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- clinical and pharmacological aspects

Doctoral Thesis

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Optimalisering av opioidbehandling ved kreftsmerter -kliniske og farmakologiske aspekter

Smerter er det hyppigste og mest fryktede symptomet hos pasienter med kreft og deres pårørende. 80 % av pasienter med langtkommet kreft opplever smerter. Selv ved behandling med sterke smertestillende medikamenter som morfin eller oksykodon (opioider), er det hele 10–30 % som opplever smerte og/eller uakseptable bivirkninger. Hos disse pasientene er det et alternativ å bytte til et annet opioid som metadon, men det er i dag begrenset kunnskap om hvordan et slikt bytte bør foregå. En annen utfordring er at mange kreftpasienter opplever plutselige episoder med intense smerter av relativt kort varighet, såkalte gjennombruddsmerter. For å oppnå tilfredsstillende behandling av gjennombruddsmerte trengs smertestillende medikamenter som virker raskt, og har kort virketid for å unngå unødige bivirkninger.

Målene med denne avhandlingen var 1) å sammenlikne om det å bytte fra morfin/oksykodon til metadon «over natten» (stopp-og-start-metoden) hos kreftpasienter med smerter/bivirkninger er mer effektivt og sikrere enn et gradvis bytte over tre dager (3-dagers-metoden) og 2) å finne mer grunnleggende kunnskap om et nytt mulig medikament for gjennombruddsmerter: opioidet fentanyl gitt som nesespray.

42 kreftpasienter ble randomisert ved fire sykehus i Norge til å bytte til metadon ved stopp-og-start-metoden eller 3-dagers-metoden. Metadondose ble beregnet i forhold til tidligere dose morfin eller oksykodon. Smerteintensitet, bivirkninger og alvorlige hendelser ble registrert i 14 dager etter byttet. Opioidkonsentrasjoner i blodet ble også målt. To studier med fentanyl nesespray ble gjennomført: I den første ble 19 kreftpasienter med gjennombruddsmerter fra tre land randomisert til å få to av tre mulige doser med fentanyl nesespray. Fentanyl konsentrasjonsanalyser ble gjort 15 ganger i løpet av fem timer etter at medikamentet ble gitt, begge gangene. I den andre studien fikk 12 eldre menn som ikke hadde brukte opioider før, én dose med fentanyl nesespray. Det ble tatt 13 blodprøver både fra arterier og vener den første timen etterpå. Tolerabilitet og vitale funksjoner som respirasjon og blodtrykk ble registrert i begge fentanylstudiene.

Resultatene fra studiene viser at et bytte til metadon med stopp-og-start-metoden ikke var mer effektivt, eller like sikkert som et bytte over tre dager i denne pasientgruppen med langtkommet kreftsykdom og høye opioiddoser. Pasientene i stopp-og-start-gruppen rapporterte verken lavere smerteintensitet eller mindre bivirkninger. Stopp-og-start-gruppen hadde flere pasienter som falt ut av studien, og det var tre alvorlige hendelser i denne gruppen. Det var ingen alvorlige hendelser i 3-dagers-gruppen. Dette indikerer at et gradvis bytte over tre dager er ønskelig hos disse pasientene. Fentanyl nesespray ble godt tolerert både hos de som brukte opioider og de som ikke brukte opioider fra før. Fentanyl ble raskt tatt opp i blodet (7-15 min). Dette støtter forventningen om at fentanyl nesespray kan være velegnet til å behandle gjennombruddsmerter.

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"Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."

Thomas Sydenham (1624-1689)

Table of contents

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Kristin Moksnes Husby

Asker, December 2011

List of papers

I. Moksnes K, Dale O, Rosland JH, Paulsen O, Klepstad P, Kaasa S**. How to switch from morphine or oxycodone to methadone in cancer patients? A randomised clinical phase II trial.** Eur J Cancer 2011;47: 2463-2470.

II. Moksnes K, Kaasa S, Paulsen Ø, Rosland JH, Spigset O, Dale O. **Serum concentrations of opioids when comparing two switching strategies to methadone for cancer pain.** Eur J Clin Pharmacol 2012, Feb 29 Online ahead of print, DOI 10.1007/s00228-012-1228-3.

III. Kaasa S, Moksnes K, Nolte T, Lefebvre-Kuntz D, Popper L, Kress HG. **Pharmacokinetics of intranasal fentanyl spray in patients with cancer and breakthrough pain.** J Opioid Manag 2010; 6: 17-26.

IV. Moksnes K, Fredheim OM, Klepstad P, Kaasa S, Angelsen A, Nilsen T, Dale O. **Nasal fentanyl - is there a significant arterio-venous difference?** Eur J Clin Pharmacol 2008; 64:497-502.

Abbreviations

AE	Adverse effect
am	after midnight
APS	American Pain Society
ATC	Around the clock
AUC	Area under the curve
AUC_c	Area under the curve dose corrected
ASA	American Society of Anesthesiologists
BPI	Brief Pain Inventory
BTP	Breakthrough pain
CPACS	Cancer Pain Assessment and Classification System
CI	Confidence interval
CL	Clearance
C_{max}	Concentration maximum
CNMP	Chronic non-malignant pain
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
C_{ss}	Concentration at steady state
CYP	Cytochrome P450
d	day
EAPC	European Association for Palliative Care
ECG	Electro cardiogram
ECS_CP	Edmonton Classification System for Cancer Pain
EORTC	European Organization for Research and Treatment of Cancer
EPCRC	European Palliative Care Research Collaboration
ESAS	Edmonton Symptom Assessment Scale
FBT	Fentanyl buccal tablet
FPNS	Fentanyl pectin nasal spray
h	hour
HPLC	High pressure liquid chromatography
IASP	International Association for the Study of Pain
im	intramuscular
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
in	intranasal
InF	Intranasal fentanyl
IR	Immediate release
iv	intravenous
LC-MS	Liquid chromatography - mass spectrometry
LOQ	Limit of quantification
k	elimination constant
KPS	Karnofsky performance status
Meth	Methadone
min	minutes
MMSE	Mini Mental Status Examination
Mo	Morphine
M6G	Morphine- 6-glucoronide
M3G	Morphine-3-glucoronide
NMDA	N-methyl-D-aspartate
NNH	Number needed to harm
NRS	Numerical rating scale

NSAID	Non steroid anti-inflammatory drug
OATPs	Organic Anion Transporting polypeptides
OTFC	Oral transmucosal fentanyl citrate
Ox	Oxycodone
PD	Pharmacodynamic
Pgp	P-glyco protein
PI	Pain intensity
PID	Pain intensity difference
PK	Pharmacokinetic
PRC	Palliative Research Center
QT_c	QT time corrected for heart rate: $QT_c = QT/\sqrt{RR}$
RCT	Randomized controlled trial
SAE	Serious adverse event
SAG	Stop and go
sc	subcutaneous
SD	Standard deviation
sl	sublingual
SR	Slow release
$t_{1/2}$	Elimination half-life
T_{max}	Time to maximum serum concentration
TPAT	Trondheim Palliative Assessment Tool
VAS	Verbal assessment scale
VRS	Verbal rating scale
V_d	Volume of distribution
vs	versus
WHO	World Health Organization
3DS	3-days switch

Sammendrag

Smerter er et fryktet symptom hos pasienter med kreft og deres pårørende. 80 % av pasienter med langtkommet kreft opplever kreftsmerter, og hele 10-30 % opplever smerte og/eller uakseptable bivirkninger til tross for behandling med et sterkt opioid som for eksempel morfin. Hos disse pasientene er et bytte til et annet opioid som metadon et behandlingsalternativ. Mange strategier for opioid-bytte til metadon er foreslått, men ingen randomiserte studier eksisterer. Et alternativ er stopp-og-start-metoden hvor en starter rett på ny metadondose samtidig som det første opioidet avsluttes. Det er hevdet at pasientene da får raskere smertelindring (raskere stabil metadon konsentrasjon) og at bivirkningene forsvinner raskere (raskere eliminasjon av det første opioidet og metabolitter) enn ved 3-dagers-metoden hvor det nåværende opioidet trappes ned over tre dager, og overlappes med tilsvarende dose metadon hver dag.

En stor andel av pasienter med langtkommet kreft opplever plutselige episoder med intense smerter av relativt kort varighet til tross for at opioider lindrer bakgrunnsmerten effektivt; såkalte gjennombruddsmerter. Standard behandling for gjennombruddsmerter har vært ”hurtigvirkende” opioid-tabletter som morfin ved behov. På grunn av lang tid til effekt og langsom utskillelse fra kroppen har effektprofilen til opioid-tabletter passet dårlig med gjennombruddsmertenes tidsprofil. Det ideelle medikamentet mot gjennombruddsmerte tas raskt opp, har rask tid til effekt, skilles raskt ut og må kunne håndteres av pasienten selv. Fentanyl er et svært potent opioid (kan gis i små volum), er fettløselig (tas raskt opp gjennom nesen) og har rask tid til effekt.

Målet for denne avhandlingen var 1) å teste hypotesen om at stopp-og-start-metoden ved bytte fra morfin/oksykodon til metadon hos kreftpasienter med smerter/bivirkninger er mer effektiv og like sikker som 3-dagers-metoden ved å måle smerteintensitet, bivirkninger, opioidkonsentrasjoner og alvorlige hendelser og 2) å studere farmakokinetikken til fentanyl gitt som nesespray og toleransen for medikamentet i målgruppen. Farmakokinetiske parametre fra arterielle og venøse blodprøver ble også sammenliknet.

42 kreftpasienter på morfin/oksykodon-behandling fra fire sykehus i Norge ble randomisert til å bytte til metadon på en av to måter; stopp-og-start-metoden eller 3-dagers-metoden. Beregnet metadondose var avhengig av morfin/oksykodon dosen de sto på. Smerteintensitet ble registrert av pasientene før intervensjon, samt dag 3 og 14. Bivirkninger, alvorlige hendelser og opioiddoser ble registrert daglig i 14 dager. Det ble også tatt blodprøver før opioid-byttet (dag 1), dag 2, 3, 4, 7 og 14 til analyser av morfin (med aktiv metabolitt M6G), oksykodon og metadonkonsentrasjoner. To studier med fentanyl nesespray ble gjennomført. I den første ble 19 kreftpasienter med gjennombruddsmerter fra tre land ble randomisert til 2 av 3 doser (50, 100 eller 200 μg) med fentanyl nesespray. Blodprøver til fentanyl konsentrasjonsanalyser ble tatt 15 ganger ila 5 timer etter administrasjon på to forskjellige dager. Vitale funksjoner som respirasjon, oksygen- metning i blodet og blodtrykk ble registrert. I den andre studien fikk 12 mannlige pasienter som skulle til prostata eller blære operasjon, og som ikke

brukte opioider fra før, en dose med 50 µg fentanyl nesespray. Den første timen etter at sprayen var gitt, ble 13 blodprøver tatt fra både arterier og vener. I tillegg ble tolerabilitet og vitale funksjoner registrert.

Resultatene i denne avhandlingen viser at de pasientene som byttet til metadon med stopp-og-start-metoden ikke rapporterte lavere smerteintensitet enn pasientene i 3-dagers-gruppen, til tross for at de var mer eksponert for metadon de tre første dagene etter byttet. Det var ingen signifikant forskjell mellom gruppene i antall pasienter som hadde stabile metadonkonsentrasjoner dag 4. Pasientene i stopp-og-start- gruppen rapporterte heller ikke mindre bivirkninger, tross mindre eksponering for morfin, M6G og oksykodon de første tre dagene, enn i 3-dagers-gruppen. Det var signifikant flere som falt ut av studien (11 mot 3) og tre alvorlige hendelser (to døde og en hadde alvorlig respirasjons depresjon) i stopp-og-start-gruppen sammenliknet med 3-dagers-gruppen. Dette indikerer at stopp-og-start-metoden ikke er sikker for denne pasientgruppen med langtkommet kreft og høye opioiddoser. Resultatene indikerer at et bytte over tre dager hos kreftpasienter med høye opioiddoser er ønskelig, og at pasientene må observeres i mer enn fem dager ved bytte til metadon uavhengig av metode.

Nasalt fentanyl ble godt tolerert både av pasienter som brukte opioider og de som ikke brukte opioider fra før. Fentanyl ble raskt tatt opp i blodet fra neseslimhinnen (venøse prøver 9-15 min og arterielle prøver 7 min), slik at disse studiene støtter forventningen om at fentanyl nesespray kan være velegnet for å behandle kreftrelaterte gjennombruddsmerter. Arteriell maksimum konsentrasjon var to ganger høyere og tid til maksimum konsentrasjon var 5 min kortere enn i venøse prøver, og de korrelerte ikke. Det er det arterielle blodet som forsyner hjernen med fentanyl, og arterielle prøver vil være mer presise når man skal forsøke å anslå tid til smertelindrende effekt.

Summary

Pain is a symptom feared by cancer patients and their relatives. 80 % of patients with advanced cancer experience cancer pain, and as much as 10-30 % experience pain and/or acceptable adverse effects despite treatment with a strong opioid such as morphine. A switch to methadone is an alternative in these patients. Several switching strategies to methadone have been proposed, but no randomized trials are performed. The stop and go procedure in which the initial opioid is stopped and methadone is started is believed to give a shorter time to pain relief (a shorter time to stable methadone concentrations) and ease of adverse effects more rapidly (a fast elimination of the initial opioid and metabolites) than the 3-days switch in which the current opioid is gradually reduced over three days, and the methadone dose increased in corresponding doses.

A majority of patients with advanced cancer experience a sudden onset of intense pain with short duration despite effective treatment of the background pain; breakthrough pain (BTP). The standard treatment of BTP has been "short-acting" opioid tablets such as morphine taken by mouth as needed. Because of a long time to effect and a slow elimination from the body, the effect profile of opioid tablets has not been corresponding with the characteristics of BTP. The ideal drug for BTP is rapidly absorbed (short time to effect) and eliminated, and it should be easy to administer for the patients. Fentanyl is an extremely potent (it can be administered in small volumes), it is fat-soluble (rapidly absorbed through the nasal mucosa) and has a fast onset of action.

The aims of this thesis were to test the hypothesis that the stop and go method when switching from morphine/oxycodone to methadone in cancer patients with pain/adverse effects is more effective than, and as safe as the 3-days switch by measuring pain intensity, adverse effects and opioid serum concentrations of the respective opioids. Secondly, the aim was to study the pharmacokinetics of intranasal fentanyl, its tolerability, and safety in the target population. Pharmacokinetic parameters of fentanyl were compared between blood samples drawn from arterial or venous samples.

42 cancer patients on morphine/oxycodone in four hospitals in Norway were randomized to a switch to methadone by one of the two switching strategies; stop and go or the 3-days switch. A dose-dependent conversion ratio was used. Pain intensity was recorded by the patients at baseline, on day 3 and day 14. Adverse events and opioid doses were recorded daily for 14 days. Blood samples were drawn before the switch (day 1) and day 2, 3, 4, 7, and 14 for analyzes of morphine (with the active metabolite M6G), oxycodone and methadone concentrations. Two studies on nasal fentanyl were performed: 1) 19 cancer patients from three countries, treated with strong opioids and experiencing BTPs were randomized to 2 of 3 doses (50, 100 or 200 μg) of nasal fentanyl. Venous blood samples for fentanyl concentration analysis were drawn 15 times during the five hours after administration, and vital signs such as respiration, oxygen saturation in blood, and blood pressure, were registered on two different days. 2) 12 elderly, male patients scheduled for prostate or bladder surgery, not using opioids, received a dose of 50 μg of nasal fentanyl.

Both arterial and venous blood samples were drawn 13 times, and tolerability and vital signs were recorded the first hour after administration.

The results in this thesis show that the patients that switched to methadone by the stop and go method did not report lower pain intensity than those switched by the 3-days strategy, despite being exposed to more methadone the first three days after the switch. The number of patients with stable methadone concentrations day 4 was not significantly different in the two groups. Neither did the patients in the stop and go group report less adverse events, even though they had a lower exposure of morphine, M6G or oxycodone than the 3-days switch group, the first three days after the switch. Significantly more patients dropped out of the stop and go group (11 to 3), and there were three serious adverse events in this group (two died and one severe respiratory depression day 5) compared to the 3-days switch group. These findings indicate that the stop and go strategy is not safe in these patients with advanced cancer and high opioid doses. The 3-days switch is recommended in cancer patients on high opioid doses, and patients need to be observed for more than five days after the switch regardless of switching strategy.

Nasal fentanyl was well tolerated by both opioid naïve and opioid tolerant patients. Fentanyl was rapidly absorbed from the nasal mucosa (venous 9-15 min and arterial 7 min). These studies support the expectation that nasally administered fentanyl is a possible treatment for breakthrough pain. Time to maximum concentrations of fentanyl was 5 min shorter and maximum concentrations twofold higher in the arterial samples compared to the venous samples, and these were not correlated. The arterial blood supplies the brain with fentanyl. Arterial samples are more precise when trying to predict time to pain relief.

Introduction

1.1 Cancer

Cancer includes many diseases, varied illness trajectories, and rapidly changing therapeutic landscape. Twenty-eight million people are living with cancer (Union for international Cancer Control, http://www.uicc.org/general-news/globocan-2008). According to the World Health Organization (WHO), cancer accounted for more than 7 million deaths in 2008 and death rates are estimated to rise to 17 million deaths in 2030(WHO 2008). The incidence rate of cancer in Norway (27 520 in 2009) has increased by 7% in men, and 3% in women from the past five-year period (2000-2004) until the last (2005-2009)(Cancer Registry of Norway). Traditionally, cancer care was divided into two phases; the anti-neoplastic treatment (cure and prolongation of life) and the later symptomatic/palliative phase aiming at improvement of quality of life(Maltoni and Amadori 2001). Today, palliative care is more integrated during the whole course of the illness(Ferris et al., 2009; Harrison et al., 2009; Kaasa and De Conno 2001).

1.2 Cancer pain

Pain is one of the most frequent symptoms in cancer patients(Teunissen et al., 2007) and it is the symptom most feared by cancer patients (Johansen et al., 2005; Morris et al., 1986; Portenoy 2011). Cancer pain may be caused by direct tumor involvement, diagnostic procedures and by various treatment strategies applied (e.g. radiation, surgery, chemotherapy, symptom management drugs)(McGuire 2004). It is also influenced by subjective perception influenced by culture(Lasch 2000), thought and psychosocial factors of the patient(Hoogendoorn et al., 2000; Rollman et al., 2004). Dame Cecily Saunders used the term “total pain” to include the physical, psychological, social and spiritual components of pain in terminally ill cancer patients(Saunders 1964). The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”(IASP 2011).

1.2.1 Classification

Cancer pain is complex and multidimensional and can be classified in several ways; such as its intensity, duration, origin, pathophysiology, as response to opioids or in association with a condition(Knudsen et al., 2009; Portenoy 2011). Patients with cancer often have several types of pain at the same time and at more than a single site and a large number of cancer pain syndromes have been identified(Caraceni and Portenoy 1999; Caraceni and Weinstein 2001; Portenoy 1992; Portenoy and Lesage 1999).

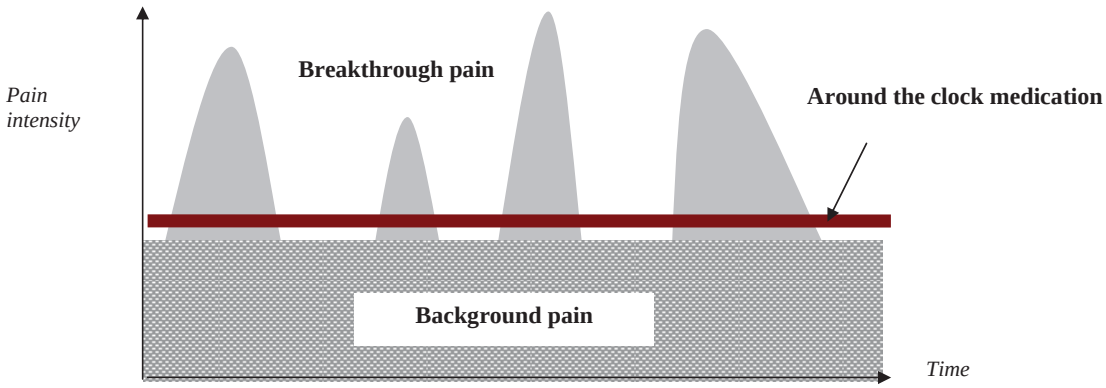
There are mainly three broad categories of pain mechanisms; nociceptive, neuropathic and idiopathic pain. Nociceptive pain is associated with activation of nociceptors after somatic or visceral tissue damage. Pain caused by a lesion or disease of the somatosensory nervous system is defined as neuropathic pain, while idiopathic pain has

no apparent underlying cause(IASP 2011). Neuropathic pain in cancer patients is most commonly a combination of inflammatory, neuropathic, ischemic, infiltrative, and compression mechanisms that involve one or more anatomic sites(Lema et al., 2010; Urch and Dickenson 2008).

According to duration, pain can be classified as acute or chronic. Acute pain serves as a warning system of potential damage. It is the normal, predictable, physiological response to an adverse chemical, thermal or mechanical stimulus with sudden onset(Carr and Goudas 1999). In contrast, chronic cancer pain (also termed baseline, persistent or background pain) is described as present for more than 12 hours a day during the previous week (or would be present if not taking analgesia).

In addition to chronic pain, a large number of patients with relatively stable and adequately controlled background pain experience breakthrough pain (BTP)(Portenoy et al., 1999a). BTP may be defined as "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain"(Davies et al., 2009), and is caused by cancer, cancer complications, treatments or comorbidities. However, there is no international consensus concerning the definition of BTP(Haugen et al., 2010). In a recent systematic review on BTP other terms such as incident pain, incidental pain, episodic pain and transitory pain or a combination was reported(Haugen et al., 2010). Three principal categories of BTP are described: spontaneous pain, incident pain (with an evident precipitating cause of event such as activity) and end-of-dose failure(Mercadante 2011). The end-of-dose failure is however now rather considered as inadequately controlled background pain(Davies et al., 2009; Mercadante 2011). In a recent study on BTP characteristics in 320 cancer patients, the median number of episodes was 3/day, the median duration of a BTP episode was 60 min, with 15 min to the peak of pain intensity (PI) and 60% reported the episodes as severe(Davies et al., 2011b). In sum, BTP is characterized by a fast onset, usually reaching a peak of intensity within three minutes, is often severe, with a duration of approximately 30 minutes (less than an hour in 90 % of the episodes)(Mercadante et al., 2002; Portenoy and Hagen 1990; Portenoy et al., 1999a; Zeppetella et al., 2000; Zeppetella and Ribeiro 2003) (fig 1).

Fig. 1 BTP and background pain



A high prevalence of BTP is associated with more severe pain(Caraceni et al., 2004) and most patients with BTP have greater chronic pain intensity as measured on the Brief Pain Inventory (BPI)(Caraceni et al., 2004). BTP significantly impacts the patients' quality of life as it is associated with poor overall pain control(Bruera et al., 1995a), increased levels of depression and anxiety(Fortner et al., 2002; Taylor et al., 2007), a high probability of dying, need a change of opioids or side effects(Greco et al., 2011). Patients with BTP experience more pain-related hospitalizations, more emergency room visits and more outpatient visits(Abernethy et al., 2008).

There is no international consensus on how to classify cancer pain(Caraceni and Weinstein 2001; Fainsinger and Nekolaichuk 2008; Knudsen et al., 2009). A recent systematic review(Knudsen et al., 2009) on cancer pain classification identified six standardized classification systems, three of these were systematically developed and partially validated(Fainsinger and Nekolaichuk 2008; Hwang et al., 2002; Merskey 1994), but none was widely applied. With the aim to validate the Edmonton Classification System for Cancer Pain (ECS-CP) Fainsinger et al. reported that in patients with advanced cancer (n=1100) from palliative care sites in six countries; younger age, neuropathic pain, incident pain, psychological distress, addictive behavior and initial pain intensity were significantly associated with days to achieve pain control(Fainsinger et al., 2010). Also, psychosocial factors such as fear, anxiety, depression, and lack of sleep have been reported to increase cancer pain(Anderson et al., 2003; Portenoy et al., 1994). The working proposals in international standards from experts in the European Palliative Care Research Collaborative (EPCRC) are that pain intensity, pain mechanism, breakthrough pain, and psychological distress are core domains to be included in a classification

system, and that the ECS-CP should be regarded as the template for further development(Kaasa et al., 2011). A consensus on classification may improve pain treatment in cancer care(Kaasa 2010).

1.2.2 Prevalence of pain and quality of treatment

In two recent reviews(Deandrea et al., 2008; van den Beuken-van Everdingen et al., 2007) and one pan-European telephone survey on cancer-related pain (n=5084)(Breivik et al., 2009) around 50 % of patients in all stages of cancer report pain. In patients with incurable cancer, as much as 70% report pain (Teunissen et al., 2007; Wilson et al., 2009). Not only is there a high prevalence of cancer pain, the pain intensity is high. In a review of 52 studies on cancer pain over the last 40 years and in a cross sectional European survey; more than 1/3 of patients with cancer in all stages of the disease graded their pain as moderate to severe(Klepstad et al., 2005b; van den Beuken-van Everdingen et al., 2007).

In a one day prevalence study of hospitalized cancer patients Holtan et al. found that 30% of those who had severe pain (> 5 on an 11-point numerical rating scale (NRS)) were not on opioids and some of these did not receive any analgesics at all(Holtan et al., 2007). Cleeland et al. surveyed the intensity of pain in 1308 outpatients with metastases, and observed that 42% of those with pain, were not given adequate analgesic treatment(Cleeland et al., 1994). The inadequacy of cancer pain treatment was also demonstrated by an IASP Task Force on cancer pain survey which reported that 67% of 1095 patients treated by pain specialists experienced worst pain intensity (PI) ≥ 7 on a 11-point NRS during the day prior to the survey (Caraceni and Portenoy 1999). The cancer pain prevalence varies greatly between different types of cancer, and also within the cancer disease trajectory, and setting. When comparing pain treatment by in-patient hospices and National Health Service hospitals in the UK from the relatives perspective, 80.6% (n=25) reported treatment relieved pain in hospices and 38.7 % (n=12) in the hospitals(Addington-Hall and O'Callaghan 2009).

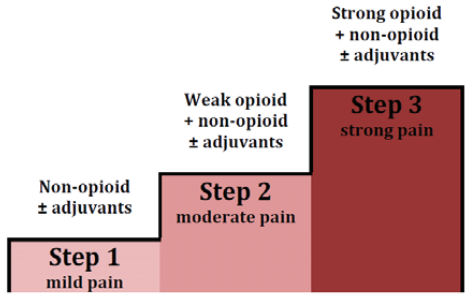
BTP has been reported in 40-93% of patients with advanced cancer depending on the setting and the definition used to identify it(Caraceni et al., 2004; Fine and Busch 1998; Greco et al., 2011; Mercadante et al., 2010; Patt and Ellison 1998; Portenoy and Hagen 1990; Swanwick et al., 2001; Zeppetella et al., 2000). A task force of the IASP involved a total of 1095 patients in 24 countries reported a prevalence of BTP of 64.8%(Caraceni and Portenoy 1999). In a recent prospective, longitudinal study of 1801 cancer patients, 40.3% reported BTP at baseline and most did not receive rescue therapy at all(Greco et al., 2011). The data suggest that moderate to severe cancer pain requiring the use of opioids is either untreated or undertreated for millions of cancer patients worldwide.

1.2.3 Principles of cancer pain treatment

The overall aim of cancer pain treatment is to eliminate the cause of the pain when possible, and if not possible, to relieve pain to the patient's satisfaction, so that he or she can function effectively and eventually die free of pain(WHO 1996). Most pain states of

cancer can be treated by careful assessment of the syndrome components and underlying pathophysiology, and with appropriate use of simple therapies(Ventafridda et al., 1987; WHO 1996). Opioids are the mainstay in cancer pain treatment, with the World Health Organization (WHO) analgesic ladder (fig 2) as the basic approach(WHO 1996).

Fig. 2 WHO pain ladder for treatment of cancer pain
(Figure made by Trine Andreassen)



The WHO ladder is based on severity of pain intensity and states that non-opioids (paracetamol or NSAIDs) should be administered for mild pain, followed by step II opioids ("weak opioids" such as codeine or dextropropoxyphene) for mild to moderate pain and then if required, a step III opioid ("strong opioids" with morphine as first choice) in increasing doses until pain relief or dose-limiting side effects occur.

During the last decade much attention has been given to improve pain treatment. Fourteen guidelines on cancer pain management, published after 2000 were recently reviewed and compared by Pigni et al.(Pigni et al., 2010). Significant variation in relevant topics, such as the role of morphine as the first-line drug was found. There is a lack of evidence to support current clinical practice in opioid treatment(Pigni et al., 2010). In addition there are often local standards for each department, center or country(Klepstad et al., 2005b). The European Association for Palliative Care (EAPC) has published detailed recommendations on the use of opioids in cancer pain treatment based on the WHO analgesic ladder. These were published in 1996, first revised in 2001, and are now under revision again(Caraceni 2011; Expert Working Group of the European Association for Palliative Care 1996; Hanks et al., 2001). Twenty-two systematic literature reviews of relevant topics in cancer pain treatment are performed(Pigni et al., 2010). At the time when this thesis was planned, the EAPC recommendations were: morphine should be the drug of choice and oral administration preferred. The dose should be tailored to the individual patient with the simplest method of dose titration, with dose of normal release morphine given every four hours and the same dose for BTP given as often as required (BTP management is further outlined in a later section). If patients experience intolerable side effects before achieving pain relief, a change to an alternative opioid or a change of route should be considered(Hanks et al., 2001).

1.3 Opioids in cancer pain

1.3.1 History

Opioids are among the oldest and most effective drugs known, with references to their use back to 4000 B.C. when the opium poppy was cultivated by Sumerians who referred to it as *Hul Gil*, the "joy plant". Ancient Egyptian papyrus records mention opium as treatment for cancer pain around 1300 B.C. History traces the drug's astounding impact on world culture - from its religious use to the earliest medical science to the opium wars. However, more has been learned about these agents, during the last 30 years, than in the preceding hundreds of years.

1.3.2 Clinical aspects of pharmacokinetics and pharmacodynamics of opioids

Opioid is a generic term for chemical substances binding to opioid receptors; naturally occurring alkaloids (opiates such as morphine and codeine from the poppy seed), semi-synthetic opioids (created from the natural opiates hydromorphone and oxycodone) or fully synthetic opioids (fentanyl and methadone). Opioids may be classified by their function as agonists (morphine, oxycodone, fentanyl, methadone and hydromorphone), partial agonists (buprenorphine), or antagonist (naloxone). The various opioids differ in ways of possible routes of administration, absorption from the gastrointestinal tract, distribution, and elimination (Hanks and Reid 2005; Inturrisi 2002; Paice 2007).

Opioids receptors were discovered independently by three research groups in 1973(Pert and Snyder 1973; Simon et al., 1973; Terenius 1973). Mu (μ), kappa (κ), and delta (δ) opioid receptors represent the originally classified receptor subtypes, with opioid receptor like-1 (ORL1) being the least characterized. All four receptors are G-protein coupled and activate inhibitory G proteins(Al-Hasani and Bruchas 2011). The opioid receptors are found within the central nervous system (CNS) and in the peripheral tissues(Janson and Stein 2003; Kieffer and Gaveriaux-Ruff 2002; Mansour et al., 1988).

Pharmacokinetics (PK) is the study of drug disposition, and deals with the process of absorption, distribution, and elimination (metabolism and excretion) (what the body does to the drug). Pharmacodynamics (PD) describes the effects of a drug (what the drug dose to the body) and is often concerned with the relation between concentration of the drug and its effect .

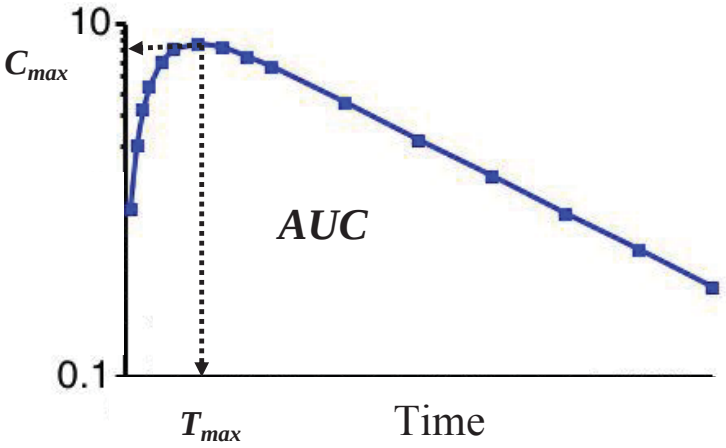
1.3.2.1 Absorption, distribution and elimination

Drugs are administered intravascular (intravenously (iv) or intra-arterially) or extravascular. Extravascular modes of administration include the oral, nasal, sublingual, buccal, intramuscular, dermal, pulmonary, and rectal routes; which all requires absorption. *Absorption* is defined as the process where unchanged drug proceeds from site of administration to site of measurement within the body. Two factors decide the extent of absorption; the characteristics of the drug and way of administration (enteral or

parenteral (excluding intravenous administration)). Oral transmucosal, intranasal, and intrapulmonary administration are a mixture of enteral and parenteral routes through which the administered drug can be absorbed enterally due to swallowing, and parenterally via the buccal or sublingual mucosa(Davies 2006). Lipid-soluble drugs (such as fentanyl) diffuse easily across membranes and these can also be delivered transdermally or transmucosally, while water-soluble opioids such as morphine and oxycodone pass at slower rates. A solid drug, encounters several barriers and sites of loss during gastrointestinal absorption; incomplete dissolution, low intestinal permeability, and metabolism in the gut lumen or by enzymes in the gut wall. Removal of drug as it first passes the liver further reduces absorption (first pass metabolism). The absorption phase lasts until no more drug is absorbed to the blood. Once absorbed, a drug is distributed to the various organs influenced by how well an organ is perfused with blood, organ size, binding of drug within blood and in tissues, and permeability of tissue membranes. *Distribution* is the process of reversible transfer of a drug to and from the site of measurement (usually blood). During the distribution phase, changes in the concentrations of a drug in plasma reflect primarily movement of drug within, rather than loss from the body. Opioid distribution within the vascular compartment following absorption is a function of plasma protein binding and lipophilicity. As an example; morphine is moderately protein bound (30%), in contrast to fentanyl which is both highly protein bound (80-85%) and lipophilic. There are two main distribution barriers; the brain-blood barrier and the placenta barrier. The blood-brain barrier is a permeability barrier to passive diffusion of substances from the bloodstream to various regions of the CNS. The extent of this transport depends on the molecular charge, weight, and its lipophilicity. With time, equilibrium of drug in tissue with that in plasma is established, and eventually, changes in the drug plasma concentration reflect a proportional change in the concentration of drug in all tissues and, hence, the amount of drug in the body. The decline of the plasma concentration is then due to only to elimination; the elimination phase. *Elimination* is the irreversible loss of drug from the site of measurement. A drug is eliminated either by metabolism or excretion. Most drugs are eliminated by a first-order process, in which the amount of drug eliminated is directly proportional to the serum drug concentration. There is a linear relationship between rate of elimination and serum drug concentration. Although the amount of drug eliminated in a first-order process changes with concentration, the fraction of a drug eliminated remains constant. As an example of metabolism process; opioids are primarily metabolized through two enzyme systems; the UDP-glucuronosyltransferases (UGTs) and the cytochrome (CYP) 450 system. The CYPs responsible for the metabolism of methadone remains controversial, CYP2B6 and CYP3A4 are suggested as main pathways, with less involvement of CYP1A2 and CYP2D6(Crettol et al., 2006; Eap et al., 2002; Kharasch et al., 2004c; Kharasch et al., 2009; Totah et al., 2008). In contrast to methadone, morphine is metabolized by the uridine-diphosphate-glucuronosyltransferase 2B7 (UGT2B7) into the two principle metabolites morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G)(Coffman et al., 1997; Milne et al., 1996). Oxycodone is metabolized mainly via CYP3A4 to the inactive noroxycodone and via CYP2D6 to the active oxymorphone(Gronlund et al., 2010; Lalovic et al., 2006; Zwisler et al., 2010). Oxymorphone is an active metabolite, but its contribution to the efficacy of oxycodone is uncertain(Mayyas et al., 2010; Zwisler et al., 2010). Fentanyl is mainly metabolized via

the CYP3A4 to norfentanyl, respectively(Feierman and Lasker 1996; Labroo et al., 1997). Once metabolized, renal excretion account for approximately 90% of the excretion of most opioid metabolites via urine. Elimination will be affected by liver or renal dysfunction, and might lead to reduced doses or a switch of drug.

Fig 3. Time concentration curve of a drug given orally (semilog)



The rising position of a plasma-concentration curve is the absorption phase (where distribution and elimination also takes place), and the declining portion, the elimination phase (where the elimination constant (k) and the terminal half-life ($t_{1/2}$) can be calculated

1.3.2.2 Pharmacokinetic parameters

Using a *non-compartmental method* the $C_{max,}$ T_{max} and area under the plasma drug concentration-time curve (AUC) can be directly read out of a concentration-time graph (fig 3). Compartment-free methods do not assume any specific compartmental model and produce accurate results also acceptable for bioequivalence studies. Exposure of a drug may be expressed as *AUC,* which is the area under the plot of plasma concentration of drug against time after drug administration. AUC may also be used to describe individual variations, and interactions. The serum concentrations of drugs that are administered periodically are often measured as *trough concentrations*; the concentration just before the administration of the next dose.

Different routes of administration result in different *times to maximum concentration (C_{max}).* The absorption across biological barriers before entry into vascular compartment after oral dosing determines the *time to maximum concentration (T_{max})* compared to the iv

route. T_{max} is often used to predict *time to effect* of the drug as it is related, although the effect of the drug starts before the peak concentration (if not delay from blood till site of action is not too long). For drugs with the vascular system as its effect site, T_{max} values are a good approximation to time to effect, whereas T_{max} values may differ significantly from time to effect for drugs acting at other effect sites, for example in the CNS as transport from blood to effect site also takes time. When estimating C_{max} and T_{max}, venous blood samples are most commonly studied. However, during the early distribution phase, arterio-venous differences in serum concentrations have been reported for several drugs such as remifentanil and heroine after intravenous administration(Chiou 1989b; Hermann et al., 1999; Rentsch et al., 2001) with a shorter T_{max} and a higher C_{max} in the arterial samples.

The volume of distribution (V_d) is a pharmacological term used to quantify the distribution of a drug between plasma and the rest of the body at steady state. It is defined as the theoretical volume in which the total amount of drug in the body would need to be uniformly distributed to produce the observed blood concentration of a drug. Volume of distribution is depending of physiochemical factors such as lipophilicity, pKa, molecular size, and physiological factors of the drug such as binding to serum proteins. Exemplified, morphine and oxycodone are moderately protein bound (30% and 45%, respectively), in contrast to fentanyl and methadone which is both highly protein bound (80-85%) and lipophilic. V_d is used to relate plasma concentration to amount of drug in the body during the elimination phase. *Clearance (CL)* is a descriptive term used to evaluate efficiency of drug removal from the body. It is not an indicator of how much drug is being removed; it only represents the theoretical volume of blood which is totally cleared of drug per unit time. Because clearance is a first-order process, the amount of drug removed depends on the concentration. The elimination rate constant (k) represents the fraction of drug eliminated per unit of time.

The elimination/terminal *half life ($t_{1/2}$)* of a drug is the time needed for the plasma concentration of a substance to be eliminated to the half. The elimination half-life is a parameter controlled by plasma clearance and extent of distribution. A long terminal half-life can be associated to a large volume of distribution (V_d) or/and attributable to a small plasma clearance ($t_{1/2}$ = 0.693 (ln 2) * Volume of distribution (V_d)/ Plasma clearance (CL)).

The main clinical application of terminal half-life is to select an appropriate length for the dosing interval in circumstances of multiple dose administration; it allows prediction of drug accumulation and the time taken to reach *steady state concentration* (C_{ss}). It takes approximately $t_{1/2}$ times five to reach steady state. In steady state the drug elimination equals drug availability. When a drug is administered every 12 h the serum concentrations of the drug rises and falls. In steady-state this cycle is repeated identically in each administration interval, and the steady state serum concentration then describes the average drug concentration during an inter-dose interval. It is more common to refer to the half-life, than to the elimination rate constant of a drug. The elimination rate constant (k) may simply be regarded as the fractional rate of drug removal. A simple way to express the efficiency of drug elimination is to consider the numerical value of the

slope (λ_z) of the terminal phase. The decay of a drug following first-order pharmacokinetics being exponential, the terminal half–life is obtained by: $t_{1/2}=0.693/\lambda z$.

The fraction of the drug (%) that enters the systemic circulation is called the *bioavailability*. The intravenous (iv) administration does not require absorption and has a 100% *bioavailability*. Oral bioavailability of methadone, morphine, oxycodone and bioavailability of oral transmucosal fentanyl (OTFC) are presented in table 1. A low bioavailability can be the result of low absorption from the intestine or a high *first pass metabolism (*by gut wall enzymes, and hepatic enzymes). Also the P-glycoprotein (Pgp) efflux pump may affect the bioavailability of opioids(Mercer and Coop 2011). Pgp transports substances from the intracellular to the extracellular space to protect cells from toxicity and limit the access of drugs to the CNS (Aquilante et al., 2000; Hassan et al., 2009; Mercer and Coop 2011). What opioids are substrates for Pgp is not yet established (Kharasch et al., 2004b; King et al., 2001; Thompson et al., 2000).

Table 1. Metabolites, T_{max}, $t_{1/2}$ and bioavailability of oral morphine and oxycodone (both IR), methadone and oral transmucosal fentanyl citrate (OTFC)

	Metabolites	***T_{max}***	***$t_{1/2}$***	***Bioavailability***
Morphine	M6G (active), M3G and normorphine	1-3h	2-3.5 h	20-35 %[a] (Collins et al., 1998; Gourlay et al., 1986; Hasselstrom and Sawe 1993; Hoskin et al., 1989; Sawe et al., 1985)
Oxycodone	Oxymorphone (active), noroxycodone and α and β oxycodole, noroxymorphone	1-2h	2-3 h	60-87 %[a] (Leow et al., 1992; Poyhia et al., 1992; Reder et al., 1996)
Methadone	EDDP and EMDP	1.5-2.8 h	24 (13-50 h)	70-90 %[a] (Dale et al., 2004; Gourlay et al., 1986)
Fentanyl (OTFC)	Norfentanyl and hydroxyfentanyl	20-24 min	1 h	40-50 % (Egan et al., 2000; Streisand et al., 1991)

Studies including cancer patients (Gourlay, Sawe and Leow), both cancer patients and healthy volunteers (Collins), and healthy volunteers only (Hasselstrom, Hoskin, Poyhia, Reder, Dale, Egan and Streisand).

1.3.3 Interindividual variability

The doses of opioids needed for pain relief vary between individuals(Hanks and Reid 2005; McQuay et al., 1990). The therapeutic dose for morphine may extend from 15 to 1500 mg per day(Hanks and Reid 2005). Even in relatively homogenous patient cohorts, dosage requirements vary substantially(Ashby et al., 1997; Aubrun et al., 2003). Many explanations to this are purposed, such as differences in drug bioavailability, metabolism, efficacy(Hanks and Reid 2005; Inturrisi 2002; Mercadante 1998), in the intensity of pain stimuli and perception(Collin et al., 1993; Glare and Walsh 1991), age, gender, body fat, muscle wasting, cancer-diagnosis, status of liver and kidney function, disease comorbidities and concurrent medications(Hall et al., 2003; Laird et al., 2009; Paice

2007). A number of studies, reviews and textbooks have addressed the role of genetic variants, especially polymorphisms in genes encoding proteins involved in opioid pharmacology(Davis et al., 2009; Galvan et al., 2011; Ikeda et al., 2005; Kasai et al., 2008; Klepstad et al., 2005a; Lacroix-Fralish and Mogil 2009; Lotsch and Geisslinger 2006; Somogyi et al., 2007; Stamer et al., 2005). Explorations of opioid receptor subtypes (μ, δ, and κ, ORL1 with splice variants) and their properties(Pan et al., 2005; Pasternak 2005), identification of twenty different endogenous opioid peptides which differed in receptor affinity(Akil et al., 1998; Bodnar and Klein 2006), the multiple opioid receptor signaling regulations at multiple levels(Law et al., 2000), receptor cross-talk(Charles et al., 2003) and differences in Pgp-activity (several substances including many of the chemotherapeutic drugs can alter the expression)(Baker et al., 2005) makes the picture complex. However, the genetic studies in which some of this knowledge originates have been criticized of having small samples, the findings are not replicated, and several candidate genes have not been studied(Hirschhorn et al., 2002; Kim et al., 2009; Skorpen et al., 2008). Even the best established gene variation supposed to influence opioid efficacy (in the μ-opioid receptor gene OPRM1) have been questioned in a meta-analyzes(Walter and Lotsch 2009). In a recent European genetic association study of 2294 cancer patients on different strong opioids, 112 single nucleotide polymorphisms (SNPs) in 23 candidate genes proposed to influence opioid efficacy were studied. None showed significant association with opioid dose(Klepstad et al., 2011). Genetic variability is also suggested to affect the degree of side effects of opioids. However, no clear genetic association has been established(Klepstad et al., 2011). So far, there is no clear evidence that genetic markers can be used to predict opioid efficacy, or adverse effects in palliative care patients(Skorpen et al., 2008).

1.3.4 Side effects

The incidence and severity of side effects from the administration of opioids can play an important role in the success or failure of pain management in patients with cancer pain (Cherny et al., 2001). The evidence of opioid related side effect prevalence is restricted to reports of specific side effects, and numbers are often confounded by the contribution of comorbidities or concurrent medication (McNicol et al., 2003). Common opioid-related side effects are constipation(Panchal et al., 2007), sedation(Young-McCaughan and Miaskowski 2001), nausea and vomiting (Redmond and Glass 2005), and cognitive dysfunction(Ersek et al., 2004). Less frequent side effects include dry mouth(Meuser et al., 2001), loss of appetite(Morley et al., 1983), urinary retention, perceptual distortion(Daeninck and Bruera 1999), respiratory depression(Dahan et al., 2010), and myoclonus(O'Mahony et al., 2001). Of 23 symptoms, only constipation, erythema and dry mouth were assessed as being most frequently caused by the analgesic regimen in a longitudinal symptom prevalence study in cancer patients treated by the WHO cancer pain guidelines (n=594)(Meuser et al., 2001). In a recent cross-sectional study from 143 palliative care centers in 21 European countries, 3030 cancer patients (whereof 2064 on opioids according to the WHO pain-ladder) were generalized weakness 50%, fatigue 48%, anxiety 28%, constipation 18%, depression 18% and dyspnea 15%(Laugsand et al., 2009). Furthermore, one-third to half of these patients did not receive any treatment

aimed to reduce the symptom intensity. Symptom intensity is also found to often being underestimated by providers(Laugsand et al., 2011).

With all opioids, respiratory depression is potentially the most serious opioid side effect. Opioid-induced respiratory depression is believed to be mediated largely by the μ-opioid receptors. Opioids administered to mice lacking these receptors, did not induce respiratory depression(Dahan et al., 2001). Respiratory depression is however rare in patients on long term opioid treatment(McQuay 1999). The different opioids are reported to cause comparable degrees of respiratory depression at equianalgesic doses. Although the complex pharmacokinetics of methadone may place patients at a higher risk of hypoventilation than other opioid agonists(Lipman 2005). Several cases of overdose and severe respiratory depression, have been reported in relation to switching to methadone(Benitez-Rosario et al., 2006; Elsayem and Bruera 2005; Ettinger et al., 1979; Fredheim et al., 2006b; Hernansanz et al., 2006; Hunt and Bruera 1995; Oneschuk and Bruera 2000; Watanabe et al., 2002). Management of respiratory depression includes discontinuing opioids, and initiating naloxone infusion(Cherny et al., 2001; Dahan et al., 2010).

Little is known about which patients are at risk of opioid side effects. According to an Expert Working Group of the EAPC Research Network, there is little reproducible evidence suggesting than one opioid agonist has a better side effect profile than another and that there is very limited evidence to suggest differences in side effects associated with a specific route of administration (Cherny et al., 2001). However, small studies have observed differences in side effects between opioids(Ahmedzai and Brooks 1997; Campora et al., 1991; Clark et al., 2004; Cooper et al., 1999; Lauretti et al., 2003; Yang et al., 2010) and when comparing routes(Babul et al., 1998). It is not evident whether this is a route-or drug-related effect. Sex, race, and increasing age are all factors suggested to influence the development of side effects(Cepeda et al., 2003). In patients with impaired renal function there is delayed clearance of the active metabolite M6G(Osborne et al., 1993). Anecdotally, high concentrations of M6G have been associated with toxicity(Hagen et al., 1991; Osborne et al., 1986; Sjogren et al., 1993). The serum concentrations of morphine, M6G, or M3G could not predict pain intensity, cognitive function, nausea or tiredness in 263 cancer patients receiving oral morphine (Klepstad et al., 2003). No association were observed between side effects, pain and serum concentrations of morphine or its metabolites in 40 cancer patients with pain(Klepstad et al., 2000), this was confirmed in a study on 46 cancer patients with pain(Quigley et al., 2003).

There remains a scarcity of randomized controlled trials in the area of management of opioid side effects(Cherny et al., 2001; McNicol et al., 2003). Several guidelines, mostly based on aggregated clinical experience and expert recommendations, describe how to treat opioid side effects(Benyamin et al., 2008; Cherny et al., 2001; Larkin et al., 2008; McNicol et al., 2003; Swegle and Logemann 2006). Dose reduction, change of route, switching the opioid, and prescription of symptomatic drugs are the main strategies used by physicians to reduce opioid side effects(Cherny et al., 2001).

1.3.5 Tolerance, dependency and addiction

Widely accepted definitions of these phenomena in patients on long term opioid treatment are lacking(Ballantyne 2007a; Savage et al., 2003). Clinical *tolerance* might be defined as the reduced effect for equivalent dose, or the requirement of increased doses to attain the same effect(Savage et al., 2003). This effect is primarily caused by pharmacodynamics changes. This is however, not shown in clinical studies, and progression of disease is often used to explain the increasing opioid dose over time(Collin et al., 1993). Tolerance to side effects such as tolerance to nausea, vomiting, respiratory depression and sedation usually develops within days or weeks, with an exception of constipation(Jage 2005). 'Cross-tolerance' implies that subjects tolerant to one opioid will be tolerant to another and is limited to drugs acting at the same receptors. Incomplete cross tolerance among μ-receptor ligands might reflect their differing selectivity for different μ -receptor subtypes(Pasternak 2001). Misuse attaches a stigma to opioid use, and a fear tolerance and addiction exist(Ballantyne 2007b; Paice et al., 1998). Addiction is associated with drugs capable of producing reward. Despite the use of high opioid doses, addiction is rare in the cancer population(Hojsted and Sjogren 2007; Levy 1994; McQuay 1999). Physical dependence is the withdrawal syndrome when the drug is significantly reduced or stopped, and is an almost obligate result of long-term use of opioids in patients irrespective of underlying pain syndrome. Opioid analgesia should therefore not be discontinued abruptly.

1.3.6 Methadone

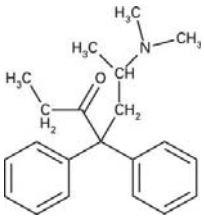
1.3.6.1 History

Methadone was developed in 1938, and was filed in 1941(Fishman et al., 2002). According to myth it was developed to relieve anticipated shortage of morphine during World War II. Due to its long half-life and low cost, methadone had an important role in the treatment of pain until the introduction of slow-release (SR) formulations of other opioids in the early 1980s. Methadone was at that time primarily available as a mixture with an unpleasant taste, and consequently lost popularity after the introduction of other slow-release formulations. Methadone has had two major indications; in pain management and in opioid maintenance therapy for opioid addicts in order to prevent abstinence reaction and relapse to misuse. Currently, methadone has had a renaissance in the treatment of pain as a second line opioid, when other opioids fail(Quigley 2004).

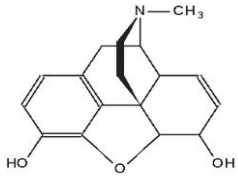
1.3.6.2 Basic properties

Methadone is a synthetic opioid whose structure is quite different from that of morphine; 6-demethylamino-4.4-diphenyl-3heptanone and it is basic with a pKa of 9.2 (fig 4).

Fig. 4 Structural formula of methadone and morphine



Methadone



Morphine

Methadone is commercially available as tablets, capsules, solution for oral administration and solution for intravenous administration. In healthy volunteers methadone has been administered intranasally and in solution for rectal administration, but local irritation was observed for the nasal route(Dale et al., 2002b; Dale et al., 2004). Clinical use of custom made suppositories has also been reported(Bruera et al., 1995b; Ripamonti et al., 1995; Watanabe et al., 1996). Methadone administered subcutaneously may cause local reactions (Bruera et al., 1991a). Thus the intravenous route is preferable for parenteral administration. (Manfredi et al., 1997). Commercially available formulations of methadone are racemic mixtures of R- and S-methadone (levomethadone and dextromethadone, respectively), though in Germany, only the R-enantiomer has traditionally been used.

Methadone is entirely absorbed in the gastrointestinal tract, but the mean oral bioavailability is about 80 % (because of first pass metabolism). The bioavailability is far higher than for the other opioids used in palliative care (Dale et al., 2002b; Gourlay et al., 1986) (table 1). Methadone binds to α1-glycoprotein in plasma, and only about 10% of methadone remains unbound (Felder et al., 1999; Garrido et al., 2000; Gourlay et al., 1986). Owing to high lipid solubility 98 % of methadone reaching the central compartment is rapidly distributed to tissues, and only 1-2 % remain in the blood compartment at steady state(Ferrari et al., 2004). Methadone has a rapid initial distribution phase (2-3h), and a prolonged elimination phase with a terminal half-life ranging from about 13-50 h (Dale et al., 2002b; Inturrisi 2002). The long half-life is caused by the large volume of distribution for methadone, the high affinity to tissue, and lipophilicity. Time required reaching steady state, and thus maximum effect will vary from about 35 to 350 hours (13.5 days). Data has shown low correlation between methadone dose and steady state serum concentrations both in patients in opioid maintenance therapy and in patients with chronic non-cancer pain(de Vos et al., 1995; Fredheim et al., 2007). Methadone is detected in serum within 30 min after oral intake, with a maximum serum concentrations (T_{max}) after oral intake between 2-4 hours (Dale et al., 2002b). It is commonly sited that the interindividual variability of the pharmacokinetics of methadone is larger than that of other opioids(Nicholson 2007; Weschules and Bain 2008).

Methadone activates μ, κ, and δ opioid receptors, possesses moderate antagonistic effect to the NMDA receptor (both enantiomers), and strongly inhibits reuptake of serotonin and noradrenalin in the CNS (S-methadone) (Codd et al., 1995; Ebert et al., 1995;

Gorman et al., 1997; Kristensen et al., 1995). The NMDA mechanism is suggested in animal studies to play an important role in the prevention of opioid tolerance, and potentiating of opioid effects(Davis and Inturrisi 1999; Ebert et al., 1995; Ebert et al., 1998; Gorman et al., 1997).

Methadone is metabolized mostly through microsomal liver enzymes, but also in the intestinal wall to the two inactive metabolites; 2-ethylidene-1.5-dimethyl-3.3-dipenylpyrolidine (EDDP) and 2-ethyl-5methyl-3.3-dipenylpyrodine (EMDP). The CYPs responsible for the metabolism of methadone remains controversial, CYP2B6 and CYP3A4 are suggested as main pathways, with less involvement of CYP1A2 and CYP2D6(Crettol et al., 2006; Eap et al., 2002; Kharasch et al., 2004c; Kharasch et al., 2009; Totah et al., 2008). The CYP 3A4 pathway in animals has recently been questioned(Kharasch et al., 2008; Kharasch et al., 2009). There is a large interindividual variability (20-100 folds) in methadone clearance(Eap et al., 2002; Foster et al., 2000). Methadone is excreted mainly via the alimentary tract, but also via the kidneys depending on the urine pH. Methadone can be administered to patients with renal impairments (Bellward et al., 1977; Rostami-Hodjegan et al., 1999).

1.3.6.3 Interactions and QT-prolongation

The metabolism of methadone by CYP3A4 and 2B6 implies the possibility of numerous drug-drug interactions, and both enzyme inhibition and induction are possible(Ferrari et al., 2004) with a possible increase or decrease of the serum methadone concentration and effects. The most relevant interactions for patients with chronic pain are outlined in a review on clinical pharmacology of methadone(Fredheim et al., 2008), with most of the drugs being psychoactive or antineoplastic. Particular attention should be paid to antibiotic treatment with the potent CYP 3A4 inhibitors macrolides and ciprofloxacin(Aminimanizani et al., 2001; Davis et al., 1996; Herrlin et al., 2000; Westphal 2000). In animal studies, inhibition of Pgp are reported to have impact on the methadone serum levels(Ortega et al., 2007; Rodriguez et al., 2004), while reports on the impact of Pgp and methadone concentration in man are conflicting(Coller et al., 2006; Crettol et al., 2006; Kharasch et al., 2004b). However, a drug such as paroxetine is suggested to inhibit major metabolic pathways for methadone in addition to its inhibitions of Pgp in patients on methadone maintenance treatment(Begre et al., 2002).

Methadone is known to block potassium channels required for rapid cardiac muscle repolarization (increasing the QT time), which may explain the associated risk of arrhythmia, particularly the potentially lethal torsade de pointes arrhythmia(Viskin 1999). The reported frequency of methadone induced long QT time varies between 7% and 83%, depending on the patients population and the methadone dose (Fredheim et al., 2006a; Krantz et al., 2003; Krantz et al., 2005; Martell et al., 2005; Pearson and Woosley 2005; Reddy et al., 2010). However, critical QT_c prolongation (exceeding 500 msec or increases exceeding 60 msec) occurs infrequently(Krantz 2008). In the few studies reporting QT time in cancer patients, a QT prolongation is described in up to 28% of the patients with only a few > 500 msec, and no arrhythmias are reported. (Kornick et al., 2003; Reddy et al., 2004; Reddy et al., 2010). The evidence concerning the influence of

methadone on QTc has been conflicting, and the risk of developing arrhythmia is not yet established(Heppe et al., 2010).

1.4 Opioid switching to methadone

1.4.1 Definition, indications and rationale

Opioid switching or opioid rotation is the practice of substituting one strong opioid for another when there is an unacceptable unbalance between pain relief and side effects from the first opioid. Major indications for switching the opioid are(Daeninck and Bruera 1999; de Stoutz et al., 1995):

- Pain is controlled, but the patient experiences intolerable side effects.
- Pain is not adequately controlled, but it is impossible to increase the dose due to side effects.
- Application problems such as swallowing difficulty, vomiting, or local irritation exists.
- Pain is not adequately controlled by rapid increasing the dose of opioids.

The last point remains controversial, as further escalating the dose could provide appropriate analgesia. Pure agonist opioids have no ceiling effect, which suggests that only side effects will limit a further escalation of the opioid dose. However, a rapid opioid escalation has been recognized as a negative predictive factor for the clinical response(Mercadante and Portenoy 2001).

Methadone is the most commonly applied second line opioid in the treatment of cancer pain or chronic non-malignant pain when other strong opioids fail to provide acceptable pain relief or side effects (Cherny and Foley 1996; Fredheim et al., 2008; Lawlor et al., 1998; Quigley 2004; Weschules and Bain 2008). The few studies providing data on the patients former opioid treatment are retrospective, and often incomplete regarding how long opioids are used before the switch to methadone, which opioids have been tried before the switch and how long methadone is utilized after the switch(de Stoutz et al., 1995; Kloke et al., 2000; Muller-Busch et al., 2005). The opioid history prior to a switch to methadone will depend on what causes the pain, which opioids and formulations are available due to restrictions, cost and setting/level of care. In a retrospective study within a tertiary cancer care center, the opioid history of 273 cancer patients where the WHO recommendations for cancer therapy were strictly followed; 68.9 % used morphine initially, 16.5% fentanyl, 11% buprenorphine and 2.9% used levomethadone. As many as 37.5% changed their opioid once, 21.4% changed twice, 6.8% three times and one patient five times(Kloke et al., 2000). A recent pharmacoepidemiological study, from a Norwegian prescription database on methadone switching, found that 77% of the cancer patients that switched to methadone received more than one dispensed methadone prescription, and that 31.5% had tried two or more strong opioids prior to the switch to methadone(Fredheim et al., 2011).

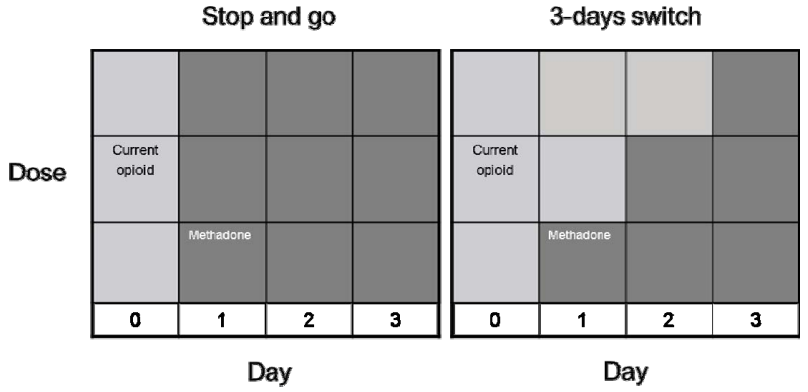
The biological mechanisms of the effect of opioid switching are not fully understood. Several different mechanisms have been suggested including differences in opioid receptor binding profiles, effects on receptors other than the μ-opioid receptor, effects from active metabolites and differences in pain conditions. The keystone to success of opioid switching is often explained by the concept of incomplete cross-tolerance between opioids(Cherny et al., 2001; Indelicato and Portenoy 2002; Mercadante 1999). In addition, genetic influence on individual responses to different opioids are reported and reviewed(Klepstad et al., 2005a; Lacroix-Fralish and Mogil 2009; Lotsch and Geisslinger 2006; Lotsch et al., 2009; Somogyi et al., 2007). Inter-individual responses to opioids are further outlined in a previous section of this introduction.

Opioid switching has become an established practice for the management of cancer related pain, and the maneuver is recommended by experts of the EAPC(Hanks et al., 2001), an interdisciplinary expert panel in the USA(Fine and Portenoy 2009) and in major text books on cancer pain(Bruera and Portenoy 2003; Davis et al., 2009; Fallon et al., 2010; Hanks et al., 2009). While opioid switching is generally recognized, there are several unresolved questions when switching the opioid; which opioid, switching strategy and equianalgesic dosage should be applied? Few studies have evaluated the outcomes of sequential opioid trials, and there are no specific data on the optimal order of administration(Muller-Busch et al., 2005).

1.4.2 Switching strategies

Several switching strategies are purposed and found effective when switching to methadone. However, no method is found to be superior and no randomized trials have compared the strategies (Weschules and Bain 2008). Two commonly used switching strategies at the time when this thesis was planned can be described as the “stop and go” (SAG) and “the 3-days switch method” (3DS) (Leppert 2009; Mercadante and Bruera 2006) (fig 5). In the 3DS strategy, also referred to as the Edmonton model(Bruera and Neumann 1999; Chhabra and Bull 2008; Lawlor et al., 1998), the dose of the primary opioid is tapered stepwise over three days (one third reduction each day) and substituted with the equianalgesic doses of methadone (Fredheim et al., 2006b; Lawlor et al., 1998; Ripamonti et al., 1997).

Fig5. The stop and go strategy (SAG) and the3-days switch (3DS) strategy when switching to methadone



When switching according to the SAG strategy, the initial opioid is terminated and immediately replaced with an equianalgesic dose of methadone (Mercadante et al., 1999). The SAG strategy is claimed to allow rapidly effective analgesia and stable plasma concentration of methadone with quick side effect resolution because of elimination of pervious opioid and metabolites(Mercadante et al., 2003; Soares 2005). 3DS proponents claim that the procedure prevents accumulation of methadone, especially in patients on high opioid doses(Lawlor et al., 1998; Ripamonti et al., 1998a). Neither of the claims have been exposed to a randomized study design(Dale et al., 2011). Other switching strategies include a switch during a week (Morley et al., 1993), gradually during several (Hagen and Wasylenko 1999; Hays and Woodroffe 1999), and a "methadone ad libitum" strategy (Cornish and Keen 2003; Tse et al., 2003). Nauck et al. reported a German model of switching from high morphine doses (≥ 600 mg/d) to methadone, where the current opioid was stopped, and 5-10 mg of R-methadone given po every 4 hours, with the same rescue dose given as needed. After 72 hours the patients' dosing intervals are adjusted to every 8 hours(Nauck et al., 2001).

1.4.3 Equianalgesic ratios

At the time when this thesis was planned, commonly recommended equianalgesic dose ratios from morphine (Mo) to methadone (Meth) were 1:1 to 4:1(Inturrisi and Hanks 1998; Mercadante et al., 1999). Several studies of opioid switching have, however, reported dose ratios which are substantially higher and with large interindividual variations (Gagnon and Bruera 1999; Lawlor et al., 1998; Ripamonti et al., 1998a; Ripamonti et al., 1998b). In seven patients with preswitch morphine doses above 1165 mg/day, a mean morphine: methadone ratio of 17:1 has been reported, with range 12:1 to 88:1 (Lawlor et al., 1998). Some studies of opioid switching have applied dose dependent dose ratios from 3:1 to 20:1(Ayonrinde and Bridge 2000; Fredheim et al., 2006b; Ripamonti et al., 1998b), while others have applied a fixed dose ratio of 5:1 for pre

switch morphine doses as high as 400 mg/day (Mercadante et al., 1999). An alternative approach to using equianalgesic tables, is the use of algorithms to determine the proper methadone dose(Morley and Makin 1998; Plonk 2005). There are strong indications that the differences in ratios may be explained by dose-dependency (Ayonrinde and Bridge 2000; Lawlor et al., 1998; Ripamonti et al., 1998b). However, also interindividual differences in pharmacokinetics as drug-drug interactions may influence dose ratios (Anderson et al., 2001). Moreover, trial design (sequential or parallel), trial population (acute pain, non malignant pain or cancer pain, opioid naïve or tolerant) and measurements of pain response will play a significant role in reported relative potencies (Berdine and Nesbit 2006). Benitez-Rosario et al. analyzed dose ratio predicting factors in cancer patients when switching from morphine to methadone, and found that the reasons for switching and the previous opioid doses were predictive factors and should be used to select the right methadone dose(Benitez-Rosario et al., 2009). Weschules et al. concluded in a recent review of studies on opioid conversion ratios used with methadone between 1966 and 2006 (N=730) that there was no evidence to support one method of rotation to methadone over another, and 46-89% of rotations were reported as successful(Weschules and Bain 2008).

Only three studies report switching from methadone to an alternative opioid(Lawlor et al., 1998; Moryl et al., 2002; Walker et al., 2008). The direction of opioid switching is important, as the conversion factors that result are not necessarily equivalent when switching the opioid in the opposite direction. Walker et al. reported retrospective data from 29 cancer patients (mean methadone dose 35 mg/d) with a mean dose ratio of oral methadone to oral morphine of 1:4.7 and from iv methadone to oral morphine 1:13.5(Walker et al., 2008). Lawlor et al. reported a sub analysis of six patients switched from oral methadone to morphine with a median ratio of 1:8.25(Lawlor et al., 1998). Moryl et al. switched 13 patients at a tertiary cancer center from methadone to different opioids and reported that the initial dose of the second opioid in eight of the 13 patients was lower than equianalgesic dose recommended by the American Pain Society (APS) (Me: Mo=1:3.3), while the dose at 24 h exceeded the APS recommended doses in 11 patients. Only one was successfully maintained on the second opioid. The 12 others were switched back to methadone because of side effects(Moryl et al., 2002).

1.4.4 Studies on switching to methadone

The studies on opioid switching to methadone are heterogeneous; the main difference between studies are in preswitch opioid dose (and various opioids), switching strategies, and definitions and measurements of outcomes. The switches are often not only a switch to and from different opioids, but also a switch of route with reporting of pooled results. In a systematic Cochrane review on opioid switching published in 2004 no randomized controlled trials (RCTs), but 52 uncontrolled trials were found, of which 14 were prospective(Quigley 2004). Quigley stated that reporting bias was highly probable as only one study reported potential problems with switching(Moryl et al., 2002). However, it was also concluded that opioid switching appeared to be effective, both in terms of improving pain control and reducing opioid related side effects. It was called for better controlled studies(Quigley 2004). This has also been the conclusion in more recent

reviews on opioid switching in cancer patients(Mercadante and Bruera 2006; Vadalouca et al., 2008) and also when including studies on chronic non-cancer patients(Weschules and Bain 2008). A recent systematic review of opioid switching to improve pain control or reduce side effects (after 2003) which built on the review from Quigley et al. included 11 papers whereof none were RCTs/meta-analyzes(Dale et al., 2011). The studies had a groups size of 10-32 patients, a variety of opioids, switching strategies and ratios were studied, observation period varied greatly (4 days to 4 weeks) and switching strategies and the level of evidence was graded D (Grade's approach(Atkins et al., 2004)). Both prospective and retrospective studies have reported switches to methadone from morphine alone in cancer patients(Benitez-Rosario et al., 2009; Mercadante et al., 2003; Mercadante et al., 1999; Mercadante et al., 2001; Morley et al., 1993; Ripamonti et al., 1998b; Tse et al., 2003) and in non-cancer patients(Fredheim et al., 2006b). No studies have reported on switches from oxycodone alone, but switches from oxycodone have been included in studies describing pooled data.(Ripamonti et al., 1998a; Sawe et al., 1981; Thomsen et al., 1999). To further describe the different outcomes and strategies used in studies including switches from morphine or oxycodone to methadone in cancer patients; more details are displayed in table 2.

Table 2. Studies including switches from morphine/oxycodone to methadone in cancer patients

Study ID	Design	Preswitch drug (N) before Meth	Preswitch ratio Mo: Meth	Participants, Baseline Mo dose	Switching strategy	Observation time	Outcomes	Results
(Sawe et al., 1981) Inpatients 1 center	Pros	Ox(2) Various	-	Cancer, 14, Severe pain	Stop and titration	7 d	Investigate effectiveness of fixed dose of Meth (10 mg/d). Decreased PI and AEs	Patient controlled regimen effective and safe. 11/14 complete or almost complete pain control. Steady state meth trough concentrations after 2-3 d (7-fold variation d5). 3 failures
(Ripamonti et al., 1998b) Inpatients 1 center	Pros	Mo (38)	4:1 (<90mg/d) 6:1 (90-300 mg/d) 8:1 (> 300 mg/d)	Cancer, 38, 145 mg/d (range 30-800), nociceptive pain, no anti-cancer treatment, no liver/kidney disease	3DS Meth titrated day by day	1-7 d (?) until equianalgesia	Dose ratios PI before, during and after (Therapy Impact Questionnaire, TPQ 1-4) Number of days to achieve equianalgesia	< 90 mg Mo median 2 d until equianalgesia, 90-300 mg Mo median 3 d and ≥ 300 mg Mo median 5.5 d. The lower the preswitch dose, the fewer days to reach equianalgesia with meth. 49 enrolled. Median dose ratio 7.75:1 (range 2.5:1-14.3:1).Median PI unchanged the first week. Median 3d for equianalgesia
(Ripamonti et al., 1998a) In- and outpatients 2 centers	Retro	Ox (15) Mo (15) Hydromorphone (37-all inpatients) Various	-	Cancer, 88 (51 outpatients and 37 inpatients), opioid toxicity ± pain	-	-	Equianalgesic dose ratio between oral meth and other opioids in two different cohorts. Analgesia (VAS 0-100) (inpatients) and integrated pain score (IPS) (outpatients)	Meth more potent than described previously, ratio correlates with preswitch opioid dose. Pooled data: Sign. reduction of PI: Inpatients: 5.0 reduced to 3.9, Outpatients 39.2 to 25.6
(Lawlor et al., 1998) Inpatients 1 center	Retro	Mo (14) Meth (6)	10:1	Cancer, 19 (20 rotations) 1165 mg/d (range 85-24027), cancer with pain rotated to or from meth	3DS	Until stabilized meth dose (min 4 d)	To determine the equianalgesic Mo: Meth ratio. PI (VASP 0-100)	Median ratio Mo: Meth= 11.36 (range 5.98-16.27) Median 5 d to reach stable Meth doses. Strong corr. between dose ratio and previous Mo dose. No sign difference in mean PI ratings before and after rotation
(Mercadante et al., 1999) Outpatients/ home care 1 center	Pros	Mo (24)	5:1	Cancer, 24, 125 mg/d, not advanced disease or short life expectancy. Poorly responsive to Mo	SAG Rescue as needed	3d	To investigate effects of abrupt switch. Distress score (sum of symptom intensity), AEs 0-3 (not at all to awful), PI (VAS 0-10)	SAG is safe and effective. 19/24 successful switch, PI form 5.7 to 3.8 (stat sign). Distress score from 5.1 to 3.6 (stat sign). 5 dropouts
(Ayonrinde and Bridge 2000) Outpatients 1 center	Pros	Mo (6) Ox (1) Various (7)	3:1 (<100 mg) 5:1 (101-300 mg) 10:1 (301-600 mg) 12:1 (601-800 mg) 15:1 (801-1000 mg) 20:1 (> 1001	Cancer (10) and non-cancer (4), Neuropathic pain, 30-1140 mg/d. Severe pain with side effects.	"SAG" Loading dose (25-50%) for 2 d, and titration. Initial dosing interval 6h-increasing to 12 h	7-60 d	Not defined	Improved analgesia within one day in 79% of patients, and achievement of maintenance dose within three days in 64% of patients. Significant sedation seen in two patients, - not further described (meth given sc).

			mg)					
(Mercadante et al., 2001) In- and outpatients 1 center	Pros	Mo (52)	4:1 (<90 mg/d Mo) 8:1 (90-300 mg/d Mo) 12:1 (> 300 mg/d Mo)	Cancer, 52, 159 mg/d, PI >4 (NRS 0-10). No anti cancer treatment, cognitive failure or kidney/liver disease	SAG and titration	Until stabilized dose (3-5d)	Reducing PI < 4 and AEs to a clinical acceptable level. PI (VAS 0-10), AEs Likert type scale 0-3 (none to severe). Distress score (DS)=Sum of symptom intensity was used	Effective switch in 80 % after 3.65 d. PI mean 6.15 to 3.06 (sign), Sign reduction of nausea, drowsiness, constipation and DS. 2 patients excluded (1 incomplete data and 1 poor compliance)
(Mercadante et al., 2003) In- and outpatients 1 center	Pros	Mo (10)	5:1	Cancer, 10, 317 mg/d (CI 22-612), NRS> 4 and/or AEs despite symptomatic treatment	SAG	4 d	Plasma concentrations of Mo, M6G, M3G and Meth Pain: PI (NRS 0-10) or pain relief AE: confusion, myoclonus, drowsiness (VRS 0-4)	Plasma concentrations: Mo, M3G and M6G almost eliminated after 3 d. Meth stabilized after 2 d. Pain: PI mean 6.9 reduced to 2.9 (p>.05) within 1-2d AEs: Not reported separately. 50% needed about 20% increase of methadone doses
(Tse et al., 2003) Inpatients 1 center	Pros	Mo (37)	12:1 (max 30 mg/dose)	Cancer, 37, 120 mg/d (30-600), terminal patients with pain or AEs	Ad libitum (1/12 of baseline Mo dose given as required (max 30 mg Meth. Min 3h between doses)	14 days/ (until pain control	To evaluate effectiveness of rotation: PI d7. Pain (VRS 0-4, no pain to overwhelming). AEs: unchanged, improved or resolved	10 dropouts (4 died, 1 stopped all opioids, 1 moved, 4 could not take oral route). 88.9% good pain control d7 (range 1-11d), all d11. 88.6% of AEs resolved. Ad libitum effective
(Auret et al., 2006) In- and outpatients, Multicenter (No. not defined)	Pros	Mo (15)	6:1	Cancer, 15, 178 (SD 126) mg/d	SAG	15 d (mean 8.3 d)	To investigate relation between s-concentrations of Mo before and Meth after .Worst pain (BPI) and side effects	2 patients withdrawn, one died day 7. Worst pain improved by ≥ 20% in 6/13 patients (46%), mean Mo: Meth ratio was 5.2 (SD 2.8). No relationship between pain and s-concentrations
(Benitez-Rosario et al., 2009) Inpatients 1 center	Retro	Mo (54)	5:1 (82%) 10:1 (18%)	Cancer, 54, 220 mg/d (range 30-1000), successfully switched from Mo to meth and stable dose d10	SAG and titration (every 48-72 h by ± 30-50%)	10d	Factors influencing the Mo: Meth ratio d10	Median Mo: Meth ratio 5:1 (range 2:1-15:1).Reason for switching (P/AEs) and preswitch Mo dose were sign. predictive for ratio
(Parsons et al., 2010) Outpatients 1 center	Retro	Strong opioid (not specified)	5:1 (<90 mg/d), 8:1 (91-300 mg/d), 12:1 (> 301 mg/d)	Cancer, total 189, 89 rotated (47%), 100 mg/d (range 60-185), receiving methadone as 1 line or rotated to methadone because of pain	SAG	23-60d (two follow-up visits)	Safety when initiating meth or rotating to meth in outpatients. Pain, nausea and drowsiness (ESAS-NRS 0-10) Other AEs not reported in ESAS: present if reported by physician.	Pooled data. 85% success rate of the rotations. Constipation and nausea improved sign. Other AEs did not increase after rotation. Median time between first visit and follow up was 15 d (range 10-25). 7 dropouts (all failures). Outpatient rotations are safe and effective

							Complete success were ≥ 2 points or ≥ 30% reduction and/or disappearance of AEs	
(Mercadante et al., 2003) In- and outpatients 1 center	Pros	Mo (10)	5:1	Cancer, 10, 317 mg/d (CI 22-612), NRS> 4 and/or AEs despite symptomatic treatment	SAG	4 d	Plasma concentrations of Mo, M6G, M3G and Meth Pain: PI (NRS 0-10) or pain relief AE: confusion, myoclonus, drowsiness (VRS 0-4)	Plasma concentrations: Mo, M3G and M6G almost eliminated after 3 d. Meth stabilized after 2 d. Pain: PI mean 6.9 reduced to 2.9 (p>.05) within 1-2d AEs: Not reported separately. 50% needed about 20% increase of methadone doses

Retro= retrospective study, Pros= prospective study, Mo= morphine, Meth= methadone, F=female, M= male, AE= adverse effect, and PI= pain intensity

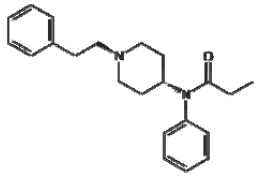
Only two studies had reported plasma concentrations of methadone after a switch from morphine/oxycodone when this thesis was planned(Mercadante et al., 2003; Sawe et al., 1981). Mercadante et al. switched 10 cancer patients (mean age 65.9 years, M8/F2) on a mean dose of morphine of 317 mg/d (CI 22-612) with pain and/or intolerable side effects to methadone, using the SAG strategy and a fixed ratio of 5:1 (Mo: Meth). Blood samples were obtained at 9am (1-2 h after the morning dose of methadone). Stable methadone concentrations were reported after 1-2 days and almost complete removal of morphine and metabolites within three days. Pain intensity (NRS 0-10) was reduced from a mean of 6.9 to 4.2 after one day of methadone treatment and observational time was three days(Mercadante et al., 2003). Only one study describes plasma concentrations of methadone after a switch from oxycodone (2/14 patients) in cancer patients(Sawe et al., 1981). The switching strategy was patient controlled (fixed dose of 10 mg as needed) and trough methadone concentrations were at steady state after 2-3 days. Plasma concentrations of methadone varied seven-fold after four to five days. 11/14 reported complete or almost complete pain relief at day six. Later, Auret et al. reported that steady state of venous trough R-methadone concentrations was achieved after 3.7-7.7 days in 11/13 advanced cancer (in-and out-) patients after a switch from morphine to methadone because of pain or side effects (SAG with a fixed ratio of 6:1) in an uncontrolled prospective study(Auret et al., 2006). 6/13 patients reported a clinically significant improvement of worst pain by ≥20%. Fredheim et al. switched 12 out-patients with non-malignant pain from morphine to methadone by the 3DS strategy(Fredheim et al., 2007). Steady state of methadone and complete elimination of morphine and metabolites were achieved after one week.

1.5 Nasal fentanyl and breakthrough pain

1.5.1 History and pharmacological aspects of fentanyl

Fentanyl is a highly lipid-soluble, short-acting, synthetic opioid (fig. 6), that was synthesized by Dr. Janssen in 1960 and was first used during general anesthesia. In the mid 1990s, fentanyl saw its first widespread use in cancer pain with the clinical introduction of the transdermal patch(Stanley 1992). In the 90s interest for fentanyl given transmucosally in palliative care arose. Most commonly, fentanyl is administered as iv bolus and continuous iv infusion. However, other modes of administration such as subcutaneous, intraspinal (epidural and intrathecal), transdermal, buccal, and intranasal are also utilized in clinical practice(Davis 2010).

Fig 6. Structural formula of fentanyl



Fentanyl is a pure μ-receptor agonist and it is 50-100 times more potent than morphine(Prommer 2009). When given orally, fentanyl is absorbed through the gastrointestinal tract and undergoes extensive intestinal and hepatic first-pass metabolism, making it less bioavailable (32%) and other routes more preferable(Labroo et al., 1997; Streisand et al., 1991). Fentanyl absorption via the mucosal surface is pH dependent. An alkaline pH leads to a larger proportion of the dose absorbed, and a shorter T_{max}(Weinberg et al., 1988). Fentanyl has a V_d about 4L/kg, estimates of terminal $t_{1/2}$ range from about 1.5 to 6 h (15 h in geriatric patients) and total body clearance (CL) ranges from 0.4 to 2.4 L/min(Lim et al., 2003; Mather 1983). Once absorbed into the systematic circulation, fentanyl passes rapidly across the blood-brain barrier(Shafer and Varvel 1991). Fentanyl has been suggested being a Pgp substrate in mice and humans(Kharasch et al., 2004a; Thompson et al., 2000), and genetic polymorphisms in the gene that encodes for Pgp have been suggested to affect the clinical effects of fentanyl(Park et al., 2007; Thompson et al., 2000). Fentanyl is metabolized in the liver (90%) and in duodenum mainly via CYP3A4 to pharmacologically inactive metabolites, such as norfentanyl and hydroxyfentanyl, which are excreted in the urine(Feierman and Lasker 1996; Labroo et al., 1997; Tateishi et al., 1996). Significant interactions may occur when fentanyl is administered concomitantly with CYP3A4 inhibitors(Hallberg et al., 2006; Saari et al., 2008). Also, CYP3A4 inducers, have been reported to interact with fentanyl by increasing the clearance(Morii et al., 2007; Takane et al., 2005).

1.5.2 Pharmacological breakthrough pain management

Breakthrough pain (BTP) is a heterogeneous phenomenon commonly managed with short acting oral opioids as “rescue medication” in addition to the fixed-schedule opioid regimen used to control the background pain. The EAPC recommendation on BTP treatment at the time when this thesis was planned, was to use the same opioid as the four-hourly dose of normal-release morphine, when necessary(Hanks et al., 2001). Oral opioids have, however, a delayed onset to analgesia relative to peak of pain for most BTP episodes, and have a long duration of effect (4-6h), which means that they are active for much longer than required to treat a typical BTP episode(Portenoy and Hagen 1990; Zeppetella 2008; 2009b). The oral rescue dose for BTP management has been assumed to have some relation to the around the clock (ATC) dosage, and 10-20% of the daily opioid dose have been recommended as starting doses(Benedetti et al., 2000; Cormie et al., 2008; Hanks et al., 2001; Zeppetella 2009b). However, the effective opioid dose is reported to be poorly related to the total daily dose of opioids(Christie et al., 1998; Portenoy et al., 1999b; Portenoy et al., 2006; Zeppetella and Ribeiro 2006). In one study the effective BTP opioid dose size varied from 1%-71% of the total daily dose of opioids (Hagen et al., 2007). This indicates that a successful BTP opioid dose should be determined by titration(Davies et al., 2009; Zeppetella 2011; Zeppetella and Ribeiro 2006).

Apart from the oral route, other routes such as the intravenous(Mercadante et al., 2004), subcutaneous(Enting et al., 2005), rectal(De Conno et al., 1995), and intrathecal(Hassenbusch et al., 2004) may be used to administer opioid analgesics for BTP.

The oral transmucosal fentanyl citrate (OTFC) was the most extensively studied novel route of BTP medication at the time when this thesis was planned(Christie et al., 1998; Coluzzi et al., 2001; Farrar et al., 1998; Portenoy et al., 1999b), and this became the first medication developed specifically for treating cancer and non-cancer BTP in opioid tolerant patients(Panagiotou and Mystakidou 2010). OTFC consists of a fentanyl-impregnated lozenge (available from 200 to 1600 μg), and requires that it be rubbed on the buccal surface until dissolved (usually within 15 min)(Aronoff et al., 2005). As the lozenge dissolves, approximately 25% is rapidly absorbed while 75% is swallowed, and a third is absorbed through the GI tract(Aronoff et al., 2005). The T_{max} varies from 20-40 min (range 20-480 min) and meaningful pain relief within 15 min is reported in controlled studies (Coluzzi et al., 2001; Mystakidou et al., 2006). The bioavailability of OTFC in healthy volunteers is 50% compared to iv fentanyl(Streisand et al., 1991). OTFC has been compared to normal release morphine(Coluzzi et al., 2001), morphine given intravenously(Mercadante et al., 2007b) and to placebo(Farrar et al., 1998), with the conclusion that OTFC had a significantly faster onset of analgesia and reduced PI more effectively. In a review of three OTFC trials involving 257 cancer patients, responses did not correlate with age, BMI, pain mechanism, ATC opioid dose or opioid dose used to treat BTP prior to the studies(Hagen et al., 2007). Studies on OTFC has recently been thoroughly reviewed with the conclusion that it has a rapid onset to analgesia, and appears to be superior to oral morphine in the treatment of BTP(Davis 2010; Portenoy 2011; Zeppetella 2011).

In the late 90s, there was an increasing interest in the nasal administration of opioids, primarily because of the possible rapid onset of action and that nasal administration could be performed by the patients themselves. The nasal route could also be acceptable to patients with dysphagia, nausea/vomiting, impaired gastrointestinal function, or xerostomia(Dale et al., 2002a; Shelley and Paech 2008). As many as 75% of patients with late stage cancer have reduced salivary flow and/or impaired function(Chaushu et al., 2000; Davies et al., 2011b; Davies and Vriens 2005; Sweeney et al., 1998) and xerostomia is an adverse effect related to morphine(White et al., 1989), and it might be a problem when administering OTFC(Davies and Vriens 2005). Other forms of administrating fentanyl was therefore of interest when treating BTP, and PK studies of intranasal fentanyl were needed.

1.5.3 Intranasal fentanyl

1.5.3.1 Characteristics of the nose and intranasal drug administration

The nasal cavity has a surface area of 150-180 cm2 and internal volume of 15-20 ml(Dale et al., 2002a). Blood flow to the nasal mucosa is extensive, and is considered to be greater per cm^3 tissue than in muscle, brain and liver. The thin mucosa, blood supply and fenestrated capillaries differ from the oral mucosa and are an advantage to drug absorption. The pH of the nasal cavity ranges between 5.5 and 6.5, which influences drug ionization and absorption. Drugs absorbed from the nasal cavity will bypass gastrointestinal and hepatic presystemic elimination. No fat deposits to delay systemic absorption or alter drug half life exist. There is theoretically a rapid access to the

subarachnoid space by way of perineural spaces around the olfactory sensory nerve(Dale et al., 2002a; Wu et al., 2008). Nasal administration of drugs may be challenging, as the maximum volume before run off to pharynx is 150µl. This indicates that the opioids administered nasally need to be highly concentrated(Dale et al., 2002a). Local toxicity might be a problem, and penetration enhancers might be expected to cause local irritation(Hjortkjaer et al., 1999).

1.5.3.2 PK of intranasal fentanyl

The first PK studies of intranasal fentanyl (InF), were randomized, crossover trials in young non-cancer patients(Lim et al., 2003; Striebel 1993) (table 3). The Striebel et al. study compared in fentanyl with iv fentanyl in a double-blinded fashion(Striebel 1993). The patients were young (mean 31.5 years), healthy volunteers. A dose of approximately 50µg of fentanyl was given (12 sprays a 0.09 ml, pH 4-5). Ten venous plasma samples were drawn from 5-120 min after administration. Striebel et al. reported a mean T_{max} of 14 min (range5-40 min) and high bioavailability of 71%, but with considerable interindividual variation. The major problem with this study was that 90 µl doses given 12 times using both nostrils was needed to deliver the dose of 50 µg. Lim et al., used a more convenient volume of 0.18 ml with 50µg of fentanyl citrate comparing two in formulations with different pH with iv administration (non-blinded)(Lim et al., 2003). 19 postoperative females from 27 to 63 years participated. Six venous serum samples were taken during the first 15 min after administration. T_{max} was found between 4 and 10 min (formulation with a pH of 6) and between 4 and 11 min (pH 8). The bioavailability was 55% with the pH 6 formulation, which was not statistical significantly different from 71% with the pH 8 formulation.

Besides fentanyl, other opioids such as nasal morphine(Fitzgibbon et al., 2003; Pavis et al., 2002), sufentanil(Good et al., 2009; Jackson et al., 2002), alfentanil(Duncan 2002) and the derivative ketamine(Carr et al., 2004) have been studied in cancer patients with BTP.

The more recent PK studies on nasal fentanyl used a more appropriate volume of 100µl and a buffer to reach the desirable pH for intranasal administration (pH6-8) have been used(Christrup et al., 2008; Fisher et al., 2010a; b; Foster et al., 2008; Veldhorst-Janssen et al., 2010). Christrup et al. performed a randomized, double-blind, double-dummy crossover study, where 24 opioid-naïve third molar extraction patients received a dose of 75, 100, 150 or 200 µg of fentanyl citrate in or iv(Christrup et al., 2008). The T_{max} was double (approximately 12 min) compared to iv. The same study reported by Foster et al. found a bioavailability of 89% after InF(Foster et al., 2008). Fisher et al. compared three different InF formulations of fentanyl citrate (pectin, chitosan and chitosan-poloxamer 188) to OTFC in 18 healthy volunteers in a randomized, open cross-over study(Fisher et al., 2010a). They were dosed with three nasal sprays (100 µg in 100 µl) and OTFC 200 µg under naltrexone blockade to avoid centrally mediated opioid effects. Venous blood samples were collected before and 15 times up to 1440 min. The mean dose-normalized $AUCs_{0-\infty}$ and the bioavailability were significantly higher for the InF compared to OTFC. Fisher et al. also conducted a single-dose study comparing 100, 200, 400 and 800 µg of InF to OTFC in 16 healthy volunteers(Fisher et al., 2010b). Venous blood samples were

collected up to 48 hours post-dosing. The study demonstrated that the InF plasma profile had a shorter T_{max} and higher C_{max} than OTFC. Two subjects withdrew because of adverse effects. The most commonly reported adverse effects were mild or moderate nasal discomfort or headache. However, only subjects who were more tolerant to fentanyl progressed to higher doses. Veldhorst-Janssen et al. compared InF to placebo in healthy women(Veldhorst-Janssen et al., 2010). A single dose of 0.05 mg/0.1 mL or 0.1mL placebo was administered 10 min before removal of drains post operative. Eight of 17 patients receiving fentanyl reported ≥ one adverse event, while 9 of 16 reported this in the placebo group. The PK studies on InF are presented in more detail in table 3. All studies displayed in the table reported that InF had a short T_{max} and that it was well tolerated.

None of the above PK studies have studied cancer patients with BTP, and they have all studied venous concentrations. More than 40 compounds have been reported to exhibit significant or marked blood sampling site dependence in concentration after dosing in humans and animals(Chiou 1989a). Due to rapid absorption intranasal administration share PK characteristics with iv drug administration, and significant arterio-venous differences in serum concentrations are reported after iv administration of other opioids(Hermann et al., 1999; Rentsch et al., 2001). Also arterio-venous differences in serum concentrations after intranasal administration (nicotine) are reported(Guthrie et al., 1999). To be able to use PK parameters as predictors of the clinical effect, arterial samples may be more appropriate than venous samples. The PK characteristics that might predict time to and level of relief, the most appropriate parameters are $T_{max,}$ $C_{max,}$ exposure (AUC), and bioavailability.

Table 3 Pharmacokinetic studies of intranasal (in) fentanyl

	Study design	Patients	Fentanyl dose, volume and blood samples post-dosing	PK variables	T_{max} Mean (min-max)	C_{max} Mean (min-max)	Bio-availability	Major results
(Striebel 1993)	Randomized, double-blind, crossover (in vs. iv)	8 healthy volunteers, sex not reported, 31.5 years (range 28-37)	Total of 54 µg (12 sprays a 0.09 ml with 4.5 µg). 10 venous plasma samples from 5-120 min	T_{max}, C_{max}, $t_{1/2}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$	14.3 min (5-40)	0.18 ng/ml (0.09-0.26)	71%	Rapid concentration rise and high bioavailability
(Lim et al., 2003)	Randomized, crossover trial (two in formulations vs. iv)	19 postop. F, 10 pH6 (38.5 years, range 27-47) and 14 pH8 (42.5 years, range 33-63)	50 µg (0.18 ml), (pH 6 fentanyl citrate in ionized form, pH 8 50 % fentanyl base). 6 venous serum samples from 2-15 min	T_{max}, C_{max}, $t_{1/2}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, CL	4.2-10 min (pH 6), 4.8 - 11.4 min (pH 8)	0.33 ng/ml (pH6), 0.37 ng/ml (pH8)	55% (pH6) 71% (pH8)	A higher pH did not alter results. Absorption of InF is rapid
(Christrup et al., 2008)	Randomized, double-blind, double-dummy, 2-way, crossover (in vs. iv)	24 opioid naïve, 13F/11M, 24.1 years, third molar extraction patients	1 of 4 doses: 75, 100, 150 and 200 µg, 100µl, fentanyl citrate. 14 venous plasma samples from 0-180 min	T_{max}, C_{max}, $t_{1/2}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, CL, V_d, C_{ss}	10.8 (75 µg)-13.8 min (200 µg) vs. 6 min iv	0.7 ng/ml (75 µg) -1.7 ng/ml (200 µg) and 0.9-2.6 ng/ml iv	-	Onset and duration of analgesia was not sign. different between in and iv administration. Both well tolerated
(Foster et al., 2008) (same study as Christrup)	As above	As above	As above	PK and PD correlation of in and iv fentanyl	13 min (pooled data)	1.2 ng/ml (pooled data)	89%	Duration and effect related to dose. InF absorption was rapid and almost complete
(Fisher et al., 2010a)	Phase I, single dose, randomized, open-label, crossover (3 in formulations vs. OTFC)	18 healthy volunteers, 5F/13M, 29.8years (range 18-50)	5 treatments: 100, 200, 400 and 800 µg, 100µl, and 200 µg of OTFC. 16 venous plasma samples from 0-24h	T_{max}, C_{max}, $t_{1/2}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$	Median 10-20 min, OTFC 90 min	337-647 pg/ml, 2.3 fold higher than OTFC	Relative to OTFC: 122-154%	All InF formulations showed sign. increased systemic exposure and reduced time to peak plasma values compared to OTFC
(Fisher et al., 2010b)	Phase I, single-dose, open, five-period, cross-over study (4 doses of InF vs. OTFC)	16 healthy volunteers, 8M/8F, 39 (SD16) years	100, 200, 400 and 800 µg, 100µl, and 200 µg of OTFC. 18 venous plasma samples from 0-48h	T_{max}, C_{max}, $t_{1/2}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$	Median 15-21 min	After 100 µg: 352 (SD 180) pg/ml	Relative to OTFC: 103-163%	InF has shorter T_{max}, higher C_{max} and greater bioavailability than OTFC. Well tolerated.
(Veldhorst-Janssen et al., 2010)	Randomized, double-blind, single dose (in vs. placebo)	36 F, 39.2 years, drain removal after breast reduction	50 µg in 100 µl. 7 venous plasma samples from 0-120 min	T_{max}, C_{max}, $t_{1/2}$	13.8 min	Estimated 0.18 ng/ml, measured 0.22 ng/ml (below the therapeutic window)	-	InF sign. more effective than placebo the first h, but not later. Well tolerated

Research questions

This thesis addresses two emerging principles of cancer pain management:

- How to switch from one opioid to methadone when patients on high doses of opioids experience an imbalance between pain and side effects
- Exploring the pharmacokinetic (PK) profile of nasal fentanyl spray as a novel principle of treatment of cancer breakthrough pain

More specifically, the thesis answers the following research questions:

In a randomized, open, multicenter, parallel group study, the principle of an opioid switch from morphine or oxycodone to methadone was addressed with the following main research questions:

1) Is the stop and go (SAG) switching strategy more effective than, and as safe as the standard 3-days switch (3DS)?
2) What is the pharmacological profile of the respective opioids, and how can it guide clinical interpretations and clinical practice of a methadone switch?

In a randomized, open, multicenter, cross-over trial and an open pharmacokinetic trial, the pharmacological and clinical features of nasal fentanyl were addressed as follows:

3) How fast is the maximum concentration of fentanyl achieved after nasal administration?
4) Does opioid naïve and opioid exposed subjects tolerate nasal fentanyl?
5) Is there a significant difference between the early venous and arterial pharmacokinetics of nasal fentanyl?

Material and methods

1.6 Patient cohort

This thesis is based on studies performed in three patient cohorts. Two studies included cancer patients on opioids for cancer pain (Study A: paper I, II and study B: paper III), while one study included opioid naïve patients scheduled for transurethral resection of the prostate or urinary bladder (Study C: paper IV). All studies included patients > 18 years with no history of substance abuse. An overview of characteristics is given in table 3. The reason for choosing these cohorts was to include patients that were representative for the target population of an opioid switch or BTP treatment.

The 42 cancer patients included in study A(paper I and II) were both in-and out patients, and were recruited in representative centers for these patients in Norway; the departments of palliative care, oncology or surgery at four hospitals in Norway between June 2004 and March 2008. Ninety per cent were included from palliative care units, and only one patient was an out-patient. The patients in need of an opioid switch were identified by the investigator/physician or staff on the different units. Forty five patients were enrolled, whereof three did not meet the inclusion criteria. Inclusion criteria were cancer patients treated with morphine or oxycodone for more than a week, no cognitive failure (if not opioid related), and experiencing cancer related pain (considered to be untreatable with further opioid titration by the physicians) and/or opioid side effects. Data on one patient in the 3DS group were not retrieved, as the study center could no longer participate. Three patients had prolonger QT_c time (2 SAG and 1 3DS), and were excluded before the intervention. One inclusion was a protocol violation (SAG), and one patient withdrew the consent (SAG). Thirty-five patients received methadone (SAG 16 and 3DS 19), and were included in the pain, adverse effects and final dose ratio analysis if still included on the days of measurement. In the PK analyses, the patients still included at the day of measurement were included, except for the samples from one patient (3DS) who was excluded from all analyses of morphine and M6G as there was a technical error in the analysis of morphine. Six patients dropped out in the SAG group after the intervention, and one in the 3DS group. Samples from the patients completing the study (n=28, SAG 10 and 3DS 18) were included in the interindividual variation of steady state concentrations of methadone, morphine and oxycodone. More details on the dropouts are outlined in the respective papers (I and II).

In study B (paper III), 19 cancer patients with BTP while taking stable opioid treatment (other than fentanyl, methadone or buprenorphine) for their background pain were recruited in three centers (oncology and palliative care units) in France, Austria and Norway. They had a minimum life expectancy of three months, an ability to receive nasal drugs. The patients had no condition that could compromise intranasal absorption of fentanyl. Exclusion criteria were impaired respiratory function, severe hepatic or renal impairment, psychiatric abnormalities, and conditions with known risk to increase intracranial pressure, pregnancy, or women who were lactating. Concomitant chemotherapy, palliative radiotherapy (excluding facial radiotherapy), were allowed. Two patients had quantifiable concentrations of fentanyl pre-dosing) and were excluded from

the assessment of dose-proportionality. One patient was excluded from the 200 µg summary of mean dose-corrected AUCs and C_{max} versus PK analysis set, because of insufficient concentration data preventing reliable estimation of PK parameters. All 19 patients were included in the safety and pharmacokinetics analysis sets, and none discontinued participation in the trial.

Twelve opioid naïve males were recruited by an investigator from the Department of Urology at St- Olav's Hospital, Trondheim, Norway in study C (paper IV). The patients were scheduled for transurethral resection of the prostate gland or bladder, were in ASA group 1-3 (American Society of Anesthesiologists' physical status classification 1-5), had no nasal disease, or nasal cold within last two weeks or anemia (hemoglobin < 11 g/dl). All patients completed the study and were included in the analyses.

Table 4. Overview of patient cohorts in this thesis

Study	***Patients***	***N***	***Sex*** *(% men)*	***Age (y)*** *Mean(range)*	***Paper***
A	Cancer patients with pain/AEs[a]	42	52	59.5 (38-76)	I + II
B	Cancer patients with BTP	19	63	57.8 (39-68)	III
C	Opioid naive males[b]	12	100	69.1 (47-84)	IV

[a] AEs= adverse effects
[b] Scheduled for prostate/bladder surgery

1.7 Study design

Study A was a randomized, open-label, parallel group, prospective, multicenter, clinical trial (paper I and II). The patients were randomized to one of two switching strategies (SAG and 3DS), and then followed during the next 14 days. Racemic methadone was administered every 8h as capsules or mixture (produced by St. Olav's Hospital Pharmacy). Adjuvant non-opioids and anti-cancer treatment were maintained. The methadone dose was calculated from the oral morphine equivalent dose (last 24 h, including mean rescue dose given last 48h) using a dose-dependent conversion ratio(Ayonrinde and Bridge 2000; Ripamonti et al., 1998a) displayed in table 5. (For conversion: parenteral morphine: oral morphine =1:3, and oral oxycodone: oral morphine =1:2).

Table 5. Dose dependent switching table

Baseline equivalent morphine dose (mg)	**Protocol ratio Mo:Meth**
30-90	4:1
91-300	6:1
301-600	8:1
601-1000	10:1
> 1000	12:1

Patients demographics were recorded by the physician/investigator at baseline, and opioid dose changes and rescue were recorded daily. Patients performance status was rated with the Karnofsky Performance status (KPS)(Yates et al., 1980) (paper I and II). Pain intensity was recorded by the patients using the Brief Pain Inventory (BPI)(Cleeland and Ryan 1994) short version before 12 am at baseline, day 3 and 14. The items analyzed were average PI (paper I) and PI now (paper I and II). Level of drowsiness, nausea, loss of appetite, and dry mouth were reported (paper I) daily by the patients before 12 am using the Norwegian version of the Edmonton Symptom Assessment Scale (ESAS)(Bruera et al., 1991b); Trondheim Palliative Assessment Scale (TPAT). The Mini Mental State Examination (MMSE)(Folstein et al., 1975) was used to observe cognitive function in the methadone switch study (paper I) at baseline and day 3. Three ECTs were obtained to supervise QT_c-prolongation (baseline, between day 4-7 (same dose ≥2 days) and day 14. Collection of blood samples are further described below.

Study B was a randomized, open-label, two periods, multicenter, PK crossover trial (paper III). The patients were randomized to two of three doses of InF (50, 100 or 200 µg) delivered as single doses. One dose was administered at each of the two treatment days. The treatment visits were separated by at least 48 h, and participation in the trial was limited to a maximum of 14 days. Pharmacokinetic blood samples were drawn, and blood pressure, peripheral oxygen, respiratory rate, and continuous heart rate were monitored for 5 hours after each dose. The patients received their opioid treatment for background pain as usual. InF was not scheduled to coincide with the occurrence of BTP episodes, and the patients were allowed to take rescue analgesics (besides fentanyl, methadone or buprenorphine) during the trial. Clinically significant changes in monitoring procedures and vital signs (recorded at baseline, 10, 15, 30, 60, 120, 180 and 300 min post dosing), in the opinion of the investigator, were classified as adverse effects. Patients were able to report adverse effects up to 48 h post-dosing during a follow-up phone call from the investigator.

The patients in the last study in this thesis (C) received a dose of 50 µg of nasal fentanyl about 90 min before scheduled surgery. This was an open PK trial (paper IV).
Blood was drawn simultaneously from an artery and a vein from cannulas in the upper limb from baseline and then 12 times during the first 60 min post-dose (9, 15, 20, 30 and 60 min after drug administration). Vital signs were recorded at baseline, 6, 13, 30, and 55 min post dosing. Nasal discomfort was reported by the patients at baseline and 10, 40, and 60 min after drug administration.

1.7.1 Randomization

In study A (paper I+II), the databased randomization (central telephone) was stratified by hospital (block size of two) and allocation was concealed until intervention was assigned. The patients were randomized to the SAG or the 3DS switching strategy. In study B (paper III), the patients were randomly assigned to one of six dose sequences, and did receive two of the three nasal fentanyl (NAF) dose levels over the course of two

treatment periods. A randomization list was generated where each dose sequence included two doses of NAF administered at either the low dose or high dose first. Patients were randomized according to the next dose sequence allocation on the randomization list, however, replacement patients were allocated a new randomization number from the bottom of the randomization list, using the highest available randomization number with the same dose sequence allocation as the patient who dropped out of the trial.

1.8 Assessment tools

In this thesis the patients reported pain and adverse affects, while demographics, cognitive function, vital signs and performance status were assessed by the investigators. The assessment tools for measuring pain intensity (Brief Pain Inventory), adverse effects (Norwegian version of Edmonton Symptom Assessment Scale), cognitive function (Mini Mental Status Examination) and performance status(Karnofsky Performance Status) are enclosed in the appendix and are described in further detail in the following pages.

1.8.1 Brief Pain Inventory short form (BPI)

The BPI short form (referred here as BPI) has mainly replaced the full version in use. The BPI is a self-report pain assessment tool with 15 items and is designed to measure the subjective intensity of pain and the impairment caused by pain the last 24 hours(Cleeland and Ryan 1994). It is sensitive to changes in pain(Lydick et al., 1995) and is recommended as a pain measurement tool by the Expert Working Group of the EAPC(Caraceni et al., 2002). The scales are all numerical rating scales (NRS) from zero (no pain/impairment) to ten (worst imaginable pain or impairment). The Norwegian translation has shown satisfactory psychometric properties in patients with cancer pain (Klepstad et al., 2002).

1.8.2 The Edmonton Symptom Assessment Scale (ESAS)

The ESAS is a nine-item patient-rated symptom visual analogue scale (VAS) developed for use in assessing the symptoms of patients receiving palliative care. Patients rate the severity of the following nine symptoms: pain, activity, nausea, depression, anxiety, drowsiness, lack of appetite, well-being, and shortness of breath on a 10-cm line (Bruera et al., 1991b). The ESAS is validated in palliative cancer patients (Chang et al., 2000) and in several clinical and cultural settings(Carvajal et al., 2011; Chang et al., 2000; Moro et al., 2006; Nekolaichuk et al., 2008; Philip et al., 1998). The most frequently used Norwegian version of the ESAS was used in this thesis. It differs from the original by including dry mouth and a second question of pain at rest and at movement. The patients are asked to report 10 items on a NRS from 0-10 (none-worst possible) of how they are today regarding; pain at rest, pain when movement, drowsiness, shortness of breath, nausea, dry mouth (xerostomia), anxiety/uneasiness, loss of appetite, depression/sadness and well-being (overall, how are you feeling today?).

1.8.3 Karnofsky Performance Status (KPS)

Performance status was rated with the KPS in paper I and II, which is an observer rated scale designed to measure the level of patient activity and medical care requirements. It contains 11 categories ranging from 0 % (death) to 100 % (normal performance). The KPS has shown good validity as a global indicator of the functional status of patients with cancer (Yates et al., 1980). The scale classifies the functional impairment of patients, and is also associated with prognosis in individual patients, with lower scores associated with worse survival(Evans and McCarthy 1985). Cancer patients with lower Karnofsky Performance Status (≤ 80) have more symptoms than patients with higher performance status(Portenoy et al., 1994).

1.8.4 Mini Mental State Examination (MMSE)

The MMSE assess cognitive function and is a standardized cognitive screening examination which is valid, reliable and able to document changes in cognitive function (Folstein et al., 1975). The scores range from 0 to 30, with higher scores indicating better cognitive function. A score of ≤ 23 is most widely used as a cut-off value considered to indicate cognitive failure(Mitchell 2009; Pereira et al., 1997). The feasibility of MMSE has been demonstrated in patients with terminal cancer (Pereira et al., 1997).

1.8.5 Vital signs

Blood pressure (mmHg), respiratory rate (RR/min) and peripheral oxygen saturation (pO_2%) levels were monitored using standard procedures in the nasal fentanyl studies (paper III and IV).

1.8.6 Rating of nasal symptoms

The patients scored their nose discomfort and level of sedation on two equal four-point verbal rating scales (VRS) (0=no, 1= mild, 2= moderate and 3= severe) in study C (paper IV).

1.9 Opioid concentrations – analysis and quantification

All serum and plasma in this thesis were analyzed with a high-performance liquid chromatography-mass spectrometry (LC/MS) or a multiple stage or tandem LC-MS/MS. These are sensitive and selective analytical techniques that combines the physical separation capabilities of liquid chromatography (LC) with the mass separation of the analytes and detection of their mass-to-charge (m/z) values in the mass spectrometry (MS). LC-(MS/MS) mass analyzers are used in series to improve quantitative results (selectivity) and structural information. Handling of the samples, limits and further details of quantification of serum opioids are further outlined in the respective papers (II, III and IV).

1.9.1 Pharmacokinetic (PK) analysis

In paper II trough serum samples were collected in the morning at trough before the switch to methadone on day 1 and day 2, 3, 4, 7 and 14 before the methadone dose was given. $AUCs_{day1-4}$ were estimated with the trapezoidal method(Rowland and Tozer 2010). Since the preswitch morphine doses apparently were unequal in the two groups, the AUCs were dose-corrected (adjusted as if every patient received the same dose of the drug during day 0- day 3; methadone 100 mg, morphine 1000 mg, and oxycodone 500 mg). The doses were chosen according to the mean dose of the opioid at baseline. However, the factor chosen is not important, as it only is used to make a ratio, and that this was done identically in the two groups. AUC was adjusted as follows: AUC_c = measured AUC x (100 mg/ total administered methadone dose (mg) from day 0 to 3) for total methadone. The same equation was used for the AUC_{cs} of morphine and M6G with the doses adjusted to 1000 mg, and 500 mg for the oxycodone doses.

In paper III venous blood samples were drawn at baseline and 2, 4, 6, 9, 12, 15, 20, 25, 40, 60, 90, 120, 180, and 300 minutes after fentanyl administration. Simultaneous arterial and venous blood samples for analysis of fentanyl were drawn at baseline and at 1, 3, 5, 7, 9, 13, 15, 20, 25, 35, 45 and 60 minutes after drug administration in paper IV. In paper III and IV fentanyl C_{max} and T_{max}, (both papers), AUC_{0-5h} and AUC_{0-t^*} (III), $AUC_{0-60min}$ (IV)) and $t_{1/2}$ (III) were calculated with non-compartmental methods using the WinNonlin (version 5.0.1 software, Pharsight Corporation Mountain View, CA, USA). The patients included in the PK analyses in paper III had assessable (including 120-minute time point or peak concentration and estimation of elimination rate) PK profile for at least one dose.

- = time of last measurable concentration above the lower limit of quantification

Dose proportionality was assessed by examining log-transformed, dose normalized C_{max} and AUC_{0-5h} using a linear mixed-effects analysis of variance (ANOVA) model and the power model analysis approach.

1.10 Statistics

All data is reported as means, medians, ranges or 95% CIs, mean difference between groups (with CIs), frequencies (n (%)) or fractions as appropriate in the papers in this thesis. The criterion of .05 was used to define statistically significance (all papers) and a difference of ≥ 2 on the 11 point NRS was defined as clinically significant (paper I)(Farrar et al., 2001). In general, most demographic- and disease-related data of the cancer patients were not normally distributed; hence nonparametric methods were used when analyzing these variables in this thesis. The statistical analyses in all papers were performed using the Statistical Package for Social Science (SPSS) statistical software version 11.0, 17.0 and 18.0 (SPSS Inc., Chicago, Il, USA). The statistical methods used in each of the different studies included in this thesis are described in further detail in the respective papers.

1.11 Ethics and approvals

All studies were carried out in accordance with the principles of the Helsinki declaration and were approved by The Regional Committee for Medical Research Ethics, Health Region Central Norway. Study B was in addition conducted in accordance with the European Parliament and of the Council of April 4, 2001 and all regulatory requirements. Study A and C was also approved by The Norwegian Social Science and Data Services and the Norwegian Medicines Agency. Patients in all studies were included after written informed consent was obtained. The methadone switch study was registered in Clinical.Trials.gov with id: NCT0014496.

1.12 Financial support

Kristin Moksnes Husby received grants from the Research Council of Norway and the Norwegian Cancer Society. Nasal fentanyl was supplied for free by Nycomed Pharma in study C (paper IV), as the firm at this point had decided not to pursue further studies on this preparation. However, with new owners the focus changed, and Nycomed Pharma (Denmark) sponsored study B (paper III) - no personal grant was received.

Results and summary of papers

1.13 Paper I

How to switch from morphine or oxycodone to methadone in cancer patients? A randomized phase II trial

The aim of this prospective, open, parallel-group, multicenter, phase II RCT trial was to compare two switching strategies when switching cancer patients with pain/adverse effects from morphine/oxycodone to methadone. The hypotheses being: patients allocated to the stop and go (SAG) strategy, in which the current opioid is terminated and an equianalgesic dose of methadone is started, have lower pain intensity day 3 compared to patients switching stepwise over three days (3DS), and SAG is as safe as the 3DS.

Cancer patients from four Norwegian hospitals (both in- and outpatients) where an opioid switch was indicated were randomized. The methadone dose was calculated using a dose-dependent conversion ratio (table 5). Pain intensity was recorded at baseline, on day 3 and 14. Adverse effects, serious adverse events and opioid doses were recorded daily for 14 days. Primary outcome was average pain intensity day 3. Secondary outcomes were pain intensity now and adverse effects day 3 and 14 and number of serious adverse events.

Forty-two patients (19 females and 22 males, mean age 60 years (range 38-76 years) were randomized, and 16 (SAG) and 19 (3DS) patients received methadone. The mean preswitch morphine doses were SAG 900 mg/day and 1330 mg/day, respectively. No differences between groups were found in mean average pain intensity day 3 (mean difference 0.5 (CI -1.2-2.2); SAG 4.1 (CI 2.3-5.9) and 3DS 3.6 (CI 2.9-4.3) or in pain intensity now. The SAG group had more dropouts (11 patients, 38%) compared to the 3DS group (3 patients, 5%) and three serious adverse events (two deaths (myocardial infarction and pulmonary embolism) and one severe respiratory arrest). No serious adverse events were observed in the 3DS group. One patient was withdrawn because of prolonged QTc time (> 480 msec) (3DS) after receiving methadone, but none exceeded the limit of 500 msec.

The SAG patients reported a trend of more pain, had more dropouts and three serious adverse events compared to the 3DS group, which indicate that the SAG strategy is not safe, and that it should not replace the 3DS when switching from high doses of morphine or oxycodone to methadone. These findings underline the importance of conducting randomized trials, even in a very sick cohort of cancer patients. Even more it gives important information to the clinicians of the importance of being careful when subscribing new opioids in frail patients receiving high opioid doses.

1.14 Paper II

Serum concentrations of opioids when comparing two switching strategies to methadone for cancer pain

The aim of this part of the methadone switch study was to compare pharmacokinetic aspects of two switching strategies from morphine or oxycodone to methadone; the stop and go (SAG) and the 3-days switch (3DS).

Trough serum concentrations of total methadone, the enantiomer R-methadone, morphine and its metabolite morphine 6-glucurodnide (M6G) and oxycodone were measured the day of the switch (day 1), day 2, 3, 4, 7, and 14. Primary outcome was the number of patients with methadone concentrations in apparent steady state on day 4 (defined as concentration ≥ 90% of the methadone concentration on day 7, when steady state could be assumed). Secondary outcomes were exposure to opioids (expressed as dose corrected area under the curves (AUC_{cs}) the first three days, interindividual variability of the serum concentrations of the respective opioids, and correlation between total methadone concentrations and pain intensity on day 3.

Thirty-five patients received methadone (16 in the SAG group and 19 in the 3DS group) and were included in the concentration analysis. The median preswitch morphine equivalent doses were 620 mg/day (range 350-2000 mg/day, SAG) and 800 mg/day (range 90-3600 mg/day, 3DS) (p=0.43). In the SAG group 42% (5/12) of the patients reached apparent steady state of total methadone concentrations day 4 compared to 22% (4/18) in 3DS group (p=0.42). The SAG group was significantly less exposed to morphine, M6G and oxycodone and significantly more exposed to total methadone the first three days after the switch. Serum opioid concentrations of the respective opioids or metabolites were not significantly higher in the dropouts in the SAG group (n=6) compared to the median of the group. However, two of the patients with SAEs had much higher dose corrected concentrations of total methadone than the median of the SAG group. One of these suffered from severe respiratory depression on day 5. The interindividual variation of dose-corrected concentrations at steady state of methadone, morphine and oxycodone for the patients that completed the study (19 switched from morphine and 9 from oxycodone) were not significantly different from another (cross over in the same subjects). Low correlation was found between total methadone concentrations and pain intensity day 3 and 14. Total methadone concentrations were highly correlated to the R-methadone concentrations.

The SAG group was initially more exposed to methadone, and less to the replaced opioids. The serum concentrations of methadone were not correlated to pain intensity, and SAEs cannot be predicted from serum concentrations of methadone. Interindividual variability of methadone at steady state is similar to that of morphine and oxycodone. Moreover, there may be a significant interindividual variability in conversion doses for methadone, consequently patients switched to methadone should be followed closely the first five days regardless of switching strategy.

1.15 Paper III

Pharmacokinetics of intranasal fentanyl spray in patients with cancer and breakthrough pain

The aim of this randomized, open-label, two-period, cross-over, multicenter trial was to investigate the pharmacokinetics, tolerability and safety of intranasal fentanyl spray (InF)

in patients with cancer and breakthrough pain (BTP). This study was a part of the development of nasal fentanyl by Nycomed Pharma.

Adult patients with cancer who received opioid treatment for chronic background pain and experienced BTP were randomly assigned to receive one of six InF dose sequences (2 of 3 doses): 50 and100 μg; 100 and 50 μg, 50 and 200 μg, 200 and 50 μg, 100 and 200 μg, or 200 and 100 μg. The InF dose-range was expected to meet the clinical needs of most patients with BTP. InF was administered independently of BTP episodes as a single dose in one nostril and each dose was separated by at least 48 hours. Venous blood samples for fentanyl analysis were collected at baseline and 2, 4, 6, 9, 12, 15, 20, 25, 40, 60, 90, 120, 180 and 300 minutes after InF administration. Blood pressure, peripheral oxygen saturation, and respiratory rate were assessed eight times during each of the two treatment periods (5 hours each).

Among the 19 patients (7 males and 12 females, mean age 57.8 (range 39-68) years) randomized and recruited in Austria, France, and Norway, mean venous fentanyl plasma concentrations increased in a dose-dependent manner, peaking for all InF dose strengths 9–15 min after InF administration. Median T_{max} values were 15, 12, and 15 min for the 50, 100, and 200 μg dose strengths of InF, respectively. Mean values for C_{max} were 0.351 (±0.226), 0.595 (±0.400) and 1.195 (±0.700) ng/ml for the three doses respectively. Over the entire 50–200 μg range C_{max} appeared to increase slightly less than proportionally to InF dose. Six patients (31.6%) experienced adverse events during a treatment period. The majority of these adverse events were mild in severity and none were considered to be severe. No patients discontinued participation in the trial.

For true dose-proportionality doubling the InF dose should produce a doubling of the retrospective PK parameters. If exposure is dose proportional, it means that clearance is constant over that same dose interval. This is why it is important to test for dose proportionality. In study B (paper III), the detected fentanyl concentrations (reason unknown) prior to InF administration in two patients, reduced the degree of proportionality within the dose range studied. Excluding these two from the analyses, demonstrated that the $AUC_{0\text{-}5h}$ appeared dose proportional for 50 and 100 μg InF dosages, and C_{max} appeared dose-proportional across the 50-200μg InF dosage range. C_{max} dose-proportionality cannot be confirmed as this study (B) was not powered to make conclusive statements for C_{max} values. Furthermore, the study was not designed for AUC up to infinity. To conclude, strict dose-proportionality for these parameters was not demonstrated.

This study demonstrates that InF has a fast systemic penetration and has a good tolerability and safety profile in patients with cancer and BTP.

1.16 Paper IV

Early pharmacokinetics of nasal fentanyl: is there a significant arterio-venous difference?

The primary aim of this study was to investigate the arterio-venous differences in pharmacokinetics of nasally administered fentanyl during the first hour after administration. A secondary aim was to document the tolerability of 50 μg of nasal fentanyl in opioid-naïve middle-aged to elderly patients.

Twelve male patients (median age 70.5 (range 47-84) years) scheduled for transurethral resection of the prostate gland received a single intranasal 100 μl dose of 50 μg fentanyl citrate in one nostril. The study sample reflected the patient population that is candidates for nasal fentanyl treatment of BTP. Simultaneous arterial and venous blood samples were drawn at baseline and 1, 3, 5, 7, 9, 13, 15, 20, 25, 35, 45 and 60 min after drug administration. Respiratory rate, peripheral oxygen saturation, continuous heart rate, invasive blood pressure, sedation and symptoms of nose/throat discomfort (VRS 0-3) were recorded.

Arterial fentanyl concentrations increased more rapidly and to a higher concentration than the venous concentrations. The arterial $AUC_{0\text{-}60}$ of 21 (±5.7) min*ng/ml was approximately 30% larger than the venous of 15 (±4.1) min*ng/ml, arterial C_{max} (0.83 (±0.26) ng/ml) nearly twice as high the venous (0.47 (±0.15) ng/ml), and the arterial T_{max} (7.0 (±1.3) min) about five minutes shorter than the venous (11.6 (±3.3) min) (all p-values $\leq$0.005). Correlations between arterial and venous T_{max} and C_{max} were poor. No significant adverse events were observed and no discomfort reported.

With reference to BTP, the most important period is the first hour after administration of the opioid. The pharmacokinetic parameters estimated from arterial samples differed significantly from the venous ones indicating that venous parameters are poor predictors of arterial values, and that arterial values may give a more precise estimate when predicting time to effect in the early phase after intranasal fentanyl. Despite a trivial dose of 50 μg of fentanyl in the conjunction of anesthesia, the finding that 50μg of nasal fentanyl was well tolerated by opioid naïve middle aged to elderly male patients is important since nasal fentanyl will be self-administered by the patients and without strict professional observation.

Discussion

This thesis addresses two principles of cancer pain management; how to switch from one opioid to another and exploring the pharmacokinetic (PK) profile of nasal fentanyl spray as a novel principle of treatment of BTP. The work spans from clinical outcomes to basic science on a pharmacokinetic level. The included papers indicate that cancer patients on high opioid doses should not be switched to methadone by the SAG strategy, as this was not safe in these patients. Intranasal fentanyl is rapidly absorbed through the nasal mucosa, and it is well tolerated both in opioid tolerant and opioid naïve patients. These results support that intranasal fentanyl have pharmacokinetics that are favorable for the treatment of patients with cancer suffering from BTP. In addition, significant differences between venous and arterial concentrations of fentanyl were found, indicating that arterial samples are more precise than venous samples when predicting time to onset of action in fast acting drugs such as fentanyl. Increased understanding of opioid pain treatment may enable clinicians to individualize pain management and avoid unnecessary suffering.

1.17 Methodological considerations

1.17.1 Study population

The multidimensionality of the cancer pain experience is characterized by fluctuations in pain intensity and variable responses to treatment, along with the challenge of disease progression and existential suffering. In a survey of 1000 palliative care patients the median number of symptoms per patient was 11 (range 1-27)(Walsh et al., 2000). This means that extrapolation of data from animal research, healthy volunteers or studies in patients with non-cancer pain may have limited relevance for clinical cancer pain(Kongsgaard and Werner 2009). Furthermore, studies including cancer pain patients often include patients early in the disease trajectory or in a more stable condition than those who could potentially benefit from the new treatment regimens. These factors limits the generalizability to the palliative care population(Kaasa and De Conno 2001). Cancer care and palliative care centers differ across Europe, regarding both demographics and disease related characteristics of admitted patients and regarding how symptoms (e.g. pain) are treated(Kaasa et al., 2007; Klepstad et al., 2005b), and these differences may obviously influence the reported prevalence and intensity rates. This thesis aimed at including patients that were representative for the target group and rather wide inclusion criteria were applied; cancer patients in need of an opioid switch (A), cancer patients who are opioid tolerant with BTPs (B) and elderly opioid naive males scheduled for prostate/bladder surgery (C).

The RCT on methadone switching (A) is the first controlled trial on opioid switching and it is on the border of what is possible to conduct as it included frail cancer patients on high opioid doses. The included patients had a mean age of 60 years (range 38-76 years), 98% were Caucasian, and 54% were men. No single cancer diagnosis dominated any of the groups. Forty-one per cent had concomitant diseases, the mean Karnofsky

performance status was 60 %, and 85 % had metastatic disease. Mean months since cancer diagnosis was 34 (range 2-202months). More than 32 % received anti cancer treatment, and all used concomitant medication. Approximately 20% had tried more than one opioid prior to the switch. Mean baseline equianalgesic morphine doses were 900 mg/day (range 650-2000mg/day) in the SAG group, and 1330 mg/day (range 90-3840 mg/day) in the 3DS group, with 71% of the patients receiving methadone having equianalgesic morphine doses > 600 mg/day. The groups were similar as to the key demographic variables, except time on WHO step III opioids (SAG 9.1 months and 3DS 23.6 months).The strength of this cohort is that it reflects the population in need of an opioid switch, in contrast to other studies on opioid switching where cancer patients with low mean baseline morphine doses (125-160 mg/day) have been included, and patients with anticancer treatment, poor liver/kidney function and brain metastases excluded(Mercadante et al., 1999; Mercadante et al., 2001; Ripamonti et al., 1998b). This is further outlined in the discussion under research question one. This underlines the importance of classifying the cohorts in clinical cancer pain studies, and that an agreement on a common classification system is needed to allow for comparability between studies.

The patients in study B were also chosen to represent the candidates for nasal fentanyl treatment for BTP. These patients had cancer pain treated with an opioid for background pain, and 18 patients (95%) treated at least one episode of BTP at any time during the trial. The mean age was 58 years (range 39-68 years) and seven (37%) were men. Seventeen were Caucasian (89%), three patients (16%) had metastases and concomitant cancer treatment was allowed. The patients in study C were all male, with a median age of 70 years (range 47-84 years). They all had chronic diseases which required concomitant medication. Ideally, females should have been included also in study C. The sample size, however, would still not have allowed the investigation of gender differences. These cohorts are in contrast to most other pharmacokinetic studies where young healthy volunteers are studied(Christrup et al., 2008; Dale et al., 2002b; Fisher et al., 2010b; Striebel 1993), with no concomitant diseases or medications.

1.17.2 Study design

There are few RCTs in palliative care, although urgently needed since there are a large number of patients who are treated for symptoms and other challenges during the last year of their lives. The difficulties in conducting RCTs in palliative care include pain fluctuations, polypharmacy, organ dysfunction, impaired cognitive function, limited accrual rates, patient compliance and the duration of trial versus limited life expectancy(Kongsgaard and Werner 2009). Conducting these trials can be like shooting at a moving target(Paice et al., 2010). In addition to the complexity of the disease with many symptoms, health care providers or relatives may act as gatekeepers(Bond Sutton et al., 2003). Studies on this patient group are therefore commonly retrospective or descriptive. This does not imply that patients generally are reluctant to participate in RCTs. White and coworkers have shown that patients with advanced cancer are interested in participating in RCTs that focus on symptom control(White et al., 2008). Furthermore, two studies on attitudes toward research reported that both palliative care patients and

staff were in favor of research participation, both for altruistic reasons and to improve their own care and treatment(Pautex et al., 2005; Ross and Cornbleet 2003). Still, good-quality controlled trials are especially difficult to conduct in patients who are in the terminal phase of cancer(Kongsgaard and Werner 2009) and studies will be adversely affected by high dropout-rates. The achievable accrual rate of patients is often less than half of what is estimated(Dugas et al., 2009). In 2006, Bell et al conducted a systematic review of pain trials (morphine, oxycodone, hydromorphone) in adult cancer patients from 1966-2005 and found 34 double-blinded RCTs(Bell et al., 2006). Twenty-nine of these reported a dropout-rate over 10%, with 12 studies exceeding 30%. Six trials had a withdrawal rate of 40% or more. Most studies had small group sizes (around 20 patients), and a duration around two weeks. In a recent systematic review on opioid switching in cancer patients(Dale et al., 2011), no RCTs were found, and the evidence level was graded D (Grade's approach(Atkins et al., 2004)).

Although switching the patients to one opioid and then back again (N=1 studies, a cross-over design), may provide strong evidence, they may be challenging to perform in very sick patients as they require longer study periods than parallel group studies. The parallel design trial was chosen in study A to compare two switching strategies to methadone. The parallel study design is less dependent on anticipation of disease progression; it is simple, and is preferred when evaluating subjective outcomes such as pain. Blinding is important in clinical research, as the expectations of patients and investigators can influence findings, especially in palliative care where there is subjectivity in symptom assessment. Blinding in RCTs is considered gold standard when comparison of two different treatments or a comparison to placebo is performed, especially when subjective outcomes are studied(Day and Altman 2000). However, the relevance of blinding will vary according to the clinical trial context. In study A, blinding could have been performed theoretically, but it would have made it far more complex and presumably impossible to run. Possible bias may manifest in the decision to withdraw a patient from the study. Two patients were withdrawn by the physician in the SAG group after allocation, but before they had started the intervention. This might be a sign of physicians' fear and reluctance to switch a patient on very high opioid doses so abruptly, although this is only speculations. Although the design of this study was strong, a slow accrual of subjects and considerable number of dropouts reduced its statistical power.

In study B (paper III) a crossover design was applied (each patient received two doses of intranasal fentanyl). A crossover design reduces the sample size and the within-subject variation is restricted. A crossover design may be useful as it increases the power of the study and uses the same patient as his/her own control. When studying cancer patients with disease progression a crossover trial needs a short duration in order to reduce the number of withdrawals. The therapeutic effect of intranasal fentanyl cease shortly after it is discontinued (short "washout" period and little risk of carryover effect) making the crossover design suitable. This study was not blinded as the outcomes were mostly objective.

Multicenter studies were performed to be able to recruit enough patients within a shorter period of time.

The model used in study C was chosen for several reasons; first, ethics committees in Norway have been reluctant to approve studies with controlled substances in healthy volunteers. The use of arterial cannulas may have been questioned. Second, in our opinion differences in arterio-venous concentrations have little relevance beyond the first hour. This allowed us to conduct this study in patients without interfering with the busy every day schedule in the operating rooms. A shortcoming was that it was not possible to provide adequate conditions for a pharmacodynamic outcome such as pupillometry commonly used in volunteers(Dale et al., 2002a).

1.17.3 Assessment of cancer pain and adverse effects

Ideally, pain and adverse effect assessment should be brief, precise, easy to implement in the clinic/trial, and specifically targeted to the patient population. When deciding on assessment tools several issues need to be taken into consideration; such as validity (does the instrument measure what it intends to measure?), reliability (does the instrument produce the same results when repeated in the same population?) and inter observer reliability (does the instrument produce the same results when used by different investigators)(Jensen 2003). Other methodological considerations for assessment tools are the ability to detect clinically relevant differences (between patients and over time), that it is appropriately translated, whether the tool has been formally validated in the appropriate population, and if the responses to a tool are known for the general population. Valid and reliable assessment of pain is essential for both effective pain treatment, and in clinical trials(Jensen 2003; Kaasa et al., 2008).

How cancer pain is classified affects how it should be assessed(Breivik et al., 2008). A consensus-based methodology that standardizes symptom classification and assessment, is still not routinely applied in clinical trials or clinical practice(Caraceni et al., 2005; Kaasa et al., 2011; Knudsen et al., 2009). Different approaches and different tools flourish in the research literature(Hjermstad et al., 2009), and superiority of any tool has not yet been demonstrated(Kaasa et al., 2008). As an example, a systematic review found eight versions of the NRS with fifteen different descriptors used to anchor the extremes(Hjermstad et al., 2011), which clearly proves the difficulty in comparing studies. In a literature review (1999-2002) on cancer pain assessments in clinical trials, Caraceni et al. found that 68% used VAS, NRS or VRS (unidimentional) and that 10% used non validated measure methods (Caraceni et al., 2005). The inadequate assessment of pain and lack of documentation are thought to be the greatest barriers to effective pain relief(Herr et al., 2004). The Initiative on Methods, Measurements and Pain Assessment in Clinical Trials (IMMPACT) aims at introducing a standard outcome assessment and reporting in pain clinical trials of chronic non-malignant pain. The IMMPACT group has published recommendations concerning the choice of outcome measures and instruments(Dworkin et al., 2008; Haythornthwaite 2010). The recommendations from an expert working group of the EAPC on the measurement of pain in palliative care research are an 11-point NRS, a 100 millimeters Visual analogous scale (VAS) or a Verbal rating scale (VRS) as unidimentional assessment of pain while the short form of the Brief pain inventory (BPI) or the Mac Gill Pain Questionnaire is recommended for the

multidimensional assessment of pain (Caraceni et al., 2002). One of the aims of the European Palliative Care Research Collaboration (EPCRC) is to develop an international classification system for cancer pain and assessment. The proposed name for this system is Cancer Pain Assessment and Classification System (CPACS)(Kaasa et al., 2011). As of today, this is based on empirical data collection, literature reviews, expert consensus surveys and input from patient focus groups and surveys. The domains that are suggested as most relevant outcomes in clinical practice and research are: pain intensity, pain relief and temporal pattern(Kaasa et al., 2011). Pain intensity at initial assessment is reported to be a significant predictor of pain management complexity, and length of time to stable pain control(Fainsinger et al., 2009).

Pain intensity and adverse effects were recorded by the patients in this thesis. Self -report is the gold standard for assessment of both the presence and the severity of pain (Portenoy and Lesage 1999). The instruments used in this thesis were chosen as they are widely recognized, reliable and validated (except the TPAT), but also to comply with the current practice for symptom assessment. Pain intensity (PI) was reported using an 11-point NRS (study A). The scales were anchored as 'no pain/impairment' to 'worst imaginable pain/impairment', which has shown satisfactory psychometric properties in patients with cancer(Klepstad et al., 2002). Average PI during the last 24 h was measured in paper I, which is now recommended as the standard for the classification system for cancer pain(Kaasa et al., 2011). PI now was also measured in this thesis (paper I and II), and used in correlations with trough serum concentrations. Whereas pain intensity ratings ask patients to rate the intensity of felt pain, pain relief ratings ask patients to rate how much relief from pain they have experienced. A critical review on the validity and reliability of pain measures in cancer pain reported that relief ratings also have been shown to be sensitive to the effects of treatment(Jensen 2003). The proposed recommendations from the EPCRC if change in pain over time is to be monitored, is pain intensity as the primary outcome, and that the difference between initial and subsequent assessments should be evaluated(Kaasa et al., 2011).

The tool used for assessing adverse effects in study A (paper I) (ESAS), is validated in palliative cancer patients(Chang et al., 2000), and in several clinical and cultural settings(Carvajal et al., 2011; Chang et al., 2000; Moro et al., 2006; Nekolaichuk et al., 2008; Philip et al., 1998). It was chosen because ESAS is a widely used, and well-known self-reporting tool for assessment of symptoms in palliative care(Nekolaichuk et al., 2008), and it may be used for day-to-day monitoring of treatment effect and change in symptoms(Bruera et al., 1991b). The Norwegian version of ESAS (TPAT) is however, not validated. A recent study in Norwegian cancer patients (using the same version as in this thesis) found that errors and misunderstandings do occur when completing the ESAS(Bergh et al., 2011), especially in the items of anxiety, depression and appetite. Contextual factors, such as mood and time of day, influenced the answers. It may be that some of the patients in this thesis interpreted a low score as equivalent to little appetite, without realizing that their answer reflected the opposite. However, this could be the case in both groups. A shortcoming of our study is that the Norwegian modifications to the ESAS may limit the comparison to other studies. ESAS was recently revised (ESAS-r), and this version is found to be significantly easier to understand(Watanabe et al., 2011).

1.17.4 Power considerations

Study A was initially designed to detect a difference of two days to achieve pain relief ≤ 4 (NRS 0-10) monitored by ESAS, and sample size calculations were made accordingly (sample size = 40 patients). Because the Norwegian version of the ESAS had an additional item of pain (pain while movement and pain at rest), average PI and PI now from the BPI was later chosen and it was subsequently decided to make assessments only at baseline, day 3 and 14, with the primary outcome being average PI day 3. We placed emphasis on estimation of effects, with the uncertainty due to sample size being made explicit by wide confidence intervals, rather than p-values which could be misleading because of possible type II errors (paper I). The experience from this study and the lack of randomized trials published on this topic reflect that conducting scientifically sound trials in this population is challenging and that one need to sample according to a 50-75% attrition rate. The inclusion rate in this study was slow, considering the high number of patients in need of an opioid switch, and that three centers included patients. The main reason for this was the difficulty of implementing the procedures into the clinical routine on ward, and that the inclusion rate heavily depended on the investigators being present.

Formal sample size calculations were not performed in the explorative intranasal fentanyl studies, as the required background data were not available. However, the sample size in PK studies is usually between 10 and 20 individuals (table 3).

1.17.5 Sampling, drug analyses and pharmacokinetics

Total methadone, R-methadone, morphine, M6G, oxycodone and fentanyl were analyzed in this thesis, as they are suggested to have analgesic effect. While there is a relationship between the morphine dose and the plasma levels of morphine, M3G and M6G, the data are conflicting regarding the association with clinical effect of these metabolites(Hammoud et al., 2011; Penson et al., 2005; Quigley et al., 2003). However, even though it is widely stated that M6G contributes substantially to the analgesic effect of morphine in humans, the data are less consistent than in animals(Lotsch and Geisslinger 2001; Penson et al., 2005). M3G displays very low affinity for opioid receptors, has no analgesic activity and other clinical effects of this metabolite is not yet elucidated(Andersen et al., 2003; Penson et al., 2000; Penson et al., 2005). M3G was therefore not included in the analyses. S-methadone together with normorphine, oxymorphone, EDDP, and EMDP were not included in the analyzes, as they have no significant analgesic activity and other clinical effects are not yet elucidated(Andersen et al., 2003; Auret et al., 2006; Fredheim et al., 2007; Mayyas et al., 2010; Zwisler et al., 2010).

When performing pharmacological analyzes the struggle to standardize the sampling is important. In the methadone switch study the blood samples were taken at trough before the morning opioid dose before and up to 14 days after the switch. The trough time point is the most standardized sample time, since only elimination is taking place and consequently other individual differences affecting serum concentrations are minimized. In addition, other opioids where chosen for rescue than the opioid used at baseline to get

the “true” concentration of the estimated dose. Many factors may complicate the concentration analysis, such as use of rescue and interindividual day-to-day variation. Factors such as food intake, gastric retention, malabsorption, interacting drugs, vomiting and variability of first-pass metabolism will influence the PK observations during oral administration. In the PK studies, the patients had not eaten before the administration of fentanyl. In study B, they received food after the sample taken at 180 min, when only one sample at 300 min remained. However, when the drug was administered nasally, most of these factors were less relevant. In the methadone study, the samples were taken in the morning before the first morning dose, and most patients had not eaten before the morning sample.

Regarding the PK analysis, emphasis was on the first hour in study B and C. To get accurate C_{max} and T_{max}, initial sampling had to be frequent. In study C, the aim was to detect arterio-venous differences the first hour, and more frequent sampling was needed. Although $t_{1/2}$ is of limited interest, it gives en indication of the potential for accumulation with frequent dosing. Sampling needs to exceed three times the expected $t_{1/2}$ to be adequate.

All serum and plasma analyses in this thesis were carried out using a liquid chromatography- tandem mass spectrometry (LC-MS/MS) system. This is a commonly used analytical technique when quantifying drugs in biological samples, and it is reckoned to be the “state of the art” with the use of internal standards. The liquid chromatography system separates compounds in a complex matrix, and the mass spectrometry act as a very specific and sensitive detector by measuring the mass-to charge ratio of charged particles. Thus, this system has the ability to separate and quantify compounds with a high specificity and sensitivity.

Compartmental models are commonly used in pharmacokinetics to explain drug disposition. Most drugs are not totally confined to the circulation and do diffuse into the tissues, and consequently 2- or 3- compartments are needed to adequately describe their disposition. However, the PK parameters wanted in this thesis were C_{max}, T_{max} and AUCs, and a non-compartmental method was chosen as it does not assume any specific compartment model and produce accurate results without assumptions.

The computation of the area under the curve (AUC) is a frequently used method in pharmacokinetic research to comprise information that is contained in repeated measurements over time(Pruessner et al., 2003). The studies were not designed to obtain AUC up to infinity. AUCs were dose corrected as if every patient received the same dose of the drug in paper II, as to correct the difference in preswitch doses in the two groups. This is a common way of correcting for the use of different doses in different individuals, and is also used in the palliative literature(Andreassen et al., 2011).

In study A, one could assume that all patients were in steady state of methadone concentrations on day 7. Steady state was defined as total methadone concentrations of day 4 $\geq$ 90% of the concentration on day 7(Katz and Kelly 1993).

The uncertainty in the relation between the observed serum concentration and the actual concentration at effect site (CNS) is a shared limitation in all the included studies as in most pharmacological studies.

1.17.6 Ethics

It has been argued that palliative care patients are too ill and too vulnerable to allow meaningful scientific research (de Raeve 1994). Dying patients are especially vulnerable, adequate informed consent may be difficult to obtain, balancing research and clinical roles are difficult, and the risks and benefits of palliative research are difficult to assess(Casarett and Karlawish 2000; Cohen and Mount 1992; Kaasa and De Conno 2001). Furthermore, health care providers or relatives may act as gatekeepers(Bond Sutton et al., 2003).

The patients in study A and B in this thesis experienced pain (background or BTP) and/or adverse effects. The suffering might create a sense of desperation; they were willing to try anything they were offered. They might have felt compelled to participate in research by gratitude, or dependence on a provider or institution (Cohen and Mount 1992). A patient's ability to give consent may be temporarily affected, such as right after they have received the diagnosis etc.(Tait and Hardy 2006). The patients included in this thesis had had time to assimilate the implications of the diagnosis and the necessity for treatment. However, a patient who is profoundly fatigued, who has uncontrolled symptoms (e.g. pain or nausea) or is suffering from side-effects of medication (e.g. drowsiness from opioids) may well not have the capacity to consent until he or she has been properly palliated, the side-effects of treatment have been controlled, or both(Tait and Hardy 2006). The patients were carefully informed that they would receive the best treatment also without enrolment. It would be unethical not to pursue evidence based medicine also in this patient group.

Especially in pharmacokinetic studies, it might be hard to find the benefit for the participating patients, and easier to see how the results might benefit future patients. The patients in study B (paper III) were offered InF for BTP after the study was completed following a compassionate use protocol. In study C (paper IV) risks of an arterial cannula was taken into consideration and patients that could benefit from the arterial cannula and from the small dose of fentanyl as pre-medication were included (paper III).

Study B was initiated and organized by Nycomed Pharma. Funding by pharmaceutical industry may represent a source of bias as their agenda not necessarily conform to that of clinicians. Numerous studies show that when the pharmaceutical industry sponsors clinical trials, the results are systematically biased in favor of the sponsor's product (Als-Nielsen et al., 2003; Wynia and Boren 2009). Our study group received a grant for participating in the study. However, no personal grants were received and we were free to influence the analysis process and writing the paper. In addition, this was a PK study with hard endpoints, which is less influenced by interpretation. Study C was initiated, organized and published without influence from Nycomed Pharma, other than that they made the fentanyl sprays available.

1.18 Discussion and interpretation of research question 1-5

1.18.1 Research question 1

Is the SAG switching strategy more effective than, and as safe as the 3DS strategy?
Opioid switching has become an established practice for the management of cancer pain. However, the newly revised cancer pain treatment guidelines from the EPCRC(Caraceni et al., 2011, accepted Lancet Oncology), conclude that the data including no randomized trials on opioid switching(Dale et al., 2011; Quigley 2004) permit a weak recommendation of opioid switching. In this thesis two switching strategies are compared in a RCT. The main finding was that the stop and go (SAG) approach when switching to methadone from morphine or oxycodone was associated with a trend of more pain, a higher number of dropouts and serious adverse events than with the 3-days switch (3DS) strategy in cancer patients on high opioid doses. Since few patients (n=28 of 42) completed the study – the confidence intervals were wide and consequently no firm conclusions could be made with regard to group differences or group similarity for the primary outcome; average PI day 3.

In previous uncontrolled studies on the SAG strategy it has been reported that the SAG approach rapidly improves pain relief(Ayonrinde and Bridge 2000; Leppert and Luczak 2005; Mercadante et al., 2003; Mercadante et al., 1999; Mercadante et al., 2001; Mercadante et al., 2005; Mercadante et al., 2009a; Moryl et al., 2005; Parsons et al., 2010). Mercadante et al. reported successful switches (PI $\leq$ 4 on NRS 0-10) in 80% of 52 patients within 3.65 days in one study(Mercadante et al., 2001) and after only 24 h in 46 % of 24 patients in another study(Mercadante et al., 1999). The inabilities of this study to reproduce the findings from the above and previous studies(Mercadante et al., 2003; Mercadante et al., 1999; Mercadante et al., 2001) may partly be a cohort effect. We included very sick cancer pain patients, which may have different outcomes than patients included earlier in the disease trajectory. In our study 33/35 patients used opioid doses >300 mg (49 % > 1000 mg) and few exclusion criteria were employed. Other studies on opioid switching from morphine have included cancer patients with low mean baseline morphine doses (125-160 mg/day), and excluded patients with anticancer treatment, poor liver/kidney function and brain metastases(Mercadante et al., 1999; Mercadante et al., 2001; Ripamonti et al., 1998b). Moryl et al. has delivered the only real critical paper to opioid switching, with only 1/13 successfully maintained on the second opioid after a switch from methadone. These patients were also on high preswitch opioid doses (mean 515 mg/day)(Moryl et al., 2002). This may indicate that low-dose switches represent a different population than in high-dose populations, and that an increase of the primary opioid would be a better alternative than a switch in some cases. In our study, as many as 12 patients switched the opioid because of pain. The background for this was not further outlined, and it might be that also these patients could increase the baseline opioid dose. The doses in themselves were however high before the switch.

The most common indication for the switch was a combination of pain and adverse effects in both groups. The physicians concluded that these patients were in need of an opioid switch. Still, both groups in this study reported a low average score on pain and AEs at baseline (all variables except average PI < 4 (NRS)). Based on interference with function, Serlin et al. found that mild pain correspond to 1-4 on a 11-point NRS, moderate pain corresponds to 5-6 and severe pain corresponds to 7-10 (Serlin et al., 1995). Adequately controlled pain should be rated as 'none' or 'mild' (NRS 1-4) (Davies et al., 2009; Paul et al., 2005; Serlin et al., 1995). One of the reasons to the surprisingly low score on both pain and AEs in this cohort might be a 'response shift'; they relate symptom intensity more to what they expect at that stage of disease than to the absolute intensity of a symptom(Carr et al., 2001). Also, discrepancies may result from several factors, including the effectiveness of the patient's coping skills. For 11-point (0-10) NRS a reduction of 2 or 30% has been demonstrated to be clinically significant(Farrar et al., 2001). The expert proposals of the EPCRC are that a reduction of ≥ 50% should be considered a 'substantial decrease' and that ≥ 30% 'a meaningful decrease' in PI. This means that a pain reduction of 1 (11 point NRS) is considered a meaningful decrease if the baseline PI is 1-3. This complies with the subjective experience of the investigators in study A, that the patients did experience pain relief and side effect resolution. The power to detect a difference in PI is shown to be higher with a high baseline score(Farrar et al., 2001).

Equianalgesic conversion ratio

Equianalgesic tables are derived largely from single-dose studies, expert opinion, and in non-cancer patients(Pereira et al., 2001). Equianalgesia is expressed as the dose ratio between two opioids which produces equivalent analgesia. However, opioid switches are made to improve pain relief rather than to obtain equivalent pain relief. For this reason it has been suggested to use the term "initial conversion ratios" instead of "equianalgesic doses" when addressing dose ratios for switching between opioids(Mercadante and Bruera 2006). Equianalgesic ratio is used in this thesis since this is the most commonly used term.

Several equianalgesic ratios for morphine and methadone have been proposed and found effective such as a fixed 5:1 ratio(Auret et al., 2006; Mercadante et al., 1999), or dose dependent ratios ranging from 1:1 to 20:1(Ayonrinde and Bridge 2000; Lawlor et al., 1998; Ripamonti et al., 1998b). The final ratios between the preswitch morphine dose and the final methadone dose in the present study support the conclusions of Bruera et al and later Ripamonti et al. that the relative potency of methadone increases in patients on higher preswitch doses(Bruera et al., 1996; Ripamonti et al., 1998a; Ripamonti et al., 1998b), and the recent belief that the methadone equivalent for morphine is not fixed, but is linearly related to dose as in concurrence with the findings in this study(Lawlor et al., 1998; Pereira et al., 2001). Both groups used rescue doses regularly during the trial indicating that titration of methadone might be more aggressive than in this protocol. The switching table explored could be further differentiated in the lower and upper morphine equivalent groups. In the 15 patients switched from oxycodone in this thesis, the ratio used to find the equivalent morphine dose was 2:1. Oxycodone is an opioid analgesic that closely resembles morphine, and the efficacy and tolerability of oxycodone are similar to

morphine(Reid et al., 2006). In a systematic review on opioid conversion ratios the morphine: oxycodone ratio was recommended as 1:1.5 instead of 1:2(Mercadante and Caraceni 2011). The choice of ratio might have caused the patients that switched from oxycodone to receive a higher methadone dose than those switched from morphine. However, this was the case in both groups and the number of patients switching from oxycodone was similar in the two groups (8 and 7).

Evidence of dangers of inconsistent equianalgesic ratios is sparse. Opioid clinical trials are often performed in highly selected patients, rarely blinded, seldom powered to adequately detect adverse events, and usually conducted by pain specialists familiar with proper opioid-dosing strategies. In addition, trials with the purpose of detecting fatal or serious side effects would be marred with ethical concerns. Patient-specific factors such as potential drug-drug interactions, opioid history, pain severity, and functional status, genetic make up, and medical conditions, among others, are not accounted for in conversion tables. Taken together, these shortcomings comprise a considerable barrier to the calculation of the equianalgesic methadone dose. The overestimation of methadone requirements was exemplified by the one patient experiencing severe respiratory depression in this study. Since prospective serum samples of morphine and methadone were available in this patient (paper II), it could be determined that pharmacokinetic factors related to the switch probably could explain his respiratory depression. Thus the major cause of this incident was that the commonly used conversion ratio overestimated his methadone requirement by 30% as the patient after all, later did well on a lower dose of methadone. This indicates that the conversion dose at least in some patients may be difficult to predict, even though strict conversion protocols are followed. In the end, it may be less important to determine the exact opioid ratio than it is to assure that the patient is an appropriate candidate for methadone conversion. The high success-rate in most studies in a recent review on methadone ratios was not directly associated with the opioid ratio or switching method applied, but rather a result of the monitoring provided and the subsequent dose titration(Weschules and Bain 2008).

Dropouts and safety

The higher rate of dropouts after intervention in the SAG group (38%) and three SAEs, are of grate concern, and indicate that the SAG strategy is not safe in this patient cohort. It might be that this is not related to the switching strategy alone, but rather a coincidence or a result of different groups. Even though five patients in the SAG group did not receive the allocated treatment and two of the SAEs were apparently disease related, three SAEs in this small group raises concerns. The high number of SAEs in the SAG group is supported by the findings by Auret et al. who switched 15 patients from morphine to methadone using the SAG strategy (fixed methadone: morphine ratio 6:1)(Auret et al., 2006). Five patients (33.3 %) dropped out and one died. Severe sedation was also reported in one patient (day 5) with chronic non-malignant pain switched by the 3DS strategy(Fredheim et al., 2006b). Similar risk of SAEs has not been reported in other SAG studies(Mercadante et al., 2003; Mercadante et al., 1999). The dropouts and SAEs are further discussed under research question 2. Taken together, these results indicate that the safety of the SAG strategy is not safe in patients with short life expectancy on high doses of opioids and it should not replace the 3DS in routine clinical practice. However,

this study only addresses one SAG approach and other "as needed" SAG approaches have been claimed effective(Morley and Makin 1997; Tse et al., 2003), but no randomized trials are performed.

The results of this thesis indicate that the patients in need of an opioid switch, on high opioid doses, should be admitted to the hospital/expert setting during the first five days of the switch. Owing to reported cases of delayed serious adverse effects such as sedation and respiratory depression (Ettinger et al., 1979; Hernansanz et al., 2006; Hunt and Bruera 1995; Watanabe et al., 2002), hospitalization during an opioid switch is also recommended by other authors (Ripamonti et al., 1997; Scholes et al., 1999). Also monitoring of vital signs during initiation of methadone therapy are proposed(Watanabe et al., 2002). On the other hand, others find that outpatient switching to methadone is safe if there is a close follow-up, and both the patients and their primary caregivers have been educated about the possible complications (Hagen and Wasylenko 1999; Hernansanz et al., 2006; Mercadante et al., 1999; Parsons et al., 2010).

It might be that a more flexible use of SAG strategy when switching to methadone is a better choice in these patients; the current opioid could be stopped, and the methadone dose (dose-dependent as done is this study) changed according to the clinical response may provide the optimal treatment in patients receiving high doses of morphine or oxycodone. This is in concordance with the newly revised cancer pain treatment guidelines from the EPCRC(Caraceni et al., 2011, accepted Lancet Oncology), which recommend that the opioid dose needs to be titrated to clinical response. They state that the existing conversion ratios are specific for patients who have satisfactory analgesia from the first opioid, therefore when the opioid switching is due to unsatisfactory analgesia and/or excessive side effects the dose should be lower than that calculated from published equianalgesic ratios(Caraceni et al., 2011, accepted Lancet Oncology). Also, that the conversion ratio from oral morphine to oral methadone is dose dependent and varies widely (Mercadante and Caraceni 2011), and is therefore not included in the recommendations.

Limitations

Study A was underpowered, and because of the low completion rate,- the confidence intervals were wide, and no firm conclusions coul be made with regard to group differences for the primary outcome PI day 3. In addition, 10 SAG patients completed the study and were compared with 18 3DS patients, with obvious statistical implications. One may question whether the groups are different in this trial. The mean preswitch equianalgesic dose of morphine is higher in the 3DS group than in the SAG group (1330 mg to 900 mg) indicating that the patients receive the same methadone dose already from day two. The patients in the 3DS group have used opioids for a longer period of time (23.9 months to 9.1 months), and more patients have metastases than in the SAG group (95% to 76%). On the other hand, both groups score equally on baseline recordings of PI and AEs (NRS) and when comparing the median preswitch dose in the patients that receive methadone, the differences are smaller (SAG 720 mg/day vs. 3Ds 960 mg/day).

There is an ongoing debate on how to define the target population(Kaasa et al., 2008). The cancer pain experienced by the patients in this thesis was only described by pain intensity level, and not further classified as to the patients pain mechanism (with or without neuropathic pain), breakthrough pain, psychological distress, pain location and other relevant symptoms such as sleep, depression and anxiety. These domains are suggested as important domains in the new classification proposal CPACS(Kaasa et al., 2011). This might cover a selection problem, and the comparison with other cancer pain samples may be difficult.

Factors that could have made this study better; higher power, describing the pain and the cause of switch (analyzing subgroups) more thoroughly, and record PI every day so that time to PI <4 could be measured. In addition, three dropouts could have been avoided had the QTc-time limits been a part of the inclusion criteria and before the randomization took place. Still, this trial had a strong design, and managed to include severely sick patients.

1.18.2 Research question 2

What is the pharmacological profile of the respective opioids, and how can it guide clinical interpretations and clinical practice of a methadone switch?
The pharmacokinetic differences between the groups were not reflected in a lower mean score of pain or side effects in the SAG group, than in the 3DS group. No significant relation between trough serum concentrations and PI levels were found.

Mercadante et al. claimed that a more rapid clearance of morphine and its metabolites for the SAG approach would result in less side effects, and that a shorter time to stabilization of the methadone concentration would give faster pain relief(Mercadante et al., 2003). This was not supported by this study. As expected, more patients were in apparent steady state of total methadone concentrations on day 4 in the SAG group than in the 3DS group. Moreover the SAG group had a higher exposure to methadone and less exposure to morphine and oxycodone the first three days. However, these pharmacokinetic differences were not reflected in a lower mean pain score in the SAG group than in the 3DS group. Mercadante et al. reported that 9/10 cancer patients had stable plasma concentrations of methadone after 1-2 days after a SAG switch(Mercadante et al., 2003). However, the patients were observed for four days only, the blood samples were taken in the absorption phase 1-2 h after methadone administration, and steady state was defined as a higher methadone concentration day 2 than day 3, which seems to be a too short period of time. In the present study only 42% (SAG group) and 22% (3DS group) reached stable total methadone concentrations on day 4 (i.e. 3 days after switch). This was in accordance with the results in the study by Auret et al., also using the SAG strategy, but sampling at trough, reporting that the patients were in steady state after 4-8 days(Auret et al., 2006). Our finding is also in agreement with the long elimination half-life of methadone, indicating steady state after about 5-6 days, corresponding to 5 times the elimination half-life of methadone.

The only significant difference in the opioid serum concentrations between groups was the concentrations on day 2. The lack of significant differences the other days might be a type II error because of a small sample size, but it might also be a factor that the 3DS group had a higher preswitch opioid dose than the SAG group. Nevertheless, the results support previous findings that the methadone dose cannot predict the serum concentrations of methadone(Eap et al., 1998; Fredheim et al., 2007).

A consequence of the relatively long elimination half-life of methadone is that the onset of overdose symptoms is delayed, and insidious. The patient that experienced an overdose displayed sedation already on day 3, followed by severe respiratory depression two days later. The methadone dose should have been stopped at day 3, not just reduced. Previous reports of sedation and/or respiratory depression during methadone treatment(Benitez-Rosario et al., 2006; Ettinger et al., 1979; Fredheim et al., 2006b; Hunt and Bruera 1995; Megarbane et al., 2007) together with the case of sedation in this study, strongly suggest that patients should be observed closely during the first five days on methadone regardless of switching strategy applied. Also, if signs of overdose appear; stop dosing and start with a reduced dose of methadone again when signs of toxicity have disappeared.

This study found low correlations of PI and the trough concentrations of methadone on day 3 and 14. This supports the findings by Auret et al. with no simple correlation between worst pain and trough methadone plasma concentrations(Auret et al., 2006). Mercadante et al., reported no differences in plasma concentration pattern of the two opioids between patients considered responders and non-responders when switching from transdermal fentanyl to methadone(Mercadante et al., 2007a). This was also the conclusion in a study on non-cancer chronic pain patients(Fredheim et al., 2007). However, in these studies as well as in this thesis, some patients might have developed a high degree of opioid tolerance prior to the opioid switch. Consistent with such a phenomenon, no simple relationship between plasma concentrations of morphine, oxycodone, metabolites or metabolite ratios and clinical effects in cancer patients has been identified in previous studies(Klepstad et al., 2003; Quigley et al., 2003; Wolff et al., 1995). A relationship between blood concentrations and effects of oxycodone has, however, been found in single dose studies in healthy volunteers(Benziger et al., 1997; Kaiko et al., 1996). The effects were assessed with a drug effect questionnaire, and by assessing mood, pupil size changes and respiratory rate in both studies. Kaiko et al. also showed that those with the highest “drug effect” had the highest incidents of opioid-related side effects and the highest oxycodone plasma concentrations(Kaiko et al., 1996). These findings are not confirmed in clinical trials on cancer patients. Heiskanen et al. recorded pain intensity, subjective drug effect and adverse effects and assessed oxycodone, morphine and metabolites concentrations at trough, and at 1,3 and 5 h after administration(Heiskanen et al., 2000). No relationship between clinical findings and opioid concentrations was found. Interestingly, Andreassen et al. reported that serum concentrations of oxycodone in cancer patients were higher in treatment failures than in treatment successes (Andreassen et al., accepted for publication in Journal of Pain and Symptom Management June 2011, DOI: 10.1016/j.jpainsymman.2011.05.008).

Relative deviation of individual concentrations from the group mean of trough concentrations at steady state of methadone was not more variable than that of morphine or oxycodone. The concerns regarding variable pharmacokinetics of methadone and numerous drug interactions that are often emphasized when predicting equianalgesic doses and risk of accumulation, were thereby not supported in this study. However, the patient experiencing severe respiratory depression and the other dropouts did not complete the study, and were thus not included in the above figures.

The total methadone concentration (R- and S-methadone) is most often studied(Kristensen et al., 1995), although the R-methadone enantiomer is considered to be responsible for the analgesic effect. In this study the R-methadone concentrations were highly correlated to the total methadone concentrations, indicating that total methadone concentrations might be sufficient in most cases.

The changes in serum concentrations may be less important than the exposure to the CNS; the site of action. CSF methadone levels vary significantly between individuals for dose; they have been reported to be 2-73% of serum levels in humans(Max et al., 1985; Rubenstein et al., 1978). Wolff et al. found that there is a significant inter-individual variability in the CSF/plasma ratio for morphine which may obscure plasma concentration-effect relationships(Wolff et al., 1995). However, a relation between pain relief and steady state concentrations of morphine in the CSF in cancer patients following epidural administration was not found in a study by Samuelsson et al(Samuelsson and Hedner 1991). Clearance of morphine and M6G from the CNS is probably much slower than the cerebral wash-in of methadone(Lotsch et al., 2009). The initial total cerebral burden of opioids after a switch may be higher in the SAG patients than in the 3DS patients. If true, this favors the 3DS switch, especially in patients on high opioid doses.

1.18.3 Research question 3

How fast is the maximum concentration of fentanyl achieved after nasal administration?
Rapid onset of action is of great importance in treating BTP, as the pain is often severe, reach peak intensity on average 3-5 minutes, and has a short duration(Portenoy et al., 1999a; Zeppetella et al., 2000). The traditional orally administered opioids are commonly used as rescue in cancer patients, although peak plasma levels ranges from 30-90 min(Gourlay et al., 1986; Leow et al., 1992), with an onset of analgesia after approximately 20-30 min post-dosing(Portenoy and Hagen 1990; Zeppetella 2008; 2009a). Oral transmucosal fentanyl citrate (OTFC) was developed to improve treatment of BTP, with venous T_{max} values varying from 20 to 91 min in healthy volunteers and cancer patients, and with a meaningful pain relief after 15 min(Coluzzi et al., 2001; Darwish et al., 2007; Egan et al., 2000; Mystakidou et al., 2006; Streisand et al., 1991). This indicated that that OTFC could be more appropriate for BTP than orally administered morphine and equivalents.
The two pharmacokinetic studies on intranasal fentanyl (InF) published at the time when this thesis was planned, reported mean venous T_{max} between 4 and 14 min(Lim et al., 2003; Striebel 1993) after administration of 50µg, and indicated that the nasal route of administration could provide a rapid onset of pain relief. This was supported by the two

studies on nasal fentanyl in this thesis, which demonstrated a fast systemic uptake of the nasally administered fentanyl in opioid naïve and opioid tolerant patients (study B and C, paper III and IV). Fentanyl was quickly absorbed through the nasal mucosa, attaining peak venous plasma concentrations within a median time (T_{max}) of 12–15 minutes for the three intranasal fentanyl spray dosage strengths (50,100 and 200 µg of fentanyl), and of 7 min in arterial samples after 50 µg of nasal fentanyl. Importantly, serum concentrations of fentanyl were detectable at just 2 min post-dosing (the first time-point measured). These findings are confirmed in more recent PK studies on InF where T_{max} from 11-21 min are reported(Christrup et al., 2008; Fisher et al., 2010a; b; Foster et al., 2008; Veldhorst-Janssen et al., 2010). The T_{max} observed in our, and these studies, shows good agreement with the mean value measured in healthy individuals, wherein a median time to onset of pain relief of 7 min was observed(Christrup et al., 2008).

Fisher et al. compared three nasal formulations, each containing 100 µg in 100 µl with different properties to OTFC(Fisher et al., 2010a). He concluded that all these nasal formulations demonstrated significant increased systemic exposure and reduced times to peak plasma values compared with OTFC. This indicates that the transmucosal bioavailability of fentanyl may depend on both formulation and the location of a transmucosal application. Factors contributing to variability in PK parameters in the studies may be explained by differences in spray device used; different volumes, formulations, different degree of run-off (also affected by patients' position), ionization, dosage and in different analytical methods(Veldhorst-Janssen et al., 2009). The different formulations used may also explain the differences when comparing C_{max} values.

1.18.4 Research question 4

Does opioid naïve and opioid exposed subjects tolerate nasal fentanyl?
Intranasal administration of fentanyl at doses of 50–200 µg were found to be well tolerated by the opioid tolerant patients (study B), and 50 µg of InF was well tolerated in the opioid naïve patients (study C). No dose-related trends in adverse events were evident. In addition, no treatment related serious AEs were reported and no patient discontinued due to AEs.

In study B, 26.3 % (5 patients) reported AEs considered being treatment related. Nausea and hypoxia were the only AEs reported for more than one patient. In study C, one patient needed oxygen when the saturation fell to 90%. However, the drop was not significant as his baseline saturation was 93%. Finally, none of the patients reported nasal discomfort or taste experiences. The latter being important, as bad taste might reduce patient compliance. Furthermore, the safety of use of fentanyl would be expected to be even better in patients given fentanyl for BTP as pain give some protection against opioid induced respiratory depression(Borgbjerg et al., 1996).

An intravenous dose of 50 µg fentanyl is trivial in conjunction with anesthesia; however, this takes place under strict professional observation. This is not the case when fentanyl is self administrated nasally by the patient. Frequent dosing carries a risk of accumulation, which may cause significant adverse events. Although less fentanyl will reach the

systemic circulation compared to intravenous administration, there are some concerns also related to possible additional mechanisms for uptake to the brain from the nasal area as discussed previously(Dale et al., 2002a; Dale et al., 2006).

Today, two formulations of intranasal fentanyl have reached the market in parts of Europe; the Fentanyl Pectin Nasal Spray (Nasal Fent®) and the intranasal fentanyl spray (Instanyl®), both with BTP as the only indication. It has also been studied with other indications than BTP, such as post operative pain treatment(Veldhorst-Janssen et al., 2010), acute pain in children(Borland et al., 2007; Cole et al., 2009; Galinkin et al., 2000), breathlessness(Sitte 2009), and burns(Finn et al., 2004). InF are tried in nociceptive pain(Zeppetella 2000), it is compared to OTFC(Mercadante et al., 2009b) and placebo (Kress et al., 2009). The prevalence of side effects was 19.8% (22/111) during the efficacy period of three weeks with nausea as the most frequently reported adverse effect (4.5%). These results was confirmed in placebo controlled RCTs(Curtiss 2011; Portenoy et al., 2010; Taylor et al., 2010) and in comparison to oral morphine(Davies et al., 2011a). Other transmucosal preparations than OTFC of fentanyl have been studied lately, such as the fentanyl buccal tablets (FBT)(Darwish et al., 2010), fentanyl buccal soluble film (FBSF)(Vasisht et al., 2009; 2010), and sublingual administration(Bredenberg et al., 2003; Lennernas et al., 2005). All avoid first pass metabolism, and the buccal and sublingual mucosa are more permeable than other locations in the mouth(Zhang et al., 2002). Vissers et al. undertook a meta-analysis if six RCTs that compared InF with OTFC, fentanyl buccal tablets (FBT), and oral morphine for BTP(Vissers et al., 2010). The end-point was reported PID on a 10-point NRS up to 60 min post dosing. InF provided the greatest reduction in pain relative to placebo. All trials on InF for the treatment of BTP have confirmed its usefulness, and the long-term tolerability has been good(Radbruch et al., 2011). InF and BTP management in cancer patients are recently reviewed(Davis 2010; Leppert 2010; Panagiotou and Mystakidou 2010).

1.18.5 Research question 5

Is there a significant difference between the early venous and arterial pharmacokinetics of nasal fentanyl?

Knowledge of arterio-venous differences is important with respect to the relationship between serum concentrations and the prediction of the analgesic effect of opioids such as fentanyl. The major finding of this part of the thesis (Study C, paper IV) was that pharmacokinetic parameters estimated from arterial samples differed significantly from the venous ones, with $AUC_{0\text{-}60}$ and C_{max} being larger and T_{max} shorter in arterial samples. In this study the correlations between arterial and venous $AUC_{0\text{-}60min}$ were found, while the correlations were poor for T_{max} and C_{max}. This indicates that venous pharmacokinetic parameters not only deviate from arterial values, but that they are also poor predictors of arterial values.

The significant arterio-venous differences comply with reports before this study was conducted; showing significant arterio-venous serum concentration differences after nasal administration of nicotine in human volunteers(Guthrie et al., 1999). This was also

reported after intravenous administration of other opioids(Hermann et al., 1999; Rentsch et al., 2001). Also studies performed more recently confirm our findings; a study of 17 healthy volunteers receiving M6G iv, arterio-venous concentration differences were apparent(Olofsen et al., 2010). In a randomized, open-label crossover study, 27 healthy volunteers received a tablet of 400 μg of buccal fentanyl. Arterial and venous samples were drawn simultaneously from 17 of the subjects (mean 22.8 years) before and during the next four hours (17 times) after administration. The maximum plasma concentrations in the arterial samples were approximately 60% higher, and occurred 15 min earlier, than in the venous samples(Darwish et al., 2006). This indicates that nasal administration, due to the rapid absorption, share pharmacokinetic characteristics with intravenous drug administration.

The effect site equilibration time is the temporal dissociation between the serum (central compartment) concentration and the apparent effect site (effect compartment) concentration of a drug. The effect site equilibration explains the delay between the arterial serum time concentration curve and the effect-curve. Since venous concentrations do not predict arterial concentrations, arterial samples will be more precise when predicting onset time of analgesia. Venous samples will also underestimate concentrations at effect site (CNS) and time to C_{max} in the CNS. However, some claim that oral opioids is effective despite the delays in peak serum concentrations(Cleary 1997). The incongruity between response and venous pharmacokinetics where analgesia precedes the rise in venous blood levels, have been attributed to the placebo effect(Farrar et al., 1998; Portenoy et al., 1999b). However, it might be that this incongruity can be explained by the earlier arterial rise.

The different sites of blood sampling might lead to different interpretations of data, particularly across studies(Chiou 1989a). Thus, the method of blood collection needs to be clearly defined, and the comparison of PK profiles across studies using arterial sampling cannot be made with those using venous sampling(Darwish et al., 2006). Even though PK results from venous samples may be less accurate for prediction of time to onset of action, this is still the most commonly applied sample site in PK/PD studies. Obtaining arterial samples may be painful, technically difficult and can result in complications including: bleeding, aneurysm formation, thrombosis of the artery, infection and at the most extreme loss of function of the extremity. For these reasons and to compare T_{max} between studies, venous samples were used in paper III in this thesis. Second, differences in arterio-venous concentrations have little relevance beyond the first hour. This means that arterial sampling is only relevant for fat-soluble drugs with a fast onset of action.

1.19 BTP management today

Several expert recommendations have addressed the issue of BTP management and concluded that the evidence is limited. (Davies et al., 2009; Hanks et al., 2001; Mercadante et al., 2002). A recent systematic review comparing InF to other opioids for BTP management concluded that InF is expected to provide the greatest improvement in the treatment of BTP(Vissers et al., 2010). Nicholson et al. have recently published a

review of different routes of opioid delivery for cancer BTP(Nicholson and Agarwala 2011). In comparison with oral morphine or placebo, transmucosal, buccal, sublingual, and intranasal fentanyl have been shown to provide rapid analgesia and are available for clinical use in most countries. All the studies performed with these delivery systems have recommended that these drugs should be administered to opioid-tolerant patients receiving doses of oral morphine equivalents of at least 60 mg(Mercadante 2011). It should be taken into consideration, that the analgesic effects of these preparations cannot be reliably assessed in BTP as the pain may peak prior to the onset and resolve before the end of the fentanyl action(Hagelberg and Olkkola 2010; Portenoy et al., 1999a).

A recent systematic review (update of(Zeppetella and Ribeiro 2006)) on opioids for the management of BTP in adults with cancer pains, as part of the European Palliative Care Collaborative (EPCRC) opioid guideline project retrieved nine RCTs, whereof most were industry sponsored(Zeppetella 2011). Based on this review, the new EAPC recommendation on BTP management is: “breakthrough pain can be effectively managed with either oral, immediate release opioids or buccal or intranasal fentanyl preparations. In some cases buccal or intranasal fentanyl preparations are preferable to the immediate release oral opioids because of their more rapid onset of action and shorter duration of effect”(Caraceni et al., 2011, accepted Lancet Oncology).

Conclusions

Based on the papers included in this thesis the following answers to the research questions are:

How to switch from morphine or oxycodone to methadone when the patients experience an imbalance between pain and side effects on high doses of opioids

1. Is the stop and go switching strategy more effective than and as safe as the standard 3-days switch?

- No benefit of the SAG strategy was observed compared to the 3DS strategy in respect to better pain control or reduction of side effects.
- The SAG group had more dropouts and serious adverse events compared to the 3DS group. This indicates that the SAG strategy is not safe in these patients.
- The SAG strategy in cancer patients with advanced disease, complex pain features, and high opioid doses, is not to be recommended.

2. What is the pharmacological profile of the respective opioids and how can it guide clinical interpretations and clinical practice of a methadone switch?

- The patients in the SAG group were significantly more exposed to methadone and less to the previous opioids, than the 3Ds group the first three days after the switch. This did, however, not result in better pain control or reduction of side effects in the SAG group.
- 42% (SAG) and 22% (3DS) of patients had apparent steady state of methadone concentrations on day 4, and one SAG-patient experienced severe respiratory depression day 5. This indicates that patients need to be observed for more than five days (when steady state may be assumed) independently of switching strategy.
- The dropouts (including the SAEs) did not have significantly higher methadone concentrations than the median of the rest of the SAG group. The SAEs cannot be predicted from serum concentrations. Increasing sedation/tiredness should lead to discontinuation of methadone until awakening, and not just a reduction of methadone dose.
- Low correlations were found between total methadone concentrations and PI day 3 in both groups.
- Serum concentrations of methadone were not more variable, than that of morphine or oxycodone.
- Total methadone concentrations were highly correlated to R-methadone concentrations, indicating that analyzing total methadone concentrations might be sufficient, despite the fact that the R-methadone enantiomer is the analgesic isomer.

Exploring the pharmacokinetic profile of nasal fentanyl spray as a novel principle of treatment of cancer breakthrough pain

3. How fast is the maximum concentration of fentanyl achieved after nasal administration?

- Nasal fentanyl provided a rapid uptake with a venous fentanyl concentration peak for all doses (50, 100 and 200 μg) from 9 to 15 min after administration and this complies with its rapid onset of action.

4. Does opioid naïve and opioid exposed subjects tolerate nasal fentanyl?

- Nasal fentanyl was well tolerated by cancer patients with breakthrough pain and by opioid-naïve, elderly men. This together with the short time to peak concentrations, indicate that this can be a suitable treatment for cancer breakthrough pain.

5. Is there a significant difference between the early venous and arterial pharmacokinetics of nasal fentanyl?

- The pharmacokinetic parameters estimated from arterial samples differed significantly from the venous ones, with the exposure the first hour (AUC_{0-60}) and the C_{max} of fentanyl being larger and the T_{max} concentration shorter in arterial samples. The correlation was strong for AUC_{0-60} (0.78) but weaker for C_{max} (0.60) and T_{max} (0.14).
- This indicates that venous pharmacokinetic parameters not only deviate from arterial values, but that they are also poor predictors of arterial values. Analyses from arterial blood samples may give a more precise estimate when predicting time to effect in the early phase after intranasal fentanyl.

Future perspectives

The findings presented in this thesis are only initial steps to elucidate the complexity of cancer pain treatment. With analgesic strategies integrated into a palliative plan of care, there is increasing hope that patients can experience cancer with a minimum of suffering. Nonetheless, the treatments used, have very little supporting evidence and there continues to be a pressing need for more research to provide comparative and long-term data to current and novel treatment strategies. A systematic review of studies on cancer symptoms reported in palliative care journals from 2009-2010, found that of the 1569 articles published, only 5.86% (92 articles) were on cancer pain(Kumar 2011), and the challenges are many. Establishment of an international, academically based network of centers that have the skills and resources to conduct multicenter studies in palliative care patients are needed. One effort is The European Palliative Care Research Centre (PRC), which was officially launched in October 2009, with the aim to coordinate groups and individual researchers across Europe, North America and Australia. The PRC is based upon an open invitation for all active researchers in palliative care to participate (http://www.ntnu.edu/prc).

Opioid switching

Most studies on opioid switching have evaluated a switch to methadone, but no RCTs have compared the efficacy and adverse effects profile of methadone to other opioids. Future studies should aim at determining what patients will benefit from an opioid switch, what the indications should be, and what opioid should be chosen as the second line opioid. Further research should compare different opioids, switching strategies and routes of administration in RCTs. A strategy where the current opioid is stopped and the new opioid started by titration might be a choice of strategy and should be studied. Furthermore opioid switching has not been compared to other treatment options when treatment with a step three opioid fails to provide acceptable balance between pain relief and side effects.

Nasal fentanyl versus other BTP treatment strategies

There is a limitation of nasal application that absorption of fentanyl can be influenced by nasal obstruction/rhinitis. As many as 44% of 320 cancer patients on opioids reported regular nasal problems in a multi-center European study(Davies et al., 2011b). The implication of this and irritability of the nasal mucosa after long term use is not yet established. RCTs comparing nasal fentanyl to other BTP treatments should be performed. Other indications of intranasal fentanyl than BTP should be explored. Issues of tolerance, and drug abuse should be addressed in future clinical trials.

Standardized classification and assessment of pain

The aim is a better selection of the right patient for the right treatment, and the ability to compare results across studies. It has been suggested that a consensus on classification may improve pain treatment in cancer patients(Kaasa and Caraceni 2010). In order to characterize the study population precisely and thus increase the external validity, a common minimum dataset for patient description should be applied in all studies. Furthermore, an agreement on outcome measures for pain intensity and adverse effects

should be standardized, including the time points for the observations. This would make meta-analysis possible. Furthermore, several of the existing, validated questionnaires are too long in order to be used in the daily routine or be repeated frequently during follow-up. The European Palliative Care Research Center (http://www.epcrc.org/) is in the process of trying to improve the classification of pain. The intention is to agree on assessment tools and new cancer pain guidelines(Kaasa et al., 2011).

Access to pain treatment

The knowledge of cancer pain treatment needs to reach all cancer patients no matter country, setting or physician. Limited knowledge is, however, not the only problem. A survey from 46 developing countries conducted by IASP identified barriers to good pain management; lack of education in pain management, low priority by government agencies, limited drug availability caused by cost implications and restrictions but also poor patient compliance(IASP). By 2020 the WHO estimates that 70% of new cancer cases will be in developing countries, with most patients presenting with late stages of disease(Ramsay 2001). Although adequate pain treatment is considered a human right, health care systems in many countries have yet to view pain management in this context. Research that may illuminate how to improve education, raise resources, and improve cancer pain treatment in all parts of the world is warranted.

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How to switch from morphine or oxycodone to methadone in cancer patients? A randomised clinical phase II trial

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ABSTRACT

Aim: Opioid switching is a treatment strategy in cancer patients with unacceptable pain and/or adverse effects (AEs). We investigated whether patients switched to methadone by the stop and go (SAG) strategy have lower pain intensity (PI) than the patients switched over three days (3DS), and whether the SAG strategy is as safe as the 3DS strategy.

Methods: In this prospective, open, parallel-group, multicentre study, 42 cancer patients on morphine or oxycodone were randomised to the SAG or 3DS switching-strategy to methadone. The methadone dose was calculated using a dose-dependent ratio. PI, AEs and serious adverse events (SAEs) were recorded daily for 14 days. Primary outcome was average PI day 3. Secondary outcomes were PI now and AEs day 3 and 14 and number of SAEs.

Results: Twenty one patients were randomised to each group, 16 (SAG) and 19 (3DS) patients received methadone. The mean preswitch morphine doses were 900 mg/day in SAG and 1330 mg/day in 3DS. No differences between groups were found in mean average PI day 3 (mean difference 0.5 (CI −1.2–2.2); SAG 4.1 (CI 2.3–5.9) and 3DS 3.6 (CI 2.9–4.3) or in PI now. The SAG group had more dropouts and three SAEs (two deaths and one severe sedation). No SAEs were observed in the 3DS group.

Conclusion: The SAG patients reported a trend of more pain, had significantly more dropouts and three SAEs, which indicate that the SAG strategy should not replace the 3DS when switching from high doses of morphine or oxycodone to methadone.

1. Introduction

Pain is a prevalent symptom in cancer patients.[1,2] Opioids may provide pain control in 85–90% of these patients,[3] still a large number of cancer patients have unacceptable high pain intensity.[2,4] A change of route or a switch to another opioid have been recommended to improve pain and/or opioid related adverse effects (AEs).[5,6]

Despite the low level of evidence, opioid switching is recommended by experts,[5,7] as well as by major textbooks on cancer pain.[8,9] The rationale behind the opioid switch is not fully understood. However, pharmacogenetic variability,

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pharmacodynamic and pharmacokinetic factors such as incomplete cross-tolerance to the analgesic effect amongst opioid agonists or the metabolic clearance of the previous toxic opioid with AE resolution may contribute.[10–12] Whilst opioid switching is generally recognised, there are several unresolved questions; which opioid to use?, what is the optimal switching strategy? and which equianalgesic dosage should be applied?

Methadone is the most commonly applied secondary opioid.[13,14] It has no active metabolites, high oral bioavailability and its elimination is largely independent of renal function. Dosing may be challenging due to a long terminal half-life (13–50 h),[15,16] potential drug-drug interactions and the risk of arrhythmia.

The dominating switching strategies are the 'stop and go' (SAG) where the current opioid is immediately replaced by methadone[17–21] and the '3-days switch' (3DS) where the dose of the current opioid is reduced stepwise by 1/3 every day and substituted with 1/3 of the equianalgesic dose of methadone over three days.[22–24] The 3DS is the standard approach as it may avoid methadone accumulation and toxicity, especially in patients on high doses.[23,25] SAG has been proposed to be safe, and more effective than 3DS.[18] Advocates for SAG argue that a rapid switch gives faster onset of analgesia and reduction of AEs.[18]

Several equianalgesic conversion ratios for morphine and methadone have been proposed and found effective such as a fixed 5:1 ratio,[19,26] or dose-dependent ratios ranging from 1:1 to 20:1.[23,27,28] However, no randomised trials on opioid switching to methadone have been published[13,29]. The studies have primarily been done in patients receiving less than 350 mg morphine limiting their validity for advanced, frail cancer patients who are switched from 800 to 1500 mg morphine equivalence doses.

In order to evaluate the effect and safety of the SAG strategy compared to the standard 3DS when switching from morphine or oxycodone to methadone in cancer patients, a randomised study was conducted with the following hypotheses: Patients allocated to the SAG strategy have lower PI than the 3DS patient's day 3, and SAG is as safe as 3DS.

2. Patients and methods

2.1. Trial design, randomisation and masking

This was a prospective, open, parallel group, multicentre randomised controlled phase II trial. The randomisation (central telephone) was stratified by hospital (block size of two) and allocation was concealed until interventions were assigned. Observation time was 14 days. The Regional Committee for Medical Research Ethics approved the study and it was conducted according to the Helsinki declaration. Informed and written consent was obtained. This trial is registered in ClinicalTrials.gov id: NCT0014496.

2.2. Patients and setting

Cancer patients >18 years, treated with morphine or oxycodone (>1 week) and having increasing pain considered to be untreatable with further opioid titration and/or having opioid related adverse effects were eligible. In- and out-patients (if observed by next of kin) were recruited from four hospitals in Norway; Telemark Hospital, Haraldsplass Deaconess Hospital, Kristiansund Hospital and St. Olav's University Hospital.

2.3. Switching procedure

In SAG patients the current morning opioid dose was replaced by an estimated equianalgesic dose of methadone at day 1 (Fig. 1). In 3DS patients, the current opioid dose was reduced by 1/3 and substituted with 1/3 of an equianalgesic dose of methadone each day and then discontinued from day 3 (Fig. 1). Racemic methadone was administered every eight hours as capsules or mixture (10, 20, 50 and 100 mg produced by St. Olav's Hospital Pharmacy). No titration was recommended until day 5 (4 days after the switch). The rescue dose

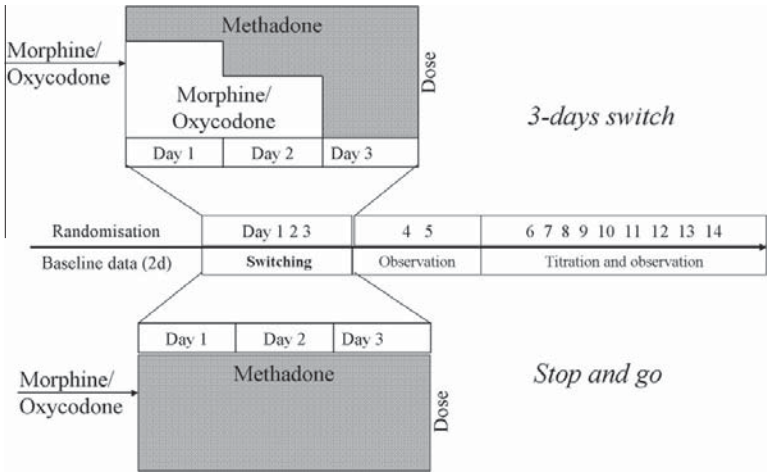

Fig. 1 – Study design. Note that day 1 is the day of the switch.

was 1/6 of the baseline opioid dose. Adjuvant non-opioid analgesics and anti-cancer treatment were maintained stabile.

The methadone dose was calculated from the oral morphine equivalent dose (last 24 h, including mean rescue dose last 48 h) using a dose-dependent conversion ratio (Table 1). (For conversion: parenteral morphine: oral morphine = 1:3 and oral oxycodone: oral morphine = 1:2).

2.4. Data collection

Patient demographics and clinical characteristics were recorded by the physician/investigator at baseline. Opioid dose changes and use of rescue were recorded daily.

Patients reported average pain intensity (PI) last 24 h and PI now before 12 am at baseline, day 3 and 14 on a numerical rating scale (NRS, 0 = no pain and 10 = worst pain imaginable) using the brief pain inventory (BPI).[30] AEs (nausea, drowsiness, loss of appetite and dry mouth) today were recorded daily (NRS 0–10) before 12 am using a Norwegian version of the Edmonton Symptom Assessment System (ESAS).[31]

The Mini Mental State Examination (MMSE) was used to assess cognitive function at baseline and day 3. Three electrocardiograms (ECG) were obtained to supervise QT-prolongation (baseline, between day 4–7 (same dose $\geqslant$2 days) and day 14). The preswitch rate-corrected QT_c-interval (Bazett formula) estimated by the physician had to be <480 ms for patients not at-risk and <460 ms for patients at-risk of arrhythmia before methadone was introduced. Patients with QT_c-intervals above these values at inclusion or who reached a QT_c-interval >500 ms after the switch were excluded.

2.5. Statistics and outcomes

The trial was initially designed to detect a difference of two days to achieve pain relief ($\leqslant$4 (NRS 0–10)), and sample size calculations were made accordingly. However, it was subsequently decided to make assessments only at baseline, day 3 and 14, with the primary outcome being average PI day 3 with pain now, drowsiness, nausea, loss of appetite and dry mouth day 3 and 14 as secondary outcomes. We placed emphasis on estimation of effects, with the uncertainty due to sample size being made explicit by wide confidence intervals, rather than *p*-values which could be misleading because of the possible type II errors.

All data are reported as means, 95% confidence intervals (CI), ranges, medians or frequencies (*N* (%)) as appropriate. Spearman's correlation (*r*) was used to compare the preswitch morphine: methadone doses and ratios with the final doses and ratios. Statistical software SPSS 17.0 was used in all analysis.

3. Results

3.1. Patients

Forty-two patients were randomised from June 2004 to March 2008, 21 to each group (CONSORT flowchart Fig. 2). The two study groups had similar patients' characteristics (Table 2) except time on WHO step 3 opioids (SAG mean 9.1 months and 3DS 23.6 months, mean difference 14.4 (CI −26.6 to −2.3)). Both groups had high mean preswitch equianalgesic morphine doses; SAG 900 mg/day (CI 650–1150) and 3DS 1330 mg/day (CI 820–1840).

More SAG patients dropped out of the study than 3DS patients (11 versus 3, respectively, RR = 3.3 (CI 1.1–8.5)). Three of the dropouts in SAG were SAEs (2 died and 1 severely sedated), none in the 3DS group. The number needed to harm (NNH) in the SAG group was seven; which means that every seventh patient will experience a SAE. Dropout reasons are shown in Table 3.

3.2. Pain and adverse effects

No differences were found between groups in means of average PI day 3 (mean difference 0.5, CI −1.2–2.2) as shown in Table 4. The 3DS reported a clinically significant lower average PI than SAG with mean difference of 2.1 (CI −0.8–5.0) at day 14 and the SAG group reported a trend of increasing pain during the 14 days.

The secondary outcomes; mean PI now and mean AEs day 3 and 14 showed no significant differences between group means (Table 4). All mean AE scores were below four from baseline through day 14 in both groups, and no group had a clinically significant reduction of AEs. The mean differences between groups day 3 were for drowsiness 0.0 (CI −1.3–1.6), for nausea 0.1 (CI −1.0–1.0), for loss of appetite 1.2 (CI −1.1–3.5) and for dry mouth 0.6 (CI −1.2–2.3) (Table 4).

3.3. The switching table

This study confirms that the stabilised dose of methadone (day 14) is highly correlated to the preswitch morphine dose ($r = 0.80$). The protocol ratios used at baseline and the final ratios (preswitch morphine dose: methadone dose at day 14) after titration were correlated ($r = 0.63$), however, the ratios

Table 1 – Dose dependent switching table and distribution of patients in each dose group, *n* = 35.

Baseline morphine dose (mg)	Protocol ratio Mo:Me[a]	Final ratio[b] Mo:Me Mean (min–max)	N Stop and go/3-days switch
30–90	4:1		0/0
91–300	6:1	4:1 (3.3–4.7)	1/1
301–600	8:1	7.5:1 (4.4–10)	4/4
601–1000	10:1	11.7:1 (7.1–17.3)	5/3
>1000	12:1	14.2:1 (8.6–26.7)	6/11

[a] Mo = morphine, Me = methadone.
[b] Baseline Mo:Me day 14.

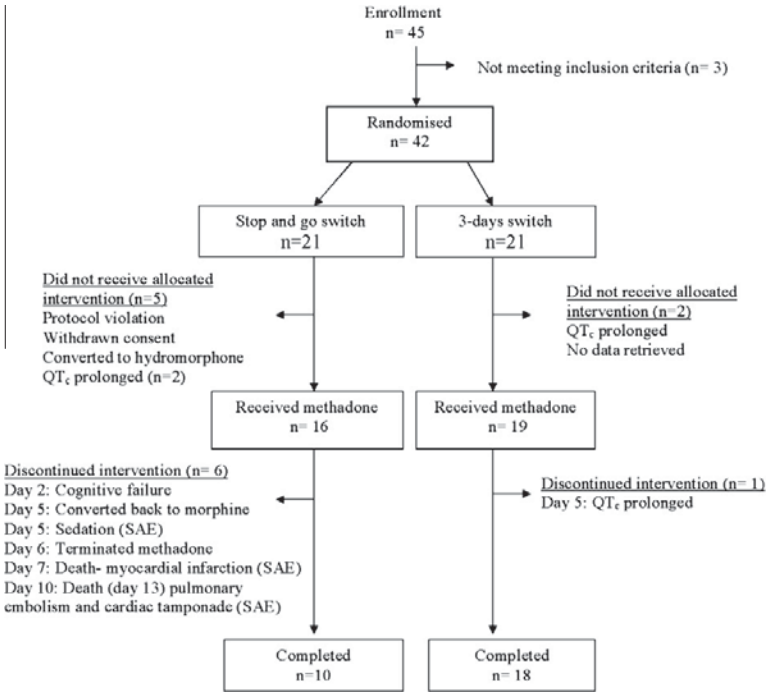

Fig. 2 – CONSORT flowchart.

varied substantially within each morphine dose equivalent, especially for the patients on high opioid doses where the ratios varied from 8.6:1 to 26.7:1 (Table 1). The final median methadone doses were lower than the estimated methadone doses preswitch; SAG from 80 to 65 mg and 3DS from 106 to 90 mg.

3.4. *Rescue*

The 3DS-patients reported two-fold more rescue episodes per day than the SAG-patients all 14 days. The mean difference in total number of rescue episodes the first 3 days was 4.0 episodes (CI −8.2–0.1).

3.5. *QT-interval*

The final (d14) average QT_c was 416 ms (CI 379–446) ($n = 6$) (15 ms increase from baseline) in SAG, whilst the average QT_c was 407 ms (CI 372–443) ($n = 9$) (5 ms decrease from baseline) in 3DS.

4. Discussion

The main finding in this randomised phase II trial was that the stop and go (SAG) approach when switching to methadone from morphine or oxycodone was associated with a trend of more pain, a higher number of dropouts and serious adverse events than with the 3-days switch (3DS) approach in cancer patients on high opioid doses. Since few patients ($n = 28$) completed the study – the confidence intervals are wide and consequently no firm conclusions can be made with regard to group differences or group similarity for the primary outcome, namely average PI day 3.

In a recent systematic review on opioid switching in cancer patients[29] no RCTs were found, and the evidence level was graded D (Grade's approach[32]). The experience from this study and the lack of randomised trials published on this topic reflect that conducting scientifically sound trials in this population is challenging and one need to sample according to a 50–75% attrition rate. Second, this cohort of patients are difficult to recruit in intervention studies due to the complexity of the disease with many symptoms, often short life-expectancy and health care providers that may act as gatekeepers. This raises a need for pragmatic trials recognising the possible methodological limitations met in the most severe sick patients compared with studies including more healthy patients. The relevant population for many interventions in cancer patients, exemplified by this study's research question, is the patients at the very end of life where scientific rigour is difficult. Studies in these patients, give clinically important information that cannot be achieved in other populations. Also, because the number of such cases successfully identified and recruited into studies are low, many centres need to take part in order to obtain a sufficient number of patients in due time (2–3 years).

In previous uncontrolled studies on the SAG strategy it has been argued that this approach will rapidly improve pain relief.[19,20,33,34] Mercadante et al. reported successful switches (PI $\leqslant$ 4 on NRS 0–10) in 80% of 52 patients within 3.65 days in one study[20] and after only 24 h in 46% of 24 patients in another study.[19] This observation was not confirmed in the

Table 2 – Patient demographics and clinical characteristics ($n = 41$)[a].

	Stop and go $n = 21$	3-days switch $n = 20$[a]
Gender F/M	9/12	10/10
Age (years, CI)	61 (58–65)	58 (54–63)
Ethnicity (*n*)		
Caucasian	20	20
Latin American	1	0
Baseline pain intensity		
Mean (CI)	5.4 (4.1–6.6)	5.5 (4.4–6.5)
Karnofsky performance status (%)		
Mean (CI)	59 (53–65)	60 (52–67)
Min–max	30–80	30–90
MMSE baseline		
Mean (CI)	28.3 (26.3–30.2)	28.3 (26.7–29.8)
Cancer diagnosis (*n*)		
Breast	2 (9.5%)	0
Prostate	4 (19%)	3 (15%)
GI	3 (14.3%)	6 (30%)
Lung	3 (14.3%)	4 (20%)
Gynaecologic	2 (9.5%)	1 (5%)
Other	7 (33.3%)	4 (20%)
Double diagnosis	0	2 (10%)
Metastatic (M1)	16 (76%)	19 (95%)
Concomitant disease (*n*)		
None	11 (52.3%)	13 (65%)
Cardiac	5 (23.8%)	4 (20%)
Anaemia	0	2 (10%)
Lung	2 (9.5%)	0
Rheumatism	1 (4.8%)	1 (5%)
Other	5 (23.8%)	4 (20%)
Cancer treatment last weak (*n*)		
None	11 (52.4%)	13 (65%)
Chemotherapy	0	2 (10%)
Radiation	2 (9.5%)	0
Surgery	0	0
Hormone	2 (9.5%)	2 (10%)
Combination	2 (9.5%)	3 (15%)
Missing	4 (19%)	1 (5%)
Concomitant medication ($n > 5$)		
Paracetamol	11 (52.4%)	18 (90%)
Steroids	7 (33.3%)	9 (45%)
Anticonvulsants	8 (38.1%)	11 (55%)
Laxatives	3 (14.3%)	5 (25%)
Benzodiazepines	3 (14.3%)	6 (30%)
Main indication for switch *n* (%)		
Pain	4 (19%)	8 (40%)
Adverse effects	2 (9.5%)	1 (5%)
High dosage	1 (4.8%)	0
Combination	12 (57%)	11(55%)
Current opioid (*n*)		
Morphine	13 (61.9%)	12 (60%)
Oxycodone	8 (38.1%)	7 (35%)
Fentanyl	0	1 (5%)
Preswitch equianalgesic morphine dose (mg)		
Mean (CI)	900 (650–1150)	1330 (820–1840)
Min–max	350–2000	90–3840
Median	690	1200

[a] Data on one patient in the 3-days switch group was not retrievable.

Table 3 – Patients that dropped out after the intervention ($n = 7$).

Switching strategy	Day of dropout	Reason	Gender age	Baseline opioid	Equianalgesic preswitch opioid dose (mg/day)
SAG	2	Cognitive failure	Female 60 y	Morphine	1200
SAG[a]	5	Sedation and respiratory arrest (reversed with Naloxone) (SAE[c])	Male 59 y	Morphine	1080
SAG	5	Switched back to morphine; pain and drowsiness	Female 68 y	Oxycodone	1580
SAG	6	Terminated all medications at home	Female 61 y	Oxycodone	640
SAG	7	Died from myocardial infarction (SAE)	Male 72 y	Morphine	510
SAG	10	Died from cardiac tamponade and pulmonary embolism (SAE)	Female 58 y	Morphine	640
3DS[b]	5	QT_c prolonged	Male 69 y	Oxycodone	1800

[a] SAG = stop and go.
[b] 3DS = 3-days switch.
[c] SAE = serious adverse event.

Table 4 – Average pain intensity (last 24 h), pain intensity now and adverse effects (last 24 h) at baseline, day 3 and 14 (11-point NRS) in the patients receiving methadone ($n = 35$), means (95% CIs).

	Baseline	Day 3	Day 14
Average pain intensity			
Stop and go	4.6 (3.5–5.7)	4.1 (2.3–5.9)	4.9 (2.1–7.7)
3-Days switch	4.7 (3.6–5.8)	3.6 (2.9–4.3)	2.8 (1.8–3.9)
Mean difference (CI)	−0.8 (−1.6–1.5)	0.5 (−1.2–2.2)	2.1[a] (−0.8–5.0)
Pain intensity now			
Stop and go	2.9 (1.9–4.0)	3.3 (1.6–5.0)	3.3 (1.9–4.7)
3-Days switch	4.2 (3.1–5.2)	2.8 (1.7–3.9)	2.6 (1.6–3.7)
Mean difference (CI)	−1.2 (−2.7–0.2)	0.5 (−1.4–2.3)	0.7 (−1.0–2.3)
Drowsiness			
Stop and go	3.5 (2.0–5.0)	2.7 (1.5–3.9)	2.9 (0.9–4.8)
3-Days switch	3.3 (2.0–4.5)	2.7 (1.7–3.6)	2.9 (1.8–4.0)
Mean difference (CI)	0.2 (1.7–2.1)	0.0 (−1.3–1.6)	0.0 (−2.0–1.9)
Nausea			
Stop and go	1.5 (0.5–2.6)	1.0 (0.3–1.7)	1.3 (0.8–3.3)
3-Days switch	1.6 (0.2–2.5)	0.9 (0.3–1.7)	0.7 (0.1–1.5)
Mean difference (CI)	0.2 (−1.4–1.8)	0.1 (−1.0–1.0)	0.6 (−1.1–2.1)
Loss of appetite			
Stop and go	3.9 (1.7–6.0)	3.9 (1.7–6.0)	2.9 (0.4–6.1)
3-Days switch	2.9 (1.9–3.9)	2.7 (1.7–3.7)	2.7 (1.4–4.1)
Mean difference (CI)	1.0 (−1.4–3.3)	1.2 (−1.1–3.5)	0.2 (−2.6–2.8)
Dry mouth			
Stop and go	2.7 (0.7–4.6)	3.0 (1.5–4.5)	1.6 (−0.2–3.3)
3-Days switch	3.1 (1.9–4.4)	2.4 (1.7–3.7)	2.0 (1.2–2.8)
Mean difference (CI)	−0.4 (−2.5–1.7)	0.6 (−1.2–2.3)	−0.4 (−1.9–1.1)

[a] Clinically significant difference between groups ($\geqslant 2$).

present study where the SAG approach was associated with a trend of more pain overall during the 14 day period.

The higher rate of dropouts after intervention in the SAG group (38%) and three SAEs raise the question whether SAG is less safe than 3DS (5% dropout and no SAEs) in this cohort. However, five patients in the SAG group did not receive the allocated treatment and two of the SAEs were disease related. This might not be related to the switching strategy alone, but rather a coincidence or a result of different groups. Still, the accumulation of dropouts and SAEs in one group raises concerns. The high number of SAEs in the SAG group is supported by the findings by Auret et al. who switched 15 patients from morphine to methadone using the SAG strategy (fixed methadone: morphine ratio 6:1). Five patients (33.3%) dropped out and one died.[26] Severe sedation was also reported in one patient (d5) with chronic non-malignant pain switched by the 3DS strategy.[35] Similar risk of SAEs has not been reported in other SAG studies.[18,19] Thus, the observation time of three to five days in some studies might be too short to observe accumulation of methadone or adverse effects. Also

some studies include patients on relatively low doses of opioids before the switch. Taken together, the safety of the SAG is questionable in patients with short life expectancy on high doses of opioids and it should not replace the 3DS in routine clinical practice. However, this study only addresses one SAG approach and other 'as needed' SAG approaches have been claimed effective,[36,37] but no randomised trials are performed.

The inability of this study to reproduce the findings from the above and previous studies[19,20] may be a cohort effect. In this study 33/35 patients used opioid doses >300 mg (49% > 1000 mg) and few exclusion criteria were employed. Only 3/52 used doses of morphine >300 mg in the study by Mercadante et al. and patients with anticancer treatment, poor liver/kidney function and brain metastases were excluded.[20] In contrast, the present study included very sick cancer pain patients which may have different outcomes than patients included earlier in the disease trajectory. These observations underline the importance of classifying the cancer cohorts in clinical cancer pain studies, and that a common system needs to be agreed upon.

The final ratios between the preswitch morphine doses and the final methadone doses in the present study support the conclusions of Bruera et al. and later Ripamonti et al. that the relative potency of methadone increases in patients on higher preswitch doses[24,25,27] and that there are strong indications that the differences in dose ratios are dose-dependent.[23] Both groups used rescue regularly during the trial indicating that a more aggressive titration of methadone might be more appropriate. It is important to acknowledge that the reported equianalgesic dose ratios are really ratios between an opioid dose, which provide unacceptable AEs in the presence of uncontrolled pain and the methadone dose which provided adequate pain control with an acceptable level of AEs.

5. Conclusion

The level of evidence remains low for the most treatment strategies during end of life care. The present study underlines the importance of conducting controlled studies before changes in treatment strategies are implemented into guidelines and/or clinical practice. The observations in this study including the severe SAE in the SAG group give no support for replacing the 3DS switch with the SAG approach in seriously ill patients using high doses of opioids.

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Conflict of interest statement

None declared.

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Paper II

Is not included due to copyright

Paper III

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Paper IV

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Appendix

Karnofsky performance status (KPS)

Brief Pain Inventory (BPI)

Norwegian version of ESAS (TPAT)

Mini mental state examination (MMSE)

KARNOFSKY INDEX

Kriterier for aktivitesstatus ved skjelettmetastatisk kreftsykdom

Utfører normal aktivitet, trenger ikke spesielt stell	100%	Normal. Ingen plager eller subjektive tegn på sykdom.
	90%	Klarer normal aktivitet, sykdommen gir lite symptomer.
	80%	Klarer med nød normal aktivitet. Sykdommen gir en del symptomer.
Ute av stand til å arbeide. Klarer seg hjemme, greier personlig stell. Trenger varierende grad av hjelp.	70%	Klarer seg selv, ute av stand til normal aktivitet aller aktivt arbeid.
	60%	Trenger noe hjelp, men klarer stort sett å tilfredstille egne behov.
	50%	Trenger betydelig hjelp og stadig medisinsk omsorg.
Ute av stand til å greie seg selv. Avhengig av pleie. Sykdommen i progresjon.	40%	Ufør, trenger spesiell hjelp og omsorg.
	30%	Helt ufør, hospitalisering nødvendig, men fare for død er ikke overhengende.
	20%	Svært syk, hospitalisering og understøttende behandling nødvendig.
	10%	Moribund, dødsprosessen er i rask fremmarsj.
	0%	Død

40857

Brief Pain Inventory

Pasientnr. ☐☐☐ Dato ☐☐.☐☐.☐☐☐☐

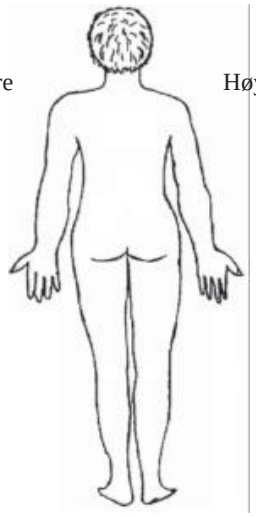
1. Gjennom livet har de fleste av oss hatt smerter (som lett hodepine, forstuelser eller tannpine). Har du i dag smerter av et annet slag enn slike dagligdagse smerter.

☐ Ja ☐ Nei

2. Vil du skravere de områdene på kroppen hvor du har smerter. Marker med et kryss der du har mest vondt.

Høyre Venstre

Venstre Høyre



3. Vennligst sett ring rundt det tallet som best beskriver de sterkeste smertene du har hatt i løpet av de siste 24 timer.

0 1 2 3 4 5 6 7 8 9 10

Ingen smerter — Verst tenkelige smerter

4. Vennligst sett ring rundt det tallet som best beskriver de svakeste smertene du har hatt i løpet av de siste 24 timer.

0 1 2 3 4 5 6 7 8 9 10

Ingen smerter — Verst tenkelige smerter

5. Vennligst sett ring rundt det tallet som best angir hvor sterke smerter du har i gjennomsnitt.

0 1 2 3 4 5 6 7 8 9 10

Ingen smerter — Verst tenkelige smerter

6. Vennligst sett ring rundt det tallet som best angir hvor sterke smerter du har akkurat nå.

0 1 2 3 4 5 6 7 8 9 10

Ingen smerter — Verst tenkelige smerter

Vennligst snu arket

7. Hvilken behandling eller medisiner får du for å lindre smertene dine?

8. I hvor stor grad har behandling eller medisiner lindret smertene dine de siste 24 timene?
Vennligst sett en ring rundt det prosenttallet som viser hvor stor smertelindring du har fått.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Ingen lindring **Fullstendig lindring**

Sett en ring rundt det tallet som for de siste 24 timene best beskriver hvor mye smertene har virket inn på :

9. Daglig aktivitet

0 1 2 3 4 5 6 7 8 9 10
Ikke påvirket **Fullstendig påvirket**

10. Humør

0 1 2 3 4 5 6 7 8 9 10
Ikke påvirket **Fullstendig påvirket**

11. Evne til å gå

0 1 2 3 4 5 6 7 8 9 10
Ikke påvirket **Fullstendig påvirket**

12. Vanlig arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)

0 1 2 3 4 5 6 7 8 9 10
Ikke påvirket **Fullstendig påvirket**

13. Forhold til andre mennesker

0 1 2 3 4 5 6 7 8 9 10
Ikke påvirket **Fullstendig påvirket**

14. Søvn

0 1 2 3 4 5 6 7 8 9 10
Ikke påvirket **Fullstendig påvirket**

15. Livsglede

0 1 2 3 4 5 6 7 8 9 10
Ikke påvirket **Fullstendig påvirket**

Tusen takk for hjelpen!

26096

Seksjon lindrende behandling
Kreftavdelingen, St.Olav

Initialer

Pasientnr

Trondheim Palliative Assessment Tool

Dato . .

Tidspunkt

Fyll ut skjemaet før kl 12 og etter kl 18 hver dag

Dag

Hvordan har du det i dag?

Smerte - i ro

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Smerte - ved bevegelse

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Slapphet

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Kvalme

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Tungpust

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Munntørrhet

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Matlyst

Meget bra 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Angst/uro

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Trist / deprimert

Ingen 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Alt tatt i betraktning, hvordan har du det i dag?

Meget bra 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Utfylt av: _____

Ikke utfylt fordi: _____ (sov, trøtt,glemte det.....)

51610

Minimental status

Morfinbehandling og morfinmetabolitter

Pasient nr. ☐☐☐

Dato ☐☐.☐☐.☐☐☐☐

1. ORIENTERING	Skår	Maksimal skår
Hvilket år er det?	☐	1
Hvilken måned er det?	☐	1
Hvilken årstid er det?	☐	1
Hvilken dato er det i dag?	☐	1
Hvilken dag er det idag?	☐	1
I hvilket land er vi nå?	☐	1
I hvilken landsdel er vi nå?	☐	1
I hvilken by er vi nå?	☐	1
I hvilket sykehus er vi nå? (Hva er din hjemmeadresse?)	☐	1
I hvilken avdeling er vi nå? (Hvilket postnummer har du?)	☐	1
2. LÆRING Si 3 ord. Bruk 1 sekund til å uttale hvert ord. OST - SYKKEL - BOK. Be pasienten gjenta alle 3 ordene. Gjenta ordene, inntil pasienten har lært dem, og kan huske dem Noter antall forsøk ☐	☐	3
3. ABSTRAKT TENKNING Stav ordet SVERD baklengs. Ett poeng for hver riktig bokstav sagt i den rette rekkefølge. Alternativt: Start med tallet 100. Trekk fra 7, rekk fra 7 igjen, og fortsett subtraksjonen i alt 5 ganger.	☐	5
4.KORTTIDHUKOMMELSE Kan du si meg de ordene du skulle huske for litt siden? (OST - SYKKEL - BOK)	☐	3
5. HØYERE KORTIKALE FUNKSJONER		
Vis fram en blyant. Hva er dette?	☐	1
Vis fram en klokke. Hva er dette?	☐	1
Gjenta følgende setning: "Aldri annet enn om og men."	☐	1
Ta et stykke papir med din høyre hånd. Brett det over på midten og legg det på gulvet.	☐	3
Les og utfør: "Lukk øynene dine."	☐	1
Skriv en setning.	☐	1
Kopier denne tegningen.	☐	1
Total skår	☐☐	30

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43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

1990

52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

1993

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

1997

124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs

1998

132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.

134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

1999

141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

2000

158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.

163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

2001

178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS

193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

2002

201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

2003

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN

218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

2004

235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES

245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

2005

248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

2006

269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT

273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN
297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

2007

298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY
303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
304. Lasse Løvstakken: SIGNAL PROCESSING IN DIAGNOSTIC ULTRASOUND: ALGORITHMS FOR REAL-TIME ESTIMATION AND VISUALIZATION OF BLOOD FLOW VELOCITY
305. Elisabeth Olstad: GLUTAMATE AND GABA: MAJOR PLAYERS IN NEURONAL METABOLISM
306. Lilian Leistad: THE ROLE OF CYTOKINES AND PHOSPHOLIPASE A_2S IN ARTICULAR CARTILAGE CHONDROCYTES IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS
307. Arne Vaaler: EFFECTS OF PSYCHIATRIC INTENSIVE CARE UNIT IN AN ACUTE PSYCIATHRIC WARD
308. Mathias Toft: GENETIC STUDIES OF LRRK2 AND PINK1 IN PARKINSON'S DISEASE
309. Ingrid Løvold Mostad: IMPACT OF DIETARY FAT QUANTITY AND QUALITY IN TYPE 2 DIABETES WITH EMPHASIS ON MARINE N-3 FATTY ACIDS
310. Torill Eidhammer Sjøbakk: MR DETERMINED BRAIN METABOLIC PATTERN IN PATIENTS WITH BRAIN METASTASES AND ADOLESCENTS WITH LOW BIRTH WEIGHT
311. Vidar Beisvåg: PHYSIOLOGICAL GENOMICS OF HEART FAILURE: FROM TECHNOLOGY TO PHYSIOLOGY
312. Olav Magnus Søndenå Fredheim: HEALTH RELATED QUALITY OF LIFE ASSESSMENT AND ASPECTS OF THE CLINICAL PHARMACOLOGY OF METHADONE IN PATIENTS WITH CHRONIC NON-MALIGNANT PAIN
313. Anne Brantberg: FETAL AND PERINATAL IMPLICATIONS OF ANOMALIES IN THE GASTROINTESTINAL TRACT AND THE ABDOMINAL WALL
314. Erik Solligård: GUT LUMINAL MICRODIALYSIS
315. Elin Tollefsen: RESPIRATORY SYMPTOMS IN A COMPREHENSIVE POPULATION BASED STUDY AMONG ADOLESCENTS 13-19 YEARS. YOUNG-HUNT 1995-97 AND 2000-01; THE NORD-TRØNDELAG HEALTH STUDIES (HUNT)
316. Anne-Tove Brenne: GROWTH REGULATION OF MYELOMA CELLS
317. Heidi Knobel: FATIGUE IN CANCER TREATMENT – ASSESSMENT, COURSE AND ETIOLOGY
318. Torbjørn Dahl: CAROTID ARTERY STENOSIS. DIAGNOSTIC AND THERAPEUTIC ASPECTS
319. Inge-Andre Rasmussen jr.: FUNCTIONAL AND DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING IN NEUROSURGICAL PATIENTS
320. Grete Helen Bratberg: PUBERTAL TIMING – ANTECEDENT TO RISK OR RESILIENCE ? EPIDEMIOLOGICAL STUDIES ON GROWTH, MATURATION AND HEALTH RISK BEHAVIOURS; THE YOUNG HUNT STUDY, NORD-TRØNDELAG, NORWAY
321. Sveinung Sørhaug: THE PULMONARY NEUROENDOCRINE SYSTEM. PHYSIOLOGICAL, PATHOLOGICAL AND TUMOURIGENIC ASPECTS
322. Olav Sande Eftedal: ULTRASONIC DETECTION OF DECOMPRESSION INDUCED VASCULAR MICROBUBBLES
323. Rune Bang Leistad: PAIN, AUTONOMIC ACTIVATION AND MUSCULAR ACTIVITY RELATED TO EXPERIMENTALLY-INDUCED COGNITIVE STRESS IN HEADACHE PATIENTS
324. Svein Brekke: TECHNIQUES FOR ENHANCEMENT OF TEMPORAL RESOLUTION IN THREE-DIMENSIONAL ECHOCARDIOGRAPHY
325. Kristian Bernhard Nilsen: AUTONOMIC ACTIVATION AND MUSCLE ACTIVITY IN RELATION TO MUSCULOSKELETAL PAIN

326. Anne Irene Hagen: HEREDITARY BREAST CANCER IN NORWAY. DETECTION AND PROGNOSIS OF BREAST CANCER IN FAMILIES WITH *BRCA1*GENE MUTATION
327. Ingebjørg S. Juel : INTESTINAL INJURY AND RECOVERY AFTER ISCHEMIA. AN EXPERIMENTAL STUDY ON RESTITUTION OF THE SURFACE EPITHELIUM, INTESTINAL PERMEABILITY, AND RELEASE OF BIOMARKERS FROM THE MUCOSA
328. Runa Heimstad: POST-TERM PREGNANCY
329. Jan Egil Afset: ROLE OF ENTEROPATHOGENIC *ESCHERICHIA COLI* IN CHILDHOOD DIARRHOEA IN NORWAY
330. Bent Håvard Hellum: *IN VITRO* INTERACTIONS BETWEEN MEDICINAL DRUGS AND HERBS ON CYTOCHROME P-450 METABOLISM AND P-GLYCOPROTEIN TRANSPORT
331. Morten André Høydal: CARDIAC DYSFUNCTION AND MAXIMAL OXYGEN UPTAKE MYOCARDIAL ADAPTATION TO ENDURANCE TRAINING

2008

332. Andreas Møllerløkken: REDUCTION OF VASCULAR BUBBLES: METHODS TO PREVENT THE ADVERSE EFFECTS OF DECOMPRESSION
333. Anne Hege Aamodt: COMORBIDITY OF HEADACHE AND MIGRAINE IN THE NORD-TRØNDELAG HEALTH STUDY 1995-97
334. Brage Høyem Amundsen: MYOCARDIAL FUNCTION QUANTIFIED BY SPECKLE TRACKING AND TISSUE DOPPLER ECHOCARDIOGRAPHY – VALIDATION AND APPLICATION IN EXERCISE TESTING AND TRAINING
335. Inger Anne Næss: INCIDENCE, MORTALITY AND RISK FACTORS OF FIRST VENOUS THROMBOSIS IN A GENERAL POPULATION. RESULTS FROM THE SECOND NORD-TRØNDELAG HEALTH STUDY (HUNT2)
336. Vegard Bugten: EFFECTS OF POSTOPERATIVE MEASURES AFTER FUNCTIONAL ENDOSCOPIC SINUS SURGERY
337. Morten Bruvold: MANGANESE AND WATER IN CARDIAC MAGNETIC RESONANCE IMAGING
338. Miroslav Fris: THE EFFECT OF SINGLE AND REPEATED ULTRAVIOLET RADIATION ON THE ANTERIOR SEGMENT OF THE RABBIT EYE
339. Svein Arne Aase: METHODS FOR IMPROVING QUALITY AND EFFICIENCY IN QUANTITATIVE ECHOCARDIOGRAPHY – ASPECTS OF USING HIGH FRAME RATE
340. Roger Almvik: ASSESSING THE RISK OF VIOLENCE: DEVELOPMENT AND VALIDATION OF THE BRØSET VIOLENCE CHECKLIST
341. Ottar Sundheim: STRUCTURE-FUNCTION ANALYSIS OF HUMAN ENZYMES INITIATING NUCLEOBASE REPAIR IN DNA AND RNA
342. Anne Mari Undheim: SHORT AND LONG-TERM OUTCOME OF EMOTIONAL AND BEHAVIOURAL PROBLEMS IN YOUNG ADOLESCENTS WITH AND WITHOUT READING DIFFICULTIES
343. Helge Garåsen: THE TRONDHEIM MODEL. IMPROVING THE PROFESSIONAL COMMUNICATION BETWEEN THE VARIOUS LEVELS OF HEALTH CARE SERVICES AND IMPLEMENTATION OF INTERMEDIATE CARE AT A COMMUNITY HOSPITAL COULD PROVIDE BETTER CARE FOR OLDER PATIENTS. SHORT AND LONG TERM EFFECTS
344. Olav A. Foss: "THE ROTATION RATIOS METHOD". A METHOD TO DESCRIBE ALTERED SPATIAL ORIENTATION IN SEQUENTIAL RADIOGRAPHS FROM ONE PELVIS
345. Bjørn Olav Åsvold: THYROID FUNCTION AND CARDIOVASCULAR HEALTH
346. Torun Margareta Melø: NEURONAL GLIAL INTERACTIONS IN EPILEPSY
347. Irina Poliakova Eide: FETAL GROWTH RESTRICTION AND PRE-ECLAMPSIA: SOME CHARACTERISTICS OF FETO-MATERNAL INTERACTIONS IN DECIDUA BASALIS
348. Torunn Askim: RECOVERY AFTER STROKE. ASSESSMENT AND TREATMENT; WITH FOCUS ON MOTOR FUNCTION
349. Ann Elisabeth Åsberg: NEUTROPHIL ACTIVATION IN A ROLLER PUMP MODEL OF CARDIOPULMONARY BYPASS. INFLUENCE ON BIOMATERIAL, PLATELETS AND COMPLEMENT
350. Lars Hagen: REGULATION OF DNA BASE EXCISION REPAIR BY PROTEIN INTERACTIONS AND POST TRANSLATIONAL MODIFICATIONS
351. Sigrun Beate Kjøtrød: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN ASSISTED REPRODUCTION

352. Steven Keita Nishiyama: PERSPECTIVES ON LIMB-VASCULAR HETEROGENEITY: IMPLICATIONS FOR HUMAN AGING, SEX, AND EXERCISE
353. Sven Peter Näsholm: ULTRASOUND BEAMS FOR ENHANCED IMAGE QUALITY
354. Jon Ståle Ritland: PRIMARY OPEN-ANGLE GLAUCOMA & EXFOLIATIVE GLAUCOMA. SURVIVAL, COMORBIDITY AND GENETICS
355. Sigrid Botne Sando: ALZHEIMER'S DISEASE IN CENTRAL NORWAY. GENETIC AND EDUCATIONAL ASPECTS
356. Parvinder Kaur: CELLULAR AND MOLECULAR MECHANISMS BEHIND METHYLMERCURY-INDUCED NEUROTOXICITY
357. Ismail Cüneyt Güzey: DOPAMINE AND SEROTONIN RECEPTOR AND TRANSPORTER GENE POLYMORPHISMS AND EXTRAPYRAMIDAL SYMPTOMS. STUDIES IN PARKINSON'S DISEASE AND IN PATIENTS TREATED WITH ANTIPSYCHOTIC OR ANTIDEPRESSANT DRUGS
358. Brit Dybdahl: EXTRA-CELLULAR INDUCIBLE HEAT-SHOCK PROTEIN 70 (Hsp70) – A ROLE IN THE INFLAMMATORY RESPONSE ?
359. Kristoffer Haugarvoll: IDENTIFYING GENETIC CAUSES OF PARKINSON'S DISEASE IN NORWAY
360. Nadra Nilsen: TOLL-LIKE RECEPTOR 2 –EXPRESSION, REGULATION AND SIGNALING
361. Johan Håkon Bjørngaard: PATIENT SATISFACTION WITH OUTPATIENT MENTAL HEALTH SERVICES – THE INFLUENCE OF ORGANIZATIONAL FACTORS.
362. Kjetil Høydal : EFFECTS OF HIGH INTENSITY AEROBIC TRAINING IN HEALTHY SUBJECTS AND CORONARY ARTERY DISEASE PATIENTS; THE IMPORTANCE OF INTENSITY,, DURATION AND FREQUENCY OF TRAINING.
363. Trine Karlsen: TRAINING IS MEDICINE: ENDURANCE AND STRENGTH TRAINING IN CORONARY ARTERY DISEASE AND HEALTH.
364. Marte Thuen: MANGANASE-ENHANCED AND DIFFUSION TENSOR MR IMAGING OF THE NORMAL, INJURED AND REGENERATING RAT VISUAL PATHWAY
365. Cathrine Broberg Vågbø: DIRECT REPAIR OF ALKYLATION DAMAGE IN DNA AND RNA BY 2-OXOGLUTARATE- AND IRON-DEPENDENT DIOXYGENASES
366. Arnt Erik Tjønna: AEROBIC EXERCISE AND CARDIOVASCULAR RISK FACTORS IN OVERWEIGHT AND OBESE ADOLESCENTS AND ADULTS
367. Marianne W. Furnes: FEEDING BEHAVIOR AND BODY WEIGHT DEVELOPMENT: LESSONS FROM RATS
368. Lene N. Johannessen: FUNGAL PRODUCTS AND INFLAMMATORY RESPONSES IN HUMAN MONOCYTES AND EPITHELIAL CELLS
369. Anja Bye: GENE EXPRESSION PROFILING OF *INHERITED* AND *ACQUIRED* MAXIMAL OXYGEN UPTAKE – RELATIONS TO THE METABOLIC SYNDROME.
370. Oluf Dimitri Røe: MALIGNANT MESOTHELIOMA: VIRUS, BIOMARKERS AND GENES. A TRANSLATIONAL APPROACH
371. Ane Cecilie Dale: DIABETES MELLITUS AND FATAL ISCHEMIC HEART DISEASE. ANALYSES FROM THE HUNT1 AND 2 STUDIES
372. Jacob Christian Hølen: PAIN ASSESSMENT IN PALLIATIVE CARE: VALIDATION OF METHODS FOR SELF-REPORT AND BEHAVIOURAL ASSESSMENT
373. Erming Tian: THE GENETIC IMPACTS IN THE ONCOGENESIS OF MULTIPLE MYELOMA
374. Ole Bosnes: KLINISK UTPRØVING AV NORSKE VERSJONER AV NOEN SENTRALE TESTER PÅ KOGNITIV FUNKSJON
375. Ola M. Rygh: 3D ULTRASOUND BASED NEURONAVIGATION IN NEUROSURGERY. A CLINICAL EVALUATION
376. Astrid Kamilla Stunes: ADIPOKINES, PEROXISOME PROFILERATOR ACTIVATED RECEPTOR (PPAR) AGONISTS AND SEROTONIN. COMMON REGULATORS OF BONE AND FAT METABOLISM
377. Silje Engdal: HERBAL REMEDIES USED BY NORWEGIAN CANCER PATIENTS AND THEIR ROLE IN HERB-DRUG INTERACTIONS
378. Kristin Offerdal: IMPROVED ULTRASOUND IMAGING OF THE FETUS AND ITS CONSEQUENCES FOR SEVERE AND LESS SEVERE ANOMALIES
379. Øivind Rognmo: HIGH-INTENSITY AEROBIC EXERCISE AND CARDIOVASCULAR HEALTH
380. Jo-Åsmund Lund: RADIOTHERAPY IN ANAL CARCINOMA AND PROSTATE CANCER

2009

381. Tore Grüner Bjåstad: HIGH FRAME RATE ULTRASOUND IMAGING USING PARALLEL BEAMFORMING
382. Erik Søndenaa: INTELLECTUAL DISABILITIES IN THE CRIMINAL JUSTICE SYSTEM
383. Berit Rostad: SOCIAL INEQUALITIES IN WOMEN'S HEALTH, HUNT 1984-86 AND 1995-97, THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
384. Jonas Crosby: ULTRASOUND-BASED QUANTIFICATION OF MYOCARDIAL DEFORMATION AND ROTATION
385. Erling Tronvik: MIGRAINE, BLOOD PRESSURE AND THE RENIN-ANGIOTENSIN SYSTEM
386. Tom Christensen: BRINGING THE GP TO THE FOREFRONT OF EPR DEVELOPMENT
387. Håkon Bergseng: ASPECTS OF GROUP B STREPTOCOCCUS (GBS) DISEASE IN THE NEWBORN. EPIDEMIOLOGY, CHARACTERISATION OF INVASIVE STRAINS AND EVALUATION OF INTRAPARTUM SCREENING
388. Ronny Myhre: GENETIC STUDIES OF CANDIDATE TENE3S IN PARKINSON'S DISEASE
389. Torbjørn Moe Eggebø: ULTRASOUND AND LABOUR
390. Eivind Wang: TRAINING IS MEDICINE FOR PATIENTS WITH PERIPHERAL ARTERIAL DISEASE
391. Thea Kristin Våtsveen: GENETIC ABERRATIONS IN MYELOMA CELLS
392. Thomas Jozefiak: QUALITY OF LIFE AND MENTAL HEALTH IN CHILDREN AND ADOLESCENTS: CHILD AND PARENT PERSPECTIVES
393. Jens Erik Slagsvold: N-3 POLYUNSATURATED FATTY ACIDS IN HEALTH AND DISEASE – CLINICAL AND MOLECULAR ASPECTS
394. Kristine Misund: A STUDY OF THE TRANSCRIPTIONAL REPRESSOR ICER. REGULATORY NETWORKS IN GASTRIN-INDUCED GENE EXPRESSION
395. Franco M. Impellizzeri: HIGH-INTENSITY TRAINING IN FOOTBALL PLAYERS. EFFECTS ON PHYSICAL AND TECHNICAL PERFORMANCE
396. Kari Hanne Gjeilo: HEALTH-RELATED QUALITY OF LIFE AND CHRONIC PAIN IN PATIENTS UNDERGOING CARDIAC SURGERY
397. Øyvind Hauso: NEUROENDOCRINE ASPECTS OF PHYSIOLOGY AND DISEASE
398. Ingvild Bjellmo Johnsen: INTRACELLULAR SIGNALING MECHANISMS IN THE INNATE IMMUNE RESPONSE TO VIRAL INFECTIONS
399. Linda Tømmerdal Roten: GENETIC PREDISPOSITION FOR DEVELOPMENT OF PREEMCLAMPSIA – CANDIDATE GENE STUDIES IN THE HUNT (NORD-TRØNDELAG HEALTH STUDY) POPULATION
400. Trude Teoline Nausthaug Rakvåg: PHARMACOGENETICS OF MORPHINE IN CANCER PAIN
401. Hanne Lehn: MEMORY FUNCTIONS OF THE HUMAN MEDIAL TEMPORAL LOBE STUDIED WITH fMRI
402. Randi Utne Holt: ADHESION AND MIGRATION OF MYELOMA CELLS – IN VITRO STUDIES –
403. Trygve Solstad: NEURAL REPRESENTATIONS OF EUCLIDEAN SPACE
404. Unn-Merete Fagerli: MULTIPLE MYELOMA CELLS AND CYTOKINES FROM THE BONE MARROW ENVIRONMENT; ASPECTS OF GROWTH REGULATION AND MIGRATION
405. Sigrid Bjørnelv: EATING– AND WEIGHT PROBLEMS IN ADOLESCENTS, THE YOUNG HUNT-STUDY
406. Mari Hoff: CORTICAL HAND BONE LOSS IN RHEUMATOID ARTHRITIS. EVALUATING DIGITAL X-RAY RADIOGRAMMETRY AS OUTCOME MEASURE OF DISEASE ACTIVITY, RESPONSE VARIABLE TO TREATMENT AND PREDICTOR OF BONE DAMAGE
407. Siri Bjørgen: AEROBIC HIGH INTENSITY INTERVAL TRAINING IS AN EFFECTIVE TREATMENT FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE
408. Susanne Lindqvist: VISION AND BRAIN IN ADOLESCENTS WITH LOW BIRTH WEIGHT
409. Torbjørn Hergum: 3D ULTRASOUND FOR QUANTITATIVE ECHOCARDIOGRAPHY
410. Jørgen Urnes: PATIENT EDUCATION IN GASTRO-OESOPHAGEAL REFLUX DISEASE. VALIDATION OF A DIGESTIVE SYMPTOMS AND IMPACT QUESTIONNAIRE AND A RANDOMISED CONTROLLED TRIAL OF PATIENT EDUCATION
411. Elvar Eyjolfsson: 13C NMRS OF ANIMAL MODELS OF SCHIZOPHRENIA

412. Marius Steiro Fimland: CHRONIC AND ACUTE NEURAL ADAPTATIONS TO STRENGTH TRAINING
413. Øyvind Støren: RUNNING AND CYCLING ECONOMY IN ATHLETES; DETERMINING FACTORS, TRAINING INTERVENTIONS AND TESTING
414. Håkon Hov: HEPATOCYTE GROWTH FACTOR AND ITS RECEPTOR C-MET. AUTOCRINE GROWTH AND SIGNALING IN MULTIPLE MYELOMA CELLS
415. Maria Radtke: ROLE OF AUTOIMMUNITY AND OVERSTIMULATION FOR BETA-CELL DEFICIENCY. EPIDEMIOLOGICAL AND THERAPEUTIC PERSPECTIVES
416. Liv Bente Romundstad: ASSISTED FERTILIZATION IN NORWAY: SAFETY OF THE REPRODUCTIVE TECHNOLOGY
417. Erik Magnus Berntsen: PREOPERATIV PLANNING AND FUNCTIONAL NEURONAVIGATION – WITH FUNCTIONAL MRI AND DIFFUSION TENSOR TRACTOGRAPHY IN PATIENTS WITH BRAIN LESIONS
418. Tonje Strømmen Steigedal: MOLECULAR MECHANISMS OF THE PROLIFERATIVE RESPONSE TO THE HORMONE GASTRIN
419. Vidar Rao: EXTRACORPOREAL PHOTOCHEMOTHERAPY IN PATIENTS WITH CUTANEOUS T CELL LYMPHOMA OR GRAFT-vs-HOST DISEASE
420. Torkild Visnes: DNA EXCISION REPAIR OF URACIL AND 5-FLUOROURACIL IN HUMAN CANCER CELL LINES

2010

421. John Munkhaugen: BLOOD PRESSURE, BODY WEIGHT, AND KIDNEY FUNCTION IN THE NEAR-NORMAL RANGE: NORMALITY, RISK FACTOR OR MORBIDITY ?
422. Ingrid Castberg: PHARMACOKINETICS, DRUG INTERACTIONS AND ADHERENCE TO TREATMENT WITH ANTIPSYCHOTICS: STUDIES IN A NATURALISTIC SETTING
423. Jian Xu: BLOOD-OXYGEN-LEVEL-DEPENDENT-FUNCTIONAL MAGNETIC RESONANCE IMAGING AND DIFFUSION TENSOR IMAGING IN TRAUMATIC BRAIN INJURY RESEARCH
424. Sigmund Simonsen: ACCEPTABLE RISK AND THE REQUIREMENT OF PROPORTIONALITY IN EUROPEAN BIOMEDICAL RESEARCH LAW. WHAT DOES THE REQUIREMENT THAT BIOMEDICAL RESEARCH SHALL NOT INVOLVE RISKS AND BURDENS DISPROPORTIONATE TO ITS POTENTIAL BENEFITS MEAN?
425. Astrid Woodhouse: MOTOR CONTROL IN WHIPLASH AND CHRONIC NON-TRAUMATIC NECK PAIN
426. Line Rørstad Jensen: EVALUATION OF TREATMENT EFFECTS IN CANCER BY MR IMAGING AND SPECTROSCOPY
427. Trine Moholdt: AEROBIC EXERCISE IN CORONARY HEART DISEASE
428. Øystein Olsen: ANALYSIS OF MANGANESE ENHANCED MRI OF THE NORMAL AND INJURED RAT CENTRAL NERVOUS SYSTEM
429. Bjørn H. Grønberg: PEMETREXED IN THE TREATMENT OF ADVANCED LUNG CANCER
430. Vigdis Schnell Husby: REHABILITATION OF PATIENTS UNDERGOING TOTAL HIP ARTHROPLASTY WITH FOCUS ON MUSCLE STRENGTH, WALKING AND AEROBIC ENDURANCE PERFORMANCE
431. Torbjørn Øien: CHALLENGES IN PRIMARY PREVENTION OF ALLERGY. THE PREVENTION OF ALLERGY AMONG CHILDREN IN TRONDHEIM (PACT) STUDY.
432. Kari Anne Indredavik Evensen: BORN TOO SOON OR TOO SMALL: MOTOR PROBLEMS IN ADOLESCENCE
433. Lars Adde: PREDICTION OF CEREBRAL PALSY IN YOUNG INFANTS. COMPUTER BASED ASSESSMENT OF GENERAL MOVEMENTS
434. Magnus Fasting: PRE- AND POSTNATAL RISK FACTORS FOR CHILDHOOD ADIPOSITY
435. Vivi Talstad Monsen: MECHANISMS OF ALKYLATION DAMAGE REPAIR BY HUMAN AlkB HOMOLOGUES
436. Toril Skandsen: MODERATE AND SEVERE TRAUMATIC BRAIN INJURY. MAGNETIC RESONANCE IMAGING FINDINGS, COGNITION AND RISK FACTORS FOR DISABILITY
437. Ingeborg Smidesang: ALLERGY RELATED DISORDERS AMONG 2-YEAR OLDS AND ADOLESCENTS IN MID-NORWAY – PREVALENCE, SEVERITY AND IMPACT. THE PACT STUDY 2005, THE YOUNG HUNT STUDY 1995-97

438. Vidar Halsteinli: MEASURING EFFICIENCY IN MENTAL HEALTH SERVICE DELIVERY: A STUDY OF OUTPATIENT UNITS IN NORWAY
439. Karen Lehrmann Ægidius: THE PREVALENCE OF HEADACHE AND MIGRAINE IN RELATION TO SEX HORMONE STATUS IN WOMEN. THE HUNT 2 STUDY
440. Madelene Ericsson: EXERCISE TRAINING IN GENETIC MODELS OF HEART FAILURE
441. Marianne Klokk: THE ASSOCIATION BETWEEN SELF-REPORTED ECZEMA AND COMMON MENTAL DISORDERS IN THE GENERAL POPULATION. THE HORDALAND HEALTH STUDY (HUSK)
442. Tomas Ottemo Stølen: IMPAIRED CALCIUM HANDLING IN ANIMAL AND HUMAN CARDIOMYOCYTES REDUCE CONTRACTILITY AND INCREASE ARRHYTHMIA POTENTIAL – EFFECTS OF AEROBIC EXERCISE TRAINING
443. Bjarne Hansen: ENHANCING TREATMENT OUTCOME IN COGNITIVE BEHAVIOURAL THERAPY FOR OBSESSIVE COMPULSIVE DISORDER: THE IMPORTANCE OF COGNITIVE FACTORS
444. Mona Løvlien: WHEN EVERY MINUTE COUNTS. FROM SYMPTOMS TO ADMISSION FOR ACUTE MYOCARDIAL INFARCTION WITH SPECIAL EMPHASIS ON GENDER DIFFERECES
445. Karin Margaretha Gilljam: DNA REPAIR PROTEIN COMPLEXES, FUNCTIONALITY AND SIGNIFICANCE FOR REPAIR EFFICIENCY AND CELL SURVIVAL
446. Anne Byriel Walls: NEURONAL GLIAL INTERACTIONS IN CEREBRAL ENERGY – AND AMINO ACID HOMEOSTASIS – IMPLICATIONS OF GLUTAMATE AND GABA
447. Cathrine Fallang Knetter: MECHANISMS OF TOLL-LIKE RECEPTOR 9 ACTIVATION
448. Marit Følsvik Svindseth: A STUDY OF HUMILIATION, NARCISSISM AND TREATMENT OUTCOME IN PATIENTS ADMITTED TO PSYCHIATRIC EMERGENCY UNITS
449. Karin Elvenes Bakkelund: GASTRIC NEUROENDOCRINE CELLS – ROLE IN GASTRIC NEOPLASIA IN MAN AND RODENTS
450. Kirsten Brun Kjelstrup: DORSOVENTRAL DIFFERENCES IN THE SPATIAL REPRESENTATION AREAS OF THE RAT BRAIN
451. Roar Johansen: MR EVALUATION OF BREAST CANCER PATIENTS WITH POOR PROGNOSIS
452. Rigmor Myran: POST TRAUMATIC NECK PAIN. EPIDEMIOLOGICAL, NEURORADIOLOGICAL AND CLINICAL ASPECTS
453. Krisztina Kunszt Johansen: GENEALOGICAL, CLINICAL AND BIOCHEMICAL STUDIES IN *LRRK2* – ASSOCIATED PARKINSON'S DISEASE
454. Pål Gjerden: THE USE OF ANTICHOLINERGIC ANTIPARKINSON AGENTS IN NORWAY. EPIDEMIOLOGY, TOXICOLOGY AND CLINICAL IMPLICATIONS
455. Else Marie Huuse: ASSESSMENT OF TUMOR MICROENVIRONMENT AND TREATMENT EFFECTS IN HUMAN BREAST CANCER XENOGRAFTS USING MR IMAGING AND SPECTROSCOPY
456. Khalid S. Ibrahim: INTRAOPERATIVE ULTRASOUND ASSESSMENT IN CORONARY ARTERY BYPASS SURGERY – WITH SPECIAL REFERENCE TO CORONARY ANASTOMOSES AND THE ASCENDING AORTA
457. Bjørn Øglænd: ANTHROPOMETRY, BLOOD PRESSURE AND REPRODUCTIVE DEVELOPMENT IN ADOLESCENCE OF OFFSPRING OF MOTHERS WHO HAD PREECLAMPSIA IN PREGNANCY
458. John Olav Roaldset: RISK ASSESSMENT OF VIOLENT, SUICIDAL AND SELF-INJURIOUS BEHAVIOUR IN ACUTE PSYCHIATRY – A BIO-PSYCHO-SOCIAL APPROACH
459. Håvard Dalen: ECHOCARDIOGRAPHIC INDICES OF CARDIAC FUNCTION – NORMAL VALUES AND ASSOCIATIONS WITH CARDIAC RISK FACTORS IN A POPULATION FREE FROM CARDIOVASCULAR DISEASE, HYPERTENSION AND DIABETES: THE HUNT 3 STUDY
460. Beate André: CHANGE CAN BE CHALLENGING. INTRODUCTION TO CHANGES AND IMPLEMENTATION OF COMPUTERIZED TECHNOLOGY IN HEALTH CARE
461. Latha Nrugham: ASSOCIATES AND PREDICTORS OF ATTEMPTED SUICIDE AMONG DEPRESSED ADOLESCENTS – A 6-YEAR PROSPECTIVE STUDY
462. Håvard Bersås Nordgaard: TRANSIT-TIME FLOWMETRY AND WALL SHEAR STRESS ANALYSIS OF CORONARY ARTERY BYPASS GRAFTS – A CLINICAL AND EXPERIMENTAL STUDY

Cotutelle with University of Ghent: Abigail Emily Swillens: A MULTIPHYSICS MODEL FOR IMPROVING THE ULTRASONIC ASSESSMENT OF LARGE ARTERIES

2011

463. Marte Helene Bjørk: DO BRAIN RHYTHMS CHANGE BEFORE THE MIGRAINE ATTACK? A LONGITUDINAL CONTROLLED EEG STUDY
464. Carl-Jørgen Arum: A STUDY OF UROTHELIAL CARCINOMA: GENE EXPRESSION PROFILING, TUMORIGENESIS AND THERAPIES IN ORTHOTOPIC ANIMAL MODELS
465. Ingunn Harstad: TUBERCULOSIS INFECTION AND DISEASE AMONG ASYLUM SEEKERS IN NORWAY. SCREENING AND FOLLOW-UP IN PUBLIC HEALTH CARE
466. Leif Åge Strand: EPIDEMIOLOGICAL STUDIES AMONG ROYAL NORWEGIAN NAVY SERVICEMEN. COHORT ESTABLISHMENT, CANCER INCIDENCE AND CAUSE-SPECIFIC MORTALITY
467. Katrine Høyer Holgersen: SURVIVORS IN THEIR THIRD DECADE AFTER THE NORTH SEA OIL RIG DISASTER OF 1980. LONG-TERM PERSPECTIVES ON MENTAL HEALTH
468. MarianneWallenius: PREGNANCY RELATED ASPECTS OF CHRONIC INFLAMMATORY ARTHRITIDES: DISEASE ONSET POSTPARTUM, PREGNANCY OUTCOMES AND FERTILITY. DATA FROM A NORWEGIAN PATIENT REGISTRY LINKED TO THE MEDICAL BIRTH REGISTRY OF NORWAY
469. Ole Vegard Solberg: 3D ULTRASOUND AND NAVIGATION – APPLICATIONS IN LAPAROSCOPIC SURGERY
470. Inga Ekeberg Schjerve: EXERCISE-INDUCED IMPROVEMENT OF MAXIMAL OXYGEN UPTAKE AND ENDOTHELIAL FUNCTION IN OBESE AND OVERWEIGHT INDIVIDUALS ARE DEPENDENT ON EXERCISE-INTENSITY
471. Eva Veslemøy Tyldum: CARDIOVASCULAR FUNCTION IN PREECLAMPSIA – WITH REFERENCE TO ENDOTHELIAL FUNCTION, LEFT VENTRICULAR FUNCTION AND PRE-PREGNANCY PHYSICAL ACTIVITY
472. Benjamin Garzón Jiménez de Cisneros: CLINICAL APPLICATIONS OF MULTIMODAL MAGNETIC RESONANCE IMAGING
473. Halvard Knut Nilsen: ASSESSING CODEINE TREATMENT TO PATIENTS WITH CHRONIC NON-MALIGNANT PAIN: NEUROPSYCHOLOGICAL FUNCTIONING, DRIVING ABILITY AND WEANING
474. Eiliv Brenner: GLUTAMATE RELATED METABOLISM IN ANIMAL MODELS OF SCHIZOPHRENIA
475. Egil Jonsbu: CHEST PAIN AND PALPITATIONS IN A CARDIAC SETTING; PSYCHOLOGICAL FACTORS, OUTCOME AND TREATMENT
476. Mona Høysæter Fenstad: GENETIC SUSCEPTIBILITY TO PREECLAMPSIA : STUDIES ON THE NORD-TRØNDELAG HEALTH STUDY (HUNT) COHORT, AN AUSTRALIAN/NEW ZEALAND FAMILY COHORT AND DECIDUA BASALIS TISSUE
477. Svein Erik Gaustad: CARDIOVASCULAR CHANGES IN DIVING: FROM HUMAN RESPONSE TO CELL FUNCTION
478. Karin Torvik: PAIN AND QUALITY OF LIFE IN PATIENTS LIVING IN NURSING HOMES
479. Arne Solberg: OUTCOME ASSESSMENTS IN NON-METASTATIC PROSTATE CANCER
480. Henrik Sahlin Pettersen: CYTOTOXICITY AND REPAIR OF URACIL AND 5-FLUOROURACIL IN DNA
481. Pui-Lam Wong: PHYSICAL AND PHYSIOLOGICAL CAPACITY OF SOCCER PLAYERS: EFFECTS OF STRENGTH AND CONDITIONING
482. Ole Solheim: ULTRASOUND GUIDED SURGERY IN PATIENTS WITH INTRACRANIAL TUMOURS
483. Sten Roar Snare: QUANTITATIVE CARDIAC ANALYSIS ALGORITHMS FOR POCKET-SIZED ULTRASOUND DEVICES
484. Marit Skyrud Bratlie: LARGE-SCALE ANALYSIS OF ORTHOLOGS AND PARALOGS IN VIRUSES AND PROKARYOTES
485. Anne Elisabeth F. Isern: BREAST RECONSTRUCTION AFTER MASTECTOMY – RISK OF RECURRENCE AFTER DELAYED LARGE FLAP RECONSTRUCTION – AESTHETIC OUTCOME, PATIENT SATISFACTION, QUALITY OF LIFE AND SURGICAL RESULTS; HISTOPATHOLOGICAL FINDINGS AND FOLLOW-UP AFTER PROPHYLACTIC MASTECTOMY IN HEREDITARY BREAST CANCER
486. Guro L. Andersen: CEREBRAL PALSY IN NORWAY – SUBTYPES, SEVERITY AND RISK FACTORS

487. Frode Kolstad: CERVICAL DISC DISEASE – BIOMECHANICAL ASPECTS
488. Bente Nordtug: CARING BURDEN OF COHABITANTS LIVING WITH PARTNERS SUFFERING FROM CHRONIC OBSTRUCTIVE PULMONARY DISEASE OR DEMENTIA
489. Mariann Gjervik Heldahl: EVALUATION OF NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER BASED ON MR METHODOLOGY
490. Lise Tevik Løvseth: THE SUBJECTIVE BURDEN OF CONFIDENTIALITY
491. Marie Hjelmseth Aune: INFLAMMATORY RESPONSES AGAINST GRAM NEGATIVE BACTERIA INDUCED BY TLR4 AND NLRP12
492. Tina Strømdal Wik: EXPERIMENTAL EVALUATION OF NEW CONCEPTS IN HIP ARTHROPLASTY
493. Solveig Sigurdardottir: CLINICAL ASPECTS OF CEREBRAL PALSY IN ICELAND. A POPULATION-BASED STUDY OF PRESCHOOL CHILDREN
494. Arne Reimers: CLINICAL PHARMACOKINETICS OF LAMOTRIGINE
495. Monica Wegling: KULTURMENNESKETS BYRDE OG SYKDOMMENS VELSIGNELSE. KAN MEDISINSK UTREDNING OG INTERVENSJON HA EN SELVSTENDIG FUNKSJON UAVHENGIG AV DET KURATIVE?
496. Silje Alvestad: ASTROCYTE-NEURON INTERACTIONS IN EXPERIMENTAL MESIAL TEMPORAL LOBE EPILEPSY – A STUDY OF UNDERLYING MECHANISMS AND POSSIBLE BIOMARKERS OF EPILEPTOGENESIS
497. Javaid Nauman: RESTING HEART RATE: A MATTER OF LIFE OR DEATH – PROSPECTIVE STUDIES OF RESTING HEART RATE AND CARDIOVASCULAR RISK (THE HUNT STUDY, NORWAY)
498. Thuy Nguyen: THE ROLE OF C-SRC TYROSINE KINASE IN ANTIVIRAL IMMUNE RESPONSES
499. Trine Naalsund Andreassen: PHARMACOKINETIC, PHARMACODYNAMIC AND PHARMACOGENETIC ASPECTS OF OXYCODONE TREATMENT IN CANCER PAIN
500. Eivor Alette Laugsand: SYMPTOMS IN PATIENTS RECEIVING OPIOIDS FOR CANCER PAIN – CLINICAL AND PHARMACOGENETIC ASPECTS
501. Dorthe Stensvold: PHYSICAL ACTIVITY, CARDIOVASCULAR HEALTH AND LONGEVITY IN PATIENTS WITH METABOLIC SYNDROME
502. Stian Thoresen Aspenes: PEAK OXYGEN UPTAKE AMONG HEALTHY ADULTS – CROSS-SECTIONAL DESCRIPTIONS AND PROSPECTIVE ANALYSES OF PEAK OXYGEN UPTAKE, PHYSICAL ACTIVITY AND CARDIOVASCULAR RISK FACTORS IN HEALTHY ADULTS (20-90 YEARS)
503. Reidar Alexander Vigen: PATHOBIOLOGY OF GASTRIC CARCINOIDS AND ADENOCARCINOMAS IN RODENT MODELS AND PATIENTS. STUDIES OF GASTROCYSTOPLASTY, GENDER-RELATED FACTORS, AND AUTOPHAGY
504. Halvard Høilund-Kaupang: MODELS AND METHODS FOR INVESTIGATION OF REVERBERATIONS IN NONLINEAR ULTRASOUND IMAGING
505. Audhild Løhre: WELLBEING AMONG SCHOOL CHILDREN IN GRADES 1-10: PROMOTING AND ADVERSE FACTORS
506. Torgrim Tandstad: VOX POPULI. POPULATION-BASED OUTCOME STUDIES IN TESTICULAR CANCER
507. Anna Brenne Grønskag: THE EPIDEMIOLOGY OF HIP FRACTURES AMONG ELDERLY WOMEN IN NORD-TRØNDELAG. HUNT 1995-97, THE NORD-TRØNDELAG HEALTH STUDY
508. Kari Ravndal Risnes: BIRTH SIZE AND ADULT MORTALITY: A SYSTEMATIC REVIEW AND A LONG-TERM FOLLOW-UP OF NEARLY 40 000 INDIVIDUALS BORN AT ST. OLAV UNIVERSITY HOSPITAL IN TRONDHEIM 1920-1960
509. Hans Jakob Bøe: LONG-TERM POSTTRAUMATIC STRESS AFTER DISASTER – A CONTROLLED STUDY OF SURVIVORS' HEALTH 27 YEARS AFTER THE CAPSIZED NORTH SEA OIL RIG
510. Cathrin Barbara Canto, Cotutelle with University of Amsterdam: LAYER SPECIFIC INTEGRATIVE PROPERTIES OF ENTORHINAL PRINCIPAL NEURONS
511. Ioanna Sandvig: THE ROLE OF OLFACTORY ENSHEATHING CELLS, MRI, AND BIOMATERIALS IN TRANSPLANT-MEDIATED CNS REPAIR
512. Karin Fahl Wader: HEPATOCYTE GROWTH FACTOR, C-MET AND SYNDECAN-1 IN MULTIPLE MYELOMA
513. Gerd Tranø: FAMILIAL COLORECTAL CANCER

514. Bjarte Bergstrøm: INNATE ANTIVIRAL IMMUNITY – MECHANISMS OF THE RIG-I-MEDIATED RESPONSE
515. Marie Søfteland Sandvei: INCIDENCE, MORTALITY, AND RISK FACTORS FOR ANEURYSMAL SUBARACHNOID HEMORRHAGE. PROSPECTIVE ANALYZES OF THE HUNT AND TROMSØ STUDIES
516. Mary-Elizabeth Bradley Eilertsen: CHILDREN AND ADOLESCENTS SURVIVING CANCER: PSYCHOSOCIAL HEALTH, QUALITY OF LIFE AND SOCIAL SUPPORT
517. Takaya Saito: COMPUTATIONAL ANALYSIS OF REGULATORY MECHANISM AND INTERACTIONS OF MICRORNAS

Godkjent for disputas, publisert post mortem: Eivind Jullumstrø: COLORECTAL CANCER AT LEVANGER HOSPITAL 1980-2004

518. Christian Gutvik: A PHYSIOLOGICAL APPROACH TO A NEW DECOMPRESSION ALGORITHM USING NONLINEAR MODEL PREDICTIVE CONTROL
519. Ola Storrø: MODIFICATION OF ADJUVANT RISK FACTOR BEHAVIOURS FOR ALLERGIC DISEASE AND ASSOCIATION BETWEEN EARLY GUT MICROBIOTA AND ATOPIC SENSITIZATION AND ECZEMA. EARLY LIFE EVENTS DEFINING THE FUTURE HEALTH OF OUR CHILDREN
520. Guro Fanneløb Giskeødegård: IDENTIFICATION AND CHARACTERIZATION OF PROGNOSTIC FACTORS IN BREAST CANCER USING MR METABOLOMICS
521. Gro Christine Christensen Løhaugen: BORN PRETERM WITH VERY LOW BIRTH WEIGHT – NEVER ENDING COGNITIVE CONSEQUENCES?
522. Sigrid Nakrem: MEASURING QUALITY OF CARE IN NURSING HOMES – WHAT MATTERS?
523. Brita Pukstad: CHARACTERIZATION OF INNATE INFLAMMATORY RESPONSES IN ACUTE AND CHRONIC WOUNDS

2012

524. Hans H. Wasmuth: ILEAL POUCHES
525. Inger Økland: BIASES IN SECOND-TRIMESTER ULTRASOUND DATING RELATED TO PREDICTION MODELS AND FETAL MEASUREMENTS
526. Bjørn Mørkedal: BLOOD PRESSURE, OBESITY, SERUM IRON AND LIPIDS AS RISK FACTORS OF ISCHAEMIC HEART DISEASE
527. Siver Andreas Moestue: MOLECULAR AND FUNCTIONAL CHARACTERIZATION OF BREAST CANCER THROUGH A COMBINATION OF MR IMAGING, TRANSCRIPTOMICS AND METABOLOMICS
528. Guro Aune: CLINICAL, PATHOLOGICAL, AND MOLECULAR CLASSIFICATION OF OVARIAN CARCINOMA
529. Ingrid Alsos Lian: MECHANISMS INVOLVED IN THE PATHOGENESIS OF PRE-ECLAMPSIA AND FETAL GROWTH RESTRICTION. TRANSCRIPTIONAL ANALYSES OF PLACENTAL AND DECIDUAL TISSUE
530. Karin Solvang-Garten: X-RAY REPAIR CROSS-COMPLEMENTING PROTEIN 1 – THE ROLE AS A SCAFFOLD PROTEIN IN BASE EXCISION REPAIR AND SINGLE STRAND BREAK REPAIR
531. Toril Holien: BONE MORPHOGENETIC PROTEINS AND MYC IN MULTIPLE MYELOMA
532. Rooyen Mavenyengwa: *STREPTOCOCCUS AGALACTIAE* IN PREGNANT WOMEN IN ZIMBABWE: EPIDEMIOLOGY AND SEROTYPE MARKER CHARACTERISTICS
533. Tormod Rimehaug: EMOTIONAL DISTRESS AND PARENTING AMONG COMMUNITY AND CLINIC PARENTS
534. Maria Dung Cao: MR METABOLIC CHARACTERIZATION OF LOCALLY ADVANCED BREAST CANCER – TREATMENT EFFECTS AND PROGNOSIS
535. Mirta Mittelstedt Leal de Sousa: PROTEOMICS ANALYSIS OF PROTEINS INVOLVED IN DNA BASE REPAIR AND CANCER THERAPY
536. Halfdan Petursson: THE VALIDITY AND RELEVANCE OF INTERNATIONAL CARDIOVASCULAR DISEASE PREVENTION GUIDELINES FOR GENERAL PRACTICE
537. Marit By Rise: LIFTING THE VEIL FROM USER PARTICIPATION IN CLINICAL WORK – WHAT IS IT AND DOES IT WORK?
538. Lene Thoresen: NUTRITION CARE IN CANCER PATIENTS. NUTRITION ASSESSMENT: DIAGNOSTIC CRITERIA AND THE ASSOCIATION TO SURVIVAL AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH ADVANCED COLORECTAL CARCINOMA

539. Berit Doseth: PROCESSING OF GENOMIC URACIL IN MAN AND MOUSE
540. Gro Falkenér Bertheussen: PHYSICAL ACTIVITY AND HEALTH IN A GENERAL POPULATION AND IN CANCER SURVIVORS – METHODOLOGICAL, OBSERVATIONAL AND CLINICAL ASPECTS
541. Anne Kari Knudsen: CANCER PAIN CLASSIFICATION
542. Sjur Urdson Gjerald: A FAST ULTRASOUND SIMULATOR
543. Harald Edvard Mølmen Hansen: CARDIOVASCULAR EFFECTS OF HIGH INTENSITY AEROBIC INTERVAL TRAINING IN HYPERTENSITIVE PATIENTS, HEALTHY AGED AND YOUNG PERSONS
544. Sasha Gulati: SURGICAL RESECTION OF HIGH-GRADE GLIOMAS
545. John Chr. Fløvig: FREQUENCY AND EFFECT OF SUBSTANCES AND PSYCHOACTIVE MEDICATIONS THE WEEK BEFORE ADMISSION TO AN ACUTE PSYCHIATRIC DEPARTMENT
546. Kristin Moksnes Husby: OPTIMIZING OPIOID TREATMENT FOR CANCER PAIN – CLINICAL AND PHARMACOLOGICAL ASPECTS