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

Thesis for the degree philosophiae doctor

Trondheim, May 2007

Norwegian University of Science and Technology
Faculty of Medicine
Department of Circulation and Medical Imaging

NTNU
Innovation and Creativity

NTNU
Norwegian University of Science and Technology

Thesis for the degree philosophiae doctor

Faculty of Medicine
Department of Circulation and Medical Imaging

ISBN 978-82-471-2100-9 (printed version)
ISBN 978-82-471-2114-6 (electronic version)
ISSN 1503-8181

Doctoral theses at NTNU, 2007:96

Printed by NTNU-trykk

Måling av helserelatert livskvalitet og aspekter av klinisk farmakologi ved bruk av metadon hos pasienter med kronisk smerte som ikke skyldes kreftsykdom

Langvarige smertetilstander som ikke skyldes kreftsykdom rammer en stor andel av befolkningen og fører til en betydelig reduksjon i selvrapportert helserelatert livskvalitet. Pasientene med de mest alvorlige og kompliserte smertetilstandene blir vurdert på tverrfaglige smerteklinikker. I noen tilfeller vil en del av behandlingen på en tverrfaglig smerteklinikk være bruk av morfin eller liknende medisiner. En andel av pasientene som får slike medisiner vil oppleve at de til tross for dette ikke får god nok smertelindring eller får for mye bivirkninger.

Målet for denne avhandlingen var 1.) å vurdere om livskvalitets spørreskjemaet EORTC QLQ-C30 gir nøyaktige og pålitelige målinger av helserelatert livskvalitet hos pasienter som skal vurderes på en tverrfaglig smerteklinikk 2.) å sammenligne helserelatert livskvalitet mellom pasienter på en tverrfaglig smerteklinikk og pasienter med langtkommet kreftsykdom som mottar lindrende behandling 3.) å vurdere effektene av et bytte fra morfin til metadon hos kroniske smertepasienter med utilfredsstillende balanse mellom smertelindring og bivirkning under behandling med morfin.

Data fra 288 pasienter med kroniske smerter ble samlet inn ved første konsultasjon på tverrfaglig smertesenter på St. Olavs Hospital. Disse dataene ble brukt til å vurdere nøyaktigheten og nytten av livskvalitet spørreskjemaet EORTC QLQ-C30 i denne pasientgruppen, og til å sammenligne livskvalitet med 434 pasienter med langtkommet kreftsykdom. En gruppe på tolv pasienter med utilfredsstillende balanse mellom smertelindring og bivirkninger under behandling med morfin for langvarige smerter byttet fra morfin til metadon. I oppfølgingsperioden på ni måneder ble smertelindring, helserelatert livskvalitet og kognitiv funksjon vurdert. Det ble også tatt blodprøver for å måle konsentrasjonen av morfin og metadon i blodet samt EKG for å vurdere økning i QT-tid, som kan gi økt risiko for hjerterytmeforstyrrelser.

Resultatene fra studiene som avhandlingen bygger på, viser at pasienter som kommer til behandling på tverrfaglige smerteklinikker rapporterer langt dårligere livskvalitet enn normalbefolkningen. På de fleste områder rapporterer de tilsvarende dårlig livskvalitet som pasienter som mottar lindrende behandling for langtkommet kreftsykdom. Omtrent halvparten av pasienter som byttet til metadon rapporterte en betydelig og langvarig bedring i helserelatert livskvalitet og fysisk funksjonsnivå etter byttet. Konsentrasjonen av metadon i blodet var stabil i de ni månedene pasientene ble fulgt opp. Det var en liten økning i QT-tid, men økningen var ikke stor nok til å ha klinisk betydning.

Cand.med. Olav Magnus Søndenå Fredheim
Institutt for Sirkulasjon og bildediagnostikk, NTNU

Hovedveileder: Professor Petter C. Borchgrevink
Biveiledere: Professor Stein Kaasa, professor Ola Dale og førsteamanuensis Pål Klepstad
Finansieringskilde: Samarbeidsorganet mellom Helse Midt-Norge RHF og NTNU

Ovennevnte avhandling er funnet verdig til å
forsvares offentlig for graden PhD i klinisk medisin
Disputas finner sted i Auditoriet (MTA), Medisinsk teknisk senter
torsdag 24. mai 2007, klokken 12.15

Abstract

Introduction
The patients with the most severe and complex chronic non-malignant pain (CNMP) conditions are admitted to multidisciplinary pain centres. A poor health related quality of life (HRQoL) has been documented in these patients but their HRQoL scores have to a very limited degree been compared to other patient groups. Such comparisons require the application of the same HRQoL instruments in different populations. While non-pharmacological treatment is preferred in this patient group, treatment with strong opioids is an option for some patients. After start of opioid therapy about half the patients experience an unacceptable balance between side effects and pain relief. According to research in cancer pain, a switch to methadone may improve pain control in these patients. However, there are several areas of uncertainty related to this switch in CNMP patients. It has not been evaluated in prospective studies with long-term follow up and both increased QTc time (QT time adjusted for heart rate) and autoinduction of methadone metabolism during long term treatment have been indicated in other patient populations.

Research questions
HRQoL assessment methodology in CNMP patients:

I. Is the EORTC QLQ-C30 a valid alternative to the SF-36 for assessment of HRQoL in CNMP patients?

Comparison of HRQoL scores between patient groups:

II. How is the HRQoL of CNMP patients admitted to multidisciplinary pain centre treatment compared to the HRQoL of palliative cancer patients?

Opioid switching from morphine to methadone in CNMP patients with an unacceptable balance between pain control and side effects during morphine therapy:

III. What are the effects on pain control, HRQoL, cognitive functioning and patient preference?
IV. What is the effect on QTc time?
V. Are methadone serum concentrations stable during long term treatment and are there interindividual differences in opioid metabolism?

Methods
HRQoL data were collected from 288 CNMP patients admitted to multidisciplinary pain treatment. These data were used for psychometric validation of the EORTC QLQ-C30 HRQoL questionnaire and for comparison of HRQoL with palliative cancer patients.

Twelve patients with unacceptable balance between pain control and side effects during morphine treatment for CNMP switched to methadone. Pain, HRQoL, cognitive functioning, opioid serum concentrations and QTc were evaluated at baseline and one, two, six and 13 weeks and nine months later.

Results
Internal consistency was below 0.70 for five of nine EORTC QLQ-C30 multi-item scales. Large floor or ceiling effects were seen for several scales. These weaknesses do not disrupt the picture of overall acceptable psychometric properties in this population.

Compared to palliative cancer patients, patients with CNMP reported poorer global quality of life and cognitive functioning and more pain, sleep disturbances and financial difficulties as well as equally poor physical, social and emotional functioning and equally high levels of diarrhoea, dyspnoea and fatigue.

Seven patients preferred long-term (> nine months) treatment with methadone and reported reduced pain and improved functioning while cognition was not improved. On the other hand one patient experienced sedation requiring naloxone and four patients were switched back to morphine due to poor pain control, drowsiness or sweating. Mean increase in QTc was 0.020 seconds. Serum concentrations of methadone and its metabolite EDDP were stable from the end of dose titration and during the nine months.

Conclusions

- The EORTC QLQ-C30 is a valid alternative to the SF-36 for HRQoL assessment in CNMP patients.
- CNMP patients admitted to multidisciplinary pain centres report as poor HRQoL as palliative cancer patients.
- Opioid switching to methadone causes improved pain control and HRQoL in some patients but is not beneficial to all patients and poses a risk of serious sedation.

Table of contents

Acknowledgements

During my work on this thesis I have had the privilege of receiving advice and supervision from a team of four mentors; professor Petter C. Borchgrevink, professor Stein Kaasa, professor Ola Dale and associate professor Pål Klepstad. I am very grateful for their patience, enthusiasm and support. Petter C. Borchgrevink introduced me to quality of life research and pain medicine when he supervised my student research topic. He also introduced me to the "pain and palliation research group" which is led by Stein Kaasa. Together Petter and Stein encouraged me to continue in this field of research, and I am grateful for the opportunity I was offered.

In addition to my four mentors several other co-authors have contributed highly valuable advice and assistance for the papers included in this thesis:

- Nils Inge Landrø provided the necessary neuropsychological expertise for the assessment of cognitive functioning in the methadone switch study.
- Marit Jordhøy provided the health related quality of life data on palliative cancer patients for paper II and also contributed with her experience in quality of life research.
- Peter Fayers contributed with invaluable advice for the analyses strategy and statistics for the comparison of health related quality of life between palliative cancer patients and chronic pain patients in paper II.
- Turi Saltnes was data manager for the two health related quality of life studies (paper I and II) and provided helpful advice on data analysis and presentation.
- Lars Hegrenæs assessed the ECGs in the methadone switch study and provided cardiological expert opinions for the paper on QTc time (paper V).

Data for the studies were collected at Trondheim multidisciplinary pain centre (Smertesenteret) at St Olav University Hospital. I am particularly grateful to Åse Jystad, Bjørn Hval and Gro H. Garvin for their assistance in patient inclusion and data collection.

Turid Nilsen and Trine N. Andreassen planned and performed the laboratory and analytical work in the methadone switch study. Numerous other members of the "pain and palliation research group" have contributed through specific advice and in group discussions. It is a privilege to do research with you all.

Financial support from "Samarbeidsorganet for Helse Midt-Norge og NTNU" made it possible to work full-time with research for eight months. During the final stages of the work on the thesis I was employed at Helgelandssykehuset / Sandnessjøen Hospital. I am grateful for the research leaves I was granted at the departments of medicine and surgery as well as financial support from the research board at Helgelandssykehuset. Early in the process I received financial support through a talent scholarship from the G9alt-foundation.

My parents Gerd and Magnus Fredheim have provided invaluable encouragement and support throughout the process.

List of original papers

I. Fredheim O, Borchgrevink PC, Saltnes T, Kaasa S. Validation and comparison of the Health Related Quality of Life instruments SF-36 and EORTC QLQ-C30 in assessment of patients with chronic non-malignant pain. Journal of Pain and Symptom Management. Accepted for publication.

II. Fredheim O, Kaasa S, Fayers P, Saltnes T, Jordhøy M , Borchgrevink PC. Chronic non-malignant pain patients report as poor health related quality of life as palliative cancer patients. Submitted for publication.

III. Fredheim O, Kaasa S, Dale O, Klepstad P, Landrø NI, Borchgrevink PC. Opioid switching from oral slow release morphine to oral methadone may improve pain control in chronic non-malignant pain: a nine months follow-up study. Palliative Medicine 2006; 20: 35-41.

IV. Fredheim O, Borchgrevink PC, Klepstad P, Kaasa S, Dale O. Long term methadone for chronic pain: a pilot study of pharmacokinetic aspects. European Journal of Pain. In press (Published online November 17th, 2006. DOI: 10.1016/j.ejpain.2006.09.006).

V. Fredheim O, Borchgrevink PC, Hegrenæs L, Kaasa S, Dale O, Klepstad P. Opioid switching from morphine to methadone causes a minor but not clinically significant increase in QTc time: a prospective 9 months follow-up study. Journal of Pain and Symptom Management 2006; 32: 180-185.

Abbreviations

BDI	Beck Depression Inventory
BPI	Brief Pain Inventory
CNS	Central Nervous System
CNMP	Chronic Non-Malignant Pain
CONSORT	Consolidated Standards of Reporting Trials
EAPC	European Association for Palliative Care
ECG	Electro Cardiogram
EDDP	2-Ethylidene-1,5-Dimethyl-3,3-Dipenylpyrrolidine
EMDP	2-Ethyl-5-Methyl-3,3-Diphenylpyrolidine
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, 30 item version
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health Related Quality of Life
IASP	International Association for the Study of Pain
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
LC-MS/MS	Liquid Chromatography – Tandem Mass Spectrometry
M3G	Morphine-3-Glucuronide
M6G	Morphine-6-Glucuronide
MDPC	Multidisciplinary Pain Centre
MDR1	Multi Drug Resistance Protein 1
MTMM	Multi Trait Multi Method
NMDA	N-methyl-D-aspartate
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NRS	Numeric Rating Scale
PASAT	Paced Auditory Serial Addition Test
QTc	QT time corrected for heart rate: $QTc = QT/\sqrt{RR}$
RCT	Randomized Controlled Trial
SF-36	Medical Outcome Study Short Formula 36
T_{max}	Time to Maximum Serum Concentration
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale
WHO	World Health Organization

Research questions

Health related quality of life assessment methodology in chronic non-malignant pain patients:

I. Is the EORTC QLQ-C30 a valid alternative to the SF-36 for assessment of health related quality of life in chronic non-malignant pain patients?

Comparison of health related quality of life scores between patient groups:

II. How is the health related quality of life of chronic non-malignant pain patients admitted to multidisciplinary pain centre treatment compared to the health related quality of life of palliative cancer patients?

Opioid switching from morphine to methadone in chronic non-malignant pain patients with an unacceptable balance between pain control and side effects during morphine therapy:

III. What are the effects on pain control, health related quality of life, cognitive functioning and patient preference?

IV. What is the effect on QTc time (QT time adjusted for heart rate)?

V. Are methadone serum concentrations stable during long term treatment and are there interindividual differences in opioid metabolism?

Introduction

Chronic non-malignant pain

Epidemiology

Pain is defined by the International Association for the Study of Pain (IASP) as "An unpleasant sensory and emotional experience associated with tissue damage, or described in terms of such damage" (IASP 1994b). The definition of chronic pain is less clear, but IASP has suggested that chronic pain is pain persisting beyond the normal time of tissue healing (IASP 1994a). The uncertainty in the definition of chronic non-malignant pain is reflected in the diverging inclusion criteria or case definitions in recent epidemiologic studies of chronic non-malignant pain (CNMP). While all these studies excluded patients with current malignant disease, they applied a pain duration of either three (Elliott et al. 1999;Blyth et al. 2001;Rustoen et al. 2004) or six months (Eriksen et al. 2003;Breivik et al. 2006) in their case definition.

The above mentioned differences in case definition between epidemiological studies probably contribute to the large variability in the prevalence estimates of CNMP in the population. In recent surveys from Denmark and the United Kingdom the prevalence of chronic non-malignant pain has been estimated to 19 and 47% respectively (Elliott et al. 1999;Eriksen et al. 2003). Recently a mean prevalence of 19% was reported in a study including 16 European countries and Israel, with variation in prevalence from 12 to 30% across countries (Breivik et al. 2006). An older review of pain prevalence studies from 1984 to 1994 reported prevalence estimates from 2 to 40% (Verhaak et al. 1998). Besides differences in case definition, also differences in the wording of questions and differences in the research methodology may have contributed to the diverging prevalence estimates. Nevertheless the results from the epidemiological studies indicate that the prevalence differs between countries. CNMP conditions are not necessarily of life long duration. Annual recovery rates of 5 and 9% respectively have been estimated in two different studies (Elliott et al. 2002;Eriksen et al. 2004a).

The different CNMP conditions can be sufficiently treated at different levels of the health care system depending on the severity and complexity of the pain condition. The majority of those reporting CNMP in epidemiologic surveys are not in need of specialised services. Patients with more serious conditions are treated by specialists like rheumatologists, surgeons or rehabilitation specialists, while patients with the most severe and complex conditions are admitted to tertiary line multidisciplinary pain centres (MDPCs). Overall the population reporting CNMP in epidemiological studies utilize nearly twice as much health care resources as the general population (Eriksen et al. 2004b). A high proportion is, however, dissatisfied with the investigations performed (33%) or with the treatment they have received (40%) (Eriksen et al. 2003).

Multidisciplinary treatment

Treatment in MDPCs is required for the most severe and complex CNMP conditions and is reported to reduce pain and improve physical functioning, quality of sleep and psychological well-being (Becker et al. 2000). The treatment in MDPCs aims at

rehabilitation and improved functioning, but seldom complete pain relief (Ashburn and Staats 1999). At admission patients are seen by several professionals; usually a medical doctor, a physiotherapist and a psychologist. Following this first evaluation the multidisciplinary team decides a treatment strategy or suggests treatment to be followed in the primary health care. The treatment options include education about pain, improving coping strategies, pharmacological treatment, socio-economic counselling and physiotherapy/exercise. Treatment of psychological comorbidities like depression and anxiety is important for some patients. For a minority of CNMP patients opioid therapy is indicated when all other therapeutic options have been exhausted without obtaining adequate pain relief. Like all other treatments opioid therapy does not aim at complete pain relief but at improved functioning and health related quality of life (HRQoL) (Kalso et al. 2003).

Assessment of health related quality of life, symptoms and functioning

Introduction

The concept of health related quality of life (HRQoL) as not only absence of disease is reflected in the World Health Organization (WHO) definition of health as physical, emotional and social well being (WHO 1946). CNMP patients often have several complaints and reduced functioning in addition to pain, and psychological/psychiatric comorbidities are common (Becker et al. 1997). Accordingly several domains of symptoms and functioning need to be assessed. In clinical routine a broad assessment is required in order to tailor the treatment strategy and to evaluate the therapeutic outcomes. Also in pain clinical trials it is required to assess several domains in addition to pain. These domains include physical, emotional and cognitive functioning as well as the symptoms fatigue and difficulties of sleep and socioeconomic problems (Turk et al. 2003).

Simple instruments for assessment of functioning such as the Barthel Index (Mahoney and Barthel 1965) and the Karnofsky performance scale (Karnofsky DA and Burchenal JH 1949) are regarded predecessors of more comprehensive HRQoL instruments (Fayers and Machin 2000). True HRQoL instruments developed during the most recent decades usually include a broad assessment of several domains of functioning as well as symptoms. Among the abundance of instruments an important dividing line is between generic instruments which are developed for use across patient populations and settings and the disease specific instruments. Two examples of common HRQoL instruments are the SF-36 and EORTC QLQ-C30 which were developed in the late 1980's and introduced in the early 1990's (Aaronson et al. 1993;Ware, Jr. and Gandek 1998). While SF-36 is a generic instrument, the EORTC QLQ-C30 was developed for use in cancer clinical trials. Other frequently applied generic HRQoL instruments are WHOQOL (The WHO quality of life group 1998), the Nottingham health profile (Hunt et al. 1980;Wiklund 1990), The Sickness Impact Profile (Bergner et al. 1981) and the EuroQoL (Brooks 1996). In spite of the broad spectrum of functions and symptoms assessed by the HRQoL instruments, other instruments are often added for a more thorough evaluation of certain domains. For patients with CNMP physical, emotional and cognitive functioning and pain are usually subject to more thorough evaluation both in clinical routine and in research, and several specific assessment tools are available (Turk and Melzack 2001;Turk et

al. 2003;Dworkin et al. 2005). Some HRQoL instruments have optional modules which can be added in specific patient populations. An example of an optional module is the EORTC QLQ-C30 head and neck cancer module (Bjordal et al. 1994).

Validation

Instruments for the assessment of symptoms or HRQoL need to be validated to ensure that they really measure what they are intended to, detect true changes over time and differentiate between subjects. While generic instruments are developed and validated for use across disease groups, the disease specific instruments are usually only validated in a specific population. If a disease specific HRQoL instrument shall be applied in any other patient population validation studies in this population is required. When an instrument has been translated, repeated validation is also required to ensure that the translated version performs as well as the original. The validation process includes assessment of several psychometric properties. The key psychometric properties are briefly described below.

Discrimination

Discrimination is an assessment of how well an instrument differentiates between subjects with different levels of functioning or symptom burden. When discrimination is high, the patients' responses are distributed along the whole range of the response alternatives. In a tool with poor discrimination, a large proportion of responses will be one of the extreme alternatives. Discrimination is assessed by measuring the floor and ceiling effect, which is the percentage of responses in either end of the response range. Large floor or ceiling effects indicate poor discrimination.

Responsiveness and sensitivity

The abilities to detect true changes over time and between groups are often described as responsiveness and sensitivity, respectively. However, these properties are closely related and the terms are not consistently used in the literature.

Responsiveness usually describes the ability to detect changes in one patient or a group of patients over time. When the patient experiences an improvement or deterioration in any domain covered by the HRQoL instrument, this experienced change should be reflected in an increased or reduced HRQoL score. If response ranges are narrow or the questions too vague changes might not be detected.

Sensitivity is usually used to describe how well an instrument identifies differences between groups. An instrument with a high sensitivity is able to detect a relatively small difference between groups with a modest sample size. Sensitivity is assessed by comparing the scores of different groups of patients. Populations may be divided into groups according to diagnosis, performance status and so on.

Construct validity

With the exception of global quality of life scales, each scale in a HRQoL instrument is supposed to assess one specific dimension of HRQoL. A physical functioning scale is for instance supposed to measure the construct physical functioning. Construct validation evaluates how well a scale measures the construct it is intended to measure. A simple form of construct validation is known groups validation which assesses whether groups expected to experience different levels of HRQoL report different scores. Patients who are dependent on help for their activities of daily life would for

instance be expected to report worse physical functioning than those who are not dependent on help. Another analysis strategy is assessment of convergent and discriminant validity. This strategy is based on the assumption that some HRQoL dimensions (constructs) are strongly associated while others are less strongly related. When testing convergent validity one assumes that scales measuring the same underlying or related construct have high correlation coefficients exceeding 0.40. On the opposite, by discriminant validity one assumes that scales measuring different constructs should show low correlation (<0.40). Convergent and discriminant validity is usually measured in a multi trait multi method (MTMM) analysis. In the MTMM analysis correlations between the results from different measurement methods of different traits (HRQoL dimensions) are presented. The construct validation may also include comparison of deviation from norm-data between two instruments.

Reliability

A reliable instrument has a high degree of correlation between items in multi item scales. The reliability is expressed as the internal consistency which is determined by Cronbach's coefficient (Cronbach's alpha). The coefficient value reflects both the number of items and the degree of correlation between them. Values above 0.70 usually indicate acceptable internal consistency and reliability.

External convergent validity

The external convergent validity is an assessment of the correlation between two instruments' measures of the same concept. Such correlations should be high and the correlation coefficient values should exceed the values for correlations between scales measuring different concepts. For instance correlation between two instruments' physical functioning scales should be high and substantially higher than correlation between physical functioning in one instrument and all other scales in the other instrument. The correlation coefficients required for assessment of external convergent validity are included in the MTMM analyses.

Health related quality of life and chronic non-malignant pain

HRQoL in CNMP populations has been assessed using the SF-36 both in clinical trials (Becker et al. 2000) and epidemiological studies (Becker et al. 1997;Elliott et al. 2002;Eriksen et al. 2003;Bergman et al. 2004). However, disease specific HRQoL instruments have been developed for several chronic pain conditions such as rheumatoid arthritis, ankylosing spondylitis and migraine (Martin et al. 2000;Russak et al. 2003;Doward et al. 2003) and are applied in trials in these populations. Recently the EORTC QLQ-C30 has also been applied at a MDPC treating CNMP conditions (Wincent et al. 2003).

Studies of HRQoL in CNMP patients have demonstrated that the part of the population reporting chronic pain in epidemiological surveys has a statistically and clinically significant reduction in HRQoL compared to the general population (Eriksen et al. 2003). In the minority of CNMP patients admitted to MDPCs an even larger reduction is observed (Becker et al. 1997;Wittink et al. 2004).

Due to use of different HRQoL instruments in different studies, it is difficult to compare the results both within CNMP cohorts and with other patient groups. Accordingly few such comparisons have been made. One study has indicated that patients with chronic headache experience different HRQoL from patients with

chronic low back pain in four of eight SF-36 scales (Gerbershagen et al. 2002) while patients admitted to a Danish MDPC reported SF-36 scores in the same range as patients with severe cardiopulmonary disease or major depression (Becker et al. 1997).

Comorbidities and associated symptoms in chronic non-malignant pain

As mentioned above, chronic pain patients often experience additional symptoms and reduced functioning as well as psychiatric comorbidity. In the methadone switch study cognitive functioning was assessed by three neuropsychological tests while several other symptoms were addressed using the EORTC QLQ-C30 in both the methadone switch study and the two HRQoL studies. This part of the introduction provides a brief overview over associated symptoms and comorbidities in CNMP with particular focus on cognitive functioning.

Cognitive functioning

The authors of a comprehensive review of chronic pain and neuropsychological impairment concluded that neuropsychological impairment is frequent in CNMP, particularly impairment of attentional capacity, processing speed and psychomotor speed (Hart et al. 2000). Even though data have not been presented for pain patients, data from other patient populations indicate that minor impairments in cognitive functioning may impair functioning in work as well as activities of daily life (Rao et al. 1991). The mechanism for impairment of cognitive functioning in chronic pain is not established, but several mechanisms such as neuroplastic changes, production of inhibitory substances in the central nervous system (CNS) and chronic stress reactions with increased glucocorticoid levels have been suggested. It has also been suggested that pain is an attention-demanding perceptional stimulus which competes for attentional resources. The influence from pain on cognitive functioning does not seem to be determined by pain intensity and location alone. The effects could also be mediated through other common symptoms in pain patients such as emotional distress, difficulties of sleep and fatigue.

Opioids as well as other medications may also have a sedative effect. In a study of chronic pain patients receiving long term therapy with long acting opioids patients performed significantly worse than healthy controls in continuous reaction time, finger tapping test and the paced auditory addition test (PASAT) (Sjogren et al. 2000). Among the pain patients higher pain intensity was positively correlated to PASAT scores and indicated an arousal effect from pain on working memory. The cross sectional study design does not allow conclusions on whether the impairment in cognitive functioning was caused by the chronic pain condition or the opioid treatment. A more recent study from the same group compared CNMP patients without any pain medication to CNMP patients on long term opioid therapy with long acting opioids without co-analgesics, CNMP patients only receiving antidepressants and/or anticonvulsants and CNMP patients receiving combined treatment with opioids and antidepressants and/or anticonvulsants (Sjogren et al. 2005). Testing included continuous reaction time, finger tapping test and PASAT. The overall patient population performed worse than healthy controls in continuous reaction time and finger tapping while no significant difference was observed in performance in the PASAT. The subgroup analyses indicated that patients on opioid therapy performed poorer than patients without pain medication in the PASAT. However, due to the non-

randomised design it can be questioned whether differences between the groups were caused by differences in medication or by differences in pain conditions. A quite recent review of effects on cognition from opioids in patients with chronic pain concluded that it was not determined whether the reduced cognitive functioning in CNMP patients on long term opioids was caused by the opioid treatment or confounding factors (Chapman et al. 2002). However, the available data suggested the greatest impairment shortly after start of opioids. A randomized controlled trial (RCT) of morphine for CNMP which included cognitive functioning as a secondary outcome found no change in cognitive functioning during morphine treatment compared to placebo (Moulin et al. 1996).

Other symptoms

Anxiety and depression are common comorbidities of CNMP. It is not established whether these conditions are part of the aetiology for development of CNMP conditions or reactions following the development of CNMP conditions. Hospital anxiety and depression scale (HADS) (Zigmond and Snaith 1983) scores from MDPC patient populations show mean values substantially below reference values and indicate a prevalence of 40% and 50% respectively for self reported depression and anxiety (Becker et al. 1997;Harris et al. 2003). Harris et al also reported a Beck Depression Inventory (BDI) mean score of 21.2 in CNMP patients admitted to a MDPC (Harris et al. 2003). This corresponds to the average scores of patients with mild to moderate depression (Beck et al. 1961).

Sleep disturbances are frequent among CNMP patients admitted to MDPCs. In one study only 12% of patients rated their quality of sleep as “good” during the last week before their first consultation at a MDPC while 46% reported their quality of sleep to be “fair” and 42% to be “poor” (Becker et al. 1997). 84% reported that their sleep was interrupted by pain. A review found an overall prevalence of 50 to 70% of difficulties of sleep in CNMP patients admitted to MDPCs (Menefee et al. 2000). It was speculated that pain is probably only one of several factors contributing to impaired sleep in this patient population. Other possible factors are psychological comorbidities and side effects from pharmacological treatment.

Fatigue is a prevalent symptom in cancer patients (Stone et al. 1998). Even though data from CNMP patients are sparse, there are indications that also CNMP patients experience increased levels of fatigue compared to the general population. In one study patients with chronic low back pain or neck pain reported levels of fatigue close to the levels in a diverse group of cancer patients admitted to radiotherapy when fatigue was assessed with the Multidimensional Fatigue Inventory (Fishbain et al. 2004). A recent review also reported an association between pain and fatigue in 16 of the 17 included high quality trials (Fishbain et al. 2003). This review concluded that there seems to be an aetiological relationship between pain and the development of fatigue. These findings are supported by poor scores in the vitality scale of the SF-36 among CNMP patients admitted to MDPCs (Becker et al. 1997;Wittink et al. 2004).

The pharmacological treatment of CNMP conditions poses a risk of side effects. Nausea/vomiting, constipation and drowsiness are common side effects of opioid therapy (Kalso et al. 2004). Drowsiness, dizziness and nausea/vomitting are among the frequent side effects of anticonvulsants while dry mouth, sweating and dizziness

are frequent during treatment with tricyclic antidepressants (Jensen 2002;Sindrup et al. 2005).

Assessment in clinical trials

Treatment decisions should be based on evidence from clinical research. However, single trials may have methodological weaknesses or biases and positive results may be false positives. Clinical decisions and strategies should be supported by several trials and it is commonly agreed that the highest level of evidence for medical treatment is conclusions from meta-analyses or systematic reviews of RCTs (Hadorn et al. 1996;Harbour and Miller 2001). Meta-analyses require a certain level of uniformity in outcome assessment and reporting, and lack of standardisation is a major obstacle when information from several trials is compared or combined. The Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) aims at introducing a standard for outcome assessment and reporting in pain clinical trials. The IMMPACT group first identified the core outcome domains for pain clinical trials (Turk et al. 2003) and have later published recommendations concerning the choice of outcome measures and instruments (Dworkin et al. 2005). The recommendations from the IMMPACT group are summarised in table 1.

The IMMPACT recommendations do not require that all outcomes are included in each trial, but states that the reasons for omission should be reported when domains are omitted from a study. HRQoL is not included as an outcome domain in the IMMPACT recommendations, but it is recommended to consider the inclusion of a HRQoL instrument for the assessment of self reported functioning.

Table 1: IMMPACT core outcome domains and recommended instruments.

Outcome domains	**Recommended outcome measures**
Pain	11 point numeric rating scale (NRS) *or if NRS is not feasible* Verbal rating scale (none, mild, moderate, severe) Usage of rescue analgesics
Physical functioning	SF-36 physical functioning scale *and one of the following:* A disease specific physical functioning instrument *or* Brief Pain Inventory interference items *or* Multidimensional Pain Inventory interference scale
Emotional functioning	Beck Depression Inventory *and/or* Profile of Mood States
Participant rating of improvement and satisfaction with treatment	Patient global impression of change
Symptoms and adverse effects	Passive capture of spontaneously reported adverse events and symptoms and use of open ended prompts.
Participant disposition	As recommended in Consolidated Standards of Reporting Trials (CONSORT) guidelines.

An expert working group of the European Association for Palliative Care (EAPC) has presented recommendations for the measurement of pain in palliative care research (Caraceni et al. 2002). An 11-point Numeric rating scale (NRS), a 100 millimetres Visual analogous scale (VAS) or a Verbal rating scale (VRS) is recommended for unidimensional assessment of pain while the short form of the Brief pain inventory (BPI) or the MacGill Pain Questionnaire is recommended for multidimensional

assessment of pain. The authors state that among the unidimensional measures the VRS is the easiest and VAS the most difficult for patients to comprehend. However, a VRS with few response alternatives may have a poor sensitivity and responsiveness to change. The use of a HRQoL instrument, preferably the EORTC QLQ-C30, is recommended when a broader assessment than pain is desired in palliative care research.

To allow solid conclusions from clinical trials, the study design needs to be appropriate and differences need to reach both statistical and clinical significance. Because statistically significant differences may be too small to be noticeable to the patient or too small to be worthwhile when risks, side effects and resources are also considered, the magnitude of change which is clinically significant needs to be determined. When the clinically significant change is determined it is also possible to report the proportion of patients experiencing clinically significant positive effects and the number needed to treat (NNT) can be calculated. For 11 point (0-10) NRS a reduction of 2 or of 30% has been demonstrated to be clinically significant (Farrar et al. 2001). For the EORTC QLQ-C30 HRQoL questionnaire a change of 10-20 in either direction is described by patients as a moderate change and is considered clinically significant (Osoba et al. 1998). Following these data, mean differences between groups in the same rage are also considered clinically significant, but more studies are needed to address this important topic.

In clinical research the wish for comprehensive assessment of all relevant domains needs to be balanced against the burden to the patients. A too heavy burden for the patients poses ethical dilemmas and may cause withdrawal from the study. These issues are also addressed in the IMMPACT recommendations (Turk et al. 2003).

Assessment in clinical routine

The keystone in the evaluation of pain patients is the medical history, clinical examination and supplementary investigations such as laboratory tests and diagnostic imaging. However, systematic assessment of symptoms, comorbidities and quality of life adds information which is useful in the clinical decision making. Chronic pain is as mentioned above associated with depression, reduced HRQoL, fatigue and reduced functioning as well as reduced neuropsychological performance.

No standard for symptom assessment in patients with CNMP admitted to pain clinics has been developed. Even though one MDPC have developed and validated an instrument which they recommend for routine clinical evaluation of symptoms and quality of life in CNMP patients (Rogers et al. 2000b) the applied instruments differ between clinics. Some pain clinics have developed “local” pain questionnaires, while others apply various types of questionnaires developed for research. Domains included are often pain and other symptoms, physical and role functioning, emotional distress/depression and cognitive functioning. Contrary to the situation in clinical research, information gathered for clinical use needs to be available to the clinician immediately after the questionnaire has been completed. This is an obstacle to the clinical application of HRQoL instruments like the SF-36 or EORTC QLQ-C30 containing multi-item scales. On the other hand instruments like the BPI, where scoring is not required, are suitable for clinical application.

Opioids in chronic non-malignant pain

Introduction

In this part of the introduction the use of opioids in the treatment of CNMP conditions will be discussed. Efficacy, guidelines, long term data, population data, concerns about opioid treatment, opioid switching, opioid pharmacogenetics, methadone as an analgesic and methadone pharmacology will be mentioned.

Epidemiology of opioids in chronic non-malignant pain

On average 5 and 23% of the European population reporting CNMP in an epidemiologic study received treatment with strong and weak opioids respectively (Breivik et al. 2006). A variation between countries from 0 to 13% in the use of strong opioids and from 5 to 50% for weak opioids was reported. The authors concluded that this large variation in opioid use indicates a need for better and more common guidelines. Other data on opioid consumption among patients with CNMP in the population are sparse. In a Danish study 9% and 3% of the population reporting pain in an epidemiologic survey used weak and strong opioids respectively (Eriksen et al. 2003) while the estimates for Denmark presented by Breivik et al were 8% and 11% respectively. According to Danish data 73% of patients admitted to a MDPC were receiving either weak or strong opioids at admittance (Becker et al. 1997).

Indications / guidelines

During the last years several guidelines for opioid treatment of CNMP have been published by experts, organizations and national regulatory bodies (Legemiddelverket 2002;Kalso et al. 2003;Nicholson 2003;The British Pain Society 2004). Even though clinical practice differs somewhat between countries and cultures, there is general agreement between the above mentioned guidelines that treatment should be based on the following principles:

- A thorough examination of the patient.
- All other therapeutic interventions have been tried or have been found contraindicated.
- Opioid therapy is initiated by a pain specialist after discussion with the patient's general practitioner.
- A clear agreement between doctor and patient about indications for termination of opioid treatment, possibly in the form of a signed treatment contract.
- The effect on pain and functioning needs to be evaluated at the end of a trial period and later at regular intervals.
- One doctor handles all opioid prescription to each patient.
- Use of fixed doses of long acting opioids or slow release formulations. Several opioids are available (table 2).
- No use of short acting opioids.
- A more careful approach is necessary in patients with known personal or family history of substance abuse or a poor psychosocial functioning.

Contrary to the situation in cancer pain (Hanks et al. 2001), the guidelines for opioid treatment of CNMP conditions do not allow short acting opioids for breakthrough pain. Rare exceptions are, however, made for patients who most of the time have mild

pain which does not require opioid treatment but on some rare occasions experience pain of excruciating intensity.

Table 2: Available opioids with long half time or slow release formulations.

Opioid	Formulation	Trade name in Norway
Morphine	Slow release p.o.	Dolcontin®
Oxycodone	Slow release p.o.	OxyContin®
Methadone	p.o.	Metadon®
Fentanyl	Transdermal	Durogesic®
Buprenorphine	Transdermal	Norspan®
Hydromorphone	Slow release p.o.	Palladon®
Ketobemidone	Slow release p.o.	Ketodur®
Tramadol	Slow release p.o.	Nobligan®
Dihydrocodeine	Slow release p.o.	*
Codeine	Slow release p.o.	*

* Not commercially available in Norway.

Efficacy

Recent reviews have summarized the available data from trials of opioids in CNMP conditions where other therapies fail to provide satisfactory pain relief (Ballantyne and Mao 2003;Kalso et al. 2004). Kalso et al identified and included four RCTs of intravenous opioid testing and eleven RCTs of oral opioids vs. placebo in their review (Kalso et al. 2004). Treatment periods in the latter group lasted from 4 days to 8 weeks. The included patients experienced a mean reduction in pain intensity of at least 30% while 80% experienced one or more side effects. There were large differences between studies in the reporting of outcomes other than pain. However, improved sleep was indicated while no clear trend towards improved functioning or quality of life or decreased depression was observed. In a recently published cross sectional epidemiologic study CNMP patients on long term opioid therapy reported 8 to 25 points poorer HRQoL scores in all SF-36 scales and a smaller proportion was employed (32% vs 55%) compared to CNMP patients not on opioid therapy (Eriksen et al. 2006). This finding could be a result of biases from the non-randomised study design but the authors speculate that opioid treatment may contribute to a worsening of the pain condition in the long run.

A recent review of opioids in chronic neuropathic pain identified six RCTs (Eisenberg et al. 2005). These studies reported improved pain control from opioids compared to placebo, with an average benefit of 14 millimetres on a 100 millimetres VAS. However, side effects were prevalent with number needed to harm (NNH) of 3.6 for nausea, 4.6 for constipation, 5.3 for drowsiness, 6.2 for vomiting and 6.7 for dizziness.

Studies comparing different long acting opioids or short acting versus long acting opioids for CNMP have recently been subject to a systematic review (Chou et al. 2003). The authors found evidence neither for one particular opioid being preferable nor for choosing long instead for short acting opioids. However, the review concluded that high quality trials are lacking and that the available data are inadequate for solid conclusions. In an open study published after this review a conversion from short acting or on demand opioids to a long acting opioid reduced the prevalence of breakthrough pain from 90 to 70% (Hojsted et al. 2006). This finding indicates that

stable use of long lasting opioids without on demand use of short acting opioids provides the most stable pain control. More importantly the data also showed that CNMP patients on opioid therapy must expect to experience periods of increased pain.

Data from long term follow up

Three studies in the previously mentioned review by Kalso et al also reported results from long term open label follow up lasting from seven to 24 months (Kalso et al. 2004). On average 44% of included patients were still on opioids at the end of follow up. Recently published follow up data on 160 patients (57% of patients still being alive) ten years after MDPC treatment in Denmark revealed that increase and decrease in opioid dose was equally common (Jensen et al. 2006). The patients decreasing their dose had a mean dose reduction of 70% while the patients increasing their dose had a mean increase of 64%. In three patients major dose escalation occurred with follow up doses about 1100 mg oral morphine /24h. While 89% of patients discharged on opioid therapy received a single long acting or slow release opioid at discharge, only 60% of patients receiving opioids at follow up used a single long acting or slow release opioid. The remaining patients used either a single short acting opioid (28%) or a combination of opioids (13%). 28% of patients discharged from MDCP without opioid therapy had initiated opioid therapy after discharge, and in 72% of these cases a short acting weak opioid was used. A German MDPC performed a follow up survey of CNMP patients having started opioid therapy three to nine years (average 66 months) earlier (Maier et al. 2005). It was possible to include 35% of the 345 approached patients. An opioid discontinuation rate of 15% was observed, with the majority of discontinuations occurring between a half and one year after start of opioid therapy. The reasons for discontinuation were poor efficacy in 14 of 18 patients, side effects in two patients and fear of addiction in two patients. At baseline 52% of patients received WHO step three opioids while this percentage had increased to 75% at follow up. 12% of patients received a short acting opioid in addition to long acting or slow release formulation at follow up. Of the patients taking the same opioid at follow up and baseline, a third used the same dose, 16% had decreased the dose and 27% had a slight increase in dose while 19% received what the authors described as high dose-treatment, which unfortunately was not clearly defined in the text.

Concerns

While it is documented that some CNMP patients respond well to opioids and continue treatment with quite stable doses for several years, there are still several areas of concern. These areas include the risk for development of addiction or aberrant drug behaviour, diversion of prescription opioids, dose escalation, development of abnormal pain sensitivity and influence on cognitive functioning and the immunological and endocrine systems (Savage 1999;Ballantyne and Mao 2003). It is also a concern that a majority of CNMP patients treated with opioids receive short acting opioids or a combination (Becker et al. 1997;Breivik et al. 2006). The evidence for long term beneficial effects on functioning and HRQoL is also yet to be established in high quality prospective trials with long follow-up periods, and the beneficial effect of opioids for CNMP has been questioned (Eriksen et al. 2006).

Opioid switching

Many CNMP patients do as previously mentioned, not experience an acceptable balance between pain control and side effects following start of opioid therapy. In these cases other therapeutic interventions need to be considered. However, because one of the indications for opioid treatment usually is that all other options have been exhausted, the available options are few. It has been indicated that successive trials of different opioids increase the responsiveness to opioid therapy in this patient population, and accordingly a switch of opioid might be an option when the first line opioid fails (Quang-Cantagrel et al. 2000). In the literature both "opioid rotation" and "opioid switching" describe this substitution of one opioid with another.

Even though an acceptable balance between pain control and side effects is achieved in the majority of cancer patients after adequate dose titration with a first line opioid (Ferreira KA et al. 2006), it has been reported that successive trials of different opioids increase the responsiveness to opioid therapy (de Stoutz et al. 1995;Riley et al. 2006). Recent review papers have concluded that the level of evidence for opioid switching for cancer pain is low, but that the large number of case series and open and/or retrospective studies indicate that opioid switching is effective in this population (Quigley 2004;Mercadante and Bruera 2006).

The mechanisms for the effect from opioid switching have not yet been established, but several different mechanisms can be hypothesized. These include differences between opioids in receptor binding profiles, effects on receptors other than the μ-opioid receptor, effects from active metabolites and differences in pain mechanisms between different pain conditions. In addition there is rapidly growing evidence for genetic influence on individual responses to the different opioids. Several genetic polymorphisms have been reported to influence the clinical efficacy of morphine (Klepstad et al. 2005). These are polymorphisms in genes coding for morphine metabolism (*UGT2B7*gene), the μ-opioid receptor (*OPRM* gene) and blood brain barrier transport of morphine (*MDR1* gene) as well as in non-opioid systems (*COMT* gene). Even though this genetic variability may cause clinically significant interindividual differences in the need for morphine, the polymorphism with the most important clinical impact on opioid treatment is the polymorphism which inhibits CYP2D6 formation of morphine in poor metabolisers of codeine (Chen et al. 1988;Yue et al. 1991;Lotsch et al. 2004). Preliminary models for how information about carrier status for several polymorphisms could be used to adapt morphine doses have been presented (Lotsch and Geisslinger 2006), but routine genotyping before start of morphine therapy is not yet an option. The perhaps most interesting pharmacogenetic study for opioid switching is the study by Ross et al which reported an association between polymorphisms in the *βarrestin2* gene (involved in μ-receptor signalling) and the need to switch from morphine to other opioids (Ross et al. 2005).

Methadone in pain treatment

History and areas of application

Methadone was developed in Germany in 1938 by the doctors Max Bochmuhl and Gustav Ehrhart in the Hoechst factory and the patent was filed in 1941 (Fishman et al. 2002). It is not known whether it was originally developed as an analgesic or

spasmolytic, but according to myth it was developed to relieve an anticipated shortage of morphine during World War II. When the Hoechst factory came under American control after the war, the formulation was published by the U.S. Department of Commerce. Methadone was first made commercially available by the company Eli-Lilly under the name Dolophine.

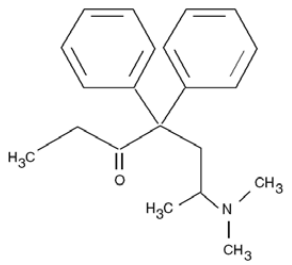
Methadone has had two major fields of application; in pain management and in opioid maintenance therapy for opioid addicts in order to prevent abstinence reactions and relapse to misuse. Methadone had an important role in the treatment of long lasting pain until the development of slow-release formulations of other opioids in the early 1980s. Until the slow release formulations were available, prescription of methadone was preferred due to its long half life; the only way of avoiding five to six daily opioid administrations. However, methadone was at that time primarily available as a mixture with an unpleasant taste, and methadone soon lost popularity after the slow release formulations of other opioids were introduced. Methadone was used for the treatment of opioid abstinence already in the 1950s. In the mid 1960s it was first used in opioid maintenance therapy in the treatment of heroine addiction (Dole and Nyswander 1965;Joseph et al. 2000). Methadone maintenance programs are more effective than programs without opioid substitution therapy in terms of decreased heroin use and retainment in rehabilitation therapy (Mattick et al. 2003). The most common alternative to methadone in opioid maintenance treatment is buprenorphine but there is no evidence supporting that buprenorphine is a better alternative than methadone in adequate doses (Mattick et al. 2004).

Methadone is cheaper than equianalgesic doses of slow release formulations of other opioids, and for some patients savings in the magnitude of 70% have been reported (Gardner-Nix 1996). However, because of variations between countries in the relative prices and interindividual differences in dose-ratios, the potential for cost reductions is variable.

Pharmacology

Methadone has the chemical structure of 6-dimethylamino-4,4-diphenyl-3-heptanone (figure 1), is lipophylic and is basic with an pKa of 9.2. The distribution volume of 3.6 L/kg is caused by an extensive tissue reservoir (Inturrisi et al. 1987). Also plasma protein binding is high, approximately 90% (Inturrisi et al. 1987), with binding to α_1-glycoprotein dominating (Eap et al. 1990). Commercially available formulations of methadone are racemic mixtures of R- and S-methadone (levomethadone and dextromethadone respectively). R-methadone is responsible for the μ-opioid receptor mediated analgesic effects of methadone (Kristensen et al. 1995). However, in vitro trials have indicated N-metyl-D-aspartate (NMDA) receptor antagonistic action from S-methadone due to non-competetive binding (Gorman et al. 1997).

Figure 1: Methadone structural formula



Methadone is metabolized primarily by the hepatic CYP 3A4 (Iribarne et al. 1996), but also by CYP 2B6 (Kharasch et al. 2004b). The metababolic activity of CYP 2D6 has been reported to play a significant role for response to methadone maintenance therapy (Eap et al. 2001), but its role in methadone metabolism has not been established. Several other CYPs have also been hypothesized to metabolise methadone (Garrido and Troconiz 1999). Even though hepatic methadone N-demetylation in vitro is not stereoselective (Foster et al. 1999), clinical studies have indicated that methadone metabolism and disposition is stereoselective (Foster et al. 2000;Foster et al. 2004). Neither the primary methadone metabolite 2-ethylidene-1,5-dimethyl-3,3-dipenylpyrrolidine (EDDP) nor the less important metabolites methadol and 2-ethyl-5-methyl-3,3-diphenylpyrolidine (EMDP) are known to be pharmacologically active. In addition to the hepatic metabolism of methadone, also intestinal first pass metabolism has been indicated (Oda and Kharasch 2001;Kharasch et al. 2004c).

P-glycoprotein also known as multi drug resistance protein 1 (MDR1) is located in several tissues including the capillary endothelium in the blood brain barrier and intestinal epithelium (Schinkel 1997). It acts as en efflux pump and at these locations it is believed to limit the concentration in the cerebrospinal fluid and oral bioavailability respectively. Experimental studies in mice have indicated methadone and several other opioids as substrates for P-glycoprotein (Thompson et al. 2000). Quinidine is known to be an inhibitor of P-glycoprotein. P-glycoprotein inhibition with quinidine increased the oral bioavailability of methadone, while it did not alter the pharmacodynamics following intravenous methadone administration in volunteers (Kharasch et al. 2004a). While polymorphisms in the gene coding for P-glycoprotein does not seem to be of clinical relevance for the pharmacokinetics of orally administered methadone (Lotsch et al. 2006) data from opioid substitution therapy indicate that genetic variability in the MDR1 gene may influence the required dose of methadone (Coller et al. 2006;Crettol et al. 2006).

Due to metabolism by CYP 3A4 and 2D6, methadone is subject to numerous possible interactions which may influence half time and serum concentration (Ferrari et al. 2004). For CYP 3A4 both induction and inhibition is possible, while CYP 2D6 can only be inhibited.

After oral administration of methadone bioavailabilities of 86% (range 75-97) is reported in healthy volunteers (Dale et al. 2002), 79% (range 60-92) for cancer patients (Gourlay et al. 1986) and 80% (range 41-99) in opiate addicts in detoxification (Meresaar et al. 1981). Time to maximum serum concentration (T_{max}) after oral intake was reported to be 2.1 hours (range 1.5 to 2.8) in one study of healthy volunteers (Dale et al. 2002) compared to 3 hours (range 1-5) in a study of opiate misusers in detoxification (Nilsson et al. 1982a). Methadone half-times between 7 and 65 hours have been reported (Gourlay et al. 1986). Urinary pH has significant influence on methadone elimination and half times (Nilsson et al. 1982b). Even though changes in urinary pH can explain changes in elimination half times in one individual, it explains only about ¼ of the interindividual variation (Rostami-Hodjegan et al. 1999).

It has been suggested that chronic methadone treatment leads to increased metabolism by autoinduction (Sawe 1986). Autoinduction has been hypothesized based on data

reporting decreasing serum concentrations during long-term methadone treatment with stable doses in opioid maintenance treatment (Verebely et al. 1975;Anggard et al. 1975;Holmstrand et al. 1978;Rostami-Hodjegan et al. 1999).

Data from patients in opioid maintenance therapy have showed low correlation between methadone dose and steady state serum concentration (de Vos et al. 1995), and that methadone dose can only explain about half the variability of methadone serum concentrations (Eap et al. 1998). Contrary to this, one study found a high correlation between daily oral methadone doses adjusted for body weight and plasma concentrations of methadone (Wolff et al. 1991). However, also the latter study reported patients with outlying serum concentrations.

Recently it has been reported that the 118A>G mutation in the *OPRM1* gene coding for the μ-opioid receptor is associated with decreased effects of levomethadone when assessed with pupillometry after a single oral dose in healthy volunteers (Lotsch et al. 2006). This study found no association between the effect of methadone and polymorphisms in the other included candidate genes which were genes coding for P-glycoproteine and CYP 3A, 2D6, 1A2, 2C8, 2C9, 2C19 and 2D6.

Interindividual differences in several of the mechanisms described above may contribute to the highly variable pharmacokinetics of methadone. The factors which may contribute to this variability are summarized in table 3.

Table 3: Factors which may contribute to interindividual variability in methadone pharmacokinetics.

Factors which may influence methadone pharmacokinetics
Tissue reservoir (body composition)
Levels of plasma proteins
Metabolic activity of involved CYPs
Urinary pH
Drug-drug interactions
First pass metabolism
P-glycoprotein activity

Equianalgesic dosing

While the traditional morphine:methadone dose ratios of 1:1 to 4:1 are still mentioned in the last editions of the major textbooks in palliative medicine and pain medicine, the readers are now warned that dose ratios in opioid switching might be higher (Hanks et al. 2004;Schug SA and Gandham N 2005). Several studies of opioid switching have reported dose ratios which are substantially higher and with large interindividual variations (Lawlor et al. 1998;Ripamonti et al. 1998a;Ripamonti et al. 1998b;Gagnon and Bruera 1999). There are strong indications that the differences in ratio may be explained by dose-dependency (Lawlor et al. 1998;Ripamonti et al. 1998b), but also interindividual differences in oral bioavailability and metabolism may influence dose ratios (Anderson et al. 2001). For very high pre switch morphine doses morphine to methadone ratios as high as 16:1 have been reported (Lawlor et al. 1998). Some studies of opioid switching have applied dose dependent dose ratios (Ripamonti et al. 1998b) while others have applied a fixed dose ratio of 5:1 (Mercadante et al. 1999).

Because studies on equianalgesic doses are performed in clinical settings, the term "equianalgesic" dosing is often inaccurate. The reason is that the indication for switching to methadone was unacceptable pain control and that methadone rapidly is titrated to the dose providing the best balance between side effects and pain control. With few exceptions the reported equianalgesic dose ratios are really ratios between an opioid dose which provided dose limiting side effects in the presence of uncontrolled pain and the methadone dose which provided adequate pain control with an acceptable level of side effects. For these reasons it has recently 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).

Methadone in cancer pain

While morphine for reasons of familiarity, availability and cost rather than proven superior efficacy remains the first choice opioid in cancer pain (Hanks et al. 2001), methadone is frequently used as an alternative opioid in opioid switching. Some RCTs have compared methadone to other opioids in the treatment of cancer pain. In a Cochrane review of these studies it was concluded that they had too short follow-up to determine if methadone could have long term benefits compared to other opioids, but that based on the available data methadone did not seem to be a better first line opioid (Nicholson 2004). However, in another Cochrane review it was concluded that methadone is the most frequently used second line opioid for cancer pain, and that opioid switching for some patients may be the only option for pain relief (Quigley 2004). Even though a large number of studies have reported the successful use of methadone in opioid switching, high quality RCTs are lacking. The switch to methadone needs to be compared to switching to other opioids and to other therapeutic interventions. Opioid switching to methadone is in spite of low level of evidence recommended in the European association for palliative care (EAPC) guidelines for "Morphine and alternative opioids in cancer pain" when other opioids fail (Hanks et al. 2001).

Methadone in chronic non-malignant pain

As in the treatment of cancer pain, methadone is primarily a second line opioid used in opioid switching in CNMP. In contrast to the situation in cancer pain, few studies have addressed opioid switching in CNMP. One case series, one case report and four studies have been published on opioid switching to methadone in CNMP patients (Gardner-Nix 1996;Thomsen et al. 1999;Hays and Woodroffe 1999;Quang-Cantagrel et al. 2000;Altier et al. 2001;Moulin et al. 2005). The first was a case series of five patients published in 1996 (Gardner-Nix 1996). Four of these patients experienced improved pain control, with NRS 2-4 on an 11 point scale several months after the switch to methadone. In a retrospective study, 17 patients were switched between methadone and other strong opioids, among them seven from morphine to methadone (Thomsen et al. 1999). Only cumulative data were reported, and the effect from switching from morphine to methadone cannot be properly judged. Another study reported improved pain control in patients switching from large doses of hydromorphone (10 patients) and morphine (2 patients) to oral methadone (Hays and Woodroffe 1999). Based on a chart review an increasing number of patients starting opioid therapy for chronic non-malignant pain, achieved more than 50% pain relief after sequential trials of different opioids including methadone (Quang-Cantagrel et al. 2000). One open prospective study included 50 patients with chronic neuropathic

pain which had not responded to an average of 2.8 previous opioids (Moulin et al. 2005). 26 of these 50 patients reported mild to complete relief of pain and 14 patients reported improved functioning at the end of follow up which was on average 14 months after the switch to methadone. Successful use of methadone in the treatment of neuropathic pain poorly responsive to morphine in one patient following a burn injury has also been reported (Altier et al. 2001). Neither RCTs nor systematic prospective studies with long time follow up have been conducted.

In addition to the studies of methadone in opioid switching, the use of methadone in the treatment of chronic neuropathic pain in the absence of malignant disease has been evaluated in one RCT and one retrospective study (Morley et al. 2003;Altier et al. 2005). 19 patients not currently on opioid therapy were included in the RCT and reported reduced VAS scores for both maximum (16 of 100 – p=0.013) and average (12 of 100 – p=0.020) pain intensity with methadone 10 mg x2 (Morley et al. 2003). In the retrospective study 13 patients taking methadone for chronic neuropathic pain were included (Altier et al. 2005). Four patients had stopped methadone due to side effects or no improvement in pain relief while the remaining nine patients were still taking methadone one year after its initiation. When patients reported their percentage of pain relief and improvements in quality of life and quality of sleep on 0 to 100% scales, mean improvements were 43% for pain intensity, 47% for quality of life and 30% for quality of sleep.

One centre in Sweden has recently published their experiences from using methadone in a program for chronic pain patients with iatrogenic opioid dependency (Rhodin et al. 2006). During eight years 60 patients had met the criteria for inclusion in the program; age above 20 years, severe CNMP, dependence on opioids for more than one year, insufficient pain relief and low quality of life. At follow up on average 34 months after start of methadone, 42 patients were still taking methadone while 18 had left the program; three due to no pain and no need for opioids, four due to intractable nausea, one due to cardiac arrhythmia, four were excluded due to addiction or diversion, one experienced no pain relief and five were dead. 36 of 42 patients reported good pain relief while the remaining patients reported moderate pain relief. Quality of life at follow up was substantially better than in patients admitted to multidisciplinary pain centres, but below norm data. Most patients experienced improved functioning.

Recently a qualitative study in 11 patients scheduled to start of methadone for CNMP evaluated patients' beliefs concerning start of methadone (Arnaert and Ciccotosto 2006). The study identified an initial acceptance phase followed by a phase focusing on to which extent patients should disclose the treatment to their friends and family. During the acceptance phase the initial belief about "methadone being for junkies" decreased as their knowledge of methadone as en analgesic as well as their trust in the doctor increased. Fear of social stigma influenced whether patients were open about their treatment to their surroundings. Important barriers to methadone treatment were thoughts like "others think I am an addict" and "methadone can harm me or my family".

Practical use

Methadone is commercially available as capsules and mixture for oral administration and in solution for parenteral administration. In experimental studies in healthy

volunteers methadone has been administered in a nasal spray device and in solution for rectal administration (Dale et al. 2002;Dale et al. 2004), but these formulations are not commercially available. Use of custom made suppositories have also been reported (Bruera et al. 1995). Methadone parenterally can cause local toxicity reactions if administered subcutaneously (Bruera et al. 1991). Thus the intravenous route is preferable for long lasting parenteral administration.

Due to its long terminal half life, methadone can be dosed less frequently than other opioids. In methadone maintenance therapy methadone is administered once daily. In contrast to this, methadone for pain is usually administered three times daily (Mercadante et al. 1999). For some patients dosing twice daily is sufficient while some patients require 6 hourly dosing to achieve stable pain control.

As methadone is rarely used as a first line opioid, therapy is usually started as part of an opioid switch. Several ways of switching to methadone have been presented. The two dominating switching strategies can be described as “stop and go” and “the 3 days method” (Mercadante and Bruera 2006). In “the 3 days method” the dose of the original opioid is decreased stepwise (a third each day) for tree days and substituted with the equianalgesic dose of methadone (Ripamonti et al. 1997;Lawlor et al. 1998). When switching according to the “stop and go” strategy, the initial opioid is abruptly terminated at the same time as an equianalgesic dose of methadone is initiated (Mercadante et al. 1999). Serum concentrations of methadone, morphine and morphine metabolites have been reported in ten patients switching from morphine to methadone in a “stop and go” manner (Mercadante et al. 2003). Minor dose adjustments were necessary and some variation in methadone serum concentrations were observed during the first three days, but improved pain control and methadone serum concentrations in what the authors considered to be therapeutic range were observed the day after the switch. Serum concentrations of morphine and morphine metabolites reached negligible levels by day tree day after the switch. The authors concluded that these data support that the “stop and go” strategy is pharmacologically sound. Other switching strategies include a gradual switch during two to four weeks (Hays and Woodroffe 1999) and a “methadone ad libitum” strategy (Tse et al. 2003). So far no studies have compared the different switching strategies, and almost all data are from studies in cancer patients.

Due to reported cases of late toxicity with sedation and respiratory depression (Ettinger et al. 1979;Hunt and Bruera 1995;Watanabe et al. 2002;Hernansanz et al. 2006) some authors have recommended that patients should be hospitalized (Ripamonti et al. 1997) and ideally with monitoring of vital signs during initiation of methadone therapy (Watanabe et al. 2002). However, others find that switching to methadone at home is safe when there is a close follow-up from the hospital and both the patients and their primary caregivers have been educated about the possible complications (Mercadante et al. 1999;Hernansanz et al. 2006). One study recommends a slow rotation during several weeks if opioid switching to methadone is performed in outpatients (Hagen and Wasylenko 1999).

Methadone and QT time prolongation

The QT time on the electro cardiogram (ECG) measures the time from the start of ventricular depolarisation to the end of ventricular repolarisation. Several drugs are known to increase the QT time trough delayed repolarisation. Such delay leads to

increased risk of arrhythmia, particularly the potentially lethal torsade de pointes arrhythmia (Viskin 1999). If QTc (QT time corrected for heart rate) exceeds 0.500 seconds there is a clinically significant risk of this arrhythmia.

In 2001 and 2002 the first cases of torsade de pointes during methadone treatment were published (Hays 2001;Krantz et al. 2002). These were followed by two more case series each including three patients with torsade de pointes during methadone treatment (Walker et al. 2003;Gil et al. 2003). The patients in both these latter studies had other known risk factors for torsade de pointes. In 2003 also a retrospective study reporting an increase in QTc of 0.042 seconds following start of methadone and a correlation between methadone dose and QTc as well as a small increase in QTc following start of morphine was published (Kornick et al. 2003). However, of 190 patients treated with methadone during the study period, ECGs before and after start of methadone were only available for 42 patients, and a selection bias is probable. In 2003 Krantz et al also published a study indicating a dose relationship between methadone dose and QTc in the 17 patients who were previously reported to have developed arrhythmia (Krantz et al. 2003). The first prospective cohort study including 193 methadone maintenance patients at baseline and 68% of these at follow up reported an increase in QTc of 0.011 seconds following start of methadone (Martell et al. 2003). Two cases of torsade de pointes during methadone therapy have also been reported in Norway (Ostvold and Topper 2005) Other cases have been reported in other national journals (Sanchez Hernandez et al. 2005). The evidence concerning the influence of methadone on QTc has been conflicting. In a retrospective study including 11% of the patients receiving methadone in a palliative care centre no indication of increased QTc was found (Reddy et al. 2004), while a cross sectional study of 83 patients being on opioid maintenance therapy with methadone for at least 6 months reported that 83% of the subjects had longer QTc than expected from reference data (Maremmani et al. 2005). Another cross sectional study including a mixed sample of 104 subjects from opioid maintenance therapy and palliative cancer care reported QTc prolongation in 32% of subjects (Cruciani et al. 2005).

Recently two prospective studies including 118 and 160 subjects in opioid maintenance therapy reported a modest increase in QTc, with mean values of 0.014 and 0.012 seconds respectively at six months follow up (Martell et al. 2005;Krantz et al. 2005). Martell et al had also included a twelve month evaluation, and reported that mean QTc had not changed significantly from six to twelve months. This study also included measurement of methadone serum concentrations in a subset of 44 patients at 12 months and found that QTc increases were significantly correlated to methadone serum concentration a year after start of methadone. Two patients reached QTc time above 500 milliseconds in this study.

None of the prospective studies have reported cases of torsade de pointes arrhythmia and the risk of developing arrhythmia is not yet established.

Methods

Patient cohorts

This thesis is based on studies performed in three patient cohorts:

1. In papers I and II patients admitted to the multidisciplinary pain centre at Trondheim University Hospital from September 1999 to January 2002 are included. During this period all patients were encouraged to complete the HRQoL instruments SF-36 and EORTC QLQ-C30 electronically using a touch screen immediately before their first consultation. Out of 602 patients admitted to the multidisciplinary pain centre for chronic non-malignant pain during the study period, complete HRQoL data were available for 286 patients (included in Paper I). EORTC QLQ-C30 was completed by two more patients, and accordingly 288 patients were included in paper II.
2. In paper II the HRQoL of CNMP patients admitted to the MDPC is compared to palliative cancer patients. From March 1995 until November 1997 patients were included in a trial of comprehensive palliative care (Jordhoy et al. 2000;Jordhoy et al. 2001). The inclusion criteria were histologically verified malignant disease, life expectancy between three and nine months, age above 18 years, completion of HRQoL data at baseline and living in one of the health care districts included in the study. The 395 included patients equal about half the number of patients dying from malignant disease in the included health care regions during the inclusion period (Jordhøy et al, Pall med 1999).
3. For inclusion in the methadone switch study (Papers III, IV and V) all patients who had started treatment with strong opioids at Trondheim multidisciplinary pain centre were evaluated. Patients were identified through the staff's knowledge of these patients. Out of 85 patients, seven were considered not suitable due to misuse of opioids and nine due to severe psychiatric comorbidity. Of the remaining 69 patients contact was established with 48. Six of these had stopped strong opioids, 20 experienced good pain control while eight did not want to participate. Two patients accepted to be included but had to withdraw prior to start of the study due to practical reasons. The remaining twelve were included in the study.

Study design

Papers I and II are cross sectional studies. HRQoL in CNMP patients was measured immediately before their first consultation at the MDPC at St. Olav University Hospital, Trondheim, Norway. HRQoL data for palliative cancer patients in Paper II were collected at trial entry (i.e. when patients were admitted to palliative care).

The methadone switch study presented in Papers III, IV and V was an open prospective pilot study without placebo treatment or randomization. Patients were followed for nine months with consultations at baseline, day one, two and three, after one, two and six weeks and at three and nine months.

EORTC QLQ-C30

The EORTC QLQ-C30 questionnaire was developed for use in cancer patients and has been validated in such patient populations (Aaronson et al. 1993). The questionnaire has been translated to Norwegian, and the Norwegian translation has proven valid and reliable in cancer patients (Kaasa et al. 1995). The instrument covers social, physical, emotional, role and cognitive functioning, global quality of life, financial difficulties and the symptoms pain, fatigue, dyspnoea, diarrhoea, constipation, difficulties of sleep, nausea/vomiting and loss of appetite. During the scoring procedure all scales are linearly transformed into scales with range zero to 100. In global quality of life and the five functioning scales a score of 100 corresponds to a high HRQoL or high functioning. For financial difficulties and the eight symptom scales a score of 100 implies maximum of the symptom in question. A change of 10 points on the 0 to 100 scales is perceived as a moderate change and considered clinically significant (Osoba et al. 1998). Following this observation a difference ≥10 between groups is also regarded as clinically significant. EORTC QLQ-C30 norm data have been published for the Norwegian general population (Hjermstad et al. 1998).

SF-36

The SF-36 questionnaire (Ware, Jr. and Sherbourne 1992) is a generic HRQoL instrument consisting of 36 questions. After the scoring procedure the results are presented in two symptom scales and six functioning scales; bodily pain, vitality, physical and social functioning, role physical and role emotional functioning, mental health and general health. All scales range from zero to 100 and a score of 100 corresponds to a high HRQoL. The questionnaire has been translated to Norwegian and the translation has been validated (Loge et al. 1998). Norm data for the Norwegian general population have been published (Loge and Kaasa 1998). In spite of its wide application in CNMP populations, particularly the responsiveness of the SF-36 in this patient population has been questioned (Rogers et al. 2000a).

Brief pain inventory

The Brief Pain Inventory (BPI) consists of numerical rating scales for pain intensity and impairment due to the pain condition (Cleeland and Ryan 1994). All scales range from zero to ten with zero being no pain/impairment and ten being the worst imaginable pain or impairment. The BPI is sensitive to changes in pain (Lydick et al. 1995) and has been validated in patients with chronic non-malignant pain (Keller et al. 2004). The Norwegian translation has shown satisfactory psychometric properties in patients with cancer pain (Klepstad et al. 2002).

Neuropsychological tests

In the methadone switch study three neuropsychological tests were used to assess the effects from the switch on cognitive functioning.

The Stroop Colour Naming Test (Spreen D and Strauss EA 1998) measures the relative speed of reading names of colours, naming colours and naming the colours of ink used to print incongruent colour names. The last task requires the ability to actively focus on the colour and override the over-learned tendency to read the word meaning. This is an adequate operationalization of selective attention, and the interference arising from such a conflict situation is called “the Stroop effect”.

The Paced Auditory Serial Addition Task (PASAT) consists of a series of digits (one through nine) which are tape recorded and presented with a certain inter stimulus interval (Spreen D and Strauss EA 1998). In the present Norwegian version of the task, two subtasks with 2.0 and 1.5 seconds inter stimulus interval, respectively, were administered (Landro et al. 2004). The subject is required to add each digit to the one immediately preceding it (the second to the first, the third to the second, and so on) and give the answer orally. The score is the percentage of correct responses. The PASAT was introduced to the subject by writing the numbers on a sheet of paper while explaining the addition rules. Then an unpaced practice session was run to familiarize the subject with the task. The actual testing was not started until the subject showed a clear understanding of the basic principle. The PASAT is a clear operationalization of the executive control aspect of working memory.

The Letter-Number Span task was selected as a measure of the capacity in working memory (Gold et al. 1997). The subjects are presented with a row of alternating letters and numbers and are asked to respond by first saying the numbers in order from 1-9, followed by saying the letters in alphabetic order. The test consists of 24 trials with increasing difficulty. The number of correctly recalled letter-number strings is recorded.

Serum concentration analyses

The effects from opioids are caused by binding to opioid receptors, primarily in the CNS. The pharmacological effects are related to the ligand concentration at the effect site. After oral administration opioids are absorbed from the gastrointestinal tract to the blood and the bioavailable fraction is further distributed to peripheral tissues including the sites of action. Due to interindividual differences in opioid pharmacokinetics and disposition, the serum concentration is a better indicator of opioid concentration at the effect site compared to opioid dose. Thus knowledge of the concentration-effect relationship may contribute to increased understanding of the dose-effect relationship for opioids. Moreover determination of serum concentrations of metabolites may contribute to increased understanding of the metabolism of the mother substance by calculating the metabolic ratio. In the case of active metabolites the determination of their serum concentrations is very important for the understanding of the dose-effect relationship.

Quantification of analytes (molecules) in serum was performed by liquid-chromatography tandem mass-spectrometry (LC-MS/MS) (Tyrefors et al. 1996;Dass C 2000). The method is based on separation of the analytes by reversed phase liquid chromatography and further identification by their difference in mass-to-charge ratio (m/e) of the ionized atoms or molecules and their fragments. Molecules have distinctive fragmentation patterns and thus the method provides high specificity.

Morphine, M3G, M6G, normorphine, methadone and EDDP were isolated from serum by solid phase extraction and separated on a Zorbax SB-18 column. The analytes were then quantitated by a validated LC-MS/MS method (Perkin Elmer 200 series HPLC system API 300 triple quadrupol mass spectrum) (Tyrefors et al. 1996). The limit of quantification was 1 ng/ml for all analytes. The standard curve range was 1-50 ng/ml for morphine and normorphine, 1-60 ng/ml for M6G and 1-500 ng/ml for M3G, methadone and EDDP. The correlation coefficients were all >0.99. Interday coefficients of variation varied from 0.1 to 7 % for the 25, 50 and 75% levels of the standardcurves.

Ethics

The use of the HRQoL data in paper I and II required no ethics committee approval. Data on the palliative cancer patients had been collected as part of a previous trial which had the necessary approval from the Regional Committee for Medical Research Ethics. The HRQoL and demographic data on CNMP patients had been collected for clinical purposes as part of clinical routine. The secretary of the Regional Committee for Medical Research Ethics, Health Region Central Norway approved the use of these data for research.

The methadone switch study (paper III, IV and V) was approved by the Regional Committee for Medical Research Ethics, Health Region Central Norway. The patients gave their informed consent to participation in the study. In the oral and written information to the patients the possible risk of sedation was emphasized and patients were instructed to contact a doctor if experiencing increasing drowsiness. During the opioid switch and the first month after the switch one of the investigators was available to the participating patients by phone around the clock. This measure was undertaken due to previous reports of severe side effects as well as the possibility that rare patients might experience severe increases in pain intensity when morphine was substituted with methadone.

The studies included in this thesis have been conducted in accordance with the Helsinki Declaration (World medical association 2000).

Summary of papers

Paper I

Validation and comparison of the Health Related Quality of Life instruments SF-36 and EORTC QLQ-C30 in assessment of patients with chronic non-malignant pain.

The aim of this study was to validate the EORTC QLQ-C30 HRQoL questionnaire in the CNMP population and to compare advantages and disadvantages between this instrument and the more widely used SF-36 HRQoL questionnaire.

The validation of the EORTC QLQ-C30 evaluated external convergent validity (how EORTC QLQ-C30 and SF-36 measures of the same concept correlated), internal consistency (reliability) in multi item scales, discrimination, sensitivity and construct validity.

Correlations between EORTC QLQ-C30 and SF-36 measures of the same concept were between 0.70 and 0.81 for all five domains covered by both instruments. Internal consistency was below 0.70 for the EORTC QLQ-C30 scales physical functioning (0.57), pain (0.68), role functioning (0.43), cognitive functioning (0.66) and nausea/vomiting (0.53) as well as the SF-36 scale role emotional functioning (0.66) while the remaining multi item scales exceeded the 0.70 limit. Large floor effects were seen for several EORTC QLQ-C30 scales, with values of 38-61% for nausea/vomiting, dyspnoea, appetite loss, constipation, diarrhoea and financial difficulties. Large floor effects were also seen for the SF-36 scales role physical functioning and role emotional functioning with values of 69 and 33 respectively. Construct validation indicated that the contents of the physical functioning scale differ between EORTC QLQ-C30 and SF-36.

Even though some EORTC QLQ-C30 scales have unsatisfactory internal consistency and some of the symptoms are of little relevancy for a majority of chronic pain patients, the EORTC QLC-30 like the SF-36 shows acceptable psychometric properties.

Paper II

Chronic non-malignant pain patients report as poor health related quality of life as palliative cancer patients.

The HRQoL of 288 CNMP patients admitted to a MDPC were compared to 434 palliative cancer patients and national norms. As HRQoL data are influenced by age and gender and these variables were unevenly distributed between the groups, age and gender adjustment was required. To adjust for age and gender differences between the two patient groups each patient's deviation from the scores of the appropriate group in the general population was computed before mean deviations from norm data were estimated and compared.

The 288 patients who completed the EORTC QLQ-C30 and met the inclusion criteria represented 48% of the 602 CNMP patients admitted to the MDPC during the study period. The included patients were on average five years younger than patients who

due to missing HRQoL data were ineligible (p <0.001, 95% CI 7.0–2.2). The percentage of females was similar, 61% and 64% respectively (chi-square test: p=0.47), as was also the distribution of pain diagnoses.

Both patient groups reported worse scores in all scales compared to the age and gender adjusted general population. When comparing the deviations from norms between the CNMP and the palliative cancer patients, the CNMP patients were found to report larger deviations (worse scores) for five scales; cognitive function (23 vs 10), global health (38 vs 31), pain (61 vs 22), sleep disturbances (36 vs 15) and financial impact (31 vs 7) as compared to the palliative cancer patients patients. The palliative cancer patients reported larger deviations (worse scores) for four scales; role functioning (53 vs 42), nausea/vomiting (20 vs 8), loss of appetite (41 vs 17) and constipation (27 vs 11) as compared to the CNMP patients. All differences were statistically significant, and except for global health, they were also clinically significant. For the remaining six functioning and symptom scales, no significant differences were found between groups.

Paper III

Opioid switching from oral slow release morphine to oral methadone may improve pain control in chronic non-malignant pain: a nine months follow-up study.

Twelve patients with poor pain control or unacceptable side effects during treatment with morphine were switched to methadone and followed for nine months in this open prospective study. Primary outcomes were patient preference of opioid and pain control while physical, cognitive and role functioning were secondary outcomes. Effects on other HRQoL domains as well as cognitive functioning were explored. BPI was used for assessment of pain, EORTC QLQ-C30 for HRQoL, Stroop, PASAT and Number Letter Span for cognitive functioning.

The morphine dose was decreased with 1/3 daily and was replaced with an equianalgesic dose of methadone over a three days period. For doses <200 mg morphine po/24h a morphine:methadone dose ratio of 4:1 was applied while a ratio of 6:1 was applied for higher doses. During switching and a one week dose titration period, patients were given additional methadone if required.

During dose titration one patient experienced sedation requiring naloxone. Four patients were switched back to morphine due to poor pain control, drowsiness or sweating. Seven patients preferred long-term (> nine months) treatment with methadone and reported reduced pain and improved functioning while cognitive functioning was not improved. EORTC QLQ-C30 symptom scales indicated a temporary increase in the nausea and vomiting scale immediately after the switch. This study brings novel information on the long term consequences for pain control, HRQoL and cognitive functioning from a switch from morphine to methadone in the treatment of chronic non-malignant pain.

Paper IV

Long term methadone for chronic pain: a pilot study of pharmacokinetic aspects.

Twelve patients treated with morphine for chronic non-malignant pain were switched to methadone. Seven of these patients continued with methadone throughout the nine

months study period and only minor dose adjustments were performed. Serum concentrations of morphine, methadone and their metabolites were measured at baseline, day one and two, after dose titration and one week, five weeks, three months and nine months after the end of dose titration.

Serum concentrations of methadone and its metabolite EDDP did not change significantly from the end of dose titration and during the nine months of follow up (repeated measures ANOVA: p=0.88 and p=0.06). Very low correlation between dose ratios and serum concentration ratios between morphine and methadone was observed. Total daily oral methadone dose at three months could not explain serum concentrations of methadone (R^2=0.06 – p=0.61). Serum-concentration of EDDP one week after the end of dose titration varied six-fold (range: 12 to 69 ng/ml), and was explained by serum concentration of methadone (R^2=0.77 – p=0.004).

At baseline traces of methadone were detected in three patients and in one of them also traces of EDDP. In one patient not reporting use of morphine or codeine after the switch, morphine-glucuronides in serum were observed at three months. In another patient M3G/morphine and M6G/morphine ratios of 215 and 36 were observed compared to average ratios of 104 and 19 in the rest of the patients. However, a rapid decline in serum concentrations of M3G and M6G was observed when morphine was substituted with methadone. In one patient the level of normorphine exceeded twice the levels in other patients while his serum-concentration of morphine was one of the lowest.

Our findings contradict that autoinduction of methadone metabolism takes place during long term treatment and supports that a 3-day opioid switch from morphine to methadone followed by a one week titration seems pharmacologically sound. Large interindividual differences in opioid metabolism were observed and the findings indicated that some CNMP patients consume other opioids in addition to the prescribed dose.

Paper V

Opioid switching from morphine to methadone causes a minor but not clinically significant increase in QTc time: a prospective 9 months follow-up study.

Twelve CNMP patients switching from morphine to methadone due to unsatisfactory pain control or intolerable side effects were followed with ECGs at baseline, two weeks after the switch and three and nine months after the switch. From the ECGs the QTc time (QT time corrected for heart rate, QTc=QT/√RR) was calculated. An experienced cardiologist measured QT time and RR intervals and screened the ECGs for factors affecting the QT time.

The mean QTc time increased from 0.416 before start of methadone to 0.436 two weeks after start of methadone (mean change =0.020, 95% CI 0.007-0.032, p=0.01). The changes in the follow-up observations of QTc time were not statistically significant (repeated measures ANOVA, p = 0.90), indicating that duration of QTc time was not associated with time from the switch to methadone. At the nine months follow-up the ECG from one patient showed a supraventricular tachycardia and could not be used for comparison of QTc time. An additional ECG obtained two months later (sinus rhythm) showed a minor increase in QTc compared to the three months

follow-up. At the 9 months follow-up ECG recordings only precordial leads were of satisfactory quality for assessment of QTc time in one patient while one patient presented a right bundle branch block. No QTc times above 0.50 seconds or episodes of arrhythmia were observed.

Discussion

Research question 1

Health related quality of life assessment methodology in chronic non-malignant pain patients:
Is the EORTC QLQ-C30 a valid alternative to the SF-36 for assessment of HRQoL in CNMP patients?

In spite of unsatisfactory internal consistency in three scales the EORTC QLQ-C30, like the SF-36, demonstrated overall satisfactory psychometric properties. In the methadone switch study the EORTC QLQ-C30 also demonstrated to be responsive to change over time in CNMP patients, as improvements in several scales were detected in the patients choosing to continue long lasting methadone therapy. The overall acceptable psychometric properties are in accordance with previous studies in cancer patients where both instruments have performed well (Apolone et al. 1998;Kuenstner et al. 2002). An advantage of the EORTC QLQ-C30 compared to the SF-36 is that EORTC QLQ-C30 also addresses cognitive functioning and a broader spectrum of symptoms. Difficulties of sleep and financial problems have a high prevalence in this patient population which may warrant evaluation in clinical routine. Nausea/vomiting and constipation are frequent side effects of opioid therapy (Kalso et al. 2004) and thus should be relevant in clinical trials as well as clinical evaluation of patients on opioid therapy, although being of minor relevance for the majority of CNMP patients.

For the symptoms nausea/vomiting, dyspnoea, appetite loss, diarrhoea and constipation floor effects of 43 to 61% were seen together with ceiling effects of 0.3 to 6.6%. This could indicate poor ability to differentiate between no symptoms and mild symptoms, but based on clinical experience it is probably at least partly a consequence of low prevalence of these symptoms in this patient population. In the EORTC QLQ-C30 scales role functioning, insomnia and financial difficulties floor effects of 13 to 38% were seen together with ceiling effects of 21 to 26%. For insomnia and financial difficulties this is probably a consequence of the narrow response range with only 4 response alternatives. For role functioning this distribution indicates that contrary to the other functioning scales, a large part of patients with chronic non-malignant pain experience either very poor or excellent role functioning.

The poorer Chronbach's alpha values observed in our study compared to validation studies in cancer patients indicate that EORTC QLQ-C30 internal consistency is higher in cancer patients than in patients with CNMP for physical functioning, role functioning and nausea/vomiting. There is no obvious explanation for these differences in internal consistency between the two patient populations but it is possible to speculate on possible explanations. A possible explanation is that chronic pain affects more specific functional areas compared to advanced cancer disease. For instance would localised pain conditions be expected to have a strong influence on some functions but less on other. Such specific impact on functioning would reduce the internal consistency.

The data indicated differences in content in the physical functioning scales between SF-36 and EORTC QLQ-C30. There are several possible explanations for this finding. While the SF-36 physical functioning scale consists of ten items, the QLQ-

C30 only contains five physical functioning items. Most of the SF-36 questions are very specific compared to the wider and vaguer questions in the EORTC QLQ-C30. While SF-36 addresses problems with walking more than one mile EORTC QLQ-C30 asks about a long walk. Another possibly important difference is that the EORTC QLQ-C30 uses carrying a suitcase as an example of strenuous activity, while the SF-36 has running and participation in sport activities as examples of strenuous activity.

A possible limitation to the validation study is that HRQoL data were only available for 48% of patients admitted to the MDPC during the study period. It is possible that patients with a very poor HRQoL are overrepresented in the group with lacking data. In this situation particularly the floor- and ceiling effects would be affected. Data for the study were collected electronically on a computer with a touch screen as part of the clinical routine. It can be hypothesized that electronic data collection could cause a selection bias because older patients who are not accustomed to computers would avoid the data collection. However, in a study comparing the paper version and a computerised version of the SF-36 two thirds of patients preferred the electronic version, the electronically collected dataset had less missing data and scores were equal (Ryan et al. 2002). When HRQoL data were collected for clinical use as part of the initial evaluation it is possible that the patients' responses could be consciously or unconsciously influenced. Reasons for this could either be a desire to justify the need for extensive treatment or a desire to be brave or tough.

Research question 2

Comparison of health related quality of life scores between patient groups:
How is the HRQoL of CNMP patients admitted to MDPC treatment compared to the HRQoL of palliative cancer patients?

The patients admitted to the MDPC reported equally poor or poorer HRQoL compared to palliative cancer patients in 11 of 15 EORTC QLQ-C30 scales. The CNMP patients' HRQoL scores in this study are in the same range as previously reported from CNMP patients admitted to other MDPCs. An earlier study using the EORTC QLQ-C30 found a mean global health status score of 33 (Wincent et al. 2003), compared to 36 for our patients. Other EORTC QLQ-C30 scores were not presented. Two previous studies using the SF-36 for HRQoL assessment found scores comparable to ours for all scales (Becker et al. 1997;Wittink et al. 2004). Although patient populations may differ between MDPC's, there is no reason to believe that the patients in the present study are worse affected than patients admitted to other MDPCs.

When interpreting the results from our and other studies it is important to recognize that patients admitted to multidisciplinary pain clinics at university hospitals are a highly selected group. Even though the patient population in our study report similar HRQoL scores as the populations admitted to similar clinics (Becker et al. 1997;Wincent et al. 2003;Wittink et al. 2004) the scores of these patients are representative neither for the large part of the population reporting chronic pain nor for patients admitted to less comprehensive pain clinics.

The equally poor or poorer HRQoL of CNMP patients compared to palliative cancer patients may partly be explained by the "Calman gap" which explains reductions in HRQoL as the difference between what is experienced and what is expected (Calman 1984;Carr et al. 2001). As CNMP patients do not have a life-threatening disease, they

may have higher expectations both to life in general and to the level of functioning than palliative cancer patients. An exception from this is the symptom pain where the large difference between the groups probably is a consequence of pain being the primary symptom in the CNMP group while not an inclusion criteria in the palliative cancer group.

A limitation for the study representativity is that HRQoL data for CNMP patients were available for only 48% of the eligible population during the study period. There may be several reasons why patients did not complete the questionnaire: some days the computer was not available or there were technical difficulties, some patients did not have time to complete the questionnaire, some were unable due to poor health and some refused. The three first reasons would probably generate random failures, and thus not affect the study validity. Data missing for the last two reasons might, however, introduce bias. As indicated by the higher age of the non-responders it is reasonable to assume that non-responders had a poorer HRQoL than those who responded.

Other factors may also have affected the comparison of HRQoL scores. The possibly most important confounder is differences in socio-demographic variables. While appropriate adjustments have been made for the differences in age and gender, direct adjustment for differences in employment status was not possible and data on other socio-demographic variables were not available. Furthermore the palliative cancer group consists of patients included in a palliative care trial from 1995 to 1997 while data for the CNMP patients were collected for clinical use from 1999 to 2001. It is doubtful that the average HRQoL in any of the groups has changed significantly in four years, but the differing purposes of the data collection may have caused a selection bias.

Research question 3

Opioid switching from morphine to methadone in chronic non-malignant pain patients with an unacceptable balance between pain control and side effects during morphine therapy:
What are the effects on pain control, HRQoL, cognitive functioning and patient preference?

This prospective open pilot study evaluated the consequences of opioid switching from morphine to methadone in cases of unsatisfactory balance between pain control and side effects during morphine therapy for CNMP. An open pilot study can not determine efficacy or NNT but can indicate whether this treatment is successful in some patients. The experience gained from pilot studies will be helpful for future RCTs. The switch was effective in about half the patients and caused improved HRQoL scores and reduced pain. However, the other half of the patients experienced increased pain or intolerable side effects after the switch. As increased levels of pain in the latter group were poorly responsive to additional doses of methadone, some patients seem to be very poor responders to the analgesic effect methadone. On the other hand the case of sedation indicates that rare patients may experience serious side effects. In open studies the placebo effect may contribute to the outcomes. However, the stable pain and HRQoL scores during the nine months of follow up with stable methadone doses indicate that the effects are long lasting and probably not a mere placebo effect. The present study confirms the previously reported positive effects from opioid switching to methadone in this patient population, but is the first study

including follow-up beyond a few weeks (Thomsen et al. 1999;Hays and Woodroffe 1999;Quang-Cantagrel et al. 2000). If the effect had not lasted beyond a few weeks after the switch it could have been questioned whether opioid switching to methadone is worthwhile as it poses a risk of increased pain as well as potentially serious adverse events.

Different ways of performing the switch from oral morphine to oral methadone have been reported in the treatment of cancer pain (Mercadante 1999;Bruera and Neumann 1999;Hagen and Wasylenko 1999). In chronic non-cancer pain a gradual switch during two to four weeks has been applied (Hays and Woodroffe 1999). The stepwise switch applied in the current study has previously only been reported in cancer patients. In the present study one patient experienced drowsiness during dose titration, nine of twelve patients needed additional methadone to achieve acceptable pain control during switching and titration and two patients withdrew due to poor pain control during the switch. The different switching strategies have not been compared, but it can not be disregarded that the switching strategy chosen in this study might have affected the frequency of side effects as well as the overall success rate.

The results are based on patient reporting. Patients have reported their opioid intake and they have completed self report instruments for the assessment of HRQoL and pain. For the first weeks of the methadone switch study the patients received from the investigator the number of methadone capsules needed until the next follow up consultation. Later methadone was prescribed to the patients. At each consultation the dosage until next consultation was decided. After the initial week of dose titration patients were not allowed to use methadone or other opioids in addition to scheduled doses. Of course there is a possibility that patients have been taking less methadone than agreed or that they on average have used the agreed dose, but with day to day variations. It is also possible that they in addition to methadone have used other opioids either from the illegal market or remnants from previous opioid treatment. Such behaviours would affect serum concentrations, self reported pain intensity and HRQoL, performance in neuropsychological tests and possibly QTc times. Data from the pharmacological part of the study give indications that some patients have at some occasions used other opioids without reporting the intake to the investigators. In a 9 months trial in outpatients who are encouraged to live normally and with opioid administration three or four times a day it is practically impossible to have absolute control over the participants' opioid intake. In theory patients in clinical trials of opioids could be followed in the same way as patients receiving methadone in opioid maintenance therapy; with frequent urine drug screenings and surveillance of opioid intake. Such rigorous follow up would require enormous resources but would more importantly put a substantial and unethical burden and stigma on the participating patients.

Self reported HRQoL and pain data could possibly be influenced by the conscious or unconscious intent of the study participants. This could be a consequence of an "eager to please" attitude. It can be speculated that such an effect is greater when the patients know that the investigator will look at the questionnaires during the consultation, as was the case in this study.

Research question 4

Opioid switching from morphine to methadone in chronic non-malignant pain patients with an unacceptable balance between pain control and side effects during morphine therapy:
What is the effect on QTc time?
The data on QTc time following the switch from morphine to methadone indicate that this switch causes a small and lasting increase in QTc time. This finding is in accordance with several previous reports from other patient populations (Martell et al. 2003;Maremmani et al. 2005;Martell et al. 2005;Cruciani et al. 2005;Krantz et al. 2005), even though the literature is not unanimous (Reddy et al. 2004). Results from the small patient cohorts studied until now are not able to evaluate the risk of Torsade de Pointes arrhythmia, but the observed increase in QTc supports that start of methadone may cause a slightly increased risk of arrhythmia.

Even though the QT time was assessed by an experienced cardiologist, manual measurements can never be exact. However, interobserver and intraobserver variability for manual assessment of QT time is reported to be low with mean variability of 12 (SD 1) and 6 (SD 6) milliseconds respectively (Tran HT et al. 1998). In cross sectional studies estimating the prevalence of QTc prolongation the prevalence will due to QT dispersion vary depending on which lead is used for assessment (Sadanaga et al. 2006). In the present prospective study the same lead was used for QT assessment at each occasion, but it can be questioned whether on each ECG the longest QT time should have been identified and used in the analyses. Diurnal variations in QTc may also affect the results (Harris and Steare 2006), while it is not established whether the time from methadone administration to the ECG is obtained affects the results. Because all ECGs were obtained at the same time of the day, these factors are not believed to affect the results significantly. On the other hand this study may have underestimated the true effect from methadone on QT times. Kornick et al. have reported an increase in QT times following start of treatment with intravenous morphine to cancer patients (Kornick et al. 2003). All patients in our study were treated with oral morphine before the start of methadone and hence may have a morphine induced increase of the QT times at baseline. Consequently, the true effect from methadone on QT time if given to opioid naïve patients may be larger than the effect demonstrated in this study.

Research question 5

Opioid switching from morphine to methadone in chronic non-malignant pain patients with an unacceptable balance between pain control and side effects during morphine therapy:
Are methadone serum concentrations stable during long term treatment and are there interindividual differences in opioid metabolism?
The results from the pharmacokinetic part of the methadone switch study indicate that serum concentrations of methadone and the primary metabolite EDDP are stable during long term treatment with stable doses of methadone. This finding oppose the hypothesized autoinduction of methadone metabolism during long term therapy (Sawe 1986). The results also demonstrate large interindividual differences in morphine and methadone metabolism. Surprisingly the results also indicated that several patients seem to have taken opioids in addition to prescribed doses before as well as after trial entry. This may affect the validity of results in all parts of the study,

but equally importantly indicates that the clinician can not trust patients to be taking only the prescribed opioid doses.

In contrast to morphine, serum concentration of methadone was not explained by dose of oral methadone in this study. This may be a type 2 error due to small sample size, but is probably a consequence of the large interindividual variability of methadone bioavailability and half times. This is supported by data from opioid maintenance therapy which have reported low correlation between methadone dose and steady state serum concentration (de Vos et al. 1995), and that methadone dose can only explain about half the variability of methadone serum concentration (Eap et al. 1998). On the other hand one study on opioid maintenance therapy found a high correlation between daily oral methadone doses adjusted for body weight and plasma concentrations of methadone, but also this study observed some outliers with unexpected serum concentrations (Wolff et al. 1991).

Serum concentrations of all xenobiotics including opioids are dependent on the time from administration/exposure to the sample is obtained. Variations are of course largest after a single dose, but serum concentrations are variable also in steady state. This variability is described by the peak/trough serum concentration ratio; the ratio between the highest and lowest serum concentration between two doses. The time from dose administration to peak serum concentration is dependent on the speed of uptake and distribution while trough values by definition are expected immediately before administration of the next dose. Serum concentrations in the methadone switch study were assessed at a standardized time of the day; between 1445 and 1530. This time of day was chosen because it corresponds with trough values when a drug is administered tree times a day (08-16-23). When some patients required methadone to be administered four times a day in order to achieve stable pain control, serum concentrations can not be considered as trough samples. Because all patients requiring four daily administrations had increased to four administrations within two weeks from the switch, the long term data form these patients are also standardized relative to drug intake in spite of being neither peak nor trough values. Accordingly the conclusion that methadone serum concentrations were stable, is valid. However, when serum concentrations are related to medicament dose the lack of standardisation could affect the validity of the results in the patients taking methadone four times daily. For patients in methadone maintenance therapy with once daily dosing the peak/trough ratio is approximately two (Hanna et al. 2005) while the ratio is expected to be considerably lower when methadone is administered three or four times a day. To avoid problems with non-standardised data for estimation of the correlation between total daily dose and serum concentration in the patients receiving methadone four times daily, they postponed their second dose two hours at the day of the three months evaluation. Accordingly the serum concentrations in all patients are trough values seven hours after administration when the relationship between total daily dose and serum concentrations was assessed. However, all results based on total methadone serum concentration need to be interpreted cautiously as levomethadone (the R-enantiomer) is responsible for the μ-opioid receptor mediated analgesic effects of methadone (Kristensen et al. 1995).

Serum concentrations may also have been influenced by metabolic interaction with other drugs. Two patients in our study were concomitantly treated with venlafaxine which is known to be an inhibitor of CYP3A4 and two patients were treated with

amitriptyline which may possibly influence methadone serum concentrations (Ferrari et al. 2004). Conclusions regarding the consequences of these possible interactions cannot be drawn due the limited number of patients.

The LC-MS/MS method is sensitive and specific and was validated according to appropriate/standard protocols. There is no reason to believe that difficulties with the assay in any way have influenced the results. When unexpected/outlying observations were made, the back-up samples were analysed. In none of these cases differences between the primary and secondary analyses were observed.

Conclusions

Based on the papers included in this thesis the following answers to the research questions can be given:

HRQoL assessment methodology in CNMP patients:

I. *Is the EORTC QLQ-C30 a valid alternative to the SF-36 for assessment of HRQoL in CNMP patients?*
   - The EORTC QLQ-C30 shows overall acceptable psychometric properties in CNMP patients.
   - EORTC QLQ-C30 is a valid alternative when a more comprehensive assessment of symptoms is desired.

Comparsion of HRQoL scores between patient groups:

II. *How is the HRQoL of CNMP patients admitted to MDPC treatment compared to the HRQoL of palliative cancer patients?*
   - CNMP patients report substantially poorer HRQoL than the general population.
   - CNMP patients report equally poor or poorer HRQoL in 11 of 15 EORTC QLQ-C30 scales compared to palliative cancer patients.

Opioid switching from morphine to methadone in CNMP patients with an unacceptable balance between pain control and side effects during morphine therapy:

III. *What are the effects on pain control, HRQoL, cognitive functioning and patient preference?*
   - It seems to improve pain control and functioning in some of the patients.
   - The patients preferring methadone for long term treatment reported improved pain control, role functioning and physical functioning while no improvement in cognitive functioning was observed.
   - All patients meeting the inclusion criteria in the trial in this thesis do not benefit from a switch to methadone and the switch poses a risk of serious adverse events like sedation.

IV. *What is the effect on QTc time?*
   - The switch is associated with a small, lasting and stable increase in QTc time in this patient population.

V. *Are methadone serum concentrations stable during long term treatment and are there interindividual differences in opioid metabolism?*
   - Serum concentrations of methadone and the primary metabolite EDDP are stable during long term methadone treatment with minor dose adjustments.
   - Large interindividual differences were observed for serum concentrations and ratios between daily total methadone dose and serum concentration.

Issues for further research

Standardisation of symptom assessment

Guidelines like the IMMPACT recommendations are one important step towards standardisation of symptom assessment. However, in spite of validity and acceptable psychometric properties today's instruments are not ideal. When comprehensive assessment is desired the burden on the patients is considerable because numerous instruments and tests are required. The consequence is that fragile patients are not included, drop out or contribute with incomplete data. One possible strategy for future assessment tools is computer based intelligent systems which are able to provide a valid and accurate description of the patient's situation from a minimum of questions. For reasons of familiarity the same instruments should be applied in research and clinical routine. Such instruments should allow assessment of specific symptoms and HRQoL as well as screening for psychiatric comorbidity.

Pain, opioids and cognitive functioning

Impaired cognitive functioning has previously been reported for CNMP patients and CNMP patients on opioids. There have been indications that increased pain intensity through an arousal effects improves some aspects of cognitive functioning, but this does not disrupt the overall picture of impaired performance in neuropsychological tests. In the methadone switch study presented in this thesis the included patients performed worse in tests of selective attention and working memory than the general population. The improved pain control was not accompanied by improved performance in the neuropsychological tests. This indicates that there is no simple association between pain intensity and cognitive functioning. Whether start of opioids affects cognitive functioning in CNMP patients in either direction needs to be addressed in prospective comparative studies.

Choice of opioid, opioid switching and pharmacogenetics

There is no solid evidence for the superiority of one opioid compared to other common first line opioids in terms of efficacy, side effects and need to switch to another opioid. Neither is there any documentation for which opioid to choose when the first line opioid fails. RCTs addressing these questions are needed both in cancer and CNMP patient populations. Most studies on opioid switching have evaluated a switch to methadone, but no trials have compared the efficacy and side effect profile of methadone to other opioids in this setting. It has recently been presented evidence for a genetic predisposition for individual responses to the different opioids. Genetic factors seem to influence both the dose required to obtain pain relief and whether acceptable pain control is achieved at all. Trials of opioid switching should include pharmacogenetics in order to identify genetic factors of clinical importance for opioid treatment. The ultimate goal might be that routine genetic testing can help the clinician decide which opioid to choose and indicate the appropriate dose.

Several cases of serious adverse events including sedation during and after a switch to methadone have been reported. The ideal switching strategy should ensure a rapid

improvement in pain control with few side effects and minimal risk of serious adverse events like sedation. Studies of serum concentrations give support to some of the presented strategies, but it is not yet established which strategy provides the most rapid improvement in pain control together with the least risk of serous adverse events. RCTs are required to compare the common switching strategies stop and go versus the three day switch. It is possible that different strategies should be applied in hospitalized patients who can be monitored closely compared to patients switching to methadone at home.

Which chronic non-malignant pain patients benefit from multidisciplinary pain clinic treatment

This thesis has demonstrated that the HRQoL of CNMP patients admitted to MDPC treatment is extremely poor. Previously it has been reported that 33 and 40% percent of the population experiencing long lasting pain are not satisfied with the investigations performed of the received treatment respectively (Eriksen et al. 2003). This might be a consequence of limited availability of MDPC treatment, when only patients with extremely poor HRQoL are admitted. Clearly everybody with long lasting pain can not be evaluated at a MDPC, but research is needed in order to determine how large proportion of CNMP patients does benefit from CNMP treatment in terms of increased functioning and quality of life. Such studies should also aim at evaluating cost-effectiveness.

Errata

1. Paper III: Two patients have not been accounted for in the flow-sheet on the second page. These two patients accepted to be included into the study, but one patient was hospitalised before start of the study and one patient could not participate due to practical reasons.

References

Aaronson, N. K., S. Ahmedzai, B. Bergman, M. Bullinger, A. Cull, N. J. Duez, A. Filiberti, H. Flechtner, S. B. Fleishman, J. C. de Haes, and . 1993, The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J. Natl. Cancer Inst. 85: 365-376.

Altier, N., D. Dion, A. Boulanger, and M. Choiniere. 2001, Successful use of methadone in the treatment of chronic neuropathic pain arising from burn injuries: a case-study. Burns 27: 771-775.

Altier, N., D. Dion, A. Boulanger, and M. Choiniere. 2005, Management of chronic neuropathic pain with methadone: a review of 13 cases. Clin. J. Pain 21: 364-369.

Anderson, R., J. H. Saiers, S. Abram, and C. Schlicht. 2001, Accuracy in equianalgesic dosing. conversion dilemmas. J. Pain Symptom. Manage. 21: 397-406.

Anggard, E., L. M. Gunne, J. Homstrand, R. E. McMahon, C. G. Sandberg, and H. R. Sullivan. 1975, Disposition of methadone in methadone maintenance. Clin. Pharmacol. Ther. 17: 258-266.

Apolone, G., A. Filiberti, S. Cifani, R. Ruggiata, and P. Mosconi. 1998, Evaluation of the EORTC QLQ-C30 questionnaire: a comparison with SF-36 Health Survey in a cohort of Italian long-survival cancer patients. Ann. Oncol. 9: 549-557.

Arnaert, A. and G. Ciccotosto. 2006, Response phases in methadone treatment for chronic nonmalignant pain. Pain Manag. Nurs. 7: 23-30.

Ashburn, M. A. and P. S. Staats. 1999, Management of chronic pain. Lancet 353: 1865-1869.

Ballantyne, J. C. and J. Mao. 2003, Opioid therapy for chronic pain. N. Engl. J. Med. 349: 1943-1953.

Beck, A. T., C. H. Ward, M. Mendelson, J. Mock, and J. Erbaugh. 1961, An inventory for measuring depression. Arch. Gen. Psychiatry 4: 561-571.

Becker, N., T. A. Bondegaard, A. K. Olsen, P. Sjogren, P. Bech, and J. Eriksen. 1997, Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center. Pain 73: 393-400.

Becker, N., P. Sjogren, P. Bech, A. K. Olsen, and J. Eriksen. 2000, Treatment outcome of chronic non-malignant pain patients managed in a danish multidisciplinary pain centre compared to general practice: a randomised controlled trial. Pain 84: 203-211.

Bergman, S., L. T. Jacobsson, P. Herrstrom, and I. F. Petersson. 2004, Health status as measured by SF-36 reflects changes and predicts outcome in chronic musculoskeletal pain: a 3-year follow up study in the general population. Pain 108: 115-123.

Bergner, M., R. A. Bobbitt, W. B. Carter, and B. S. Gilson. 1981, The Sickness Impact Profile: development and final revision of a health status measure. Med. Care 19: 787-805.

Bjordal, K., M. hlner-Elmqvist, E. Tollesson, A. B. Jensen, D. Razavi, E. J. Maher, and S. Kaasa. 1994, Development of a European Organization for Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. EORTC Quality of Life Study Group. Acta Oncol. 33: 879-885.

Blyth, F. M., L. M. March, A. J. Brnabic, L. R. Jorm, M. Williamson, and M. J. Cousins. 2001, Chronic pain in Australia: a prevalence study. Pain 89: 127-134.

Breivik, H., B. Collett, V. Ventafridda, R. Cohen, and D. Gallacher. 2006, Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. Eur. J. Pain 10: 287-333.

Brooks, R. 1996, EuroQol: the current state of play. Health Policy 37: 53-72.

Bruera, E., R. Fainsinger, M. Moore, R. Thibault, E. Spoldi, and V. Ventafridda. 1991, Local toxicity with subcutaneous methadone. Experience of two centers. Pain 45: 141-143.

Bruera, E. and C. M. Neumann. 1999, Role of methadone in the management of pain in cancer patients. Oncology (Williston. Park) 13: 1275-1282.

Bruera, E., S. Watanabe, R. L. Fainsinger, K. Spachynski, M. Suarez-Almazor, and C. Inturrisi. 1995, Custom-made capsules and suppositories of methadone for patients on high-dose opioids for cancer pain. Pain 62: 141-146.

Calman, K. C. 1984, Quality of life in cancer patients--an hypothesis. J. Med. Ethics 10: 124-127.

Caraceni, A., N. Cherny, R. Fainsinger, S. Kaasa, P. Poulain, L. Radbruch, and C. F. de. 2002, Pain measurement tools and methods in clinical research in palliative care: recommendations of an Expert Working Group of the European Association of Palliative Care. J. Pain Symptom. Manage. 23: 239-255.

Carr, A. J., B. Gibson, and P. G. Robinson. 2001, Measuring quality of life: Is quality of life determined by expectations or experience? BMJ 322: 1240-1243.

Chapman, S. L., M. G. Byas-Smith, and B. A. Reed. 2002, Effects of intermediate- and long-term use of opioids on cognition in patients with chronic pain. Clin. J. Pain 18: S83-S90.

Chen, Z. R., A. A. Somogyi, and F. Bochner. 1988, Polymorphic O-demethylation of codeine. Lancet 2: 914-915.

Chou, R., E. Clark, and M. Helfand. 2003, Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. J. Pain Symptom. Manage. 26: 1026-1048.

Cleeland, C. S. and K. M. Ryan. 1994, Pain assessment: global use of the Brief Pain Inventory. Ann. Acad. Med. Singapore 23: 129-138.

Coller, J. K., D. T. Barratt, K. Dahlen, M. H. Loennechen, and A. A. Somogyi. 2006, ABCB1 genetic variability and methadone dosage requirements in opioid-dependent individuals. Clin. Pharmacol. Ther. 80: 682-690.

Crettol, S., J. J. Deglon, J. Besson, M. Croquette-Krokar, R. Hammig, I. Gothuey, M. Monnat, and C. B. Eap. 2006, ABCB1 and cytochrome P450 genotypes and phenotypes: influence on methadone plasma levels and response to treatment. Clin. Pharmacol. Ther. 80: 668-681.

Cruciani, R. A., R. Sekine, P. Homel, D. Lussier, Y. Yap, Y. Suzuki, P. Schweitzer, S. R. Yancovitz, J. A. Lapin, L. Shaiova, R. G. Sheu, and R. K. Portenoy. 2005, Measurement of QTc in patients receiving chronic methadone therapy. J. Pain Symptom. Manage. 29: 385-391.

Dale, O., C. Hoffer, P. Sheffels, and E. D. Kharasch. 2002, Disposition of nasal, intravenous, and oral methadone in healthy volunteers. Clin. Pharmacol. Ther. 72: 536-545.

Dale, O., P. Sheffels, and E. D. Kharasch. 2004, Bioavailabilities of rectal and oral methadone in healthy subjects. Br. J. Clin. Pharmacol. 58: 156-162.

Dass C. 2000. Principles and Practice of Biological Mass Spectrometry. John Wiley & Sons Inc.

de Stoutz, N. D., E. Bruera, and M. Suarez-Almazor. 1995, Opioid rotation for toxicity reduction in terminal cancer patients. J. Pain Symptom. Manage. 10: 378-384.

de Vos, J. W., P. J. Geerlings, B. W. van den, J. G. Ufkes, and W. H. van. 1995, Pharmacokinetics of methadone and its primary metabolite in 20 opiate addicts. Eur. J. Clin. Pharmacol. 48: 361-366.

Dole, V. P. and M. Nyswander. 1965, A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. JAMA 193: 646-650.

Doward, L. C., A. Spoorenberg, S. A. Cook, D. Whalley, P. S. Helliwell, L. J. Kay, S. P. McKenna, A. Tennant, H. D. van der, and M. A. Chamberlain. 2003, Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann. Rheum. Dis. 62: 20-26.

Dworkin, R. H., D. C. Turk, J. T. Farrar, J. A. Haythornthwaite, M. P. Jensen, N. P. Katz, R. D. Kerns, G. Stucki, R. R. Allen, N. Bellamy, D. B. Carr, J. Chandler, P. Cowan, R. Dionne, B. S. Galer, S. Hertz, A. R. Jadad, L. D. Kramer, D. C. Manning, S. Martin, C. G. McCormick, M. P. McDermott, P. McGrath, S. Quessy, B. A. Rappaport, W. Robbins, J. P. Robinson, M. Rothman, M. A. Royal, L. Simon, J. W. Stauffer, W. Stein, J. Tollett, J. Wernicke, and J. Witter. 2005, Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 113: 9-19.

Eap, C. B., G. Bertschy, P. Baumann, T. Finkbeiner, M. Gastpar, and N. Scherbaum. 1998, High interindividual variability of methadone enantiomer blood levels to dose ratios. Arch. Gen. Psychiatry 55: 89-90.

Eap, C. B., F. Broly, A. Mino, R. Hammig, J. J. Deglon, C. Uehlinger, D. Meili, A. F. Chevalley, G. Bertschy, D. Zullino, M. Kosel, M. Preisig, and P. Baumann. 2001, Cytochrome P450 2D6 genotype and methadone steady-state concentrations. J. Clin. Psychopharmacol. 21: 229-234.

Eap, C. B., C. Cuendet, and P. Baumann. 1990, Binding of d-methadone, l-methadone, and dl-methadone to proteins in plasma of healthy volunteers: role of the variants of alpha 1-acid glycoprotein. Clin. Pharmacol. Ther. 47: 338-346.

Eisenberg, E., E. D. McNicol, and D. B. Carr. 2005, Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA 293: 3043-3052.

Elliott, A. M., B. H. Smith, P. C. Hannaford, W. C. Smith, and W. A. Chambers. 2002, The course of chronic pain in the community: results of a 4-year follow-up study. Pain 99: 299-307.

Elliott, A. M., B. H. Smith, K. I. Penny, W. C. Smith, and W. A. Chambers. 1999, The epidemiology of chronic pain in the community. Lancet 354: 1248-1252.

Eriksen, J., O. Ekholm, P. Sjogren, and N. K. Rasmussen. 2004a, Development of and recovery from long-term pain. A 6-year follow-up study of a cross-section of the adult Danish population. Pain 108: 154-162.

Eriksen, J., M. K. Jensen, P. Sjogren, O. Ekholm, and N. K. Rasmussen. 2003, Epidemiology of chronic non-malignant pain in Denmark. Pain 106: 221-228.

Eriksen, J., P. Sjogren, E. Bruera, O. Ekholm, and N. K. Rasmussen. 2006, Critical issues on opioids in chronic non-cancer pain: an epidemiological study. Pain 125: 172-179.

Eriksen, J., P. Sjogren, O. Ekholm, and N. K. Rasmussen. 2004b, Health care utilisation among individuals reporting long-term pain: an epidemiological study based on Danish National Health Surveys. Eur. J. Pain 8: 517-523.

Ettinger, D. S., P. J. Vitale, and D. L. Trump. 1979, Important clinical pharmacologic considerations in the use of methadone in cancer patients. Cancer Treat. Rep. 63: 457-459.

Farrar, J. T., J. P. Young, Jr., L. LaMoreaux, J. L. Werth, and R. M. Poole. 2001, Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 94: 149-158.

Fayers, P. and D. Machin. 2000. Quality of life. 1 ed. Chichester: John Wiley & Sons, ltd.

Ferrari, A., C. P. Coccia, A. Bertolini, and E. Sternieri. 2004, Methadone--metabolism, pharmacokinetics and interactions. Pharmacol. Res. 50: 551-559.

Ferreira KA, Kimura M, and Teixeira M. 2006, The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? Support. Care Cancer Online first.

Fishbain, D. A., B. Cole, R. B. Cutler, J. Lewis, H. L. Rosomoff, and R. S. Fosomoff. 2003, Is pain fatiguing? A structured evidence-based review. Pain Med. 4: 51-62.

Fishbain, D. A., R. B. Cutler, B. Cole, J. Lewis, E. Smets, H. L. Rosomoff, and R. S. Rosomoff. 2004, Are patients with chronic low back pain or chronic neck pain fatigued? Pain Med. 5: 187-195.

Fishman, S. M., B. Wilsey, G. Mahajan, and P. Molina. 2002, Methadone reincarnated: novel clinical applications with related concerns. Pain Med. 3: 339-348.

Foster, D. J., A. A. Somogyi, and F. Bochner. 1999, Methadone N-demethylation in human liver microsomes: lack of stereoselectivity and involvement of CYP3A4. Br. J. Clin. Pharmacol. 47: 403-412.

Foster, D. J., A. A. Somogyi, K. R. Dyer, J. M. White, and F. Bochner. 2000, Steady-state pharmacokinetics of (R)- and (S)-methadone in methadone maintenance patients. Br. J. Clin. Pharmacol. 50: 427-440.

Foster, D. J., A. A. Somogyi, J. M. White, and F. Bochner. 2004, Population pharmacokinetics of (R)-, (S)- and rac-methadone in methadone maintenance patients. Br. J. Clin. Pharmacol. 57: 742-755.

Gagnon, B. and E. Bruera. 1999, Differences in the ratios of morphine to methadone in patients with neuropathic pain versus non-neuropathic pain. J. Pain Symptom. Manage. 18: 120-125.

Gardner-Nix, J. S. 1996, Oral methadone for managing chronic nonmalignant pain. J. Pain Symptom. Manage. 11: 321-328.

Garrido, M. J. and I. F. Troconiz. 1999, Methadone: a review of its pharmacokinetic/pharmacodynamic properties. J. Pharmacol. Toxicol. Methods 42: 61-66.

Gerbershagen, H. U., G. Lindena, J. Korb, and S. Kramer. 2002, [Health-related quality of life in patients with chronic pain]. Schmerz. 16: 271-284.

Gil, M., M. Sala, I. Anguera, O. Chapinal, M. Cervantes, J. R. Guma, and F. Segura. 2003, QT prolongation and Torsades de Pointes in patients infected with human immunodeficiency virus and treated with methadone. Am. J. Cardiol. 92: 995-997.

Gold, J. M., C. Carpenter, C. Randolph, T. E. Goldberg, and D. R. Weinberger. 1997, Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. Arch. Gen. Psychiatry 54: 159-165.

Gorman, A. L., K. J. Elliott, and C. E. Inturrisi. 1997, The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. Neurosci. Lett. 223: 5-8.

Gourlay, G. K., D. A. Cherry, and M. J. Cousins. 1986, A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. Pain 25: 297-312.

Hadorn, D. C., D. Baker, J. S. Hodges, and N. Hicks. 1996, Rating the quality of evidence for clinical practice guidelines. J. Clin. Epidemiol. 49: 749-754.

Hagen, N. A. and E. Wasylenko. 1999, Methadone: outpatient titration and monitoring strategies in cancer patients. J. Pain Symptom. Manage. 18: 369-375.

Hanks, G., N. Cherny, and M. Fallon. 2004. Opioid analgeix therapy. Pages 316-341 *in* Doyle D, G. Hanks, N. Cherny, and Calman K, eds. Oxford textbook of palliative medicine. Oxford: Oxford University Press.

Hanks, G. W., F. Conno, N. Cherny, M. Hanna, E. Kalso, H. J. McQuay, S. Mercadante, J. Meynadier, P. Poulain, C. Ripamonti, L. Radbruch, J. R. Casas, J. Sawe, R. G. Twycross, and V. Ventafridda. 2001, Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br. J. Cancer 84: 587-593.

Hanna, J., D. J. Foster, A. Salter, A. A. Somogyi, J. M. White, and F. Bochner. 2005, Within- and between- subject variability in methadone pharmacokinetics and pharmacodynamics in methadone maintenance subjects. Br. J. Clin. Pharmacol. 60: 404-413.

Harbour, R. and J. Miller. 2001, A new system for grading recommendations in evidence based guidelines. BMJ 323: 334-336.

Harris, R. I. and S. E. Steare. 2006, A meta-analysis of ECG data from healthy male volunteers: diurnal and intra-subject variability, and implications for planning ECG assessments and statistical analysis in clinical pharmacology studies. Eur. J. Clin. Pharmacol. 62: 893-903.

Harris, S., S. Morley, and S. B. Barton. 2003, Role loss and emotional adjustment in chronic pain. Pain 105: 363-370.

Hart, R. P., M. F. Martelli, and N. D. Zasler. 2000, Chronic pain and neuropsychological functioning. Neuropsychol. Rev. 10: 131-149.

Hays, H. 2001, High dosing methadone and a possible relationship to serious cardia arrhythmias. Pain Res. Manag. 6: 64.

Hays, H. and M. A. Woodroffe. 1999, Use of methadone in treating chronic noncancer pain. Pain Res. Manag. 4: 23-27.

Hernansanz, S., C. Gutierrez, A. S. Rubiales, L. A. Flores, and M. L. del Valle. 2006, Opioid rotation to methadone at home. J. Pain Symptom. Manage. 31: 2-4.

Hjermstad, M. J., P. M. Fayers, K. Bjordal, and S. Kaasa. 1998, Health-related quality of life in the general Norwegian population assessed by the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire: the QLQ=C30 (+ 3). J. Clin. Oncol. 16: 1188-1196.

Hojsted, J., P. R. Nielsen, J. Eriksen, O. B. Hansen, and P. Sjogren. 2006, Breakthrough pain in opioid-treated chronic non-malignant pain patients referred to a multidisciplinary pain centre: a preliminary study. Acta Anaesthesiol. Scand.

Holmstrand, J., E. Anggard, and L. M. Gunne. 1978, Methadone maintenance: plasma levels and therapeutic outcome. Clin. Pharmacol. Ther. 23: 175-180.

Hunt, G. and E. Bruera. 1995, Respiratory depression in a patient receiving oral methadone for cancer pain. J. Pain Symptom. Manage. 10: 401-404.

Hunt, S. M., S. P. McKenna, J. McEwen, E. M. Backett, J. Williams, and E. Papp. 1980, A quantitative approach to perceived health status: a validation study. J. Epidemiol. Community Health 34: 281-286.

IASP. 1994a. Classification of chronic pain - descriptions of chronic pain syndromes and definitions of pain terms. Second ed. Seattle: IASP Press.

IASP. IASP definition of pain. www.iasp-pain.org/terms-p.html#Pain . 1994b. 10-7-2006b.

Inturrisi, C. E., W. A. Colburn, R. F. Kaiko, R. W. Houde, and K. M. Foley. 1987, Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. Clin. Pharmacol. Ther. 41: 392-401.

Iribarne, C., F. Berthou, S. Baird, Y. Dreano, D. Picart, J. P. Bail, P. Beaune, and J. F. Menez. 1996, Involvement of cytochrome P450 3A4 enzyme in the N-demethylation of methadone in human liver microsomes. Chem. Res. Toxicol. 9: 365-373.

Jensen, M. K., A. B. Thomsen, and J. Hojsted. 2006, 10-year follow-up of chronic non-malignant pain patients: Opioid use, health related quality of life and health care utilization. Eur. J. Pain 10: 423-433.

Jensen, T. S. 2002, Anticonvulsants in neuropathic pain: rationale and clinical evidence. Eur. J. Pain 6 Suppl A: 61-68.

Jordhoy, M. S., P. Fayers, J. H. Loge, M. hlner-Elmqvist, and S. Kaasa. 2001, Quality of life in palliative cancer care: results from a cluster randomized trial. J. Clin. Oncol. 19: 3884-3894.

Jordhoy, M. S., P. Fayers, T. Saltnes, M. hlner-Elmqvist, M. Jannert, and S. Kaasa. 2000, A palliative-care intervention and death at home: a cluster randomised trial. Lancet 356: 888-893.

Joseph, H., S. Stancliff, and J. Langrod. 2000, Methadone maintenance treatment (MMT): a review of historical and clinical issues. Mt. Sinai J. Med. 67: 347-364.

Kaasa, S., K. Bjordal, N. Aaronson, T. Moum, E. Wist, S. Hagen, and A. Kvikstad. 1995, The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. Eur. J. Cancer 31A: 2260-2263.

Kalso, E., L. Allan, P. L. Dellemijn, C. C. Faura, W. K. Ilias, T. S. Jensen, S. Perrot, L. H. Plaghki, and M. Zenz. 2003, Recommendations for using opioids in chronic non-cancer pain. Eur. J. Pain 7: 381-386.

Kalso, E., J. E. Edwards, R. A. Moore, and H. J. McQuay. 2004, Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 112: 372-380.

Karnofsky DA and Burchenal JH. 1949. The clinical evaluation of chemotherapeutic agents in cancer. Pages 196 *in* MacLeod CM, ed. Evaluation of chemotherapeutic agents. New York: Columbia University Press.

Keller, S., C. M. Bann, S. L. Dodd, J. Schein, T. R. Mendoza, and C. S. Cleeland. 2004, Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin. J. Pain 20: 309-318.

Kharasch, E. D., C. Hoffer, and D. Whittington. 2004a, The effect of quinidine, used as a probe for the involvement of P-glycoprotein, on the intestinal absorption and pharmacodynamics of methadone. Br. J. Clin. Pharmacol. 57: 600-610.

Kharasch, E. D., C. Hoffer, D. Whittington, and P. Sheffels. 2004c, Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. Clin. Pharmacol. Ther. 76: 250-269.

Kharasch, E. D., C. Hoffer, D. Whittington, and P. Sheffels. 2004b, Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. Clin. Pharmacol. Ther. 76: 250-269.

Klepstad, P., O. Dale, F. Skorpen, P. C. Borchgrevink, and S. Kaasa. 2005, Genetic variability and clinical efficacy of morphine. Acta Anaesthesiol. Scand. 49: 902-908.

Klepstad, P., J. H. Loge, P. C. Borchgrevink, T. R. Mendoza, C. S. Cleeland, and S. Kaasa. 2002, The Norwegian brief pain inventory questionnaire: translation and validation in cancer pain patients. J. Pain Symptom. Manage. 24: 517-525.

Kornick, C. A., M. J. Kilborn, J. Santiago-Palma, G. Schulman, H. T. Thaler, D. L. Keefe, A. N. Katchman, J. C. Pezzullo, S. N. Ebert, R. L. Woosley, R. Payne, and P. L. Manfredi. 2003, QTc interval prolongation associated with intravenous methadone. Pain 105: 499-506.

Krantz, M. J., I. B. Kutinsky, A. D. Robertson, and P. S. Mehler. 2003, Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. Pharmacotherapy 23: 802-805.

Krantz, M. J., L. Lewkowiez, H. Hays, M. A. Woodroffe, A. D. Robertson, and P. S. Mehler. 2002, Torsade de pointes associated with very-high-dose methadone. Ann. Intern. Med. 137: 501-504.

Krantz, M. J., C. M. Lowery, B. A. Martell, M. N. Gourevitch, and J. H. Arnsten. 2005, Effects of methadone on QT-interval dispersion. Pharmacotherapy 25: 1523-1529.

Kristensen, K., C. B. Christensen, and L. L. Christrup. 1995, The mu1, mu2, delta, kappa opioid receptor binding profiles of methadone stereoisomers and morphine. Life Sci. 56: L45-L50.

Kuenstner, S., C. Langelotz, V. Budach, K. Possinger, B. Krause, and O. Sezer. 2002, The comparability of quality of life scores. a multitrait multimethod analysis of the EORTC QLQ-C30, SF-36 and FLIC questionnaires. Eur. J. Cancer 38: 339-348.

Landro, N. I., E. G. Celius, and H. Sletvold. 2004, Depressive symptoms account for deficient information processing speed but not for impaired working memory in early phase multiple sclerosis (MS). J. Neurol. Sci. 217: 211-216.

Lawlor, P. G., K. S. Turner, J. Hanson, and E. D. Bruera. 1998, Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. Cancer 82: 1167-1173.

Legemiddelverket. Terapianbefaling: Bruk av opioider ved langvarige, non-maligne smertetilstander. SLV 2002:03. 2002. Oslo.

Loge, J. H. and S. Kaasa. 1998, Short form 36 (SF-36) health survey: normative data from the general Norwegian population. Scand. J. Soc. Med. 26: 250-258.

Loge, J. H., S. Kaasa, M. J. Hjermstad, and T. K. Kvien. 1998, Translation and performance of the Norwegian SF-36 Health Survey in patients with rheumatoid arthritis. I. Data quality, scaling assumptions, reliability, and construct validity. J. Clin. Epidemiol. 51: 1069-1076.

Lotsch, J. and G. Geisslinger. 2006, Current evidence for a genetic modulation of the response to analgesics. Pain 121: 1-5.

Lotsch, J., C. Skarke, J. Liefhold, and G. Geisslinger. 2004, Genetic predictors of the clinical response to opioid analgesics: clinical utility and future perspectives. Clin. Pharmacokinet. 43: 983-1013.

Lotsch, J., C. Skarke, J. Wieting, B. G. Oertel, H. Schmidt, J. Brockmoller, and G. Geisslinger. 2006, Modulation of the central nervous effects of levomethadone by genetic polymorphisms potentially affecting its metabolism, distribution, and drug action. Clin. Pharmacol. Ther. 79: 72-89.

Lydick, E., R. S. Epstein, D. Himmelberger, and C. J. White. 1995, Area under the curve: a metric for patient subjective responses in episodic diseases. Qual. Life Res. 4: 41-45.

Mahoney, F. I. and D. W. Barthel. 1965, Functional evaluation: The Barthel Index. Md State Med. J. 14: 61-65.

Maier, C., C. Schaub, A. Willweber-Strumpf, and M. Zenz. 2005, [Long-term efficiency of opioid medication in patients with chronic non-cancer-associated pain. Results of a survey 5 years after onset of medical treatment]. Schmerz. 19: 410-417.

Maremmani, I., M. Pacini, C. Cesaroni, M. Lovrecic, G. Perugi, and A. Tagliamonte. 2005, QTc interval prolongation in patients on long-term methadone maintenance therapy. Eur. Addict. Res. 11: 44-49.

Martell, B. A., J. H. Arnsten, M. J. Krantz, and M. N. Gourevitch. 2005, Impact of methadone treatment on cardiac repolarization and conduction in opioid users. Am. J. Cardiol. 95: 915-918.

Martell, B. A., J. H. Arnsten, B. Ray, and M. N. Gourevitch. 2003, The impact of methadone induction on cardiac conduction in opiate users. Ann. Intern. Med. 139: 154-155.

Martin, B. C., D. S. Pathak, M. I. Sharfman, J. U. Adelman, F. Taylor, W. J. Kwong, and P. Jhingran. 2000, Validity and reliability of the migraine-specific quality of life questionnaire (MSQ Version 2.1). Headache 40: 204-215.

Mattick, R. P., C. Breen, J. Kimber, and M. Davoli. 2003, Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane. Database. Syst. Rev. CD002209.

Mattick, R. P., J. Kimber, C. Breen, and M. Davoli. 2004, Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane. Database. Syst. Rev. CD002207.

Menefee, L. A., M. J. Cohen, W. R. Anderson, K. Doghramji, E. D. Frank, and H. Lee. 2000, Sleep disturbance and nonmalignant chronic pain: a comprehensive review of the literature. Pain Med. 1: 156-172.

Mercadante, S. 1999, Opioid rotation for cancer pain: rationale and clinical aspects. Cancer 86: 1856-1866.

Mercadante, S., M. Bianchi, P. Villari, P. Ferrera, A. Casuccio, F. Fulfaro, and V. Gebbia. 2003, Opioid plasma concentration during switching from morphine to methadone: preliminary data. Support. Care Cancer 11: 326-331.

Mercadante, S. and E. Bruera. 2006, Opioid switching: A systematic and critical review. Cancer Treat. Rev. 32: 304-315.

Mercadante, S., A. Casuccio, and L. Calderone. 1999, Rapid switching from morphine to methadone in cancer patients with poor response to morphine. J. Clin. Oncol. 17: 3307-3312.

Meresaar, U., M. I. Nilsson, J. Holmstrand, and E. Anggard. 1981, Single dose pharmacokinetics and bioavailability of methadone in man studied with a stable isotope method. Eur. J. Clin. Pharmacol. 20: 473-478.

Morley, J. S., J. Bridson, T. P. Nash, J. B. Miles, S. White, and M. K. Makin. 2003, Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. Palliat. Med. 17: 576-587.

Moulin, D. E., A. Iezzi, R. Amireh, W. K. Sharpe, D. Boyd, and H. Merskey. 1996, Randomised trial of oral morphine for chronic non-cancer pain. Lancet 347: 143-147.

Moulin, D. E., D. Palma, C. Watling, and V. Schulz. 2005, Methadone in the management of intractable neuropathic noncancer pain. Can. J. Neurol. Sci. 32: 340-343.

Nicholson, A. B. 2004, Methadone for cancer pain. Cochrane. Database. Syst. Rev. CD003971.

Nicholson, B. 2003, Responsible prescribing of opioids for the management of chronic pain. Drugs 63: 17-32.

Nilsson, M. I., U. Meresaar, and E. Anggard. 1982a, Clinical pharmacokinetics of methadone. Acta Anaesthesiol. Scand. Suppl 74: 66-69.

Nilsson, M. I., E. Widerlov, U. Meresaar, and E. Anggard. 1982b, Effect of urinary pH on the disposition of methadone in man. Eur. J. Clin. Pharmacol. 22: 337-342.

Oda, Y. and E. D. Kharasch. 2001, Metabolism of methadone and levo-alpha-acetylmethadol (LAAM) by human intestinal cytochrome P450 3A4 (CYP3A4): potential contribution of intestinal metabolism to presystemic clearance and bioactivation. J. Pharmacol. Exp. Ther. 298: 1021-1032.

Osoba, D., G. Rodrigues, J. Myles, B. Zee, and J. Pater. 1998, Interpreting the significance of changes in health-related quality-of-life scores. J. Clin. Oncol. 16: 139-144.

Ostvold, C. and M. Topper. 2005, [Methadone-induced heart arrhythmia]. Tidsskr. Nor Laegeforen. 125: 2021-2022.

Quang-Cantagrel, N. D., M. S. Wallace, and S. K. Magnuson. 2000, Opioid substitution to improve the effectiveness of chronic noncancer pain control: a chart review. Anesth. Analg. 90: 933-937.

Quigley, C. 2004, Opioid switching to improve pain relief and drug tolerability. Cochrane. Database. Syst. Rev. CD004847.

Rao, S. M., G. J. Leo, L. Ellington, T. Nauertz, L. Bernardin, and F. Unverzagt. 1991, Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. Neurology 41: 692-696.

Reddy, S., M. Fisch, and E. Bruera. 2004, Oral methadone for cancer pain: no indication of Q-T interval prolongation or torsades de pointes. J. Pain Symptom. Manage. 28: 301-303.

Rhodin, A., L. Gronbladh, L. H. Nilsson, and T. Gordh. 2006, Methadone treatment of chronic non-malignant pain and opioid dependence - A long-term follow-up. Eur. J. Pain 10: 271-278.

Riley, J., J. R. Ross, D. Rutter, A. U. Wells, K. Goller, B. R. Du, and K. Welsh. 2006, No pain relief from morphine? Individual variation in sensitivity to morphine and the need to switch to an alternative opioid in cancer patients. Support. Care Cancer 14: 56-64.

Ripamonti, C., C. F. de, L. Groff, M. Belzile, J. Pereira, J. Hanson, and E. Bruera. 1998a, Equianalgesic dose/ratio between methadone and other opioid agonists in cancer pain: comparison of two clinical experiences. Ann. Oncol. 9: 79-83.

Ripamonti, C., L. Groff, C. Brunelli, D. Polastri, A. Stavrakis, and C. F. de. 1998b, Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J. Clin. Oncol. 16: 3216-3221.

Ripamonti, C., E. Zecca, and E. Bruera. 1997, An update on the clinical use of methadone for cancer pain. Pain 70: 109-115.

Rogers, W. H., H. Wittink, A. Wagner, D. Cynn, and D. B. Carr. 2000a, Assessing individual outcomes during outpatient multidisciplinary chronic pain treatment by means of an augmented SF-36. Pain Med. 1: 44-54.

Rogers, W. H., H. M. Wittink, M. A. Ashburn, D. Cynn, and D. B. Carr. 2000b, Using the "TOPS," an outcomes instrument for multidisciplinary outpatient pain treatment. Pain Med. 1: 55-67.

Ross, J. R., D. Rutter, K. Welsh, S. P. Joel, K. Goller, A. U. Wells, B. R. Du, and J. Riley. 2005, Clinical response to morphine in cancer patients and genetic variation in candidate genes. Pharmacogenomics. J. 5: 324-336.

Rostami-Hodjegan, A., K. Wolff, A. W. Hay, D. Raistrick, R. Calvert, and G. T. Tucker. 1999, Population pharmacokinetics of methadone in opiate users: characterization of time-dependent changes. Br. J. Clin. Pharmacol. 48: 43-52.

Russak, S. M., C. D. Sherbourne, D. P. Lubeck, H. D. Paulus, C. F. Chiou, N. Sengupta, J. Borenstein, J. Ofman, A. Moadel, and M. H. Weisman. 2003, Validation of a rheumatoid arthritis health-related quality of life instrument, the CSHQ-RA. Arthritis Rheum. 49: 798-803.

Rustoen, T., A. K. Wahl, B. R. Hanestad, A. Lerdal, S. Paul, and C. Miaskowski. 2004, Prevalence and characteristics of chronic pain in the general Norwegian population. Eur. J. Pain 8: 555-565.

Ryan, J. M., J. R. Corry, R. Attewell, and M. J. Smithson. 2002, A comparison of an electronic version of the SF-36 General Health Questionnaire to the standard paper version. Qual. Life Res. 11: 19-26.

Sadanaga, T., F. Sadanaga, H. Yao, and M. Fujishima. 2006, An evaluation of ECG leads used to assess QT prolongation. Cardiology 105: 149-154.

Sanchez Hernandez, A. M., F. F. Atienza, M. A. Arenal, T. E. Gonzalez, C. A. Puchol, and G. J. Almendral. 2005, [Torsades de pointes during methadone treatment]. Rev. Esp. Cardiol. 58: 1230-1232.

Savage, S. R. 1999, Opioid therapy of chronic pain: assessment of consequences. Acta Anaesthesiol. Scand. 43: 909-917.

Sawe, J. 1986, High-dose morphine and methadone in cancer patients. Clinical pharmacokinetic considerations of oral treatment. Clin. Pharmacokinet. 11: 87-106.

Schinkel, A. H. 1997, The physiological function of drug-transporting P-glycoproteins. Semin. Cancer Biol. 8: 161-170.

Schug SA and Gandham N. 2005. Opioids: clinical use. Pages 443-457 *in* McMahon S and M. Kolzenburg, eds. Wall and Melzack's Textbook of pain. Churchill Livingstone.

Sindrup, S. H., M. Otto, N. B. Finnerup, and T. S. Jensen. 2005, Antidepressants in the treatment of neuropathic pain. Basic Clin. Pharmacol. Toxicol. 96: 399-409.

Sjogren, P., L. L. Christrup, M. A. Petersen, and J. Hojsted. 2005, Neuropsychological assessment of chronic non-malignant pain patients treated in a multidisciplinary pain centre. Eur. J. Pain 9: 453-462.

Sjogren, P., A. B. Thomsen, and A. K. Olsen. 2000, Impaired neuropsychological performance in chronic nonmalignant pain patients receiving long-term oral opioid therapy. J. Pain Symptom. Manage. 19: 100-108.

Spreen D and Strauss EA. 1998. A compendium of neuropsychological tests. Administration, normas and commentary. Oxford University Press.

Stone, P., M. Richards, and J. Hardy. 1998, Fatigue in patients with cancer. Eur. J. Cancer 34: 1670-1676.

The British Pain Society. Recommendations for the appropriate use of opioids for persistent non-cancer pain. 2004. London.

The WHO quality of life group. 1998, The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc. Sci. Med. 46: 1569-1585.

Thompson, S. J., K. Koszdin, and C. M. Bernards. 2000, Opiate-induced analgesia is increased and prolonged in mice lacking P-glycoprotein. Anesthesiology 92: 1392-1399.

Thomsen, A. B., N. Becker, and J. Eriksen. 1999, Opioid rotation in chronic non-malignant pain patients. A retrospective study. Acta Anaesthesiol. Scand. 43: 918-923.

Tran HT, Fan C, Tu WQ, Kertland H, Li L, Kluger J, and Chow MSS. 1998, QT measurement: a comparison of three simple methods. Ann. Noninvasive. Electrocardiol. 3: 228-231.

Tse, D. M., M. M. Sham, D. K. Ng, and H. M. Ma. 2003, An ad libitum schedule for conversion of morphine to methadone in advanced cancer patients: an open uncontrolled prospective study in a Chinese population. Palliat. Med. 17: 206-211.

Turk, D. C., R. H. Dworkin, R. R. Allen, N. Bellamy, N. Brandenburg, D. B. Carr, C. Cleeland, R. Dionne, J. T. Farrar, B. S. Galer, D. J. Hewitt, A. R. Jadad, N. P. Katz, L. D. Kramer, D. C. Manning, C. G. McCormick, M. P. McDermott, P. McGrath, S. Quessy, B. A. Rappaport, J. P. Robinson, M. A. Royal, L. Simon, J. W. Stauffer, W.

Stein, J. Tollett, and J. Witter. 2003, Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain 106: 337-345.

Turk, D. C. and R. Melzack. 2001. Handbook of pain assessment. 2 ed. New York: The Guilford Press.

Tyrefors, N., B. Hyllbrant, L. Ekman, M. Johansson, and B. Langstrom. 1996, Determination of morphine, morphine-3-glucuronide and morphine-6-glucuronide in human serum by solid-phase extraction and liquid chromatography-mass spectrometry with electrospray ionisation. J. Chromatogr. A 729: 279-285.

Verebely, K., J. Volavka, S. Mule, and R. Resnick. 1975, Methadone in man: pharmacokinetic and excretion studies in acute and chronic treatment. Clin. Pharmacol. Ther. 18: 180-190.

Verhaak, P. F., J. J. Kerssens, J. Dekker, M. J. Sorbi, and J. M. Bensing. 1998, Prevalence of chronic benign pain disorder among adults: a review of the literature. Pain 77: 231-239.

Viskin, S. 1999, Long QT syndromes and torsade de pointes. Lancet 354: 1625-1633.

Walker, P. W., D. Klein, and L. Kasza. 2003, High dose methadone and ventricular arrhythmias: a report of three cases. Pain 103: 321-324.

Ware, J. E., Jr. and B. Gandek. 1998, Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J. Clin. Epidemiol. 51: 903-912.

Ware, J. E., Jr. and C. D. Sherbourne. 1992, The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med. Care 30: 473-483.

Watanabe, S., Y. Tarumi, D. Oneschuk, and P. Lawlor. 2002, Opioid rotation to methadone: proceed with caution. J. Clin. Oncol. 20: 2409-2410.

WHO. 1946. WHO Constitution. Available at http://whqlibdoc.who.int/hist/official_records/constitution.pdf. Accessed November 17, 2006.

Wiklund, I. 1990, The Nottingham Health Profile--a measure of health-related quality of life. Scand. J. Prim. Health Care Suppl 1: 15-18.

Wincent, A., Y. Liden, and S. Arner. 2003, Pain questionnaires in the analysis of long lasting (chronic) pain conditions. Eur. J. Pain 7: 311-321.

Wittink, H., D. C. Turk, D. B. Carr, A. Sukiennik, and W. Rogers. 2004, Comparison of the redundancy, reliability, and responsiveness to change among SF-36, Oswestry Disability Index, and Multidimensional Pain Inventory. Clin. J. Pain 20: 133-142.

Wolff, K., M. Sanderson, A. W. Hay, and D. Raistrick. 1991, Methadone concentrations in plasma and their relationship to drug dosage. Clin. Chem. 37: 205-209.

World medical association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. 2000.

Yue, Q. Y., J. Hasselstrom, J. O. Svensson, and J. Sawe. 1991, Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: comparisons between extensive and poor hydroxylators of debrisoquine. Br. J. Clin. Pharmacol. 31: 635-642.

Zigmond, A. S. and R. P. Snaith. 1983, The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67: 361-370.

Paper 1

Validation and comparison of the health related quality of life instruments EORTC QLQ-C30 and SF-36 in assessment of patients with chronic non-malignant pain.

Olav Magnus S. Fredheim, MD, Petter C. Borchgrevink, MD, PhD, Turi Saltnes, MSc, Stein Kaasa, MD, PhD

Pain and palliation research group, Department of Circulation and Medical Imaging (O.M.S.F., P.C.B.) and Pain and palliation research group, Department of Cancer Research and Molecular Medicine (T.S., S.K.), Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; Department of Surgery, Sandnessjøen Hospital, Helgelandssykehuset, Norway (O.M.S.F.); and Center for Pain and Complex Disorders, Department of Anaesthesiology (P.C.B.) and Palliative Medicine Unit, Department of Oncology (S.K.), St. Olav University Hospital, Trondheim, Norway

Corresponding author:
Olav Magnus S. Fredheim
Multidisciplinary pain centre
St. Olav University Hospital
Olav Kyrresgt. 17
7006 Trondheim
Norway
olavmagn@ntnu.no
phone: +4741628318

Conflicts of interest:
Health related quality of life data were collected using a computer programme developed by Janssen-Cilag. The software was provided free of charge. Janssen-Cilag was in no other way involved in the study.

Accepted for publication in Journal of Pain and Symptom Management

Abstract

The EORTC QLQ-C30 health related quality of life (HRQoL) questionnaire was developed for use in clinical cancer trials. It has also been applied in studies of patients with chronic non-malignant pain in spite of non-documented validity. Validation of the EORTC QLQ-C30 in this patient population and comparison with the traditional first choice HRQoL instrument in chronic non-malignant pain, the SF-36, is therefore required. 286 patients admitted to the tertiary line multidisciplinary pain centre at St. Olav University Hospital in Trondheim, Norway completed both the EORTC QLQ-C30 and SF-36 at admittance. Correlations between EORTC QLQ-C30 and SF-36 measures of the same concept were between 0.70 and 0.81 for all five domains covered by both instruments. Internal consistency was below 0.70 for the EORTC QLQ-C30 scales physical functioning (0.57), pain (0.68), role functioning (0.43), cognitive functioning (0.66) and nausea/vomiting (0.53) as well as the SF-36 scale role emotional functioning (0.66). Large floor or ceiling effects were seen for several EORTC QLQ-C30 scales. While SF-36 addresses no other symptoms than pain and fatigue the EORTC QLQ-C30 also includes sleep, financial difficulties, nausea/vomiting, dyspnoea, appetite loss, constipation and diarrhoea. Even though some EORTC QLQ-C30 scales have unsatisfactory internal consistency, EORTC QLQ-C30 like the SF-36 has overall acceptable psychometric properties. The EORTC QLQ-C30 is a valid alternative to the SF-36 when a broader assessment of symptoms is desired.

Keywords: Quality of Life, SF-36, EORTC QLQ-C30, chronic pain, validation

Running title: EORTC QLQ-C30 and SF-36 in chronic pain

Introduction

During the last two decades the concept of Health Related Quality of Life (HRQoL) has become increasingly important in clinical medicine as well as medical research. This is particularly the case in chronic diseases and in patients with a limited life expectancy. Instruments used for the assessment of HRQoL need to be validated in order to ensure that they measure what they are intended to, detect true changes over time and differentiate between subjects.

HRQoL questionnaires are divided into generic and disease specific instruments. The Medical Outcome Study Short Form 36 (SF-36) questionnaire is a generic instrument which has been widely used for assessment of HRQoL in studies on chronic pain[1,2,3,4] as well as in other diseases. The use of parts of this questionnaire is recommended in the IMMPACT recommendations for pain clinical trials.[5] The European Organization for Research and Treatment of Cancer Quality of Life core questionnaire (EORTC QLQ-C30) is a disease specific instrument which has been the instrument of choice in cancer trials in Europe.[6] The two instruments are quite similar and have five domains in common; physical functioning, mental health/emotional functioning, social functioning, vitality/fatigue and pain.

While several pain clinics have used SF-36 in pain clinical trials and clinical routine, others have used EORTC QLQ-C30.[7,8] While the SF-36 was developed for use in general populations and across disease groups, the EORTC QLQ-C30 was developed and validated for use in clinical cancer trials. Accordingly the use of EORTC QLQ-C30 in patients with chronic non-malignant pain can be criticized due to lack of documented validity in this patient population. When SF-36 and EORTC QLQ-C30 have previously been compared in cancer populations both instruments displayed satisfactory psychometric properties and correlation between the five domains covered by both instruments ranged from 0.50 to 0.74.[9,10] The instruments have, however, not been compared in chronic non-malignant pain patients.

The objective of this study was to validate the EORTC QLQ-C30 for use in patients with chronic non-malignant pain and to compare it with the SF-36 in this patient population. The validation of EORTC QLQ-C30 included testing of discrimination, internal consistency, sensitivity and construct validity. Furthermore external convergent validity was measured by assessing how SF-36 and EORTC QLQ-C30 measures of the same concept correlate with each other.

Material and methods

Patients

From September 1999 to January 2002 all consecutive out-patients admitted to the multidisciplinary pain centre at St. Olav University Hospital in Trondheim, Norway completed the two HRQoL questionnaires EORTC QLQ-C30 and SF-36 immediately before their first consultation as a part of the routine evaluation. Patients with malignant disease or acute/subacute pain lasting less than six months were excluded from this study.

EORTC QLQ-C30

EORTC QLQ-C30 is a cancer-specific 30-item HRQoL questionnaire.[11] It consists of 30 questions. 24 questions form nine multi-item scales presenting various aspects of HRQoL while the remaining six are single-item scales describing different cancer relevant symptoms. During the scoring procedure raw EORTC QLQ-C30 scores are linearly transformed into 0-100 scales. For global health status and the five functioning scales a score of 100 corresponds to a high HRQoL. For financial difficulties and the eight symptoms a score of 100 implies maximum difficulty or symptom burden. Norm-data for the EORTC QLQ-C30 scores of the general Norwegian population exists along with other countries.[12,13]

SF-36

SF-36 consists of 36 questions which form 8 multi-item scales.[14] In all scales a score of 100 corresponds to a high level of functioning or less symptomatology. SF-36 norm data exist for the Norwegian general population.[15]

Data collection

The HRQoL questionnaires were completed using the computer programme Painscreen and data were entered by means of a touch-screen. Painscreen was developed by Janssen Cilag for use in Scandinavian pain centres. The questions were asked in the same order as on the paper version of the questionnaire. It was not possible to go on to the next question before an answer was given. Accordingly there are no missing data in the questionnaires. The two instruments were always presented in the same order with EORTC QLQ-C30 as the first and SF-36 as the last instrument.

Analysis strategies and statistics

Descriptive data are presented with means, SDs, medians, ranges and proportions as appropriate.

Discrimination

If discrimination is high, the patients' responses are distributed along the whole range of response alternatives. In a tool with poor discrimination, a large proportion of responses will be one of the extreme alternatives. Discrimination is measured by the floor and ceiling effect, which is the percentage of responses in either end of the response range.

Reliability

Reliability expressed as internal consistency, is a measure of how well the items in a multi-item scale interrelate. This is usually assessed by computing Cronbach's coefficient (Cronbach's alpha). The score reflects both the number of items and the degree of correlation between items. Values above 0.70 usually indicate acceptable internal consistency.

Sensitivity

The sensitivity measures how well the instrument identifies differences between groups. An instrument with a high sensitivity is able to detect a relatively small difference with a modest sample size. Sensitivity is measured by comparing the scores of different groups of patients. In this study the patient population was divided into seven broad groups according to ICD-10 pain diagnosis. Based on clinical experience, significant differences between these patient groups were expected.

Convergence between instruments

Convergence between instruments (external convergent validity) is an assessment of the correlation between SF-36 and EORTC QLQ-C30 measures of the same concept. This is included in the multi trait multi method (MTMM) analysis where Pearson's correlations are used to compute the degree of correlation. External convergent validity was assessed for physical functioning, social functioning, emotional functioning/mental health, fatigue/vitality and pain. A correlation above 0.70 between scales measuring the same concept is considered to be an indication of the same underlying concept.[16]

Construct validity

Construct validation evaluates how well an instrument measures the construct it is intended to measure. Construct validity is often divided into convergent and discriminant validity as well as comparison of deviation from norm-data.

When assessing convergent validity one assumes that scales related to the same underlying construct show high correlations. Previously correlations above 0.40 have been considered

satisfactory for convergent validity.[16] However, if correlation is too high (>0.70) it can be questioned whether the scales really measure different concepts[16] and whether the application of two highly correlated scales adds useful information compared to if only one of the scales is included. On the opposite, by discriminate validity one assumes that scales measuring different constructs should show low correlation, which means well below 0.40. Convergent and discriminant validity is assessed in a MTMM analysis. In the MTMM analysis correlations between the results from different measurement methods of different traits are presented. In the present analyses the HRQoL scales are traits and the two different instruments are methods.

As part of the construct validation deviations from the age and gender adjusted norm data for the two instruments were compared for the five domains covered by both instruments. If similar scales or items in the two instruments deviate approximately similarly from the norm, one assumes equality between instruments.

Ethics

The data were collected for clinical purposes as part of the routine evaluation of new patients at the multidisciplinary pain centre. The secretary of the Regional Committee for Medical Research Ethics approved the use of these data for research without obtaining informed consent.

Results

Patient characteristics

Out of 602 patients with chronic non-malignant pain admitted during the study period, 286 (48%) had completed both EORTC QLQ-C30 and SF-36 and were included in the analyses. Causes of missing or incomplete HRQoL data were that some days the computer was not available or there were technical difficulties, some patients did not have time to complete the questionnaire, some were unable due to poor health and some refused. The distribution between these causes is not known. The study population included 113 (39%) males and 173 (61%) females. Mean age was 45 (SD 13) years. The included patients were divided into 7 groups according to ICD-10 diagnoses; generalised pain conditions (16 %), neck pain (15 %), lumbar/thoracic pain (19 %), localised musculoskeletal pain (11 %), neuropathic pain (16 %), somatoform pain disorders (9 %) and other pain conditions (14 %). Mean EORTC QLQ-C30 and SF-36 scores of the patients in the study and standard deviations are presented in table 1 together with age- and gender adjusted norm-data. Table 2 provides a detailed overview of the ICD-10 diagnoses included in each diagnostic group and the number of patients with each ICD-10 diagnosis.

Discrimination

Floor and ceiling effects are presented in table 1. Floor effects of 15 and 20% respectively were seen for the EORTC QLQ-C30 scales social functioning and role functioning while floor effects of 38 to 61% were seen for the EORTC QLQ-C30 single items nausea/vomiting, dyspnoea, appetite loss, constipation, diarrhoea and financial difficulties. For the SF-36 scales role physical functioning and role emotional functioning floor effects were 69 and 33 respectively. Ceiling effects were respectively 23, 22 and 42% for the EORTC QLQ-C30 scales role functioning, cognitive functioning and pain. The EORTC QLQ-C30 single items insomnia and financial difficulties had ceiling effects of 21 and 25 while the SF-36 scale role emotional functioning had a 19% ceiling effect.

Internal consistency

Cronbach's alpha is computed for all multi item scales and the values are presented in table 1. Values below 0.70 are observed for the EORTC QLQ-C30 scales physical functioning (0.57), pain (0.68), role functioning (0.43), cognitive functioning (0.66) and nausea/vomiting (0.53) and the SF-36 scale role emotional functioning (0.66). The values for the remaining four EORTC QLQ-C30 multi item scales and seven SF-36 scales exceeded 0.70.

Sensitivity

The scores of the seven groups of patients are compared using one-way ANOVA, and results are presented in table 3. Both instruments detected significant differences between the groups in the physical functioning scale. EORTC QLQ-C30 also detected differences between the groups in social functioning, but such difference was not detected by the SF-36. Neither SF-36 nor EORTC QLQ-C30 separated the groups in the emotional functioning/mental health, pain/bodily pain and fatigue/vitality scales.

Convergence between instruments

For all five domains covered by both instruments, coefficients for external convergent validity met the 0.70 criteria, with values ranging from 0.70 to 0.81 (table 4). These values were as they should, well above correlation values between the different scales in each instrument (0.15-0.57). In all cases the correlation between the corresponding scales in the two instruments was higher than correlations between the scale in one instrument and the four non-corresponding scales in the other instrument.

Construct validity

In the MTMM correlation matrix in table 4 the five domains covered by both HRQoL instruments are included. With two exceptions similar patterns of the magnitude of correlations were found for the two instruments. The exceptions were observed for correlation between physical functioning and mental health/emotional functioning and pain/bodily pain. Correlation between EORTC QLQ-C30 physical functioning and emotional functioning was 0.15 compared to a correlation of 0.37 between SF-36 physical functioning and mental health. Between physical functioning and pain/bodily pain a value of 0.39 was observed for EORTC QLQ-C30 compared to 0.52 for SF-36.

As part of the construct validation the deviations from norm-data for the five corresponding domains were compared. For emotional functioning/mental health, social functioning, vitality/fatigue and pain/bodily pain the differences in deviations were 11 or less while the difference in physical functioning was 18.

Discussion

In this study the Norwegian translations of both the EORTC QLQ-C30 and SF-36 HRQoL questionnaires demonstrated acceptable psychometric properties in patients with chronic non-malignant pain. However, both instruments have advantages and weaknesses which will be discussed below.

Discrimination was good with small or moderate floor and ceiling effects in all QLQ-C30 functioning scales, but seems to be poor in several symptom scales, particularly the single item scales. For the symptoms nausea/vomiting, dyspnoea, appetite loss, diarrhoea and constipation floor effects of 43 to 61% were seen together with ceiling effects of 0.3 to 6.6%. This could indicate poor ability to differentiate between no symptoms and mild symptoms, but based on clinical experience it is probably at least partly a consequence of low prevalence of these symptoms in this patient population. In the QLQ-C30 scales role functioning, insomnia and financial difficulties floor effects of 13 to 38% were seen together with ceiling effects of 21 to 26%. For insomnia and financial difficulties this is probably a consequence of the narrow response range with only 4 response alternatives. For role functioning this distribution indicates that contrary to the other functioning scales, a large part of patients with chronic non-malignant pain experience either very poor or excellent role functioning.

For SF-36 the internal consistency was acceptable for all scales while three EORTC QLQ-C30 scales had values substantially below the 0.70 limit. The Chronbach's alpha of 0.57 for EORTC QLQ-C30 physical functioning is probably a consequence of the narrow range of responses when all questions are dichotomous (yes/no). In the last version of the questionnaire, this problem is probably reduced because there are currently four response alternatives. For the other scales with low internal consistency there are no obvious explanations. In cancer patients the EORTC QLQ-C30 internal consistency in multi item scales has been reported to be equal to SF-36 values.[9,10] The Chronbach's apha values in these comparative studies are similar to findings in other EORTC QLQ-C30 validation studies.[16] The poorer Chronbach's alpha values observed in our study indicate that EORTC QLQ-C30 internal consistency is higher in cancer patients than in patients with chronic non-malignant pain for physical functioning, role functioning and nausea/vomiting. There is no obvious explanation for these differences in internal consistency between the two patient populations but it is possible to speculate on possible reasons. A possible explanation is that chronic pain affects more specific functional areas compared to advanced cancer disease. For instance would localised pain conditions be expected to have a strong influence on some functions but less on others. This could be an

explanation for the lower correlation between the items in multi item functioning scales in this population.

Our results indicate that the sensitivities of the two instruments are about equal. In three dimensions neither of the two instruments detected differences between the seven diagnostic groups. In physical functioning both instruments detected differences while in social functioning only EORTC QLQ-C30 detected differences. It is not established whether different chronic pain conditions affect HRQoL data differently. Accordingly our results are either a consequence of poor sensitivity for both instruments or illustrate that very different chronic pain conditions have similar impact on HRQoL.

When SF-36 and EORTC QLQ-C30 were previously compared in cancer patients external convergent validity correlation values from 0.52 to 0.69 and from 0.50 to 0.74 were seen in two different studies.[9,10] This is well below values ranging from 0.70 to 0.81 in our study. In spite of these differences the overall picture from both populations is that correlation between measures of the same concept is high. However, the finding that no correlation values are close to 1.0, indicates some differences in content between the instruments.

When correlation coefficients between different EORTC QLQ-C30 scales from the present study are compared to data from cancer patients,[16] the coefficient values differ as much as 0.30. The largest difference is seen for the correlation between emotional and physical functioning with a correlation coefficient of 0.46 in cancer patients compared to 0.15 in patients with chronic non-malignant pain. Lower correlations in patients with chronic non-malignant pain compared to cancer patients were also seen between pain and physical and emotional functioning and between fatigue and physical functioning. A possible interpretation of this finding is that the levels of pain and fatigue are of less importance for the level of physical functioning, and that the level of pain is of less importance for emotional functioning in patients with chronic non-malignant pain compared to cancer patients. On the other hand the association between fatigue and emotional functioning is higher in patients with chronic non-malignant pain with a correlation coefficient of 0.55 compared to 0.36.

Differences between the two instruments in correlation between physical functioning and mental health/emotional functioning indicate that the contents of the physical functioning and/or mental health/emotional functioning scales differ between the two instruments. If the content was the same in both instruments for both scales, similar correlation coefficients would be expected together with similar deviations from norm data. Mean EORTC QLQ-C30 and SF-

36 physical functioning scores differ with respectively 31 and 49 from norm data while no significant difference in deviation from norm data is seen for emotional functioning/mental health. This indicates different contents in the physical functioning scales. While the SF-36 physical functioning scale consists of ten items, the QLQ-C30 only contains five physical functioning items. Most of the SF-36 questions are very specific compared to the wider and vaguer questions in the QLQ-C30. While SF-36 addresses problems with walking more than one mile EORTC QLQ-C30 asks about a long walk. Another possibly important difference is that the EORTC QLQ-C30 uses carrying a suitcase as an example of strenuous activity, while the SF-36 has running and participation in sport activities as examples of strenuous activity.

Unfortunately the two HRQoL instruments were only completed by 48% of patients admitted to the multidisciplinary pain centre during the study period. This could obviously have caused a selection bias in the study and reduce the external validity of the results. While we believe that technical difficulties and lack of time would exclude random patients and thus not introduce a selection bias, poor health and refusal is probably more likely in patients with poor HRQoL scores. As a selection bias can not be disproved the results from the present study should be confirmed in future studies.

The EORTC QLQ-C30 does in spite of unsatisfactory internal consistency in three scales show overall acceptable psychometric properties in patients with chronic non-malignant pain. An advantage of the EORTC QLQ-C30 compared to the SF-36 is that cognitive functioning and a broader spectrum of symptoms are addressed. SF-36 only addresses pain and fatigue while the EORTC QLQ-C30 also addresses difficulties of sleep, financial difficulties, nausea/vomiting, dyspnoea, appetite loss, constipation and diarrhoea. Some of these symptoms have a low prevalence in this patient population, but insomnia and financial difficulties are frequent complaints and should be addressed. In this study the high prevalence of difficulties of sleep and financial difficulties is reflected in the large ceiling effects and mean deviations from norm data. Nausea/vomiting and constipation, on the other hand, are of minor relevance for the majority of patients with chronic non-malignant pain, but are frequent side effects for the minority who are treated with strong opioids.[17] In conclusion the EORTC QLQ-C30 is a valid alternative to the SF-36 when a broader assessment of symptoms is desired. The application of the EORTC QLQ-C30 may also be desirable to those clinicians who deal with both cancer and non-cancer pain patients. In spite of the overall acceptable psychometric properties of both instruments the results from the present study indicate that further development of the instruments could be required in order to achieve ideal psychometric properties in patients with chronic non-malignant pain.

Table 1

EORTC-QLQ-C30 and SF-36 scores and norm data, floor- and ceiling effects and Cronbach's alpha.

Instrument	Scale	Mean	(SD)	Norm data*	Deviation from norm	Floor %	Ceiling %	Cronbach's alpha
QLQ-C30	Physical functioning	60	(24)	91	-31	1	12	0.57
	Emotional functioning	58	(24)	81	-23	1	4	0.80
	Social functioning	43	(29)	85	-42	15	5	0.75
	Role functioning	52	(33)	93	-41	20	23	0.43
	Cognitive functioning	64	(28)	87	-23	3	22	0.66
	Global Quality of life	36	(19)	73	-37	5	1	0.74
	Pain	82	(19)	21	+61	0	42	0.68
	Nausea/vomiting	12	(18)	4	+8	56	0	0.53
	Fatigue	60	(24)	29	+31	2	9	0.79
	Dyspnoea	29	(30)	13	+16	43	5	Single item
	Insomnia	57	(33)	21	+36	13	26	Single item
	Appetite loss	24	(30)	7	+17	52	5	Single item
	Constipation	22	(31)	11	+11	61	7	Single item
	Diarrhoea	20	(27)	10	+10	56	4	Single item
	Financial difficulties	41	(39)	10	+31	38	21	Single item
SF-36	Physical functioning	50	(24)	89	-49	1	1	0.89
	Mental health	60	(20)	79	-19	0	1	0.88
	Social functioning	52	(28)	86	-34	6	7	0.84
	Vitality	32	(20)	60	-28	5	0	0.81
	Bodily pain	26	(16)	76	-50	13	1	0.74
	General health	45	(21)	78	-33	0	0	0.70
	Role – physical	13	(24)	81	-68	69	4	0.70
	Role – emotional	40	(36)	84	-44	33	19	0.66

In EORTC QLQ-C30 functioning scales a high score indicates good functioning/high quality of life. High scores in EORTC QLQ-C30 symptom scales indicate worse symptoms/poor quality of life. In all SF-36 scales a high score indicates a high quality of life.

* Age and gender adjusted data from the general Norwegian population (Loge et al and Hjermstad et al).

Table 2
Detailed overview of the ICD-10 diagnoses of the included patients.

Diagnostic group	ICD-10	diagnoses	N =	%
Generalised pain conditions	M79.0	Rheumatism, unspecified (fibromyalgia)	29	10,1
N: 45 (16%)	R52.2	Other chronic pain	16	5,6
Neck pain	M54.2	Cervicalgia	29	10,1
N: 42 (15%)	S13.4	Sprain and strain of cervical spine	13	4,5
Lumbar/thoracic pain	M54.4	Lumbago with sciatica	23	8,0
N: 54 (19%)	M54.5	Low back pain	27	9,4
	M54.6	Pain in thoracic spine	4	1,4
Localised musculoskeletal pain	M16.0	Primary coxarthrosis, bilateral	6	2,1
N: 33 (11%)	M17.0	Primary gonarthrosis, bilateral	6	2,1
	M75.9	Shoulder lesion, unspecified	9	3,1
	M79.1	Myalgia	7	2,4
	R07.4	Chest pain, unspecified	5	1,7
Neuropathic pain	B02.9	Zoster without complication	1	0,3
N: 45 (16%)	G35	Multiple sclerosis	1	0,3
	G50.1	Atypical facial pain	11	3,8
	G54.6	Phantom limb syndrome with pain	1	0,3
	G54.8	Other nerve root and plexus disorders	1	0,3
	G54.9	Nerve root and plexus disorder, unspecified	1	0,3
	G56.8	Other mononeuropathies of upper limb	6	2,1
	G57.9	Mononeuropathy of lower limb, unspecified	8	2,8
	G58.0	Intercostal neuropathy	4	1,4
	G62.9	Polyneuropathy, unspecified	2	0,7
	I69.8	Sequelas of other and unspecified cerebrovaskular disease	5	1,7
	M89.0	Algoneurodystrophy	4	1,4
Somatoform pain disorders	F45.3	Somatoform autonomic dysfunction	14	4,9
N: 25 (9%)	F45.4	Persistent somatoform pain disorder	11	3,8
Other pain conditions	G43.9	Migraine, unspecified	1	0,3
N: 42 (15%)	G44.2	Tension-type headache	7	2,4
	M05.9	Seropositive rheumatoid arthritis, unspecified	1	0,3
	M54.1	Radiculopathy	10	3,5
	R10.2	Pelvic and perineal pain	22	7,7
	M76.8	Other enthesopathies of lower limb, excluding foot	1	0,3

Table 3
Scores in the five corresponding HRQoL scales of EORTC and SF-36 for the seven different groups of pain patients.

Groups of ICD 10 diagnoses	N	%		EORTC PF	SF-36 PF	EORTC EF	SF-36 MH	EORTC SF	SF-36 SF	EORTC FA	SF-36 VT	EORTC PA	SF-36 BP
Neuropathic pain	45	16	Mean (SD)	58.2 (28.5)	50.7 (29.2)	59.6 (23.6)	60.7 (21.0)	45.2 (27.0)	48.9 (29.7)	60.5 (24.5)	34.9 (20.5)	85.6 (17.3)	24.2 (19.1)
Lumbar/thoracic pain	54	19	Mean (SD)	53.0 (19.1)	42.4 (22.2)	64.4 (22.6)	64.6 (21.2)	39.2 (27.7)	53.1 (28.3)	59.5 (21.8)	34.1 (18.6)	85.2 (17.6)	25.1 (14.4)
Generalised pain conditions	45	16	Mean (SD)	56.4 (21.4)	44.1 (22.0)	55.7 (24.5)	58.2 (19.9)	41.1 (28.8)	50.6 (28.7)	64.0 (25.3)	26.6 (21.3)	84.8 (15.8)	21.7 (14.4)
Somatoform pain disorders	25	9	Mean (SD)	62.4 (28.5)	54.8 (27.7)	57.7 (26.0)	59.2 (18.9)	46.7 (28.9)	51.0 (27.0)	61.8 (25.1)	32.4 (20.0)	78.7 (25.7)	29.6 (23.9)
Neck pain	42	15	Mean (SD)	67.1 (24.1)	62.1 (21.2)	52.4 (23.5)	58.3 (18.1)	40.9 (27.1)	51.8 (23.7)	61.9 (21.1)	29.0 (17.0)	80.6 (20.8)	23.6 (12.1)
Other pain conditions	41	14	Mean (SD)	61.0 (23.2)	48.8 (21.7)	52.9 (23.8)	56.7 (22.9)	33.3 (30.7)	46.3 (27.7)	61.2 (26.9)	32.2 (22.8)	80.5 (18.2)	25.1 (13.3)
Localised musculoskeletal pain	33	11	Mean (SD)	65.5 (18.2)	54.7 (22.4)	62.9 (26.7)	63.5 (19.3)	57.0 (25.7)	61.4 (25.6)	53.5 (25.4)	34.1 (18.0)	73.7 (20.8)	32.2 (14.9)
Highest – lowest group mean				14.1	19.7	12	7.9	23.7	15.1	10.5	8.3	11.9	10.5
One-way ANOVA p-value				0.036	0.002	0.082	0.291	0.008	0.226	0.323	0.146	0.051	0.106

PF: physical function, EF: emotional function, MH: mental health, SF: social function, FA: fatigue, VT: vitality, PA: pain, BP: bodily pain

Table 4
MTMM correlation matrix

			SF-36 PF	E-C30 PF	SF-36 MH	E-C30 EF	SF-36 SF	E-C30 SF	SF-36 VT	E-C30 FA	SF-36 BP	E-C30 PA
SF-36	Physical functioning	PF										
E-C30	Physical functioning scale	PF	0.76									
SF-36	Mental health	MH	0.37									
E-C30	Emotional functioning scale	EF		0.15	0.81							
SF-36	Social functioning	SF	0.41		0.59							
E-C30	Social functioning scale	SF		0.35		0.48	0.70					
SF-36	Vitality	VT	0.33		0.57		0.58					
E-C30	Fatigue symptom scale	FA		-0.29		-0.55		-0.53	-0.74			
SF-36	Bodily pain	BP	0.52		0.40		0.56		0.49			
E-C30	Pain symptom scale	PA		-0.39		-0.39		-0.52		0.52	-0.76	
External convergent validity												

References

1. Becker N, Sjogren P, Bech P, Olsen AK, Eriksen J. Treatment outcome of chronic non-malignant pain patients managed in a danish multidisciplinary pain centre compared to general practice: a randomised controlled trial. Pain 2000;84:203-211.

2. Bergman S, Jacobsson LT, Herrstrom P, Petersson IF. Health status as measured by SF-36 reflects changes and predicts outcome in chronic musculoskeletal pain: a 3-year follow up study in the general population. Pain 2004;108:115-123.

3. Elliott AM, Smith BH, Hannaford PC, Smith WC, Chambers WA. The course of chronic pain in the community: results of a 4-year follow-up study. Pain 2002;99:299-307.

4. Elliott TE, Renier CM, Palcher JA. Chronic pain, depression, and quality of life: correlations and predictive value of the SF-36. Pain Med 2003;4:331-339.

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

6. Fayers P, Bottomley A. Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. Eur J Cancer 2002;38 Suppl 4:S125-S133.

7. Wincent A, Liden Y, Arner S. Pain questionnaires in the analysis of long lasting (chronic) pain conditions. Eur J Pain 2003;7:311-321.

8. Fredheim OM, Kaasa S, Dale O, et al. Opioid switching from oral slow release morphine to oral methadone may improve pain control in chronic non-malignant pain: a nine-month follow-up study. Palliat Med 2006;20:35-41.

9. Apolone G, Filiberti A, Cifani S, Ruggiata R, Mosconi P. Evaluation of the EORTC QLQ-C30 questionnaire: a comparison with SF-36 Health Survey in a cohort of Italian long-survival cancer patients. Ann Oncol 1998;9:549-557.

10. Kuenstner S, Langelotz C, Budach V, et al. The comparability of quality of life scores. a multitrait multimethod analysis of the EORTC QLQ-C30, SF-36 and FLIC questionnaires. Eur J Cancer 2002;38:339-348.

11. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-376.

12. Hjermstad MJ, Fayers PM, Bjordal K, Kaasa S. Health-related quality of life in the general Norwegian population assessed by the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire: the QLQ=C30 (+ 3). J Clin Oncol 1998;16:1188-1196.

13. Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer 2001;37:1331-1334.

14. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-483.

15. Loge JH, Kaasa S. Short form 36 (SF-36) health survey: normative data from the general Norwegian population. Scand J Soc Med 1998;26:250-258.

16. Kaasa S, Bjordal K, Aaronson N, et al. The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. Eur J Cancer 1995;31A:2260-2263.

17. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004;112:372-380.

Paper 2

Chronic non-malignant pain patients report as poor health related quality of life as palliative cancer patients.

Olav Magnus S. Fredheim [a,b,*], Stein Kaasa [a,c], Peter Fayers [a,d], Turi Saltnes [a], Marit Jordhøy [a,e], Petter C. Borchgrevink [a,f]

[a] *Pain and palliation research group, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway*
[b] *Department of medicine, Sandnessjøen Hospital, Helgelandssykehuset, Norway*
[c] *Palliative Medicine Unit, Department of Oncology, St. Olav University Hospital, Trondheim, Norway*
[d] *Department of Public Health, School of Medicine, University of Aberdeen, Aberdeen, UK*
[e] *Unit of Oncology and Palliative Care, Nordland Hospital, Bodø, Norway*
[f] *Centre for Pain and Complex Disorders, Department of Anaesthesiology, St. Olav University Hospital, Trondheim, Norway*

Corresponding author:
Olav Magnus S. Fredheim
Multidisciplinary pain centre
St. Olav University Hospital
Olav Kyrresgt. 17
7006 Trondheim
Norway
olavmagn@ntnu.no
phone: +4741628318

Keywords: Health related quality of life, chronic pain, EORTC QLQ-C30, SF-36, palliative care

Paper II is not included due to copyright.

Paper 3

Paper III is not included due to copyright.

Paper 4

ARTICLE IN PRESS

Available online at www.sciencedirect.com
ScienceDirect

European Journal of Pain xxx (2006) xxx–xxx

www.EuropeanJournalPain.com

Long term methadone for chronic pain: A pilot study of pharmacokinetic aspects

Olav Magnus S. Fredheim [a,c,*], Petter C. Borchgrevink [a,d], Pål Klepstad [a,d], Stein Kaasa [b,e], Ola Dale [a,d]

[a] *Pain and Palliation Research Group, Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology, 7006 Trondheim, Norway*
[b] *Pain and Palliation Research Group, Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway*
[c] *Department of Medicine, Sandnessjøen Hospital, Helgelandssykehuset, Norway*
[d] *Department of Anaesthesia, St. Olav University Hospital, Trondheim, Norway*
[e] *Palliative Medicine Unit, Department of Oncology, St. Olav University Hospital, Trondheim, Norway*

Received 13 March 2006; received in revised form 27 September 2006; accepted 27 September 2006

Abstract

Methadone is used as an alternative opioid when first line opioids fail to provide adequate pain control. Highly variable morphine:methadone dose ratios make switching challenging and little is known about the pharmacokinetics of long lasting methadone treatment for pain. Twelve patients treated with morphine for chronic non-malignant pain were switched to methadone. Seven of these patients continued with methadone throughout the nine months study period and only minor dose adjustments were performed. Serum concentrations of morphine, methadone and their metabolites were measured at baseline, day one and two, after dose titration and one week, five weeks, three months and nine months after the end of dose titration. Serum concentrations of methadone and its metabolite EDDP did not change significantly from the end of dose titration and during the nine months (repeated measures ANOVA: $p = 0.88$ and $p = 0.06$). Very low correlation between dose ratios and serum concentration ratios between morphine and methadone was observed. Large interindividual differences in serum concentrations and metabolism were observed. Our findings contradict that autoinduction of methadone metabolism takes place during long term treatment and supports that a 3-day opioid switch from morphine to methadone followed by a one week titration seems pharmacologically sound.

Keywords: Methadone; Morphine; Pharmacokinetic; Chronic pain; Opioid switch

1. Introduction

Morphine is a first line opioid in the treatment of cancer pain (Hanks et al., 2001; Wiffen et al., 2003) and chronic non-malignant pain. Switching to methadone is an alternative if morphine does not provide a satisfactory balance between pain relief and side effects (de Stoutz et al., 1995; Fredheim et al., 2006a). How-

* Corresponding author. Address: Pain and Palliation Research Group, Multidisciplinary pain centre, St. Olav University Hospital, Olav Kyrresgt. 17, 7006 Trondheim, Norway. Tel.: +47 41628318; fax: +47 73866990.
E-mail address: olavmagn@frisurf.no (Olav Magnus S. Fredheim).

1090-3801/$32
doi:10.1016/j.ejpain.2006.09.006

Please cite this article in press as: Fredheim OMS et al., Long term methadone for chronic pain: ..., Eur J. Pain (2006), doi:10.1016/j.ejpain.2006.09.006

ever, highly variable morphine:methadone dose ratios make this switch challenging and little is known about pharmacokinetic aspects of switching from morphine to long term methadone treatment. Morphine and methadone differ in several ways. Oral bioavailability for morphine is usually 25–35% (Hasselstrom and Sawe, 1993; Lotsch et al., 1999), but a range from 10% to 43% was reported by Gourlay et al. (1986). Oral bioavailability for methadone is usually 70–90%, but values from 40% to 99% are reported (Meresaar et al., 1981; Gourlay et al., 1986; Dale et al., 2004). While serum elimination half-time for morphine is 2–3 h (Sawe, 1986) methadone half-time ranges from 7 to 65 h (Gourlay et al., 1986). Methadone is metabolised to the inactive compound 2-ethylidene-1,5-dimethyl-3,3-dipenylpyrrolidine (EDDP) via CYP3A4 (Iribarne et al., 1996), but also other CYPs may metabolise methadone (Garrido and Troconiz, 1999). It has been suggested that chronic methadone treatment leads to increased metabolism by autoinduction (Sawe, 1986). Morphine is primarily eliminated by glucuronidation to morpine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) via UGT2B7 (Coffman et al., 1997), but is also *N*-demetylated to normorphine via CYP3A4 and CYP2C8 (Projean et al., 2003).

Changes in opioid and metabolite serum concentrations during and after switching from morphine to methadone in chronic pain have not previously been studied. In this study we provide data on serum concentrations of methadone and EDDP during long lasting methadone therapy and explore other pharmacokinetic characteristics of a switch from morphine to methadone.

2. Material and methods

2.1. Patients

Twelve patients with chronic non-malignant pain (age >18 years) scheduled to a change in opioid therapy from oral slow release morphine to oral methadone were included in the study. Seven of these preferred to continue with methadone throughout the nine months study period. Details on the identification and inclusion of the patients as well as the clinical outcomes from the study are reported previously (Fredheim et al., 2006a).

2.2. Design and blood sampling

During a 3-day period the morphine doses were reduced by one third each day and substituted with a daily increase of one third of the assumed equianalgesic methadone dose (Lawlor et al., 1998; Fredheim et al., 2006a). Dose ratios between morphine and methadone of four to one and six to one were applied for doses below and above 200 mg, respectively. After the switch the patients entered a one week dose-titration period and were thereafter followed for nine months. Venous blood for analyses of serum concentration of morphine and methadone and their metabolites was sampled at baseline, at day one and two of the switch, at the end of the dose titration week (one week after the switch), two weeks after the switch, six weeks after the switch and three and nine months after the switch. All samples were drawn between 1445 and 1530 h. For morphine this equalled seven hours after morning dose, while it for methadone equalled two or seven hours after last dose depending on whether methadone was administered three or four times daily. Samples for methadone at three months were always drawn seven hours after last dose. Blood samples were stored at room temperature between 1 and 2 h before centrifugation. After centrifugation (3000 rpm, 10 min) serum was transferred to cryo-tubes and stored at −20 °C until analysis.

2.3. Analysis

Morphine, M3G, M6G, normorphine, methadone and EDDP were isolated from serum by solid phase extraction. The extracted samples were then identified and analyzed by a validated LC–MS/MS method (Perkin-Elmer 200 series HPLC system API 300 triple quadrupol mass spectrum). The limit of quantification was 1 ng/ml for all analytes. The standard curve range was 1–50 ng/ml for morphine and normorphine, 1–60 ng/ml for M6G and 1–500 ng/ml for M3G, methadone and EDDP. The correlation coefficients were all >0.99. Interday coefficients of variation varied from 0.1% to 7% for the 25%, 50% and 75% levels of the standard curves.

2.4. Statistics

Mean, range and standard deviation are reported when appropriate. Simple linear regression was used when analyzing how total oral opioid doses could explain opioid serum concentrations and how serum concentrations of mother compound could explain serum concentrations of metabolites. Repeated measures ANOVA was used when testing for changes in serum concentrations of methadone and EDDP during follow-up.

2.5. Ethics

The study was conducted according to the principles of the Helsinki declaration and was approved by the Regional Committee for Medical Research Ethics, Health Region Central Norway. Patients were included after informed, written consent was obtained.

Please cite this article in press as: Fredheim OMS et al., Long term methadone for chronic pain: ..., Eur J. Pain (2006), doi:10.1016/j.ejpain.2006.09.006

3. Results

3.1. Patient characteristics

Table 1 characterizes the patients with respect to age, gender, pain diagnose, morphine dose at baseline and methadone dose after titration and at nine months. Details on opioid doses, pain relief, quality of life and cognitive functioning (Fredheim et al., 2006a), concomitant drug treatment and data on the effect on QTc-time from the switch (Fredheim et al., 2006b) have been reported previously.

3.2. Methadone and metabolites

Serum concentrations of methadone (Fig. 1) did not change significantly from the end of dose titration and throughout the study period (repeated measures ANOVA, $p = 0.88$). Serum concentrations of methadone varied fivefold (range: 114–551 ng/ml). The ratio between the total daily oral methadone dose and serum concentration of methadone varied 8-fold (range 0.10:1–0.79:1). Total daily oral methadone dose at three months could not explain serum concentrations of methadone ($R^2 = 0.06$, $p = 0.61$). Serum-concentration of EDDP (Fig. 1, lower panel) one week after the end of dose titration varied sixfold (range: 12–69 ng/ml), and was explained by serum concentration of methadone ($R^2 = 0.77$, $p = 0.004$). The serum concentrations of EDDP were stable from the end of the dose titration and throughout the study period ($p = 0.055$). One patient (E) had decreased his methadone dose from 5 mg × 4 to 2.5 mg × 4 shortly before the nine months follow-up, and a 40% decrease in methadone serum concentration is seen in this patient from three to nine months.

3.3. Morphine and metabolites

Serum concentrations of morphine and the metabolites M3G, M6G and normorphine at baseline are presented in Table 1. Morphine serum concentrations at baseline varied 15-fold, from 3.7 to 52.2 ng/ml (mean 18.1–SD 16.2). The ratio between total daily oral morphine dose and serum concentration of morphine varied 7-fold (range: 5:1–32:1). The total daily oral morphine dose explained the serum concentration ($R^2 = 0.75$, $p < 0.000$). Morphine was completely eliminated in all patients within one week. Serum concentrations of M3G and M6G were explained by serum concentrations of morphine ($R^2 = 0.790$, $p < 0.000$ and $R^2 = 0.786$, $p < 0.000$, respectively). Serum concentrations of normorphine were not explained by morphine serum concentrations ($R^2 = 0.024$, $p = 0.631$).

3.4. Morphine:methadone ratios

The ratios between total daily doses of oral morphine and methadone varied threefold (range 1.8/1–4.5/1). The ratios between serum concentrations of morphine and methadone varied fourfold (range 12.5:1–50:1). However, no significant correlation between the oral dose ratios and serum concentration ratios was seen (Pearson correlation, $R = 0.52$, $p = 0.19$).

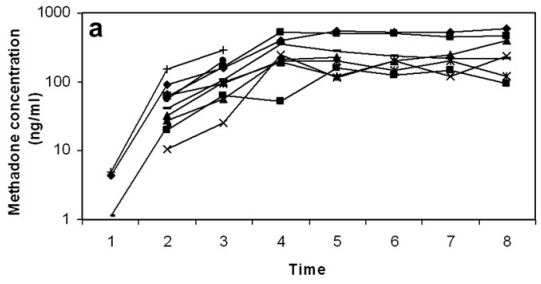
3.5. Other observations and outliers

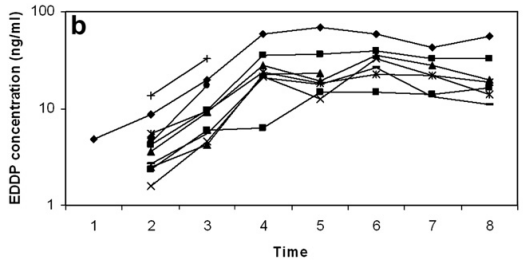
The pharmacological analyses identified some outliers and some unexpected observations were made. At baseline traces of methadone were detected in patients G, H and J and in patient J also traces of EDDP. In patient D who did not report use of morphine or codeine after the switch, morphine-glucuronides in

Table 1
Patient characteristics

ID	Gender/age	Pain diagnosis	Morphine dose baseline mg/24 h	Baseline serum concentrations				Methadone dose after titration mg/24 h	Methadone dose 9 months mg/24 h
				Morphine	M6G	M3G	Normorphine		
A	M/58	Low back pain	450	36.9	665.6	3722.0	3.5		
B	M/47	Low back pain, cox arthrosis	120	3.7	106.5	538.0	14.3	30	35
C	F/67	Low back pain	90	10.4	133.4	981.9	1.2	30	
D	M/41	Low back pain	150	9.0	123.7	605.4	0.0	85	100
E	M/64	Central pain	90	16.3	294.0	1017	2.7	20	10
F	F/70	Severe osteoporosis	50	3.8	68.9	455.2	0.0		
G	M/66	Severe osteoporosis	800	52.2	1878.2	11211.8	5.0		
H	F/77	Low back pain, radiculopathy	60	4.4	72.5	432.4	1.5		
I	M/59	Low back pain	90	7.1	171.3	961.2	0.0	30	22.5
J	F/60	Post surgery neuropathy	180	18.9	472.9	2145.6	4.0	80	90
K	F/63	Low back pain	200	40.0	538.9	3549.7	5.3	60	60
L	M/50	Low back pain	150	14.2	248.7	1745.0	1.9	70	80

Please cite this article in press as: Fredheim OMS et al., Long term methadone for chronic pain: ..., Eur J. Pain (2006), doi:10.1016/j.ejpain.2006.09.006





Time	Stage of opioid switch	Medication
1	Day 1 of switch	3/3 morphine dose, 0/3 methadone dose
2	Day 2 of switch	2/3 morphine dose, 1/3 methadone dose
3	Day 3 of switch	1/3 morphine dose, 2/3 methadone dose
4	End of dose titration	Has reached final methadone dose
5	1 week after titration	1 week on stable methadone dose
6	6 weeks after titration	6 weeks on stable methadone dose
7	3 months after titration	3 months on stable methadone dose
8	9 months after titration	9 months on stable methadone dose

Fig. 1. Semilogarithmic plot of methadone and EDDP serum concentrations during nine months methadone treatment.

serum were observed at three months. In patient G M3G/morphine and M6G/morphine ratios of 215 and 36 were observed compared to average ratios of 104 and 19 in the rest of the patients. However, a rapid decline in serum concentrations of M3G and M6G was observed when morphine was substituted with methadone. In patient B the level of normorphine exceeded twice the levels in other patients while his serum-concentration of morphine was one of the lowest.

4. Discussion

Novel information is that methadone serum concentrations are stable from the end of dose titration and during long term treatment with stable doses for pain. Serum concentrations of EDDP, the primary methadone metabolite, are also stable, indicating that methadone metabolism is not altered during long term treatment for pain. This finding contradicts the hypothesis of metabolic tolerance and autoinduction of hepatic enzymes during long term methadone therapy (Sawe, 1986). Autoinduction has been hypothesized based on data reporting decreasing serum concentrations during long-term methadone treatment with stable doses in opioid maintenance treatment (Verebely et al., 1975; Anggard et al., 1975; Holmstrand et al., 1978).

Our findings may contribute to the understanding of the interindividual differences in dose ratios when switching from morphine to methadone. In contrast to morphine, serum concentration of methadone was in this study not explained by dose of oral methadone. This may be a type 2 error due to small sample size, but is probably a consequence of the large interindividual variability of methadone bioavailability and half times. This is supported by data from opioid maintenance therapy which have reported low correlation between methadone dose and steady state serum concentration (de Vos et al., 1995), and that methadone dose can only explain about half the variability of methadone serum concentration (Eap et al., 1998). One study on opioid maintenance therapy found a high correlation between daily oral methadone doses adjusted for body weight and plasma concentrations of methadone, but also observed some patients with unexpected serum concentrations (Wolff et al., 1991).

Furthermore, we observed a low and not statistically significant correlation between morphine:methadone

Please cite this article in press as: Fredheim OMS et al., Long term methadone for chronic pain: ..., Eur J. Pain (2006), doi:10.1016/j.ejpain.2006.09.006

dose ratios and morphine:methadone serum concentration ratios. The important information here is that patients requiring the highest methadone dose relative to morphine dose were not the same as the patients with the highest methadone serum concentration relative to morphine serum concentration. However, all results based on total methadone serum concentration need to be interpreted cautiously as levomethadone (the R-enantiomer) is responsible for the μ-opioid receptor mediated analgesic effects of methadone (Kristensen et al., 1995). A 15-fold variation of morphine serum concentrations was observed while variations for methadone were five-fold. One of the possible explanations for this is that some patients have developed a high degree of opioid tolerance prior to the opioid switch and that cross-tolerance between methadone and other opioids is incomplete. Serum concentrations may also have been influenced by metabolic interaction with other drugs. Two patients in our study were concomitantly treated with venlafaxine which is known to be an inhibitor of CYP3A4 and two patients were treated with amitriptyline which may possibly influence methadone serum concentrations (Ferrari et al., 2004). There were indications that metabolism of methadone was inhibited in these patients, but conclusions cannot be drawn due the limited number of patients.

Measurement of serum concentrations of mother compound and metabolites may identify patients who differ significantly from the rest, and thus contribute to the understanding of interindividual variations in opioid pharmacology. For instance did only 8 of 12 patients metabolise morphine to normorphine. Moreover, one subject showed low morphine levels together with high normorphine levels, which may indicate that a larger proportion of morphine than usual is metabolised along this pathway in this subject. Also, very high levels of morphine glucuronides were observed in one patient, which was probably due to rapid generation from morphine, as the glucuronides were rapidly eliminated after terminating morphine.

Finally, the finding of M3G in one patient at three months after the switch indicates that this patient has used codeine or morphine in addition to methadone. Also the traces of methadone in three patients at baseline indicate that all chronic non-malignant pain patients may not adhere strictly to the treatment plan.

In conclusion, our study has indicated that methadone serum concentrations and metabolism are stable during long term treatment for pain and that large interindividual differences in methadone pharmacokinetics exist. Previously pharmacogenetic studies on morphine have to some extent explained the differences in need for morphine in cancer patients (Klepstad et al., 2005). Recently it was also reported that the 118A > G mutation in the *OPRM1* gene is associated with decreased effects of levomethadone when assessed with pupillometry after a single dose in healthy volunteers (Lotsch et al., 2006). Future studies will hopefully determine the contribution of genetic factors to the interindividual variation of the pharmacology of methadone in patients.

Acknowledgement

We are grateful for the assistance of Trine N. Andreassen, M.Sc. who performed the opioid serum concentration analyses.

References

Anggard E, Gunne LM, Homstrand J, McMahon RE, Sandberg CG, Sullivan HR. Disposition of methadone in methadone maintenance. Clin Pharmacol Ther 1975;17:258–66.

Coffman BL, Rios GR, King CD, Tephly TR. Human UGT2B7 catalyzes morphine glucuronidation. Drug Metab Dispos 1997;25:1–4.

Dale O, Sheffels P, Kharasch ED. Bioavailabilities of rectal and oral methadone in healthy subjects. Br J Clin Pharmacol 2004;58:156–62.

de Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity reduction in terminal cancer patients. J Pain Symptom Manag 1995;10:378–84.

de Vos JW, Geerlings PJ, van den Brink W, Ufkes JG, van Wilgenburg H. Pharmacokinetics of methadone and its primary metabolite in 20 opiate addicts. Eur J Clin Pharmacol 1995;48:361–6.

Eap CB, Bertschy G, Baumann P. High interindividual variability of methadone enantiomer blood levels to dose ratios. Arch Gen Psychiatry 1998;55:89–90.

Ferrari A, Coccia CPR, Bertolini A, Sternieri E. Methadone – metabolism, pharmacokinetics and interactions. Pharmacol Res 2004;50:551–9.

Fredheim O, Kaasa S, Dale O, Klepstad P, Landro N, Borchgrevink PC. Opioid switching from oral slow release morphine to oral methadone may improve pain control in chronic non-malignant pain: a nine month follow-up study. Palliat Med 2006a;20:35–41.

Fredheim O, Borchgrevink PC, Hegrenæs L, Kaasa S, Dale O, Klepstad P. Opioid switching from morphine to methadone causes a minor but not clinically significant increase in QTc: a prospective 9 months follow-up study. J Pain Symptom Manag 2006b;32(2):180–5.

Garrido MJ, Troconiz IF. Methadone: a review of its pharmacokinetic/pharmacodynamic properties. J Pharmacol Toxicol 1999;42:61–6.

Gourlay GK, Cherry DA, Cousins MJ. A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. Pain 1986;25:297–312.

Hanks GW, de Conno F, Cherny N, Hanna M, Kalso E, McQuay HJ, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Cancer 2001;84:587–93.

Hasselstrom J, Sawe J. Morphine pharmacokinetics and metabolism in humans. Enterohepatic cycling and relative contribution of metabolites to active opioid concentrations. Clin Pharmacokinet 1993;24:344–54.

Holmstrand J, Anggard E, Gunne LM. Methadone maintenance: plasma levels and therapeutic outcome. Clin Pharmacol Ther 1978;23:175–80.

Iribarne C, Berthou F, Baird S, Dreano Y, Picart D, Bail JP, et al. Involvement of cytochrome P450 3A4 enzyme in the *N*-demetyla-

tion of methadone in human liver microsomes. Chem Res Toxicol ;9:365–73.

Klepstad P, Dale O, Skorpen F, Borchgrevink PC, Kaasa S. Genetic variability and clinical efficacy of morphine. Acta Anaesthesiol Scand 2005;49:902–8.

Kristensen K, Christensen CB, Christrup LL. The mu1, mu2, delta, kappa opioid receptor binding profiles of methadone stereoisomers and morphine. Life Sci 1995;56:45–50.

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

Lotsch J, Weiss M, Ahne G, Kobal G, Geisslinger G. Pharmacokinetic modeling of M6G formation after oral administration of morphine in healthy volunteers. Anesthesiology 1999;90:1026–38.

Lotsch J, Skarke C, Wieting J, Oertel BG, Schmidt H, Brockmoller J, et al. Modulation of the central nervous effects of levomethadone by genetic polymorphisms potentially affecting its metabolism, distribution and drug action. Clin Pharmacol Ther 2006;79:72–89.

Meresaar U, Nilsson MI, Holmstrand J, Anggard E. Single dose pharmacokinetics and bioavailability of methadone in man studied with a stable isotope method. Eur J Clin Pharmacol 1981;20:473–8.

Projean D, Morin PE, Tu TM, Ducharme J. Identification of CYP3A4 and CYP2C8 as the major cytochrome P450s responsible for morphine *N*-demetylation in human liver microsomes. Xenobiotica 2003;33:841–54.

Sawe J. High-dose morphine and methadone in cancer patients. Clinical pharmacokinetic considerations of oral treatment. Clin Pharmacokinet 1986;11:87–106.

Verebely B, Volavka J, Mule S, Resnick R. Methadone in man: pharmacokinetic and excretion studies in acute and chronic treatment. Clin Pharmacol Ther 1975;18:180–90.

Wiffen PJ, Edwards JE, Barden J, McQuay HJ. Oral morphine for cancer pain. The cochrane database of systematic reviews 2003, Issue 4. Art. No.: CD003868. DOI: 10.1002/14651858. CD003868.

Wolff K, Sanderson M, Hay AWM, Raistrick D. Methadone concentrations in plasma and their relationship to drug dosage. Clin Chem 1991;37:205–9.

Please cite this article in press as: Fredheim OMS et al., Long term methadone for chronic pain: ..., Eur J. Pain (2006), doi:10.1016/j.ejpain.2006.09.006

Paper 5

Clinical Note

Opioid Switching from Morphine to Methadone Causes a Minor But Not Clinically Significant Increase in QTc Time: A Prospective 9-Month Follow-Up Study

Olav Magnus S. Fredheim, MD, Petter C. Borchgrevink, MD, PhD, Lars Hegrenæs, MD, Stein Kaasa, MD, PhD, Ola Dale, MD, PhD, and Pål Klepstad, MD, PhD

Pain and Palliation Research Group, Institute of Circulation and Medical Imaging (O.M.S.F., P.C.B., O.D., P.K.), and Pain and Palliation Research Group, Institute of Cancer Research and Molecular Medicine (S.K.), Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; and Department of Anesthesiology (P.C.B., O.D., P.K.), Palliative Medicine Unit, Department of Oncology (S.K.), and Department of Cardiology (L.H.), St. Olav University Hospital, Trondheim, Norway

Abstract

Case reports and retrospective studies suggest that methadone causes an increase in QTc (QT time corrected for heart rate) time and risk of torsades de pointes arrhythmia. No prospective studies in pain patients have been conducted, and data on whether a methadone-induced increase in QTc time persists during long-term treatment have not been reported. Eight chronic nonmalignant pain patients experiencing insufficient pain control or intolerable side effects during treatment with oral morphine switched to oral methadone and were included in this study. Electrocardiograms were obtained at baseline and at follow-up 2 weeks, and 3 and 9 months after the opioid switch. Start of methadone caused a minor but statistically significant increase in QTc time, while fluctuations in QTc during treatment with stable doses of methadone were neither clinically nor statistically significant. We observed no episodes of arrhythmias. J Pain Symptom Manage 2006;32:180–185. © *2006 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words

Methadone, QT time, arrhythmia, chronic pain, opioid switch

Introduction

A prolonged interval between the Q-wave and the end of the T-wave (QT time) at the electrocardiogram (ECG) is associated with an increased risk for arrhythmias, particularly the potentially lethal torsades de pointes arrhythmia.[1] The risk for torsades de pointes increases with increasing QTc times (QTc represents the QT time adjusted for heart rate)

Address reprint requests to: Olav Magnus S. Fredheim, MD, Multidisciplinary Pain Center, St. Olav University Hospital, Olav Kyrresgt. 17, 7030 Trondheim, Norway. E-mail: olavmagn@frisurf.no

Accepted for publication: February 15, 2006.

0885-3924/06/$–see front matter
doi:10.1016/j.jpainsymman.2006.02.010

and is clinically significant if the QTc time exceeds 0.50 seconds.[1] Several factors may influence the QTc time, including gender and the use of drugs such as antiarrhythmics, macrolides, clindamycin, antidepressants, and antipsychotic drugs. Opioid analgesics are also shown to influence the QTc time. Prolonged QTc times associated with methadone treatment have been described both during high-dose intravenous methadone administration to cancer patients and in patients receiving oral methadone in opioid maintenance programs.[2,3] QTc time increases from opioids may also be associated with other opioids, as observed in cancer patients after start of intravenous morphine.[2]

To our knowledge, the change in QTc time caused by opioid switching from oral slow-release morphine to oral methadone in the treatment of chronic nonmalignant pain has not been reported previously. Moreover, none of the reports of prolonged QT time have included more than a single ECG after the start of methadone. Thus, in this hypothesis-generating study, we report QTc times measured before opioid switching from morphine to methadone and QTc times measured 2 weeks, and 3 and 9 months after the opioid switch in patients treated for chronic nonmalignant pain. The primary outcome was increase in QTc 2 weeks after the switch to methadone.

Materials and Methods

This study was conducted according to the principles of the Helsinki Declaration and was approved by the Regional Committee for Medical Research Ethics. After obtaining written informed consent, patients with chronic nonmalignant pain (age >18 years) were included. All patients were scheduled for a change in opioid treatment from oral slow-release morphine to oral methadone. The indications for start of methadone were insufficient pain control and/or adverse effects during morphine treatment. All patients were treated by the multidisciplinary pain clinic at St. Olav University Hospital, Trondheim, Norway, and were screened for indications for an opioid switch to methadone. Twelve patients were included. Details on the identification and inclusion of patients, as well as clinical outcomes including patient preference of opioids and the effects on pain, health related quality of life, and cognitive functioning, have been reported in a separate publication.[4]

Opioid Switching

The opioid switch was performed by substituting the morphine dose during a 3-day period with the estimated equianalgesic dose of methadone. The morphine dose was decreased by one-third each day, and substituted with a daily increase of one-third of the estimated equianalgesic total methadone dose. The dose ratio between morphine and methadone shows inter-individual variation and may be dependent on dose.[5,6] Because all patients included in the study used low doses of morphine, a morphine:-methadone ratio ranging from 4:1 to 6:1 was applied. After the switch was completed, the patients entered a methadone dose-titration period of one week to achieve an optimal balance between pain control and side effects. Changes in other medications were not performed.

ECG

A 12-lead ECG was recorded at baseline 4 days before the start of the opioid switching, and at 2 weeks, and 3 and 9 months after start of methadone. The QT interval is defined as the interval between the Q-wave and the end of the T-wave. Lead II was preferred for measurement of QT time and RR interval. If the quality of Lead II precluded proper assessment, Lead I was used. The same lead was measured on the four consecutive ECGs for each individual patient. The QTc time was computed using Bazetts formula, $QTc = QT/\sqrt{RR}$. The QT times and the RR intervals were measured by a cardiologist. The ECGs were also checked for conditions affecting the validity of the measured QT time.

Statistics

Paired samples *t*-test (two-sided test) was used to test for the primary outcome, which was increase in QTc 2 weeks after the switch to methadone. The use of the paired *t*-test was based on the assumption of QTc times being normally distributed and is in accordance with a previous report.[2] Long-term change in QTc was tested with repeated measures ANOVA on the observations from the three follow-up consultations. Statistical analyses were performed using the SPSS version 11.0.

Table 1
Patient Characteristics

				Baseline Data				Methadone (mg/24 hours)		
ID	Age/Gender	Pain	Other Medications	Morphine (mg/24 hours)	$[Mg^{++}]$ mmol/L	$[K^{+}]$ mmol/L	$[Ca^{++}]$ Total mmol/L	2 Weeks	3 Months	9 Months
NR	47 M	Low back pain, cox arthrosis	Paracetamol, diazepam, loratadine, salmeterol	120	0.76	3.1	2.47	30	30	35
IY	66 F	Low back pain	Levothyroxine, paracetamol	90	0.32	4.3	2.47	35	Switched back to morphine	
VI	41 M	Low back pain	Amitriptyline, venlafaxine, paracetamol, zopiclone, salbutamol inhalant	150	0.90	4.3	2.43	85	100	100
ON	64 M	Central pain, amputation	None	90	0.63	3.9	2.43	20	20	10
AR	59 M	Low back pain	None	90	0.78	3.9	2.40	30	30	22.5
IO	59 F	Postsurgery neuropathy	Mianserin hydrochloride, amitriptyline, natrium alendronate, calcium, cholecalciferol, oestradiol	180				80	80	90
SG	62 F	Low back pain, multiple sclerosis	Salbutamol, oestradiol. dinatrium etidron, calcium	200	0.78	3.9	2.46	60	60	60
GT	40 M	Low back pain	Zopiclone, salmeterol inhalant, salbutamol inhalant, acetylsalicylic acid, valsartan, karvedilol, venlafaxine	150	0.85	4.1	2.53	70	75	80
Mean				134	0.72	3.93	2.46	51	56	57
SD				43	.194	.407	.042	25	30	35

Table 2
QT Time, RR Interval, and QTc in Seconds

Patient ID	Baseline			2 Weeks after Opioid Switch			3 Months after Opioid Switch			9 Months after Opioid Switch		
	QT	RR	QTc	QT	RR	QTc	QT	RR	QTc	QT	RR	QTc
NR[a]	0.41	0.79	0.46	0.37	0.65	0.46	0.40	1.00	0.40	0.37	0.88	0.39
IY	0.40	0.85	0.43	0.40	0.81	0.44						
VI	0.35	0.72	0.41	0.34	0.65	0.42	0.38	0.77	0.43	0.37	0.84	0.40
ON	0.35	0.69	0.42	0.40	0.83	0.44	0.34	0.69	0.41	0.35	0.70	0.42
AR[b,c]	0.37	0.79	0.42	0.43	0.93	0.45	0.47	0.90	0.49	0.48	0.92	0.50
IO	0.41	0.90	0.43	0.43	0.94	0.44	0.45	0.87	0.48	0.44	0.94	0.45
SG	0.38	1.03	0.37	0.40	0.91	0.42	0.42	1.06	0.41	0.43	1.05	0.42
GT[b,d]	0.43	1.27	0.38	0.43	1.07	0.42	0.45	1.19	0.41	0.40	0.87	0.43
Mean	0.39	0.88	0.42	0.40	0.85	0.44	0.42	0.93	0.43	0.41	0.89	0.43
SD	0.03	0.19	0.03	0.03	0.15	0.02	0.05	0.17	0.04	0.05	0.11	0.04

[a]Lead V1 was used for measurements at 9-month follow-up.
[b]Lead I was used for measurements of QT time and RR interval.
[c]Supraventricular tachycardia at 9 months. Data from new ECG 2 months later.
[d]Right bundle branch block at 9 months.

Results

Patient Characteristics

Twelve patients were switched from morphine to methadone. Four patients were switched back to morphine before the first follow-up ECG was scheduled. The switches back to morphine were not caused by arrhythmias or other cardiac symptoms. The remaining eight patients were included in this study. Age, gender, cause of pain, other medications and serum concentrations of magnesium, potassium and calcium at baseline are shown for each patient in Table 1. One patient was switched back to oral morphine before the 3-month follow-up due to profuse sweating, considered to be a treatment-related adverse effect. Pain scores on an 11-point numeric rating scale showed an average decrease of 2.9 (range 1–6) following the switch to methadone.

Doses of Morphine and Methadone

Mean oral morphine dose prior to the opioid switch (baseline ECG) was 134 mg/24 hours. Mean oral methadone dose 2 weeks, and 3 and 9 months after opioid switching was 51, 56 and 57 mg/24 hours, respectively. Daily opioid doses at baseline, 2 weeks, and 3 and 9 months for each patient are reported in Table 1.

Change in QTc Time

The heart rates, QT times, and QTc times for each patient at baseline, 2 weeks after switching to methadone and at the 3- and 9-month follow-up are presented in Table 2. The mean QTc time increased from 0.416 before start of methadone to 0.436 2 weeks after start of methadone (mean change = 0.020, 95% CI = 0.007–0.032, $P = 0.01$). The changes in the follow-up observations of QTc time were not statistically significant (repeated measures ANOVA, $P = 0.90$), indicating that duration of QTc time was not associated with time from the switch to methadone. At the 9-month follow-up, the ECG from one patient (AR) showed a supraventricular tachycardia and could not be used for comparison of QTc time. An additional ECG obtained 2 months later (sinus rhythm) showed a minor increase in QTc compared to the 3-month follow-up. At the 9-month follow-up, ECG recordings from only precordial leads were of satisfactory quality for assessment of QTc time in patient NR, and lead V1 was therefore used for measurement. Patient GT presented a right bundle branch block at the 9-month follow-up. No QTc times above 0.50 seconds or episodes of arrhythmia were observed.

Discussion

The observations from this prospective case series indicate that opioid switching from low doses of oral slow-release morphine to an equianalgesic dose of oral methadone causes a small but clinically insignificant increase in QTc time. Nine months of follow-up brought novel information indicating that changes in QTc during long-term methadone treatment

are small and neither clinically nor statistically significant in this population. However, for two patients, we observed QTc increases close to clinically significant levels.

We observed that low-dose oral methadone for chronic nonmalignant pain in otherwise healthy patients caused minor increases in QTc times. This is novel information because previous reports of increased QTc times associated with methadone treatment have been from patients treated with high doses of intravenous methadone,[2] patients receiving oral methadone for opioid maintenance therapy,[3,7,8] patients with other potential factors influencing the QT interval[9,10] or finally, patients receiving daily doses of more than 600 mg in the treatment of chronic nonmalignant pain.[9] A recent cross-sectional study including 104 patients receiving long-term methadone therapy for chronic pain or opioid maintenance therapy observed a prolongation of the QTc time in one-third of the patients. Multivariate analysis performed in this study indicated that methadone treatment was associated with prolonged QTc in males within one year of initiation of treatment.[11] In contrast to these findings, a retrospective study including 56 patients receiving low doses of methadone for cancer pain did not find increases in QTc times.[12] None of these studies investigated the time course of QTc time associated with methadone treatment. Furthermore, the conflicting findings illustrate that the additional risk associated with methadone treatment is not established.

This study may have underestimated the true effect from methadone on QT times. Kornick et al.[2] have reported an increase in QT times following start of intravenous morphine in patients with cancer pain. All patients in our study were treated with oral morphine before the start of methadone, and hence may have a morphine-induced increase of the QT times at baseline. Consequently, the true effect from methadone on QT time if given to opioid naïve patients may be larger than the effect demonstrated in this study. Ideally, QTc should be determined based on continuous QT readings to allow for possible changes in QTc during the day, but such methodology was not feasible in outpatients at a pain center.

In this study, neither arrhythmia nor cases of QTc times above 0.50 seconds were observed. However, it is important to recognize that observations obtained in a case series of eight patients cannot exclude that start of oral low-dose methadone may cause arrhythmias or clinically significant increases in QTc times. This is especially true for patients with genetic predisposition or other risk factors, such as hypokalemia, hypomagnesemia, use of diuretics, bradycardia, congestive heart failure, or concomitant treatment with drugs that predispose to increases of QTc time.[1] This relationship between methadone and risk factors for arrhythmias was supported by case reports in which at-risk patients developed torsades de pointes arrhythmia during methadone treatment.[7,9,10]

Data in the present study indicate that start of low doses of methadone caused an increase in QTc, which was not clinically significant and that QTc was stable during follow-up. This finding is supported by a previous cross-sectional study of long-lasting methadone treatment, which observed that one-third of patients had prolonged QTc but did not observe any correlation between QTc and duration of treatment.[11] However, the risk of clinically significant QTc prolongation has not yet been determined. Thus, prospective studies including patients on both high and low doses of methadone are needed. Until data from such studies are available, a cautious clinical practice might include screening patients for pathological QT intervals and known risk factors for long QT syndrome before initiating methadone treatment and before and after escalation to high-dose treatment.[13] If risk factors are present, the possible clinical benefit should be carefully balanced against the possible risk of arrhythmia.

References

1. Viskin S. Long QT syndromes and torsade de pointes. Lancet 1999;354:1625–1633.

2. Kornick CA, Kilborn MJ, Santiago-Palma J, et al. QTc interval prolongation associated with intravenous methadone. Pain 2003;105:499–506.

3. Martell BA, Ray B, Gourevitch MN. The impact of methadone induction on cardiac conduction in opiate users. Ann Intern Med 2003;139:154–155.

4. Fredheim O, Kaasa S, Dale O, et al. Opioid switching from oral slow release morphine to oral methadone may improve pain control in chronic non-malignant pain: a nine-month follow-up study. Palliat Med 2006;20:35–41.

5. Lawlor P, Turner K, Hanson J, Bruera E. Dose ratio between morphine and methadone in patients with cancer pain. Cancer 1998;82:1167–1173.

6. Ripamonti C, Groff L, Brunelli C, et al. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol 1998;16:3216–3221.

7. Krantz MJ, Lewkowiez L, Hays H, et al. Torsade de pointes associated with very-high-dose methadone. Ann Intern Med 2002;137:501–504.

8. Maremmani I, Pacini M, Cesaroni C, et al. QTc interval prolongation in patients on long-term methadone maintenance therapy. Eur Addict Res 2005;11:44–49.

9. Walker PW, Klein D, Kasza L. High dose methadone and ventricular arrhythmias: a report of three cases. Pain 2003;103:321–324.

10. Gil M, Sala M, Anguers I, et al. QT prolongation and torsades de pointes in patients infected with human immunodeficiency virus and treated with methadone. Am J Cardiol 2003;92:995–997.

11. Cruciani RA, Sekine R, Homel P, et al. Measurement of QTc in patients receiving chronic methadone therapy. J Pain Symptom Manage 2005;29: 385–391.

12. Reddy S, Fisch M, Bruera E. Oral methadone for cancer pain: no indication of QT interval prolongation or torsades de pointes. J Pain Symptom Manage 2004;28:301–303.

13. Krantz MJ, Kutinsky IB, Robertson AD, Mehler PS. Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. Pharmacotherapy 2003;23:802–805.

Dissertations at the Faculty of Medicine, NTNU

1977

1. Knut Joachim Berg: EFFECT OF ACETYLSALICYLIC ACID ON RENAL FUNCTION
2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED *IN VITRO*

1978

3. Karel Bjørn Cyvin: CONGENITAL DISLOCATION OF THE HIP JOINT.
4. Alf O. Brubakk: METHODS FOR STUDYING FLOW DYNAMICS IN THE LEFT VENTRICLE AND THE AORTA IN MAN.

1979

5. Geirmund Unsgaard: CYTOSTATIC AND IMMUNOREGULATORY ABILITIES OF HUMAN BLOOD MONOCYTES CULTURED IN VITRO

1980

6. Størker Jørstad: URAEMIC TOXINS
7. Arne Olav Jenssen: SOME RHEOLOGICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MUCOID SPUTUM FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

1981

8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS *IN VITRO*

1983

9. Tore Syversen: EFFECTS OF METHYLMERCURY ON RAT BRAIN PROTEIN.
10. Torbjørn Iversen: SQUAMOUS CELL CARCINOMA OF THE VULVA.

1984

11. Tor-Erik Widerøe: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.
12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REALTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AN STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
15. Inggard Lereim: TRAFFIC ACCIDENTS AND THEIR CONSEQUENCES.
16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.
17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OG DRUGS.

1985

18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
19. Terje Espevik: THE CYTOSKELETON OF HUMAN MONOCYTES.
20. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.
21. Ole-Jan Iversen: RETROVIRUS-LIKE PARTICLES IN THE PATHOGENESIS OF PSORIASIS.
22. Lasse Eriksen: EVALUATION AND TREATMENT OF ALCOHOL DEPENDENT BEHAVIOUR.
23. Per I. Lundmo: ANDROGEN METABOLISM IN THE PROSTATE.

1986

24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
25. Odd Arnold Kildahl-Andersen: PRODUCTION AND CHARACTERIZATION OF MONOCYTE-DERIVED CYTOTOXIN AND ITS ROLE IN MONOCYTE-MEDIATED CYTOTOXICITY.
26. Ola Dale: VOLATILE ANAESTHETICS.

1987

27. Per Martin Kleveland: STUDIES ON GASTRIN.
28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
29. Vilhjalmur R. Finsen: HIP FRACTURES

1988

30. Rigmor Austgulen: TUMOR NECROSIS FACTOR: A MONOCYTE-DERIVED REGULATOR OF CELLULAR GROWTH.
31. Tom-Harald Edna: HEAD INJURIES ADMITTED TO HOSPITAL.
32. Joseph D. Borsi: NEW ASPECTS OF THE CLINICAL PHARMACOKINETICS OF METHOTREXATE.

33. Olav F. M. Sellevold: GLUCOCORTICOIDS IN MYOCARDIAL PROTECTION.
34. Terje Skjærpe: NONINVASIVE QUANTITATION OF GLOBAL PARAMETERS ON LEFT VENTRICULAR FUNCTION: THE SYSTOLIC PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT.
35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

1989

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 CANSER.
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 OG 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