence, further studies were encouraged to explore the effects of gabapentinoids in combination with other non-opioid analgesics focusing on optimal dose, timing, and repetitive dosing before routine use of gabapentinoids in postoperative pain management would be warranted.

1.7.3 Adverse effects of gabapentinoids

In the first trials investigating the effects of gabapentinoids on acute postoperative pain, the main focus was on analgesic efficacy with limited attention paid to the incidence of adverse effects. The review by Seib et al¹¹⁹ which investigated the effects of preoperatively administered gabapentin, could not demonstrate a reduced incidence of opioid-related adverse effects, such as nausea, vomiting, and sedation, but did find significant reductions in opioid consumption and pain scores. However, several more recent systematic reviews^{120,124} found that gabapentinoids attenuated typical opioid-related adverse effects, such as nausea and vomiting. Unfortunately, with the increasing number of clinical studies, it became evident that the gabapentinoids have several worrisome adverse effects, the most prominent being a dose-dependent¹²⁵ sedative effect observed in the early postoperative period¹¹⁴ although this was not found in all studies.¹¹⁵ Moreover, the systematic reviews demonstrated an increased incidence of dizziness¹²⁴ and visual disturbances were reported in single studies.^{116,126}

1.8 Postoperative respiratory failure

One of the most serious and feared adverse events in the postoperative period is respiratory failure. This occurs when the respiratory system cannot oxygenate the blood and/or eliminate carbon dioxide from the blood. Conventionally, respiratory failure is classified as type 1, defined as an arterial oxygen tension (PaO_2) < 8 kPa (60 mmHg), or as type 2, defined as an arterial carbon dioxide tension (PaCO_2) > 6 kPa (45 mmHg).¹²⁷ Importantly, these values are not rigid and only serve as guidelines; respiratory failure must be evaluated in the light of a patient history and clinical assessment. Generally, the respiratory system consists of the gas-exchange organ, lungs, and ventilatory pump function, including the chest wall with the respiratory muscles and the central nervous control system with central and peripheral nerves. Put simply, type 1 respiratory failure is associated with various lung diseases (e.g., pneumonia) and type 2 is associated with pump failure (e.g., overdose). However, both types of respiratory failure may coexist, e.g., in patients with chronic obstructive pulmonary disease.¹²⁷

The definition of respiratory failure varies according to variations in clinical practice and in the studies,¹²⁸ but ventilatory frequency and peripheral oxygen saturation (SpO₂) are commonly used measurements because of their feasibility.¹²⁹ However, both variables may provide limited information about the potential effect of a drug on ventilatory drive, i.e., the ventilatory pump function,¹²⁸ and inspired ventilatory minute volume and arterial carbon dioxide concentration may be more useful outcomes measurements in drug studies.

Surgical patients are often at increased risk for ventilatory depression on the first postoperative day.¹³⁰ The risk factors may be multifactorial, but among the most common causes is opioid-induced ventilatory depression, which has an incidence of about 0.5%.¹²⁸ Opioids remain the agents of choice in moderate and severe pain conditions and exert dose-dependent ventilatory depressive effects by binding to μ receptors,¹³¹ thereby reducing the sensitivity of the respiratory centers to PaCO₂. The overall incidence of opioid-induced ventilatory depression may vary according to the definition used; in a review the overall incidence of respiratory impairments was 0.3% using naloxone as indicator, 1.1% when low-frequency breathing (<8 or <10 breaths/min) was used as indicator, and 3.3% and 17.0% when respiratory depression was assessed by hypercarbia and oxygen desaturation, respectively. When comparing i.m., PCA, and epidural administration of opioids, no significant differences between-groups in respiratory depression were found using ventilatory frequency as indicator.¹³² Systemic administration of opioids using patient-controlled analgesia devices has been shown to be associated with a low incidence of ventilatory depression, but the risk may increase dramatically with continuous backup administration of analgesia, higher opioid doses, increasing patient age, and major abdominal surgery.¹³³ Furthermore, the sedating effect of opioids may cause additional respiratory complications in patients at higher risk because of obesity, obstructive sleep apnea, obstructive pulmonary disease, advanced age, or critical illness.¹³⁴ Furthermore, other sedating agents, e.g. benzodiazepines and anticholinergics, may enhance ventilatory depression even further when used in combination with opioids.¹³⁵

The ventilatory effect of gabapentinoids has not been systematically evaluated. A few case reports have suggested that the gabapentinoids may cause hypoventilation and respiratory failure in patients with certain comorbidities.^{136,137}

Given the serious and potentially fatal consequences of respiratory depression in the postoperative period, as well as the increasing adjunctive use of gabapentinoids in multimodal pain management, we decided to explore the respiratory effects of gabapentinoids alone and in combination with opioids.

1.9 Postoperative cognitive dysfunction

Cognitive impairments and delirium have gained increased focus during the last years both in the intensive care units and in the postoperative setting. Delirium is often reported in critically ill patients in Norwegian hospitals,¹³⁸ and delirium is associated with increased mortality, hospital stay and long-term cognitive impairments.¹³⁹

Postoperative cognitive dysfunction (POCD) is characterized by impaired cognitive performance after surgery and may affect different domains of cognition, such as memory and executive function. Unlike delirium, which is often characterized by acute onset, disorientation, and confusion,¹⁴⁰ the symptoms of POCD are subtle and longer lasting and may be difficult to recognize without specific neurocognitive testing.¹⁴¹ According to the literature, POCD may appear during emergence from anesthesia, but may also develop later in the postoperative period, but with a decreasing incidence over time. The incidence varies widely according to the definition used and the duration and timing of assessment, ranging from 30% to 80% during the first postoperative weeks and from 10% to 60% at 3–6 months after surgery.¹⁴² A large study in elderly patients undergoing non-cardiac major surgery even found persistent POCD 1–2 years after surgery.¹⁴³

The exact etiology of POCD is not clear, but factors such as major surgery, advancing age, low educational level, and preoperative cognitive impairment have traditionally been associated with POCD.¹⁴⁴ More recently; postoperative pain, increased inflammatory activity, sleep disturbances, and environmental influences have also been discussed to negatively affect cognitive functioning.^{144,145}

In contrast, there is insufficient evidence to determine how the various types of anesthesia and anesthetic techniques used affect the risk of POCD.⁴ Studies comparing regional anesthesia with general anesthesia could not demonstrate any significant reduction in the incidence of POCD^{146,147} and reports on the effects of centrally acting agents, such as opioids, anticholinergic agents, and benzodiazepines, on POCD have not been consistent.¹⁴⁸ Overall, POCD seems to be more common than hitherto recognized and must be acknowledged as a possible postoperative complication that may impede recovery, increase morbidity, and prolong the postoperative hospital stay. Despite some progress in our understanding of its pathophysiology and etiology, clinical investigations of POCD are still in their infancy. The cognitive effects of gabapentinoids are not well investigated, and their effects when used in combination with opioids in the postoperative period are unknown.

In conclusion, the gabapentinoids, which represent a relatively new class of analgesics developed primarily for the treatment of epilepsy and later approved for neuropathic pain conditions, are now increasingly used as “off-label” adjuncts in multimodal treatment of pain. Although there is some evidence that gabapentinoids have better analgesic and opioid-sparing effects than placebo, the size of these effects varies substantially across studies and the aim of multimodal treatment, which is to achieve additive or supra-additive analgesia with a concomitant reduction in adverse effects, has yet to be met.

2 AIMS OF THE THESIS

The overall aim of this thesis was to explore the effects of pregabalin in combination with opioids, and specifically the effect on acute pain, ventilatory–, and cognitive function.

Specific aims:

1. To investigate the analgesic effects of pregabalin, remifentanyl and their combination in a crossover study in healthy volunteers. Furthermore, the study also aimed at exploring the effects of pregabalin and remifentanyl on ventilatory and cognitive function (Paper I).
2. To examine whether pregabalin 150 mg twice daily on the day of surgery and the consecutive day reduce opioid consumption. Secondly, to investigate the effect of pregabalin on postoperative pain, incisional hyperalgesia and adverse effects (Paper II).
3. To explore the cognitive effects of pregabalin 150 mg administered twice daily – on the day of surgery and on the subsequent day – using neuropsychological tests measuring visual memory, working memory, executive function, and attention (Paper III).

3 MATERIALS AND METHODS

3.1 Study populations

The participants in the experimental study (Paper I) were recruited by open invitation to students at Oslo University; twelve students (six males and 6 females) were enrolled. The inclusion criteria were healthy volunteers (ASA Classification I), aged 18 to 50 years, and a negative pregnancy test. Exclusion criteria were history of alcohol or drug abuse; any known diseases (especially cardiac or vascular disease); lung, liver or kidney disease; diabetes, use of any types of medication before or during the trial; allergy to any of the test drugs; weight >100 kilograms or BMI >30% above normal; inclusion in other studies within the last two months; or not fluent in spoken and written Norwegian.

Papers II and III were based on the same study population. Patients scheduled for donor nephrectomy were asked to participate upon admission to the ward two to four days before their surgery. Prior to hospitalization, all participants underwent extensive investigations for donor acceptance and were considered healthy with ASA Classification I–II. Inclusion criteria were acceptance for kidney donation and aged 18 to 75 years. Exclusion criteria were allergy to any of the test drugs, daily use of analgesics or sedative medications, or unfamiliarity with spoken and written Norwegian.

3.2 Study design

The experimental study (Paper I) was a randomized, placebo-controlled, blinded crossover study consisting of four different treatments: 1) pregabalin + remifentanyl, 2) pregabalin + placebo, 3) placebo + remifentanyl, and 4) placebo + placebo. Each participant received each of the four treatments in a randomized order – one treatment at the time on four different days. On every study day, cognitive tests, ventilatory measurements and experimental pain tests were performed four times: at baseline and after three predefined levels of remifentanyl/placebo infusion (levels 1 to 3) (Fig.1).

Figure 1. Timeline for each study day

Papers II and III were based on the same randomized, parallel group, placebo-controlled and blinded study. The participants received either pregabalin or placebo on the day of surgery and the day after surgery in addition to a standardized multimodal pain treatment.

All patients received 10 mg diazepam 1 h before surgery as part of the wards' standard premedication. General anesthesia was performed by the anesthesiologists in the operation theater using total intravenous anesthesia (TIVA) (IVAC Syringe Pump, Model P7000, Alaris, Cardinal Health, Switzerland) delivering 20 µg/ml remifentanil (Ultiva; GlaxoSmithKline, United Kingdom) (µg/kg/min) and 20 mg/ml propofol (Propofol; Fresenius Medical Care, Germany) (mg/kg/h). One hour after induction of anesthesia, the patients intravenously received 0.625 mg droperidol and 8 mg dexamethasone. Thirty minutes before the conclusion of the surgery, 50 µg (patients ≤ 60 kg) or 100 µg (patients ≥ 61 kg) fentanyl was given as an intravenous bolus in addition to 1 g paracetamol, and wound infiltration was treated with 5 mg/ml bupivacaine + 5 µg/ml epinephrine in a total volume of 20 ml.

3.3 Study medication

Pregabalin capsules and placebo capsules were produced at Oslo University Pharmacy, Oslo, Norway, and prepacked in numbered containers of identical appearance labeled with identical study information corresponding to each study.

In the experimental study (Paper I), two capsules of 75 mg pregabalin or placebo (totaling 150 mg) were swallowed whole with a sip of water thirteen hours before start of the trial. The same dose of two capsules, each containing 75 mg pregabalin or placebo (totaling 150 mg), was repeated 1 h before trial initiation; a total of 300 mg pregabalin or placebo capsules were given. Two trained nurses prepared the syringes (size 60 ml) containing either 20 µg/ml remifentanil (Ultiva; GlaxoSmithKline, United Kingdom) or placebo (NaCl 9

mg/ml; Braun, Germany) according to randomization and immediately before the start of each trial. Remifentanyl (20 µg/ml) was administered via target-controlled infusion (TCI) (effect-site TCI, Minto model and Alaris PK Syringe Pump; CareFusion, United Kingdom) with predefined concentrations for each level: 0.6, 1.2, and 2.4 ng/ml (TCI levels 1–3, respectively).

In the clinical study (Papers II and III), two capsules of 75 mg pregabalin or placebo (totaling 150 mg) were administered by trained nurses on the ward according to the assigned numbered container. The study drugs were swallowed whole with a sip of water 1 h before surgery, in the evening the day of surgery (21.00), in the morning on postoperative day 1 (09.00), and in the evening on postoperative day 1 (21.00), totaling 600 mg pregabalin or placebo capsules.

3.4 Randomization and blinding

A senior consultant not involved in the participants' care or the drug handling made randomized lists using a computerized randomization program (DatInf RandList version 1.2, Datinf GmbH, Germany).

In the experimental study (Paper I), the participants were randomized to one of four sequences (reduced Latin-square design), using a block randomization with a block size of four or eight. After written consent was obtained, the participants were consecutively enrolled in the study according to the numbered randomization list. The randomization was unknown to both participants and researchers, and the randomization code was not revealed to any of the investigators until all the data were collected and entered into a database.

In the clinical study (Papers II and III), a computerized randomization list stratified the participants by sex and in blocks of four or six to one of the two treatment groups. After participants provided consent, they were assigned the next consecutive participant number and provided with corresponding study medication.

3.5 Central variables

3.5.1 Experimental and surgical pain

Cold pressor pain

A cold pressor test (CPT)³² was used for pain stimulation in the experimental pain study (Paper I). A 13-liter custom-made Plexiglas container (Evoik Industries Ag, Germany) connected to a refrigerated circulator (Julabo FP40-HE; Julabo Labortechnik GmbH,

Germany) was used. The water temperature was held constant at $3^{\circ}\text{C} \pm 0.01$ as measured by a precision thermometer, and the pump flow rate was 22 to 26 l/min. The participants were asked to submerge their non-dominant hand in the water to their wrist with the fingers spread into the container for a maximum of 120 sec. Pain intensity was scored 12 times (at 5 sec after submersion and every 10 sec thereafter) using a customized and computerized Visual Analogue Scale (VAS) scoring system. The VAS consisted of a vertical bar that turned red when the patients were scrolling the cursor upwards with their dominant hand. The numeric value of the VAS score ranged from 0–100 mm, where 0 = “no pain” (lower anchor) and 100 = “unbearable pain” (upper anchor); these values were hidden from the participants. The anchors were written in Norwegian. If the participant had to withdraw the hand from the water because of unbearable pain before the test was completed, the last scores were set to 100. The CPT was performed at baseline and at each level of remifentanyl/placebo infusion (levels 1–3).

Postsurgical pain

Hand-assisted living donor nephrectomy is a standardized surgical procedure¹⁴⁹ and was performed by transplant surgeons without any unexpected or divergent events. Three incisions on the left or right side of the abdomen were used to insert and manipulate the surgical instruments, and the left or right kidney was dissected from the retroperitoneal tissue before its removal through a 10-cm horizontal incision just above the symphysis pubis. Postoperative pain was assessed at rest and with standardized movement (coughing) on a Numeric Rating Scale (NRS) of 0–10, where 0 = “no pain” and 10 = “worst pain imaginable”. Pain intensity was measured every hour for the first six hours; in the evening on the day of surgery (21.00), and at four times (09.00, 13.00, 17.00 and 21.00) 24–48 h after surgery. The data collection was performed by trained nurses in the postoperative care department and on the surgical ward (Paper II).

Pain-related sleep interference

Pain causing sleep interference was registered in patients undergoing nephrectomy in the morning (09.00) at 24 h and 48 h after surgery and was measured on an NRS of 0–10, where 0 = “pain did not interfere my sleep at all” and 10 = “pain made sleep impossible”. The data collection was performed by trained nurses on the surgical ward (Paper II).

3.5.2 Opioid consumption

Patients undergoing donor nephrectomy were treated according to standard analgesic management on the ward, consisting of opioids, steroids, paracetamol, and local anesthetics

(Papers II). Postoperative opioids were administered using a patient-controlled analgesia (PCA) device delivering boluses of 1 mg ketobemidone with a lock-out time of 8 min and a maximum dose of 7 mg ketobemidone per h (dose and lock-out time). The PCA device was stopped 48 h after surgery if the total opioid consumption was ≤ 20 mg for the last 24 h; otherwise, PCA administration was continued for the next 24 h. After the PCA device was discontinued, oral oxycodone was used for pain relief in addition to 1 g paracetamol 4 times per day. Opioid consumption was registered daily at 07.00 by a trained nurse and entered into the database by one of the investigators (MM).

3.5.3 Incisional hyperalgesia

Incisional hyperalgesia was tested twice with a handheld von Frey glass-fiber monofilament (Optihair 256 mN, Marstocknervtest, Marburg, Germany) (Paper II). The first test was conducted approximately 24 h after the end of surgery (around noon), and the second test was performed before hospital discharge 4–6 days after the last administration of test drug. The test was performed in a standardized manner¹⁵⁰ using pinprick stimulation with a von Fray hair along five imaginary lines above and to each side of the 10 cm incision above the symphysis. The tactile stimulation started outside the hyperalgesic area and progressed every 5 mm on the predefined line towards the incision. When a distinct change in tactile sensation was perceived or reported as painful, sore or a sharp sensation, the distance from that point to the incision was measured. The stimulus stopped 5 mm before the incision if no change in sensation appeared. The distances along the five trajectories were summarized and used as a surrogate variable for the hyperalgesic area. All tests were performed by one of the investigators (MM).

3.5.4 Ventilatory measurements

Spirometry

In the healthy volunteer study (Paper I), the ventilatory variables were measured using spirometry (Vmax Spectra 229; SensorMedics Corp., USA) consisting of a facial mask, a mass flow sensor, and a non-rebreathing circuit with a low-resistance breathing valve. The O₂ capnography, the O₂-sensor, and the flow sensor were calibrated daily and before every participant was assessed: the two former were calibrated against 100% O₂ and a span gas (16% O₂, 4% CO₂), and the latter was calibrated with a 3-liter syringe at low flow (0.5 l/sec), medium flow (3–4 l/sec) and high flow (7–8 l/sec). By correctly performing and accepting the calibrations, the measured ventilatory volumes were independent of the flow rates.

During spirometry, the facial mask covering the nose and mouth was carefully adjusted, and the patients were asked to relax in a semi-upright position and breathe normally for approximately 10 min. Respiratory frequency, tidal and minute volumes, and end-tidal carbon dioxide tensions (ET_{CO_2}) were registered automatically and recorded into a database. We used ET_{CO_2} as the primary outcome because this variable is highly correlated with ventilatory changes and is most commonly used in clinical practice. Measurements considered representative over a 2 min period were used for further analysis. The ventilatory measurements in Paper I were performed at baseline and at each level of remifentanil/placebo infusion (level 1–3).

3.5.5 Cognitive measurements

Cambridge Neuropsychological Test Automated Battery (CANTAB)

Cognitive measurements were performed using the Cambridge Neuropsychological Test Automated Battery, a computer-based cognitive assessment system consisting of neuropsychological tests that assess different areas of cognitive functioning, such as executive function, attention, and processing speed.¹⁵¹ Two of the main researchers (AS, MM) and a nurse from the surgical ward attended a two-day training program arranged by the manufacturer in Cambridge, United Kingdom, to become familiar with the tests and the software.

The test procedures were carried out in a quiet and undisturbed room using a tablet and a press pad placed on a table in front of the participant and with one of the researchers (MM) sitting beside the participant. The tests were run automatically, and the participants were given standardized instructions before and during the course of the tests. Predefined specific test variables were used to explore the cognitive effects of pregabalin. In Paper I, we used Rapid Visual Information Processing, and, in Paper III, we used the Motor Screening, Reaction Time, Paired Associated Learning, Rapid Visual Information Processing, Spatial Working Memory, and Stop Signal Task. The test results, including the number of errors, time measurements, and derived measurements, were automatically captured and recorded into the database. In Paper I, the cognitive tests were performed at baseline and at each level of remifentanil/placebo infusion (level 1–3), and in Paper III, the tests were carried out at baseline (1–3 days before surgery) and at 24 h and 3–5 days after surgery. A premorbid intelligence test was performed using the Norwegian version of the National Adult Reading Test.¹⁵²

Color Word Interference Test (CWIT)

This test was used in Paper I to examine the participants' ability to inhibit and sustain focus.¹⁵³ The test consists of four parts: naming of color patches, reading of color words printed in black, preventing the reading of words by naming dissonant ink colors in which those words are printed, and switching between naming dissonant ink colors and reading the words. We recorded the total completion time and number of errors for all tests. The CWIT was used in Paper I at baseline and at each level of remifentanyl/placebo infusion (level 1–3).

3.5.6 Adverse effects

In the human volunteer study (Paper I), participants were asked to report side effects such as sedation, nausea, dizziness, pruritus, headache, and diplopia at the end of each of the four treatments. The side effects were reported as incidences, and the use of antiemetics was registered.

In the clinical study (Paper II), sedation, nausea, headache, and dizziness were scored on a 0–10 NRS scale in the evening on the day of surgery and at four times (09.00, 13.00, 17.00, 21.00) 24–48 h after surgery. Additionally, the number of instances of vomiting, number of uses of antiemetics, degree of mobilization (coughing, sitting upright in bed, standing/sitting in chair, walking), and time to recovery of bowel function were recorded in the evening on the day of surgery and postoperative day 1. All adverse effects were reported as incidence rates.

3.5.7 Long-term follow-up questionnaires

A long-term follow-up was performed using questionnaires addressing persistent postsurgical pain (PPSP) at rest and during activity during the last 24 h and during the last week. The postal questionnaires were sent to the participants at 6 weeks, 6 months and 12 months after surgery. If no response was received within 2 weeks, a second equivalent questionnaire was forwarded.

3.6 Statistical analysis

The results are presented as the mean with SD or as the median with ranges and/or 25th to 75th percentiles according to normal and non-normal distribution of the data, respectively. The distributions of the variables were examined using the Shapiro-Wilk test and by inspection of the residuals using QQ-plots and histograms.

In Paper I, we used the linear mixed random intercept model to investigate the effect of the infusions and the differences between treatment groups. Mixed effects models take both fixed effects and random effects into account. Treatment groups, infusion levels and treatment-by-infusion level were used as fixed effects, whereas subjects were treated as random intercepts, and a compound symmetric correlation structure was assumed, meaning that all variances and covariances were equal.

In Paper II, the differences between treatment groups were analyzed using independent sample t-tests in normally distributed continuous variables (intraoperative data, demographics) and Mann-Whitney *U* tests in non-normally distributed data (opioid consumption, pain intensity, incisional hyperalgesia, pain-related sleep interference and PPSP). Repeated measurements of pain intensity over time were calculated as the area under the curve (AUC) to compare the difference between the treatment groups. The Chi square test for independence was used to explore the relationships among categorical variables (adverse effects, PPSP, and demographic variables), which were corrected with Fisher's exact test when appropriate.

A mixed effects negative binomial regression model was used in Paper III for over-dispersed count data (spatial working memory within errors, stop-signal task stop-go, paired associated learning), and a linear mixed random intercept model was used for normally distributed continuous data (spatial working memory strategy, rapid visual processing A', reaction time). The treatment group, time and treatment group by time were treated as fixed effects, and the subjects were used as a random effect accounting for repeated measurements within each patient. The results were reported as rate ratios and median differences with 95% confidence intervals (CIs).

3.7 Power calculation

The power calculation in the human volunteer study (Paper I) was based on an expected average difference of 10 (VAS, 0–100 mm scale) between groups. To compensate for six multiple pairwise comparisons, the α -level for the sample size calculation was set to 0.008 using Bonferroni correction (α -level = 0.05/6). Thus, to demonstrate a difference between groups, with a power of 0.8, an SD of 8.0 for the difference, and no dropouts, at least 12 participants were needed.

In Paper II, we based the sample size on results from a previous study in patients undergoing donor nephrectomy at the same institution.¹⁵⁴ Opioid consumption was the primary outcome, and a 20% difference between the groups was considered clinically

meaningful. With an expected opioid consumption of 50 mg in the control group with an SD of 15, a two-sided α -level = 0.05, and a power of 0.8, a total of 36 participants in each group was necessary. To compensate for attrition, 40 participants were included in each group.

Paper III was a secondary explorative analysis of the randomized placebo-controlled study described in Paper II. The cognitive effects of pregabalin have only been sparsely investigated earlier and, as far as we know, not in the postoperative setting; thus, the analysis was considered exploratory, and a formal power calculation could not be calculated.

3.8 Software

Statistical data analyses were performed with IBM SPSS Statistics, versions 22–24 (SPSS Inc., Chicago, IL, USA). The sample size calculations were performed using the software nQuery Advisor, Version 7.0 (Statistical Solutions, Ireland).

3.9 Approvals

The experimental and clinical studies in this thesis were approved by the privacy representatives at Oslo University Hospital, the Regional Committee for Medical Research Ethics for Eastern Norway and the Norwegian Medicines Agency. The studies were registered at EudraCT (2009-016199-55 and 2009-015316-17) and www.clinicaltrials.gov (NCT01419405 and NCT01059331) and were reported according to the CONSORT Statements. The accomplishments of the studies were in adherence with the Helsinki declaration.¹⁵⁵

4 MAIN RESULTS

4.1 Paper I

In this paper, we explored the effects of pregabalin, remifentanyl and their combinations on experimental pain, respiratory function, and cognitive function. Pain intensity (reported as the average of the last three VAS values) in the 2-minute CPT was 72 mm (95% CI 62 to 83) after placebo. Compared to placebo, pregabalin alone reduced the pain score by -10 mm (-14 to -7, $P < 0.001$). Remifentanyl exerted a dose-dependent analgesic effect, reducing the VAS score by -47 mm (-54 to -39, $P < 0.001$) at the highest TCI level (2.4 ng/mL). Pregabalin in combination with remifentanyl exerted an additive analgesic effect, reducing the VAS score by -57 mm (-64 to -50, $P < 0.001$) at the highest TCI level. Figure 2 shows the pain over time curves at baseline and at increasing levels of remifentanyl. The figure has not been presented previously.

Figure 2. Mean pain during cold pressor test during time at baseline, TCI 0.6, 1.2, and 2.4 ng/mL for the four treatments

Respiratory depression was potentiated by adding pregabalin to remifentanyl; the end-tidal carbon dioxide was 39.3 mmHg (37.2 to 41.3) with placebo but increased 1.8 mmHg (-0.9 to 4.6, $P = 0.4$) with pregabalin, 10.1 mmHg (4.9 to 15.4, $P < 0.001$) with remifentanyl, and 16.4 mmHg (11.3 to 21.5, $P < 0.001$) with the combination of pregabalin and remifentanyl at the highest TCI level.

Compared to placebo, pregabalin increased the number of errors in the CWIT ($P = 0.004$), an indicator of impaired cognitive performance. Remifentanyl reduced the psychomotor speed in the CWIT ($P = 0.029$) and the Rapid Visual Processing test ($P = 0.009$) compared to the corresponding values of placebo. The combination of pregabalin and remifentanyl impaired all tests significantly *versus* placebo. Pairwise comparisons between the combination of pregabalin + remifentanyl and placebo + remifentanyl showed no difference between the groups except for an increased number of errors in the CWIT when the combination of pregabalin + remifentanyl was administered ($P < 0.001$).

4.2 Paper II

In Paper II, the opioid-sparing, analgesic, and antihyperalgesic effects of perioperatively administered pregabalin were explored in patients undergoing laparoscopic donor nephrectomy. Compared to placebo, pregabalin significantly reduced opioid consumption 0–48 h after surgery (median mg [25th, 75th percentile]; 29.0 mg (22.0 to 45.5) vs 41.8 mg (25 to 63.6), respectively; $P = 0.04$). The pain intensity 0–48 h after surgery, calculated as area under the pain (NRS) *versus* time curve, was not significantly different between groups either at rest ($P = 0.12$) or with movement ($P = 0.21$).

Pregabalin decreased incisional hyperalgesia 24 h after surgery (median [25th, 75th percentile]; 8.5 cm (1.0 to 18.5) vs 15.5 cm (9.5 to 24.0), respectively; $P = 0.02$). Additionally, nausea ($P \leq 0.01$), the use of antiemetics ($P \leq 0.01$) and pain-related sleep interference ($P = 0.02$) were reduced with pregabalin.

4.3 Paper III

In Paper III, we explored whether 150 mg pregabalin twice daily on the day of surgery and postoperative day 1 would impair different aspects of cognitive function, measured as neuropsychological task performance, compared to placebo.

In the Spatial Working Memory within errors test, the median (25th, 75th percentile) number of errors 24 h after surgery was significantly higher with pregabalin than with placebo (1 (0,6) *versus* 0 (0,1); rate ratio [95% CI]: 3.20 [1.55 to 6.62]; $P = 0.002$). Pregabalin

significantly increased the median (25th, 75th percentile) number of errors in the Stop Signal Task Stop Go-test compared to that of placebo (3 (1,6) *versus* 1 (0,2); rate ratio 2.14 [1.13 to 4.07]; $P = 0.020$). These results indicate that when pregabalin was administered, executive function, including inhibition and working memory, was impaired compared to that of placebo. There were no significant differences between groups in the Paired Associated Learning, Reaction Time, Rapid Visual Processing, or Spatial Working Memory strategy tests.

5 DISCUSSION

5.1 Methodological discussion

5.1.1 Study design

Study population

The participants in the human volunteer study (Paper I) were recruited by advertising on a web page for students at the University of Oslo; hence, the study population consisted of a homogenous group of volunteers considered to be representative of a young healthy population.

Differences in pain perception have been observed in experimental and clinical pain studies^{156,157} suggesting that females are more sensitive to pain and are frequently represented among patients with chronic pain conditions.¹⁵⁸ In the experimental study we chose to recruit an equal number males and females. Due to small sample size, sex-specific analysis was not performed, and study of sex-differences was not the aim of the study.

The clinical study (Papers II and III) consisted of patients undergoing laparoscopic donor nephrectomy. Prior to surgery, patients were subjected to thorough investigations and were excluded for not meeting the strict requirements for donor acceptance. Accordingly, the study population consisted of patients with ASA classification I–II without comorbidities and preoperative chronic pain and thus was considered to be a homogenous patient group with comparable baseline characteristics. However, as substantially more women than men are willing to become donors, only 25 men compared to 55 females were recruited. To avoid unequal distribution among the groups, sex-stratified randomization was performed.

Group design

Both studies in this thesis were prospective, randomized, placebo-controlled studies. The first study (Paper I) was a crossover study that is considered to be favorable when investigating the efficacy of drug and drug combinations. As each participant receives all treatments, the participant is serving as his or her own control. The crossover trial is also known as the “within subject” study design, in which the inter-individual variability is eliminated, and smaller differences may be detected. Therefore, crossover trials may provide statistically and clinically valid results with fewer patients required compared to the number of patients needed for similar outcomes from parallel group trials.¹⁵⁹

Although crossover trials are advantageous in many respects, the design may also be prone to biases such as carryover effects and period effects. Carryover effects may be present if two treatments are administered shortly after each other without allowing for enough washout time between the two treatments.¹⁶⁰ Hence, the first treatment may influence the subsequent treatment and confound the results. In our study, the carryover effect was handled by establishing the washout time for a minimum of 11 times the elimination half-life of pregabalin ($T_{1/2}$, 6.3 h).⁹⁵ Thus, pharmacological carryover effects were unlikely. This does not eliminate possible psychological carryover effects; if a drug effect is experienced, the response on the next test the following day may be modified. A variance-balanced reduced Latin square design should also eliminate that potential bias.

Carryover effects should not be confused with period effects, which are independent from the treatment given, but may occur if there are changes in the subjects' basic conditions or in the conditions of measurements, such as a systematically different effect in the first period compared with the last period.¹⁶⁰ We performed a *post-hoc* statistical analysis, which did not reveal any period effects in the crossover study.

The clinical postoperative study (Papers II and III) was a parallel group study in which the participants were randomly assigned to one of the two treatment arms and received the same treatment during the whole study period. As the efficacy and side effects of each treatment are compared between the participants, this parallel group is called the “between subject” study design. Because this study design is prone to inter-variability between participants, the differences between treatment groups should be corrected for baseline differences.¹⁵⁹ The disadvantages of the parallel group design compared with the crossover design are that more participants are required and a larger amount of resources are necessary during the study. However, participation is less time consuming for each participant, which may reduce attrition and the number of withdrawals during the trial. Parallel studies are preferred by regulatory authorities for drug trials because the statistical analysis of parallel studies is easy and straightforward compared with that of crossover studies. Additionally, period effects and carryover effects are eliminated.

Experimental versus clinical study design

Experimental and clinical designs were used to explore the treatment efficacy and side effects of pregabalin. Both designs have advantages and disadvantages, but, together, they may serve as valuable and complementing study designs. The experimental study (Paper I) was strictly designed, enabling us to investigate the analgesic, ventilatory, and cognitive

effects of pregabalin alone and in combination with increasing levels of remifentanyl during the test period lasting approximately 3.5 h. In this experimental design, a standardized pain stimulus was performed. Furthermore, the experimental design allowed us to investigate the ventilatory effects of pregabalin using spirometry, which is highly sensitive to respiratory changes and provides more detailed information about ventilatory depression than peripheral oxygen saturation and respiratory frequency, which are often used in clinical studies. However, the time frame of the protocol did not allow for an extended cognitive investigation; thus, the cognitive assessment was limited to two tests.

In the clinical study, we investigated the opioid-sparing, analgesic and cognitive effects of pregabalin in combination with opioids after nephrectomy. Although the analgesic efficacy may be demonstrated under experimental conditions, the utility of the drug or drug combination must also prove advantageous in a clinical setting. Thus, the clinical study allowed us to compare the effect of pregabalin with standard treatment to that of standard treatment alone after surgery. Furthermore, compared to the experimental study, the clinical study allowed for a more thorough investigation of the cognitive effects of pregabalin, but investigating the ventilatory effects was difficult. Although multiple confounders may influence the outcome variables in a clinical study, we endeavored to reduce some of these confounders by using a homogenous group of patients undergoing the same planned and standardized surgical procedure.

Exploratory versus confirmatory design

The key difference between exploratory and confirmatory study designs is that confirmatory designs are anchored in a predefined hypothesis and seek to find the definitive answer of a research question.¹⁶¹ By contrast, the findings in an exploratory study are associations that have to be tested in additional trials. In the studies in this thesis, we tested the hypothesis that pregabalin exerts analgesic (Paper I) and opioid-sparing (Paper II) effects compared to those of placebo. The outcomes were of primary interest; thus, the studies were confirmatory with a clear hypothesis at the start of the trials. In Paper III, we investigated the perioperative effect of pregabalin on cognitive functioning. This paper was a secondary exploratory analysis of the study population in Paper II, and the outcome variable (cognitive function) was considered as a secondary variable of the primary Paper II. However, exploratory endpoints may provide valuable information about the treatment in question and may generate new hypotheses for future research.¹⁶²

Another important difference between the two study designs is that the confirmatory design is based on a calculated sample size, ensuring sufficient statistical power, while an exploratory design may not meet a predefined sample size requirement. Consequently, confirmatory designs have to adjust for multiplicity with suitable statistical methods according to the methods used in Papers I and II, whereas in exploratory trials, adjustments are not necessary, as the findings must undergo further testing to confirm the results.¹⁶¹ However, the findings in an exploratory study may be corrected for multiplicity to add information and to help interpret the results, and this was done in Paper III.

5.1.2 Validity, biases and confounders

The internal and external validity of the results are important dimensions of the trial quality. Internal validity is when the observed difference between the treatment groups is associated with the intervention to be tested. Internal validity can be flawed by systematic errors, including biases and confounders.¹⁶³ Randomization may minimize selection bias and promote internal validity, and both studies in this thesis were randomized placebo-controlled studies.

Performance bias may occur either when researchers provide additional treatment intervention to one group or if knowledge of the group allocation influences the assessment of outcome. To reduce these potential biases, both studies were double-blinded until all the data were entered into a database. In Paper I, we used a standardized protocol for intravenous drug administration that was designed to minimize the possible abrupt side effects and to reduce unblinding, and only standardized instructions were given during the test procedures.

Attribution bias because of nonadherence to protocol or loss to follow-up may reduce the statistical power of the analysis and, consequently, the internal and external validity of the results. In the clinical study (Papers II and III), more participants in the placebo group denied testing because of nausea and pain, which caused unequal sample sizes and may have biased the test results.

Confounders are differences in baseline characteristics between treatment groups and may influence the associations between the treatment and outcome measurements. We used sex-stratified block randomization with alterations of block size in the clinical parallel study to address this potential confounder. Also a crossover design may reduce confounders¹⁶⁴

External validity is defined as to what extent the results of a trial can be generalized to the whole population the sample was meant to represent.¹⁶⁵ The results in our studies are valid for healthy adult populations. In fact, there are reasons to believe that some of the outcome

variables (ventilatory depression and cognitive effects) may be even more pronounced in older patient groups and in patients with more co-morbidities. In summary, we considered the internal and external validities to be acceptable for healthy populations.

5.1.3 Treatment intervention

Pregabalin

The study medications consisting of pregabalin capsules and identical placebo capsules were produced at Oslo University Pharmacy and prepacked in identical boxes labeled with study information and randomization numbers. Accordingly, our research was completely independent from the commercial pharmaceutical industry, which should be considered advantageous.¹⁶⁶

In the study composing healthy volunteers, 150 mg pregabalin or placebo capsules were administered thirteen hours before start of the trial and 1 h before trial initiation; a total of 300 mg pregabalin or placebo capsules were given. All patients in the healthy volunteer study received the treatment drug according to the protocol. In the study of patients scheduled for donor nephrectomy, 150 mg pregabalin or placebo capsules were administered twice daily on the day of surgery and the first postoperative day by trained nurses on the ward according to the assigned numbered container; a total of 600 mg pregabalin or placebo capsules were given. In the clinical study two protocol deviations occurred in the pregabalin group: one patient received only 450/600 mg due to adverse effects (diplopia), and one patient received the 4th dose 12 h late. Equally, two protocol deviations occurred in the placebo group; one patient received only 6/8 placebo capsules, and one patient was administered the third and fourth doses simultaneously. The study drugs were swallowed whole with a sip of water.

We did not draw any blood samples to measure the plasma concentrations of pregabalin, which is a limitation of our work. However, pharmacokinetic interactions are unlikely because pregabalin undergoes almost no metabolism and has low protein binding. An earlier study demonstrated that the plasma concentration of pregabalin peaked at 1 h after administration, while the maximum CSF concentration occurred as late as 8 h after oral intake.¹⁶⁷ To achieve adequate plasma and CSF concentrations, we decided to administer pregabalin in the evening and in the morning before the experimental study (Paper I) and before surgery in the clinical study (Papers II–III).

The optimal treatment duration and dose for pregabalin in postoperative pain treatment is not clearly determined.¹⁶⁸ Based on earlier research, we decided to administer 150 mg twice daily to balance potential pain relief and to minimize the side effects. However, as only one

dose of pregabalin was used, our results are not valid for other doses. In a recent meta-analysis no differences in opioid-sparing effects were found according to dose-level (≤ 75 –300 mg) 24 h after surgery, and single versus multiple dosing seemed insignificant.¹⁶⁸

Opioids

In the human volunteer study, we used step-dose remifentanyl infusion as a template for opioids. Remifentanyl has dose-dependent analgesic effects with short onset of action and may be considered ideal in experimental studies requiring rapid changes in plasma levels in addition to fast recovery after the conclusion of the trial.¹⁶⁹ Remifentanyl's liver-independent metabolism and ultrashort T_{1/2} make this opioid increasingly used in the clinic for analgesia during the postoperative period and in the intensive care unit. In Paper I, the drug was administered via effect-site TCI (Minto model) delivering increasing concentrations of 0.6, 1.2, and 2.4 ng/ml (TCI level 1–3) at determined intervals. The doses were based on earlier research and experience in our research group and worked well without protocol deviations. The doses were comparable to steady-state continuous infusion of 0.025 to 0.1 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and proved superior to 10 mg to 20 mg IV morphine in the acute postoperative setting.^{170,171}

Ketobemidone¹⁷² delivered by PCA device was used as standard analgesic treatment in Paper II. At the patients' own discretion, boluses of 1 mg ketobemidone with a lock-out time of 8 min (maximum of 7 mg per hour), was provided. This procedure was normal at the hospital at that time. PCA is considered to provide better pain relief for individual patients than nurse-assisted pain treatment.

The detailed pump usage history and the opioid consumption were read directly from the PCA device and stored into a computer using a program from the pump manufacturer. One patient in the pregabalin group erroneously received excessive PCA boluses and was excluded in the analysis of efficacy but was included in the analysis of side effects. Only a few participants received opioids orally in the time period investigated (0–48 h), typically 5 mg or 10 mg oxycodone. For comparisons, both intravenous ketobemidone and oral oxycodone were converted to IV morphine equivalents, which are often used to compare the analgesic effects of different compounds. However, differences exist in the literature with respect to conversion ratios, which may influence the outcomes and make comparisons across studies difficult. We used the conversion tables published in Legemiddelhåndboken.¹⁷³

Placebo

Randomized placebo-controlled studies are considered the “gold standard” in clinical trials, and placebo was used as a control in both studies. However, the use of placebo as a

comparable inactive compound is not the same as administering nothing at all. Placebo definitely has nonspecific effects that should not be neglected and is a complex phenomenon that includes psychological and neurobiological effects.¹⁷⁴ The psychological aspects reflect the participant's response to the anticipation of a noticeable treatment effect, which is also maintained by the formal research environment, observation, assessment, and doctor-patient relationship among others. Furthermore, there is evidence that the use of placebo provides neurobiological effects. This has been studied in analgesic models showing that placebo causes analgesic effects by the release of endogenous opioids.¹⁷⁵ The analgesic placebo effect may even be stronger when administered after active analgesic treatment, as may be the case in a crossover trial. In an attempt to minimize such an effect, the order of the treatments was balanced with the use of a Latin square design (Paper I).

5.1.4 Consideration of tests and measurements

Assessment of pain

Cold pressor pain

The CPT is a long-established pain test widely used in experimental pain research. In the beginning, the model was criticized because of the lack of reliability^{176,177} because the water temperature could vary considerably and thereby influence the results. Today, the model has become highly standardized using devices where temperature and water circulation are well controlled. In the experimental study, we used established equipment well-known in our research group.¹⁷⁸ The CPT has been validated as a model to investigate the analgesic efficacy of different drug classes. The CPT has showed reliable for analgesics such as opioids, paracetamol, and the anticonvulsant lamotrigine and gabapentin³³ whereas for other drugs, e.g., NSAIDs and cannabinoids, the results have been more variable. However, the drug efficacy may vary according to pain modality; e.g., NSAIDs are primarily anti-inflammatory drugs that may not affect neurogenic pain, such as cold pressor pain.¹⁷⁹ The individual differences in cold pressor pain may be explained by differences in pain sensitivity in which genetic and environmental effects are important factors, while the use of different pain rating scales seems to be less important.¹⁸⁰

In the experimental study (Paper I), pain was rated on a computerized VAS (0–100), providing a repeated registration of pain intensity during the CPT with a continuous scale with the numeric values hidden from the participants. Hence, the ratings were not easily associated with a known former numeric test result that could have influenced subsequent ratings. The first rating was given 5 sec after immersion of the hand with other ratings

recorded every 10 sec thereafter, leaving the participant time to specify the pain score. All participants, except one, endured the CPT for 2 min. Taken together, our data suggested that the CPT and the computerized pain score system were easy to use and the tests were conducted mainly without unexpected events and deviances. Our repetitive testing showed that the CPT enabled reproducible and reliable pain measurements.

Postsurgical pain

The patients in the clinical study were scheduled for laparoscopic nephrectomy, which is a highly standardized procedure. The left or right kidney was free dissected using laparoscopic techniques and then removed through a 10 cm transversal incision just above the symphysis pubis. Accordingly, the surgical intervention and tissue injury were considered to be quite equal among the participants. The surgery was performed without complications, and none of the patients required a follow-up operation. All patients were anesthetized using TIVA with propofol and remifentanyl. One patient erroneously received sevoflurane anesthesia for 90 min before changing to TIVA; however, we decided to keep this participant in the study.

Laparoscopic surgical procedures may be considered a minimally invasive surgery compared to open surgery and are associated with less postoperative pain. In two studies comparing pain intensities on the first two postoperative days in patients undergoing laparoscopic or open transperitoneal donor nephrectomy at Oslo University Hospital, Rikshospitalet, both surgical techniques were associated with relatively low pain scores^{154,181}. However, other studies measuring pain on the day of surgery and consecutive postoperative days have demonstrated moderate pain after laparoscopic donor nephrectomy.^{182,183} Thus, we considered the laparoscopic donor nephrectomy procedure in healthy donors as a suitable clinical pain model.

In the clinical study, pain was assessed at rest and during movement. In earlier research on perioperative gabapentinoids, postoperative pain was often measured only at rest and not with movement. As pain during activity is the most limiting pain to recovery and mobility after surgery, we included pain assessments both at rest and during activity in our secondary outcome variable. The pain intensities were scored on the NRS (0–10), which is intuitive and simple to use in clinical practice. The NRS has demonstrated good reliability and validity in addition to high sensitivity to changes following pharmacological interventions.¹⁸⁴ The pain intensities were measured regularly at rest and with movement at 0–48 h after surgery and corresponding with the time and expected efficacy window for the drug intervention. In

addition, pain-related sleep interference was rated in the morning at 24 h and 48 h after surgery to also include a pain outcome during the night.

Assessment of ventilatory function

Most clinical studies assessing ventilatory function focus on respiratory frequency and oxygen saturation. However, spirometry is considered to be the “gold standard” when investigating ventilatory parameters but is difficult to perform in a postoperative setting. Simplistically summarized, spirometry measures the flow or volume of inhaled and exhaled air.¹⁸⁵ In addition to respiratory frequency, tidal volume, and more sophisticated parameters such as functional vital capacity (FVC) and peak expiratory flow (PEF) can be obtained. With a built-in multi-gas analyzer, end-tidal carbon dioxide (ETCO₂) can be measured simultaneously, and ETCO₂ is a sensitive measure of drug affecting the respiratory center.

To ensure high validity and reproducibility, the device and setup were checked and approved daily. The flow sensor was calibrated before every new treatment session by skilled researchers (MM, LMP) who used a 3-L calibrated syringe and a standardized test gas (16% O₂ and 4% CO₂) for volume calibration and O₂ and CO₂ calibration.

During the test procedure, the participants were sitting in a comfortable chair in a semi-upright position. A facial mask of suitable size was carefully placed over the nose and mouth to avoid leakage. All participants tolerated the mask well and were in compliance with the test procedure.

To ensure precise collection of large amounts of data, the ventilatory measurements were directly stored into the computer. End-tidal CO₂ was chosen as the primary outcome because this variable is highly sensitive to ventilatory variations and is most often used in clinical practice. During the test periods with low respiratory frequencies, the number of ETCO₂ measurements decreased accordingly. In cases of apnea periods >15 sec and significant oxygen desaturation < 92%, the participants were asked to take a deep breath, and additional oxygen was delivered. This interfering action was only necessary a few times for safety reasons but may have influenced the test results by reducing some of the ETCO₂ values.

The subjects were connected to the system for approximately 10 min each time, and data from a stable, representative 2 min period were used for further analysis. The extracted variables (ETCO₂, MV, RF) were automatically entered into the database before the randomization code was broken.

Assessment of cognitive function

The effect of pregabalin on cognitive function was studied in both the human volunteer study and the clinical study. In the experimental study, we used the CWIT to test executive functions. The CWIT is developed from the Stroop test, considered to be more demanding by including an inhibition/switching trial in addition to the former color naming and word reading.¹⁸⁶ Each part of the test was performed in the same order and with standardized instructions read by one of the investigators (MM, LMP). The number of errors and measurements of elapsed time were recorded with a pen and stopwatch. The data collection was conducted to the best of the researchers' abilities; nevertheless, minor inaccuracies cannot be excluded because of the manual nature of this test procedure.

In contrast, computerized tests may be advantageous compared to paper tests in terms of precision, speed, and reliability. Thus, in both studies, we used the Cambridge Neuropsychological Test Automated Battery to investigate different subdomains of cognitive function. In the experimental study, the Rapid Visual Processing test was used in addition to the CWIT. More tests were considered as well; however, the time frame and the study design did not allow for more intensive testing. In the clinical study, we expanded the procedure to include six different tests. This broadened test battery investigated different subdomains of cognitive function and comprised tests on executive function, attention, inhibition, processing speed, and memory. The tests were selected in collaboration with a psychologist with good knowledge of the tests (SA). The tests were conducted either in a test room or in the patient's room on the ward. During the test procedure, only standardized instructions for use were given by one of the investigators (MM).

The outcome measurements from the neurocognitive battery were captured directly into the computer and saved for further analyses, which reduced the risk for bias. Repetitive testing may cause learning effects that influence test performance. To minimize this potential confounder, the test battery consisted of different modes, ensuring different visual stimuli for each test session. In conclusion, we consider the outcome measurements to be reliable and of high internal validity in both the experimental and clinical studies.

Assessment of incisional hyperalgesia

Incisional hyperalgesia was tested in the clinical study using a modified version of the method first described by Stubhaug et al.¹⁵⁰ Because the length of the incision varied and pain sensations could not be provoked along all five trajectories in some patients, we summed the distance from the incision to the first point of hyperalgesia along the five trajectories as a

surrogate for the degree of hyperalgesia around the incisions. The mapping with von Frey hairs was performed by one investigator only (MM).

Assessment of adverse effects

The adverse effects associated with pregabalin were studied in both the experimental and clinical studies. To document the adverse event profile of a drug or a drug combination, a considerable number of participants must be included. The two studies in this thesis were not sufficiently powered to study the side effects profile of pregabalin. However, because of the off-label use of pregabalin and its combination with opioids, the adverse effects were considered important and had to be reported. Of clinical interest is also the severity of the adverse effects, which is not very often reported in clinical trials.¹⁸⁷ In the clinical study, we assessed the mean and worst experienced adverse effects on a NRS at specific time points during the first 48 h after surgery. However, because the small study population was not sufficiently powered to evaluate these outcomes, we reported the adverse effects as incidences, which were described as the number of participants experiencing the adverse effect at least once.

The time point for assessment is important when evaluating the side effects profile of a drug.¹⁸⁷ The assessments must be performed at pharmacologically rational time points according to the drug in question. In the experimental study, the participants were asked to describe any side effects after every treatment day and, at the latest, approximately 7 h after the last drug administration. In the clinical study, we assessed the side effects in the evening on the day of surgery (21.00) and four times (09.00–13.00–17.00–21.00) during the first postoperative day. Although this method of repeated assessments comprised adequate time points to measure side effects, we cannot exclude the possibility that any side effects experienced between these time points were less accurately remembered and reported.

Long-term follow-up

In the clinical study of patients undergoing donor nephrectomy, the incidences of PPSP were explored three times during the first year after surgery using a paper questionnaire sent to the participants by mail. The patients were asked to quantify pain with an NRS at rest and during movement in the area of surgery during the last 24 h and the last 7 days, which is considered adequate for immediately assessing acute postoperative pain but also pain experienced within the last 24 h or the last week. This way of asking about pain experiences in the recent past may be less exposed to recall failure, i.e., the fact that the memory of pain may be changed over time.⁵⁹

Nevertheless, the pain intensity score is only one dimension of the pain experience, as a wide variety of other qualities characterize chronic pain. Hence, the assessment of chronic pain may require more detailed assessment than that performed in our study, e.g., other diagnostic multidimensional tools such as the Brief Pain Inventory or McGill Pain Questionnaires in addition to clinical examination in which pain sensitivity was tested to different pain modalities could have to provide a multidimensional assessment of pain and a more accurate picture of the pain condition.

We emphasize that the primary aim of the clinical study was to examine the differences in opioid consumption between the treatment groups, and the number of participants included was based on this outcome. Hence, the study was not designed or powered to investigate the effect of pregabalin on PPSP.

5.1.5 Statistical considerations

Sample size/power calculation

Sample size and power are essential when designing clinical trials and must be calculated before a study is initiated. The power of a study is the probability of detecting a statistically significant difference between two treatment groups when a difference exist, which often is set to a cutoff of 0.8. The power of a study will increase with the sample size; thus, random errors can be diminished. The cutoff level of statistical significance (P-value) is often set to 0.05 (α). The P-value is “the probability of obtaining a result at least as extreme as the observed result when the null hypothesis is true.”¹⁸⁸ The null hypothesis states that there is no association or relationship between the groups investigated. However, two different errors may occur: the possibility of obtaining a significant result and rejecting the null hypothesis, even though the null hypothesis is true (Type I error), or obtaining a nonsignificant result and retaining the null hypothesis, even though the null hypothesis is false (Type II error).¹⁸⁸

In Paper I, the sample sizes were set to provide a power of 0.80 with a two-sided P-value < 0.05 . We anticipated a mean difference of 10 in the mean pain intensity (0–100 VAS) between the treatment groups. With a power of 0.80 and assuming an SD of 8.0 for the difference and no drop outs, at least 12 participants were necessary. Twelve participants were included, and all participants completed the study without dropping out.

In Paper II, the sample size was based on a similar study on pain and opioid usage at the same institution.¹⁵⁴ A difference of 20% in opioid usage between the groups was considered clinically meaningful. With an average usage of 50 mg in the control group, an SD of 15, a two-sided $\alpha = 0.05$ and a power of 0.80, we considered 36 patients in each group to be

sufficient. To compensate for attrition, 40 patients in each group were included. For the primary outcome – the opioid-sparing effect – as well for pain assessment, 39 participants in the pregabalin group and 40 participants in the placebo group were analyzed, and the difference was considered not to significantly influence the test results. However, for the variable incisional hyperalgesia (Study II) fewer participants were assessed because of nausea and pain, leading to unequal groups and a smaller sample size, which reduced the statistical power and significance of the results.

Paper III was a secondary exploratory study based on the study population in Paper II. Again, fewer patients were assessed at 24 h after surgery because of nausea and pain, which may have affected the test results. However, as outlined earlier, exploratory designs are not required to meet a predefined sample size requirement, and the findings must be subject to further investigations in appropriately designed studies with adequate power.

Multiple testing/comparisons

Adjustments for multiple comparisons are mandatory when comparing several outcomes or repeated measurements to control for the fact that significant results happen purely by chance (Type I error). Multiple comparisons may be undertaken when comparing several treatment arms, assessing multiple endpoints, or analyzing the data in different subgroups.¹⁸⁹ The number of trials that do not perform adjustments for multiple comparisons is substantial and may lead to erroneous results and conclusions.¹⁹⁰ In contrast, statistical adjustments may increase the possibility of Type II errors, which leads to the conclusion that a supposed effect or relationship does not exist when in fact it does. Adjusting for multiple comparisons in clinical trials is much debated in the literature, and there are multiple ways of performing statistical adjustments.¹⁹¹ The Bonferroni correction is a simple and often used method that is performed by changing the α -level by the number of comparisons made (α -level/ n).¹⁶¹ Although this adjustment has been criticized for being too conservative and increasing the possibility of making Type II errors, Bonferroni correction is one of the most commonly used methods and was applied in Papers I and II to adjust for pairwise comparisons.

Paper III was considered an exploratory study because no specific hypothesis could be claimed. Exploratory studies consist of multiple outcomes without “a clear structure”¹⁹² and appropriate adjustments may not exist. Thus, in exploratory studies, it should be emphasized that the results must be confirmed in further confirmation studies with a clear hypothesis and adequate power. However, it may be prudent to add an adjustment as a supplementary

analysis to acknowledge the implications of the multiple comparisons.¹⁶¹ Several modifications of the rather conservative Bonferroni method have been developed and are increasingly used for adjustments in exploratory studies. The Benjamini-Hochberg correction is one such correction that was used in study III.¹⁹³

Missing data

Missing data are defined as data that are not complete, i.e., when planned measurements are not obtained.¹⁹⁴ The reasons for missing data could be due to equipment failure, non-responders, refusal to test, or loss to follow-up, among others. Missing values are common in clinical trials and are hardly avoidable in trials based on volunteerism. However, missing data per se may not be problematic but may greatly affect the results if not identified and handled correctly.¹⁹⁵

In Papers II and III, several patients refused hyperalgesia and cognition testing on the first postoperative day because of nausea and pain, thus challenging the completion of these outcome variables. In Paper II, the cases with missing data were handled in a traditional way, i.e., participants with incomplete data were excluded. The disadvantages of this method are the reduced sample size and loss of power, the larger standard errors, and biased effects estimates. More patients were excluded from the placebo group ($n = 12$) than the pregabalin group ($n = 5$), which may have compromised the test results. The number of missing data was clearly reported, and the results were interpreted in light of these shortcomings.

In Papers I and III, we used statistical methods that take the missing values into account. The generalized linear model (GZLM) and the mixed model (MM) are both based on the concept of missing at complete random (MCAR) and missing at random (MAR) and utilize all data in the data set, therefore providing more appropriate estimate of the treatment effect and their standard errors as long as the model is correctly specified.¹⁹⁶

5.2 Ethical discussion

General considerations

The hallmarks of medical research on individuals are respect, good consequences, fairness and integrity.¹⁹⁷ Based on these principles, the researcher should plan, design, conduct, and publicize the results of a study according to the applicable national laws (“Helseforskningsloven”).¹⁹⁸ Moreover, all research must adhere to international conventions and agreements.

Study design

In Paper I, we investigated the analgesic, ventilatory and cognitive effects of pregabalin alone and in combination with increasing levels of the opioid remifentanyl. According to the protocol design, the study was not feasible in a clinical population; thus, an experimental study in healthy volunteers was performed. To reduce the number of participants, we used a crossover design in which the number of participants required for the study was minimized. However, crossover trials may be stressful and exhausting for the participants because of the long treatment period and the increased risk for attrition. In this study, none of the subjects dropped out, indicating that the study was not too demanding. Moreover, the participants were all healthy, and the test procedures were of limited duration each study day; hence, the total burden was considered acceptable.

The studies in this dissertation were placebo-controlled studies. According to the Helsinki declaration, the use of placebo causes additional considerations; placebo should only be used when no efficient treatment is available.¹⁹⁹ Additionally, there may be an ethical dilemma to change the treatment from an effective treatment to a less effective one.¹⁵⁹ In Paper II, pregabalin or placebo was given as an add-on treatment on top of the standardized pain treatment, which included PCA opioids, steroids, paracetamol, and local anesthetics. Hence, both groups received the same robust postoperative pain treatment except for the addition of pregabalin or placebo.

Justification of the studies

The primary goal of all medical research is to progress the knowledge about the development, diagnosis, and treatment of diseases.²⁰⁰ Consequently, studies on humans are necessary and unavoidable; however, the interests and safety of each individual subject are paramount in all human studies. Furthermore, it is essential that the studies should search for new knowledge to justify the research.

Gabapentinoids were first approved for antiepileptic treatment and, later, for neuropathic pain conditions. Nevertheless, gabapentinoids are currently increasingly prescribed as “off-label” adjuvants for acute pain conditions. When planning our research, we discovered that only a few studies have investigated the analgesic effect of pregabalin in acute postoperative pain and the results were inconclusive. Furthermore, we wanted to explore the side effects with an emphasis on ventilatory and cognitive function. These potential adverse effects have not been investigated previously and would provide valuable information about the use of pregabalin alone and in combination with opioids. To study these relatively

unknown adverse effects of gabapentinoids, both experimental and clinical human studies were considered necessary.

Advantages, disadvantages and safety for the participants

In the experimental study, the participants received opioids and pregabalin without experiencing pain qualifying for medical treatment only for the sake of the study. Opioids are potentially dangerous and addictive medications, and the administration of opioids to healthy young volunteers may be ethically questioned. However, it is our experience that the professional and technical approach of the research does not promote the feeling of being “high” or qualify as an adventurous setting. Importantly, the participants may experience ventilatory depression with increasing rates of opioid administration, which is one of the most feared side effects in the postoperative setting. Furthermore, unnecessary medication with pregabalin and opioids could also cause troublesome adverse effects, such as sedation, nausea, vomiting, headache, and visual disturbances, subsequently requiring medical treatment.

In Paper I, the pain response to the CPT was evaluated. The CPT causes intense, dull-aching pain, which steadily increases and may become unbearable for the participants. However, the participants were allowed to remove the hand out of the water if the pain became intolerable, providing the participants with an escape whenever needed. The participants were provided with an intravenous cannula that possibly, although unlikely, could cause phlebitis and the need for antibiotics. On the other hand, the participants were able to learn more about the research fields at Oslo University and develop insight into how a clinical study may be performed. Furthermore, they received information about the drugs and the study question. Equally, the participants in the clinical study were exposed to pregabalin, which could increase the abovementioned troublesome adverse effects such as sedation, dizziness, nausea, and visual disturbances. The participants also underwent additional clinical and cognitive testing during the hospital stay, which may have been perceived as additional stress and burden. Furthermore, the participants were asked to answer several questionnaires during and after their hospital stay. In contrast, all patients received standard analgesic treatment during the study and equally good or superior follow-up with an anesthesiologist and a nurse with respect to postoperative pain management and antiemetic treatment. The close follow-up also allowed the participants to ask other questions or discuss problems related to the treatment. Finally, fewer and milder complaints could lead to shorter hospital stays.

One of the cornerstones in all human research is to protect the participants and minimize harm. The participants in both studies were closely monitored, and side effects were reported regularly and, if required, treated according to the study protocol. Detailed plans for the treatment of adverse events were known to all the investigators, and all types of devices and resuscitation drugs were available if needed. Both studies were conducted in close relationship to the intensive care unit at Oslo University Hospital with anesthesiologist and intensivists on call. The randomization lists were kept in the immediate vicinity if unblinding became necessary.

Informed consent

Clinical research in humans is based on volunteerism, and, as a main rule, the participants have to give their written consent before enrollment in the study. The participants are within their own rights to withdraw their consent at any time point.¹⁹⁷

The experimental study was announced on the website of the University of Oslo. Interested subjects were invited to an information meeting where information about the study was provided by one of the main investigators (MM). If subjects were further interested in participating, they were provided with written and explicit information about the study and asked to read the information thoroughly. Information about the study was given at least 24 h before the start of the trial to allow for sufficient time to make a decision and to ask questions about the study.

In the clinical study, the participants were recruited among patients scheduled for donor nephrectomy. Thorough oral information about the study was given by one of the main investigators (MM), written information was provided for perusal. The information was given 1–2 days before surgery to allow the participant time to consider whether he or she wanted to participate and to discuss the study with relatives if desirable. In both studies, the volunteerism of participating was emphasized, and the opportunity to withdraw from the studies at any time point, without any reason or without any consequences, was clearly stated.

Data protection

All data were treated according to the data protection policy of Oslo University Hospital. The studies were registered in the public available data base for research studies at the hospital.

Economic independent research

Medical research is based on volunteerism, and consent to participate must be given. It is most important that the participants do not feel any type of gratitude debt to the researchers or the research institution when giving their consent to participate in the study, and payment should not be a reason for participating in clinical trials. However, there is general agreement to compensate the subjects for travel expenses and loss of earnings.¹⁹⁷ The participants in the experimental study received NOK 120 per hour paid as a gift card to a total of NOK 2000.

All studies were conducted without financial support from the medical industry, and the study medication was manufactured in the hospital pharmacy. The studies were financed by the scholarship of one of the main investigators (MM) and economic support from Inven2, a nonprofit research organization owned by Oslo University Hospital.²⁰¹

Publication

The researchers have the main responsibility to not only conduct the study according to ethical standards but also publish the results of the study and make the research results available to the public. Interestingly, about half of all research is not published; much of which presents negative or inconclusive results.²⁰² If made available, the unpublished trials could influence further research, inclusive research fields and research questions as well as contribute to meta-analyses on the research field. Papers I—III are all published in peer-reviewed journals and have been presented as abstracts and speeches at pain conferences.

5.3 Discussion of results

During the work with this thesis, the analgesic and opioid-sparing effects of pregabalin have been investigated in numerous preclinical and clinical studies. The exact mechanisms of the analgesic effect of gabapentinoids are still not clear, although animal and preclinical human studies have led to increased knowledge about the site and mechanism of action. To date, pregabalin has been used for postoperative pain treatment in various surgical fields; however, the analgesic efficacy substantially varies among single studies, the types of surgery, and drug dose administered, and the optimal treatment duration has not been elucidated.

5.3.1 Analgesic effects

In the experimental study in healthy volunteers, we found that pregabalin alone had a small but detectable analgesic effect, while remifentanyl increased analgesia in a dose-dependent manner. Moreover, co-administration of pregabalin and remifentanyl exerted

additive analgesic effects. The additivity was consistent with increasing levels of remifentanyl infusion and was equal to the theoretical sum of the individual drug effects of pregabalin and remifentanyl (combination – calculated sum; $P = 1.0$).

Experimental human pain models may be ideal to investigate the effects of drug combinations and may serve as a bridge between preclinical and clinical studies. In a study by Eckhardt et al,¹⁰² 600 mg gabapentin in combination with oral 60 mg morphine (controlled release) significantly increased the pain tolerance by 76% compared to 41% with morphine + placebo. However, gabapentin alone did not increase the tolerance to cold pressor pain compared to that of placebo. The diverging results of this study compared to ours may be explained both by the use of different drugs (even if they were both gabapentinoids) and by the different methods of pain assessment. In this previous study, pain tolerance was used as a pain outcome, defined as the maximum time the participant tolerated a specific stimulus in a given situation. Pain tolerance is a single measure that may be biased by time, pain intensity, and a separate endurance factor not associated with pain intensity.^{14,203} In Paper I, we used an automated VAS to measure pain intensity during the CPT, which may be a better way of assessing the increasing pain perception. Others have argued that not one single pain model but multiple experimental pain models should be used when investigating the efficacy of new analgesics. Accordingly, Okkerse et al²⁰⁴ found that pregabalin increased the pain tolerance threshold compared to placebo in cold pressor pain, mechanical pain, and electrical pain by 46.4%, 14.1%, and 10.8%, respectively, whereas the pain detection threshold increased by 4.1% in normal skin heat pain.

Although the experimental study design may reduce biases and confounding factors present under clinical conditions, new analgesics also have to prove their utility in clinical studies. Thus, in a clinical postoperative trial (Paper II), we investigated the analgesic effect of 300 mg pregabalin daily in combination with a robust multimodal pain regime over two consecutive days. Although our results showed numerically lower NRS scores in the pregabalin group, the results could not significantly demonstrate that pregabalin reduced pain intensity at 0–48 h after surgery. However, the analgesic effect of pregabalin alone may be difficult to measure when using the PCA method. Before surgery, patients were instructed to use the PCA device when their NRS score was ≥ 3 ; thus, we expected relatively low pain scores independent of the treatment group during the postoperative period. Consequently, we decided not to use postoperative pain as the main efficacy variable in the clinical study.

The insignificant difference in pain intensity scores between groups is in concert with many studies investigating the analgesic efficacy of gabapentinoids. In a recent, well-

designed, large study by Lunn et al,²⁰⁵ 274 patients scheduled for total knee arthroplasty received 1300 mg/d or 900 mg/d gabapentin as an adjunct to multimodal analgesia consisting of slow release acetaminophen, celecoxib, and opioids. The results did not show any analgesic advantage of adding gabapentin compared to adding placebo. One important reason for the lack of analgesic effects, as pointed out by Dahl et al,²⁰⁶ may be the use of a robust multimodal pain treatment administered to all patients. In comparison to studies investigating gabapentinoids as monotherapies, it may be difficult to demonstrate additional analgesic effects when gabapentinoids are added on the top of 3–4 other analgesics, as was the case in the study by Lunn et al and in our clinical study. We also measured pain-related sleep interference during the first two nights after surgery and observed significantly less interference in patients treated with pregabalin. The results are in line with earlier findings, and may suggest the analgesic effects of gabapentinoids in the early postoperative period.^{110,205} Another explanation for the reduced pain-related sleep interference may be the well-known sedative effects associated with gabapentinoids, which have been stated in earlier studies.

Nevertheless, other studies reported reduced pain scores in the early postoperative period.^{207,208} In a study in patients undergoing laparoscopic sleeve gastrectomy, compared to placebo, 150 mg pregabalin reduced pain at rest 24 h after surgery.²⁰⁹ In another study by Mathiesen et al,¹¹⁴ 300 mg pregabalin and 1 g paracetamol every 6 h combined with 8 mg dexamethasone reduced VAS-pain scores at rest and during swallowing after tonsillectomy.

Multiple clinical studies investigating perioperative gabapentinoids have been assessed in several recent meta-analyses and systematic reviews.^{168,210-213}

In a meta-analysis by Eipe et al, the authors proposed a “model specific” approach across various types of surgeries by dividing the surgery into “pronociceptive” (acute hyperalgesia) and “non-pronociceptive” procedures.²¹⁰ A small analgesic advantage of pregabalin and its opioid-sparing effect was found only in surgeries associated with a “pronociceptive” mechanism, including surgeries on spine, joint and amputations but especially not in abdominal surgeries. However, the meta-analysis was later criticized because of a lack of evidence-based methodology and the statistical procedures used.²¹⁴ The failure of perioperative pregabalin to elicit an analgesic effect in abdominal surgery was not confirmed in a recent meta-analysis by Mishriky et al.¹⁶⁸ In this meta-analysis, reduced pain scores were found in resting patients who underwent open abdominal, head or neck surgeries, while pain during movement was reduced in open abdominal, orthopedic and cardiac surgeries. During the last few years, increasing attention has been paid towards procedure-specific pain

management (PROSPECT),²¹⁵ and meta-analyses of specific surgical procedures have emerged. Several meta-analyses investigated the analgesic efficacy of pregabalin in abdominal studies, showing reduced pain intensity 24 h after laparoscopic cholecystectomy and gynecological surgery.^{211,216} However, other authors have claimed that the analgesic efficacy of gabapentinoids is determined by the experienced pain intensity and not by the type of surgery per se.²¹²

Pain is a multidimensional experience, and other factors, such as anxiety or depression, may significantly affect pain perception during the postoperative period. Pregabalin has demonstrated anxiolytic effects and is approved for the treatment of general anxiety disorders and significant perioperative anxiolytic effect has been suggested.^{217,218} We did not measure anxiety in our studies, which could be criticized. However, in a study using midazolam, an even stronger anxiolytic than pregabalin, no significant difference in pain intensity was demonstrated.²¹⁹ Furthermore, we did not measure depression; however, the participants in Paper I, were healthy young volunteers without known comorbidities, while the participants in Paper II were thoroughly examined mentally and physically to qualify as organ donors. Thus, preoperative depression affecting the pain intensity scores seems unlikely.

In conclusion, our experimental and clinical studies support that gabapentinoids may exert a small analgesic effect in acute postoperative pain. However, a consistent level of improved analgesia during the first 24 h after surgery and the dose and duration of the treatment, are not settled.

5.3.2 Opioid-sparing effects

The opioid-sparing effect is often used as primary outcome and as a proxy for analgesic efficacy in studies investigating gabapentinoids. Both studies in this thesis indicated opioid-sparing effects; in the experimental study, comparable analgesia was achieved with approximately 50% less remifentanyl when pregabalin was added to increasing levels of remifentanyl. Furthermore, pregabalin significantly reduced opioid consumption compared to placebo 0–48 h after surgery when added to a multimodal pain regimen. The difference was most evident during the first 24 h, reducing the opioid requirement by a mean of 10.5 mg (39%) in the pregabalin group.

The opioid-sparing effect observed in our studies is in accordance with other randomized controlled trials.²²⁰⁻²²³ In a study in patients undergoing transperitoneal nephrectomy, a single preoperative dose of 300 mg pregabalin significantly reduced the cumulative 48 h opioid consumption after surgery from 77 mg in the placebo group to 52 mg

in the pregabalin group.²²⁴ Furthermore, opioid-sparing effects were also found 24 h after surgery in patients undergoing laparoscopic sleeve gastrectomy and cholecystectomy.^{209,225} In contrast to these results, other studies could not confirm the opioid-sparing effects of pregabalin.^{115,117,226}

Similar to the pain measurements, the opioid-sparing effects of the gabapentinoids have been investigated in several meta-analyses. In the meta-analysis by Eipe et al,²¹⁰ pooled data across various surgeries showed that pregabalin reduced opioid consumption by 16% [95% CI 9 – 21] after surgery compared to placebo group. Furthermore, Mishriky et al showed that pregabalin reduced opioid consumption at 24 h by -8.27 mg [95% CI -10.08 to -6.47] across all types of surgery except for minor procedures and surgeries in the neck and head.¹⁶⁸ Additionally, in a comparable meta-analysis on postoperative gabapentin, Doleman et al found reduced opioid consumption by -8.44 mg [95% CI 7.26 to 9.42] 24 h after surgery.²¹² However, this meta-analysis has been criticized because it included all studies regardless of trial bias risk and did not focus on harmful side effects.²²⁷ Thus, in a recent meta-analysis, Fabritius et al²²⁷ graded single studies on postoperative gabapentin according to risk of bias and found that the studies with low risk could not confirm a clinically meaningful opioid-sparing effect 24 h after surgery, which was predefined as more than 5 mg morphine.

An effective pain treatment may be defined as a treatment leading to less opioid consumption, although the use of opioid consumption as an outcome variable has been debated. It has been argued that equal pain intensity in the treatment groups at a certain time point after surgery is a prerequisite for using opioid consumption as a measure of analgesic efficacy.²²⁸ In our clinical study, the pain intensity scores 0–48 h after surgery were equal among the groups, indicating that the PCA-treatment algorithm and the instruction for its use worked well. Thus, the lower opioid consumption observed in the pregabalin group must be considered relevant, indicating the opioid-sparing and analgesic effects.

Other factors influencing upon opioid consumption have been discussed. The side effects of the drugs included in a multimodal treatment may cause sedation and motor and cognitive impairments, which may influence the use of the PCA device.¹¹⁰ Additionally, patients who are intolerant to opioids may suffer from opioid-induced side effects such as nausea and vomiting, resulting in less opioid consumption even though their pain scores are still high. In our clinical study, the incidence of nausea was lower in the pregabalin group, while the differences in sedation were nonsignificant, which does not explain the lower opioid consumption in the pregabalin group 0–48 h after surgery. However, the cognitive impairments observed in the pregabalin group may have affected the frequency of PCA usage.

Our clinical study may be criticized for its lack of novel discoveries; however, it may provide some valuable information regarding patients receiving pregabalin in combination with opioids and as part of a multimodal pain regimen after laparoscopic abdominal surgery. We consider both studies to be well designed in investigating the opioid-sparing and analgesic effects of pregabalin, and the studies were conscientiously conducted. In contrast with many postoperative studies, we recorded pain intensity at rest and during movement as well as the cumulating opioid consumption. Some authors have suggested combining the pain scores and opioid consumption by constructing a composite score as a proxy for both effects.²²⁹ However, this method may not necessarily provide additional information and may be more difficult for clinicians to interpret compared to NRS scores and milligrams of opioid consumption.²³⁰

In conclusion, the opioid-sparing effect of pregabalin observed 0–48 h after surgery together with the numerically lower pain scores and the reduced pain-related sleep interference must be considered an analgesic effect. The results were also supported by the experimental study showing both the analgesic effect of pregabalin alone and the additive analgesic effect when combined with remifentanyl.

5.3.3 Ventilatory effects

Although there is increased focus on the potential side effects of pregabalin, its effects on ventilation have been poorly investigated. In a case series by Eipe et al,²³¹ the use of pregabalin for postoperative pain treatment was associated with significant respiratory depression in three postsurgical patients. The patients were all suffering from comorbidity, and the authors proposed that pregabalin may enhance sedation and thus the respiratory depressive effect in vulnerable patient groups such as patients with obstructive sleep apnea, renal failure, and head trauma as well in patients taking other medications. In our experimental study, pregabalin potentiated the respiratory depressive effect of remifentanyl in healthy young volunteers. The respiratory depression was not investigated during assessment of pain stimuli, which could have increased the respiratory drive mimicking clinical conditions. Nevertheless, postoperative pain in the clinic is most often effectively relieved by the use of analgesics to achieve predefined goals of pain treatment. In a retrospective study by Weingarten et al, the respiratory effects of long-acting analgesics were investigated in patients undergoing joint arthroplasty. Respiratory depression was defined by three clinical symptoms: hypoventilation, hypoxemia, or pain/sedation-mismatch. The results revealed that preoperatively administered gabapentin (>300 mg) and long-acting oxycodone (>10 mg) were

significantly associated with respiratory depression in the post anesthesia care unit (PACU).²³² In another retrospective study published by the same research group in patients undergoing major laparoscopic abdominal procedures, 153 out of 1000 patients experienced respiratory depression when receiving gabapentin (odds ratio [OR] of 1.47 [95% CI 1.22–1.76]).²³³ The incidence was highly associated with older age, increased doses of intraoperative opioids, prolonged stay in the PACU, and increased rate of readmission to a level of higher care. In the abovementioned studies, respiratory depression was studied using respiratory frequency, oxygen saturation, naloxone administration, and failure to extubate, among others, as outcome variables. In contrast to these somewhat observer-dependent and subjective symptoms, we used spirometry, which is considered the gold standard for respiratory evaluation and measures parameters of high accuracy, such as tidal volume, respiratory frequency, and exact ETco₂ measurements, all of which are highly sensitive to respiratory changes.

Interestingly, although in a completely different population, a Finnish group found that pregabalin was frequently involved in medico-legal death cases (2.3%). Nearly half of the deceased pregabalin cases were drug abusers, and >90% of those abused opioids. The authors proposed that pregabalin, especially in combination with opioids, may exert benzodiazepine-like properties causing central nervous system depression and, consequently, respiratory failure and death.²³⁴ The increased sedative effect and subsequent impaired ventilatory function of combinations including benzodiazepines and opioids have also been demonstrated in clinical studies.²³⁵ Although the safety profile of older analgesics is well known, the potential harmful and unintended ventilatory effects of gabapentinoids have not been adequately investigated.¹⁸⁷ In summary, increased vigilance is warranted when pregabalin is combined with other analgesics or sedatives during postoperative pain management.

5.3.4 Cognitive effects

Prevention of perioperative cognitive decline is important to reduce morbidity and enhance postoperative recovery and rehabilitation.²³⁶

Older anti-epileptic drugs have well-known and untoward cognitive effects.²³⁷ The newer gabapentinoids have also been associated with significant central nervous system adverse effects including sedation, dizziness and diplopia. Despite of that, the cognitive effects of perioperative gabapentinoids have not been investigated.

Earlier, the cognitive effects of pregabalin have been studied in a few trials composed of healthy volunteers showing reduced performance in tests assessing arousal and attention but

no impairments in psychomotor effects.²³⁸ Furthermore, in a trial using pregabalin as an add-on for the treatment of refractory partial epilepsy, reduced verbal and visual episodic memory was observed after administration of 300 mg pregabalin compared to treatment with levetiracetam alone.²³⁹ Long-time treatment with pregabalin has also been associated with subjective neurotoxic complaints.²⁴⁰ Our experimental and clinical results are in line with these findings. In the experimental study (Paper I) the test on executive functioning (using CWIT) impaired significantly when pregabalin was added to high-dose remifentanyl compared to remifentanyl alone. In the postoperative study, pregabalin impaired executive functioning including visuospatial working memory and inhibition compared to placebo. However, we did not measure the patients' self-reports on cognitive function, which would have supplemented our data and provided valuable information.

What does impaired executive function mean in clinical practice? The tests measuring visuospatial working memory and strategic choices (Paper III) are sensitive for deficits in the neural circuitry affecting the frontal lobe²⁴¹ which are essential for managing everyday tasks like handling medications and thus, adhere to treatment prescriptions.²⁴² The test-results also indicated reduced inhibitory functions in patients receiving pregabalin. The corresponding neuroanatomical structures are proposed to be sited in the fronto-striatal network and may be responsible for goal-directed and habitual inhibition across motoric and non-motoric domains. Deficits in this area may increase ataxia and the risk of falling in the postoperative period.^{243,244} In a systematic review and meta-analysis investigating the adverse effects associated with long-term use of pregabalin, impaired coordination and cognition were the most common side effects, leading the authors to the conclusion that pregabalin may influence both vestibulocerebellar- and brainstem structures as well as higher cortical functions resulting in balance disorders and risk of falling.²⁴⁵

Research have indicated that pain and cognitive functioning may interfere through actions on the same neuroanatomical and neurochemical structures.²⁴⁶ Also, cognitive processing is dependent on multiple neurotransmitters such as glutamate and its interaction with the NMDA-receptor which is essential for memory and learning.^{246,247} Thus, analgesics may affect cognition by interaction on the same structures causing treatment-related cognitive impairment. Gabapentinoids act both on spinal and supraspinal levels by dampening the release of excitatory neurotransmitters and activate noradrenergic descending pathways.^{96,248} In line with this, there are reasons to believe that the gabapentinoids may affect cognitive functions *de novo* or impair already existing cognitive dysfunction.²⁴⁶ Generally, analgesics have shown inconsistent effects on cognition,²⁴⁶ and the evidence that opioids cause

postoperative cognitive changes are limited²⁴⁹ although a few studies have demonstrated impaired attention, working- and visual memory.^{250,251}

However, multiple factors may be associated with impaired cognitive performance during the postoperative period; premorbid cognitive performance, education, age, and increased preoperative pain are all factors associated with postoperative cognitive decline.^{236,252} Furthermore, certain types of surgery, especially non-cardiac major surgery and cardiac surgery, are recognized as risk factors for postoperative cognitive decline²⁵³ and lately, systemic inflammation and the following neuro-inflammatory response are thought to play a role in cognitive impairment. Also, preceding delirium may increase the incidence of long-term cognitive decline as showed in a recent study in patients undergoing cardiac surgery.²⁵⁴

Generally, the investigation of postoperative cognitive changes has been hampered by the lack of definitions of postoperative cognitive decline. Additionally, there are a wide variety of numbers and types of cognitive tests used, differences in the criteria for cognitive changes and time periods for assessments. Recently, a recommendation for the 2018 Nomenclature of Cognitive Change Associated with Anesthesia and Surgery was published with the goal of clarifying the nomenclature and diagnostic criteria in the field of cognitive changes after anesthesia and surgery.²⁵⁵ This new classification is welcomed, and may simplify future research and comparisons between studies.

In conclusion, our findings showed that pregabalin alone and in combination with opioids may negatively affect subdomains of cognitive function. The clinical implications of our findings need further elaboration.

5.3.5 Hyperalgesia

There is increasing evidence that central sensitization plays an important role in acute pain after surgery.²⁵⁶ Sensitization of peripheral nociceptors and dorsal horn neurons may manifest as primary and secondary hyperalgesia, respectively. Hyperalgesia in relation to inflammation and opioids (opioid-induced hyperalgesia) may intensify painful stimuli.^{89,257} Additionally, hyperalgesia induced by an incision is associated with increased acute pain, as demonstrated in animal and human models.^{37,258} Gabapentinoids act by inhibiting the influx of calcium through Ca channels in the dorsal root, thus reducing the exaggerated release of excitatory neurotransmitters, which may cause central sensitization. The gabapentinoids has demonstrated antihyperalgesic properties in preclinical studies.²⁵⁹⁻²⁶¹ In an experimental study in healthy volunteers receiving 300 mg pregabalin over a 6-day period, pregabalin

significantly reduced electrical hyperalgesia compared with aprepitant.²⁶² Additionally, gabapentin reduced brush allodynia but not pinprick hyperalgesia in a human capsaicin-evoked pain model.²⁶³ However, it has been challenging to translate the findings in animal and preclinical pain models into clinical postsurgical trials. In one study of patients undergoing hip arthroplasty, the antihyperalgesic effect of pregabalin, ketamine and their combination was explored.²⁶⁴ Ketamine significantly reduced secondary hyperalgesia provoked by pinprick stimulation while pregabalin alone did not. Additionally, the combination of pregabalin and ketamine did not diminish the area of secondary hyperalgesia significantly compared with ketamine alone. In contrast, pregabalin has showed reduced remifentanyl-induced area of hyperalgesia in patients undergoing laparoscopic urologic surgery.²⁶⁵

Incisional hyperalgesia was tested after nephrectomy in our clinical study, and the results indicated a significant reduction in incisional hyperalgesia in the pregabalin group compared with the placebo group 24 h after surgery, while there was no difference between the treatment groups at hospital discharge 4–6 days after the last drug administration. In a comparable study in patients undergoing transperitoneal nephrectomy, compared with placebo, a single dose of 300 mg pregabalin reduced secondary hyperalgesia 48 h after surgery in a borderline manner ($p = 0.0497$). However, the study was small with 13 patients in each group and was considered by the authors to be underpowered for this secondary outcome.²²⁴

In summary, only a few studies have investigated the antihyperalgesic effect of pregabalin in acute postsurgical pain, and the evidence that gabapentinoids reduce incisional hyperalgesia remains limited.

5.3.6 Adverse effects

The increased use of gabapentinoids for postoperative pain has led to more attention on the associated adverse effects of these drugs.^{187,266} The primary aim of adding gabapentinoids to a multimodal pain regimen to minimize opioid use is of limited value without simultaneously reducing opioid-related side effects.²⁶⁷ Increased adverse effects may hamper recovery and prolong hospital stay. In line with this acknowledgment, the importance of the precise reporting of the adverse effects in clinical trials has been emphasized.^{187,268}

Two of the most prominent side effects of perioperative pregabalin are increased sedation and dizziness.^{168,210} In our experimental study in healthy volunteers (Paper I), more subjects reported sedation (75%) and dizziness (75%) with pregabalin than with placebo (42%

and 25%, respectively). Remifentanyl alone caused increased sedation and dizziness, while the combination of pregabalin and remifentanyl only showed minor differences compared to remifentanyl alone. In the clinical study of patients undergoing laparoscopic nephrectomy (Paper II), the incidence of sedation was equal between the groups. This was somewhat surprising, but one reason may be the concomitant administration of steroids, which may diminish the sedative effect of pregabalin as suggested in another trial that combined pregabalin and steroids for postoperative pain management.¹¹⁴

In Paper II, the incidence of nausea and the need for antiemetics were equal between groups 0–24 h after surgery, even though more opioids were administered to the placebo group. The nonsignificant result may be because all patients received PONV-prophylaxis containing steroids, ondansetron, and droperidol at the end of surgery. However, during the next 24–48 h, significantly more patients in the placebo group experienced nausea and the need for antiemetics, which may be explained by the higher total opioid consumption in the placebo group within the first 48 h after surgery. The lower incidences of postoperative nausea in patients treated with pregabalin are in concert with multiple studies and meta-analyses.^{168,210}

In addition to the well-known side effects of pregabalin, its more uncommon side effects such as vision disturbances and confusion have been recognized.^{168,269} In our experimental pain study, diplopia was registered in one patient receiving pregabalin alone and in five patients receiving remifentanyl alone. The combination did not increase the incidence of visual disturbances. In the clinical study, one patient in the placebo group and three patients in the pregabalin group experienced diplopia. On one occasion, the study drug (pregabalin) was not administered because of this disturbing side effect. A recent meta-analysis showed that per 1000 patients treated with pregabalin, 10 and 41 more patients experienced blurred vision and sedation, respectively, than those not administered pregabalin.²¹⁰ In another meta-analysis, pregabalin was associated with increased incidences of sedation (46%), dizziness (33%), and blurred vision (3.5 times more likely) compared to those of placebo.¹⁶⁸ The same side effects have been demonstrated in the use of gabapentin for postoperative pain.²¹²

The importance of an exhaustive assessment of side effects may be even more essential in novel agents developed primarily for other indications than what they are actually being used for. In a systematic review and meta-analysis,¹⁸⁷ the authors concluded that adverse events are often inadequately assessed, and in 17–18% of the studies investigating newer postoperative analgesics, the method of assessment of the adverse events was not described. Additionally, nine percent of the studies did not report adverse events at all, and only a

minority of studies assessed serious adverse events. Poor reporting was confirmed in a recent meta-analysis investigating the benefits and harms of perioperative pregabalin, showing an increased incidence of serious adverse events in patients treated with pregabalin, especially in patients treated with more than one dose of pregabalin.²¹³ However, only 22 out of 97 included trials reported serious adverse events, thus, limiting the reliability of the results.

General problems when investigating the side effects of gabapentinoids are a small cohort size, incomplete reporting, short follow-up period, and insufficient or missing reports on serious adverse events.²²⁷ In addition, a wide variety of multimodal pain regimens are used, making comparisons between the treatments difficult. Consequently, potential side effects may be inadequately investigated, and as meta-analyses mirror the studies included, the results may be flawed. Our studies were not powered to investigate the side effects of pregabalin. However, our results provide additional information on the side effects profile of pregabalin and may add power to meta-analyses in the future. However, more and larger studies that investigate the side effects profile of pregabalin are warranted.

5.3.7 Long-term follow-up

Many patients experience prolonged pain after surgery, causing suffering and reduced quality of life.³⁸ The etiology of PPSP still has to be elucidated, but preoperative pain and acute postoperative pain are considered contributing factors. Thus, initiatives to reduce the establishment of PPSP include optimal perioperative pain treatment to prevent the transition from acute to chronic pain after surgery.

The efficacy of gabapentinoids for PPSP is debated, and trials are showing mixed results. In a study by Buvanendran et al pregabalin twice daily over 14 days reduced the incidence of chronic neuropathic pain at 3 and 6 months after knee arthroplasty.¹¹⁰ Additionally, reduced pain intensity was observed 3 months after cardiac and spinal surgery,^{270,271} while other trials could not confirm this positive effect.²⁷² A recent systematic review and meta-analysis including 18 studies could not demonstrate any significant advantageous effect of pregabalin in chronic persistent pain at 3, 6, and 12 months after surgery.²⁷³ Importantly, the meta-analysis included 60% unpublished studies, corresponding to 79% of the patients, indicating that studies reporting positive results are more easily published than those reporting negative results.

In Paper II, we performed a follow-up study on PPSP at 6 weeks, 6 months and 12 months after surgery. Our results showed no differences in patient-reported pain scores between the pregabalin and placebo groups at any time point. However, it is important to

emphasize that the study was not designed or powered for this outcome; hence, the results do not allow for any conclusions concerning the efficacy of pregabalin on PPSP. However, the results may be used in systematic reviews and meta-analyses in the future. In conclusion, the efficacy of gabapentinoids on PPSP remains unclear, and evidence supporting the recommendations of their routine use is lacking.

6 CONCLUSIONS

Experimental pain model

6.1 Analgesic effects

Pregabalin exerted mild analgesia in a cold pressor pain model in healthy volunteers. Remifentanyl showed dose-dependent analgesic effect. The combination of pregabalin and remifentanyl significantly increased the analgesic effect compared to remifentanyl alone, showing additive analgesic effects of pregabalin at all TCI-levels.

6.2 Ventilatory effects

Pregabalin caused no respiratory depressive effect. Remifentanyl showed dose-dependent ventilatory depressive effect. The combination of pregabalin and remifentanyl significantly increased ventilatory depression compared to remifentanyl alone, demonstrating that pregabalin potentiated remifentanyl-induced ventilatory depression.

6.3 Cognitive effects

Pregabalin impaired tests measuring executive functioning and remifentanyl reduced processing speed. The combination of pregabalin and remifentanyl significantly impaired all tests compared to placebo and the combination affected all tests numerically more extensively compared to each single drug alone.

Post-surgical pain model

6.4 Effects on opioid consumption

Perioperative pregabalin administered as part of a multimodal pain treatment significantly reduced opioid consumption 0–48 h after surgery compared to placebo.

6.5 Analgesic effects

Perioperative pregabalin administered as part of a multimodal pain treatment did not significantly reduce pain intensity at rest or with movement 0–48 h after surgery compared to placebo.

6.6 Hyperalgesic effect

Perioperative pregabalin decreased incisional hyperalgesia significantly 24 h after surgery, but not 4–6 days after surgery compared to placebo.

6.7 Adverse effects and effects on PPSP

Perioperative pregabalin reduced nausea and use of antiemetics 24–48 h after surgery compared to placebo. Pain-related sleep interference was reduced with pregabalin the first two nights. There were no significant differences between pregabalin and placebo in persistent post-surgical pain 6 weeks, 6 and 12 months after surgery.

6.8 Cognitive effects in a surgical population

Pregabalin significantly negatively affected subdomains of executive functioning 24 h after surgery compared to placebo, including working memory and inhibition measured through neuropsychological tests.

7 CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

7.1 Clinical implications

Our studies give some support for use of pregabalin as part of multimodal pain management since we found opioid-sparing, analgesic effect and reduced postoperative hyperalgesia, sleep-interference and nausea. However, our studies also revealed potential serious side effects when pregabalin was combined with opioids, showing potentiating of opioid-induced ventilatory depression and cognitive impairments. Importantly, our studies were performed in healthy volunteers and a healthy, relatively young surgical population thus, the negative side effects observed in our studies may be more pronounced in older patients with increased comorbidity. In addition we lack knowledge about optimal timing and treatment length.

Our findings question the overall benefit of the perioperative use of pregabalin. Thus, the routine use of pregabalin for early postoperative pain cannot be supported based on the present available evidence.

7.2 Research implications

Our experimental study successfully documented an analgesic effect of pregabalin, a dose-dependent analgesic effect of the opioid remifentanyl and an additive effect when the drugs were combined. In addition, the study set-up allowed reliable ventilatory measurements. Thus, the experimental set-up can be recommended for studies of other drug combinations. Our results showing a potentiation of the ventilatory depressive effects of remifentanyl when pregabalin was administered together with remifentanyl are new and should be further investigated in a clinical setting. Well-designed prospective placebo-controlled clinical studies are warranted in the future to elucidate the ventilatory effects of pregabalin in combination with opioids. The use of spirometry and multi-gas-analyses, which provides accurate measurements on both respiratory and ventilatory functions, should be encouraged in this type of postoperative clinical research. Furthermore, the cognitive effect of pregabalin should be further investigated when used in acute and chronic pain management. Our exploratory secondary study in a healthy surgical population needs replication before any firm conclusions can be drawn, and our results may serve as a basis for the hypothesis in future research.

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Errata

Name of candidate: Marianne Myhre

Title of thesis: Analgesic, ventilatory, and cognitive effects of pregabalin and opioids

Studies in healthy volunteers and kidney donors

Abbreviations for different types of corrections:

Cor – correction of language

Page	Line	Original text	Type of correction	Corrected text
21	25	...sedating gents, ...	Cor	...sedating agents, ...
29	27	The O2 capnography, ...	Cor	The capnograph, ...

The following original references are corrected (from – to):

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