Mortality and QTc prolongation in opioid maintenance treatment

Norwegian Centre for Addiction Research (SERAF)

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PhD thesis

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Acknowledgements

When I had completed my medical training and house officer job in 2004 I accidently got a post as a physician in opioid maintenance treatment (OMT) at LAR Øst in Oslo. This triggered my interest for addiction medicine. The patients often came to me with questions regarding OMT and various health aspects. When searching in the literature, there appeared to be a lack of research and clear answers to many of these questions. At the time professor Helge Waal was my clinical supervisor and together we planned the research project which has since resulted in this thesis.

I will therefore start by thanking Helge Waal, who has been my main supervisor during this work. Thank you for your open door and availability, your encouragement and for sharing your vast knowledge with me in this process. Your lifelong dedication to addiction medicine has been an everyday inspiration.

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Katinka Anchersen
Summer 2010

List of papers

Paper 1

Mortality prior to, during and after opioid maintenance treatment (OMT): A national prospective cross-registry study

Thomas Clausen, Katinka Anchersen, Helge Waal.

Drug and Alcohol Dependence 2008; 94: 151-157.

Paper 2

Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: A mortality assessment study

Katinka Anchersen, Thomas Clausen, Michael Gossop, Viggo Hansteen, Helge Waal.

Addiction 2009; 104: 993-999.

Paper 3

Opioid maintenance patients with QTc prolongation: Congenital long QT syndrome mutation may be a contributing risk factor

Katinka Anchersen, Viggo Hansteen, Michael Gossop, Thomas Clausen, Helge Waal.

Drug and Alcohol Dependence 2010*; in press.*

Summary of research

Mortality and health aspects associated with long term use of opioid maintenance treatment (OMT) are insufficiently researched. The first study investigated mortality prior to, during and after the Norwegian OMT programme. A national OMT register was established based on the electronic record system in OMT centres in Norway. The register contained a total observation period of seven years, from January 1997 to December 2003. Based on national security numbers, these data were cross-linked with the Norwegian national death register, consisting of all Norwegian death certificates. The death certificates include one principal cause of death, and up to four underlying causes (ICD 10 codes). Only the principal cause of death was used.

There was a significant overall reduction in mortality risk between pre-treatment and in-treatment groups (hazard ratio 0.5, $P = 0.001$). The post-treatment group as a whole was not significantly different from the pre-treatment group with regards to mortality; however, a tendency toward gender differences was observed. Following treatment, males had significantly higher mortality compared to the pre-treatment levels. The post-treatment females had a non-significant tendency toward reduced mortality. A significant overall reduction in mortality risk between the pre-treatment and the intention-to-treat individuals (hazard ratio of 0.6, $P = 0.004$) was identified. Risk of overdose death was significantly reduced with OMT, both for the in-treatment group separately and in intention-to-treat analysis.

We then investigated the prevalence of corrected QT (QTc) interval prolongation in OMT. Many studies have pointed to a relation between methadone and QTc prolongation. This is associated with a type of cardiac arrhythmia known as torsades des points (TdP) that can lead to syncope and in worst case sudden death. Our aim was to assess the prevalence of QTc prolongation over 500 msec (generally considered the threshold for TdP development), to compare methadone and buprenorphine, investigate a potential dose-dependent association and possible risk factors for prolonged QTc interval.

In a cross-sectional study, we recorded electrocardiographies (ECGs) on 200 OMT patients in Oslo. 173 of these were on methadone, the rest on buprenorphine. The ECGs were assessed by a senior cardiologist, blinded for all patient details. Of the 173 patients on methadone, eight were found to have QTc interval above 500 msec. These were all on doses of 120 mg or more per day. None of the buprenorphine patients exhibited QTc prolongation. A dose-dependent association was found between methadone dose and the length of the QTc interval. There was no association detected in the analyses between age, gender or time in treatment and QTc prolongation.

The clinical relevance of QTc prolongation and whether deaths in OMT could potentially be attributed to QTc prolongation and ventricular arrhythmia was investigated. The data from the first cross-register study was examined and the stated causes of death for patients in treatment analysed. 90 deaths had occurred among the 2382 patients with 6450 total years in OMT. Only four could possibly be attributed to ventricular arrhythmia. Thus, the maximum mortality rate potentially attributable to QTc prolongation was 0.06 deaths per 100 patient years in OMT. Additionally, only one death among 3850 OMT initiations occurred within the first month of treatment.

Finally, the eight patients previously found to have prolonged QTc intervals above 500 msec were offered further cardiac investigations and management. The investigations included a new ECG at rest, exercise ECG, 24 hours ECG (Holter) and genetic testing for the five most common long QT syndrome (LQTS) mutations. Seven patients accepted genetic testing. One of these later dropped out of OMT. Six patients attended the cardiac outpatient clinic. The QTc intervals fluctuated widely over 24 hours and during exercise. Two were heterozygous carriers of mutations in LQTS1 and LQTS2 genes, respectively. Both had previous histories of cardiac symptoms, but had never been under cardiac investigations prior to the study. One had already switched to buprenorphine and started on protective beta-blocker. None of the remaining five patients, including the women with the LQTS2 mutation, wanted to switch to buprenorphine or take other cardiac protective measures. Safe cardiac management of methadone patients found to have QTc prolongation proved very difficult.

Norsk sammendrag

Dødelighet og helseproblemer knyttet til legemiddelassistert rehabilitering (LAR) er utilstrekkelig forsket på. I det første studiet undersøkte vi dødelighet knyttet til perioden før, under og etter LAR behandling. Et norsk LAR register ble etablert og inneholdt informasjon om alle som hadde søkt LAR i Norge over en syv års periode, fra januar 1997 til desember 2003. Ved bruk av personnummer ble dette registeret krysset med det norske dødsårsaksregisteret til Statistisk sentralbyrå (SSB). Kun hoveddødsårsak ble benyttet.

En signifikant totalreduksjon i dødelighet ble funnet under behandling, sammenlignet med før LAR. På totalgruppenivå var det ingen dødelighetsforskjell mellom før- og etter-LAR gruppene, mens en tendens til kjønnsforskjell ble funnet. Etter avsluttet behandling hadde menn en signifikant økt dødelighet sammenlignet med før LAR, mens kvinner hadde en ikke-signifikant tendens til lavere dødelighet. En signifikant nedgang i dødelighet ble funnet mellom før-LAR og intensjon-om-å-behandle-gruppene. Risiko for overdosedød ble redusert med LAR, både for de i behandling og for intensjon-om-å-behandle-gruppen.

Vi undersøkte også forekomsten av korrigert QT (QTc) forlengelse i LAR. Mange studier har vist til en sammenheng mellom metadon og QTc forlengelse. Dette tilknyttes en type hjertearytmi kjent som torsades des pointes (TdP), som kan lede til synkope og i verste fall brå død. Vårt mål var å undersøke forekomsten av QTc forlengelse over 500 millisekunder (ofte antatt å være terskel for TdP utvikling), å sammenligne metadon og buprenorfin, undersøke en potensiell dose-avhengighet, samt å kartlegge risikofaktorer for forlenget QTc intervall.

I vår tverrsnittsstudie tok vi elektrokardiografi (EKG) av 200 LAR pasienter i Oslo. 173 av disse sto på metadon, resten på buprenorfin. EKG'ene ble tolket av en kardiolog, uvitende om alle pasientdetaljer. Av de 173 metadonpasientene ble åtte identifisert med QTc forlengelse over 500 millisekunder. Alle disse hadde metadondose på 120 mg eller mer per dag. Ingen av buprenorfin-pasientene hadde QTc forlengelse. Et dose-avhengig forhold ble funnet mellom metadondose og lengden av QTc

intervallet. Det ble ikke funnet noen sammenheng mellom alder, kjønn eller tid i LAR og lengden på QTc intervallet.

Den kliniske relevansen av QTc forlengelse og hvorvidt dødsfall i LAR potensielt kunne tilskrives QTc forlengelse og ventrikulær arytmi ble undersøkt. Data fra det foregående kryss-registerstudiet ble nøye gjennomgått og dødsårsakene for pasienter i behandling analysert. 90 dødsfall hadde forekommet blant de 2382 LAR pasientene med til sammen 6450 år i LAR. Kun fire av disse kunne muligens tilskrives ventrikulær arytmi. Den maksimale dødeligheten som potentielt kunne tilskrives QTc forlengelse var 0.06 dødsfall per 100 personår i LAR. Av 3850 oppstarter i LAR forekom det kun ett dødsfall under den første behandlingsmåneden.

De åtte pasientene med QTc forlengelse over 500 millisekunder i tverrsnittsstudiet ble tilbudt videre hjerteutredning og behandling. Undersøkelsene inkluderte et nytt hvileEKG, belastningsEKG, 24 timers EKG (Holter) og genetisk test for de fem mest vanlige lang QT syndrom (LQTS) mutasjonene. Syv pasienter ønsket genetisk testing. En av disse droppet etterpå ut av LAR. Seks pasienter deltok i videre hjerteutredning. Alle hadde store døgnvariasjoner i QTc intervallet og også under belastning. To pasienter var heterozygote bærere av LQTS mutasjoner, henholdsvis i LQTS1 og LQTS2 gener. Begge hadde i anamnesen tidligere opplevd hjertesymptomer, men de hadde ikke blitt utredet for dette før deltagelse i studiet. En av dem hadde allerede byttet fra metadon til buprenorfin og startet under studiet på en beskyttende beta-blokker. Ingen av de resterende fem pasientene, inkludert kvinnen med LQTS2 mutasjon, ønsket overgang til buprenorfin eller andre hjertebeskyttende tiltak. Trygg hjertebehandling av metadonpasienter med QTc forlengelse viste seg svært utfordrende.

Opioid dependence: an increasing public concern

According to The world health organisation (WHO), there has been a global increase in the production, transportation and consumption of opioids, mainly heroin over the years. Heroin use has become increasingly common in North America and Europe since the 1960s.[1] From 1985 until today the worldwide production of heroin has more than doubled, or even tripled. Globally, it is estimated that 13.5 million people take opioids and of these 9.2 million use heroin.

In European countries, the average prevalence of problem opioid use in the countries providing data is estimated to be between 3.6 and 4.6 cases per 1 000 of the population aged 15–64. Assuming that this reflects Europe as a whole, it implies that about 1.4 million (1.2–1.5 million) people were problem opioid users in the EU and Norway in 2007.[2]

Mortality in opioid dependence

Mortality among untreated opioid dependants is internationally estimated with wide variations; between 1 to 4 per 100 person years.[3-6] Heroin injectors who regularly consume large amounts of different drugs, face a risk of death which may be 20 to 30 times higher than non-drug users in the same age range.[1] Relative risk and odds ratio are calculated in relation to baseline mortality in the general population, which depends upon living standards and social conditions. As these vary greatly among different populations worldwide, variations in mortality levels across different groups of illicit drug users are subsequently the result. The majority of deaths among opiate dependents are reported to be overdose related.[7-9] Other common causes of death in this group are trauma, including suicide and murder, as well as somatic causes such as blood-borne infections.[10] The number of overdoses will depend on gender, age, type of drug and drug administration, personality, general health status and the availability of treatment within the group. The extent to which drug treatment is

provided and easily accessible, will substantially influence the rates of drug-related mortality in these populations.[10]

Treatment strategies for opioid dependence

In theory there are two main types of treatment for opioid dependence; abstinence-oriented therapy and substitution therapy. There are numerous different approaches within abstinence-oriented treatment and these cover both institutionalised and out-patient based therapy. It is not within the scope of this thesis to discuss the many varieties currently used, but in summary as the phrase abstinence-oriented suggests, they all aim for a drug-free state. To reach this goal, the patient has to go from a drug-using to an abstinent state. In the period following opioid detoxification, the rates of fatal overdoses appear increased. This is assumed to be linked to loss of tolerance and the subsequent unpredictability of resumed heroin use.[11]

A recently published study by Ravndal and Amundsen pointed to an unadjusted excess overdose mortality, with a rate ratio (RR) of 15.7 (95% confidence interval (CI) of 5.3-38.3) during the first 4 weeks after discharge from inpatient facilities with various abstinence-oriented treatment approaches for opioid dependents.[12] Research has also highlighted the increased risk of overdose death in this population after prison release. One study among HIV positive injecting drug users found a relative risk of overdose during the first two weeks after release of 7.7 when compared to the next 10 weeks.[13] A study of the United States prison population found that during the first two weeks following release, the risk of any mortality was 12.7 (CI 9.2-17.4) times that of other state residents. The risk of death from overdose was particularly high; 129 (CI 89-186). [14]

A way of protecting individuals against the increased risk of opioid overdose detoxification is by using an opioid antagonist. Naloxone is a short-acting, non-selective opioid receptor antagonist. As the oral bioavailability is low, the route of effective administration is by intravenous or intramuscular injection. Due to the onset of action within minutes, this is the drug used for immediate opioid overdose reversal.[15] Naltrexone is another opioid antagonist, which is orally effective and longer-acting. A Cochrane review suggested that although oral naltrexone reduced

heroin use more that placebo and psychosocial counselling, it was not beneficial on heroin relapse or treatment retention rates.[16] Over the last decade, sustained-release naltrexone has been investigated in larger clinical trials. The results are so far promising, but the amount of evidence of its effectiveness is still limited.[17;18]

Opioid maintenance treatment for opioid dependence

The alternative to abstinence-oriented therapy is substitution treatment. Methadone was first synthesised in Germany in 1937 and during World War II it became an important analgesic, as the supply of traditional morphine was short.[19] It is a synthetic opioid agonist that binds to the opioid μ-receptor. Vincent P Dole and Marie Nyswander conducted the first studies in the 1960s, treating heroin addicted patients with methadone. The treatment was intended to replace the use of illicit opioids, mainly heroin, with this long acting agonist, without giving rise to intoxication. They emphasized that methadone could only prevent symptoms of withdrawal and craving; treatment with methadone alone would not restore the life and relations the patient had prior to the heroin addiction and it was only a mean to facilitate this rehabilitation.[20] Methadone maintenance treatment (MMT) is today the most commonly used treatment for opiate dependence worldwide, and its effectiveness on attrition and relapse prevention has been demonstrated in many studies.[21-23]

In addition to methadone, buprenorphine is the other most commonly used OMT drug. This is a synthetic opioid that also binds to the μ-opioid receptor. It is a partial agonist, which is known to reach a ceiling effect and is assumed to be less likely to produce intoxication compared to methadone. [24] Due to potential misuse and injection of buprenorphine tablets, a preparation that contains both buprenorphine and naloxone is now available.[25] Although all opioids in theory may be suitable as maintenance drugs, currently oral slow-release morphine, codeine and heroin are the other drugs widely used for opioid maintenance treatment purposes.[18]

In Europe many opioid users are enrolled in programmes providing long-term care. This is reflected in an increasing proportion of primary opioid users among drug users already in treatment. The total number of clients receiving substitution treatment in

the EU, Croatia and Norway was estimated to be about 650 000 in 2007, up from 560 000 in 2005 and 500 000 in 2003.

Opioid maintenance treatment (OMT) is generally considered to be the most important harm-reducing measure in opioid dependence,[26;27] and it is often stated that "OMT saves lives".[28;29] Although there is accumulating evidence to support this, the underlying research contains several limitations. This particularly relates to the level of risk reduction, which is highly important both in treatment policy; balancing the need for control with the need for availability and the management of individual patients.

Mortality in opioid maintenance treatment

Mortality has been included in the outcome measures of some randomized controlled trials (RCTs) with short follow-up periods up to 20 weeks, with little or no significant mortality reducing effects found.[30;31] Study designs with large samples and long-term follow-up periods are needed, but difficult to apply in RCTs, in order to thoroughly investigate the potential mortality reducing effects.[32] A systematic review published in 2005 by Amato and colleges concluded that OMT did not exhibit a significantly proven reduction in mortality.[3]

Nonetheless, the results from OMT research have been divergent on the issue. A Swedish clinical trial comparing buprenorphine maintenance to medically supervised buprenorphine withdrawal, observed a statistically significant reduction in mortality rates favouring buprenorphine maintenance.[33] The group stabilised on buprenorphine would presumably experience less abstinence and also receive some protection against overdose from the drug itself. The conclusions from this clinical trial were further limited by a rather small study size. In 1981, Gunne randomly assigned a group of intravenous heroin abusers to either methadone maintenance treatment (n=17) or no treatment (n=17) and found marked differences in mortality.[28] After a 2 years follow-up period, none of the MMT patients had died, whereas two patients died in the control group. Of the MMT patients, 12 were drug-free and the remaining five had recurrent drug problems. Among the controls, one was drug-free, 12 were continuously abusing heroin and two were imprisoned. Notably, that study

was performed in a time of policy conflict in Sweden and the group denied treatment were left in a vulnerable situation. This highlights the worrying ethical aspects of an RCT design in this setting.

The mortality-reducing effects of OMT are primarily established through observational studies. These often exclude dropouts, sometimes lack clear selection criteria for treatment or might be seen as local area studies with low generalisation.[4;34;35] Consequently, the findings are mostly applicable to those selected by the specific treatment unit and maintained in the actual treatment studied. Even well designed cohort studies face challenges with persons lost to follow-up, a commonly recognised problem in the research field of drug addiction.[36;37] Although large, long-term case-control studies would be desirable, the ethical considerations attached would not permit such an approach.

Programme characteristics such as treatment approach, inclusion and exclusion criteria may vary. Comparison of effect of OMT programmes in various countries or regions can therefore be challenging and indeed highlight the effects on mortality of different criteria for entering treatment. For example, a study from the capital of Sweden found no opiate overdose deaths in their OMT population. The Stockholm programme did not, however, include polydrug users and excluded all patients with concurrent use of drugs.[38] The in-treatment effects of such a programme may be favourable, but the external validity limited.

Today increasing numbers of people are being treated with OMT worldwide and larger studies to quantify the treatment effect on mortality is clearly called for. It is likewise important to investigate the mortality risk associated with leaving OMT.

Common effects and side-effects of opioids

Opioid receptors are found in neurones and are spread throughout the central nervous system (CNS).[39] The opioid receptors are also found in many other cells in the central and peripheral nervous systems. There are three main types of opioid receptors.[40] The μ-receptors are thought to be responsible for most of analgesic effects of opioids and are also linked to some major unwanted effects, such as

dependence, sedation and respiratory depression. The δ-receptors are probably more important in the periphery, but may also contribute to analgesia.
The Κ-receptors contribute to analgesia at the spinal level, but produce relatively few unwanted effects and do not contribute to dependence.

Depending on the physiological response from receptor binding, the opioids are divided into pure agonists, like methadone, and partial agonists/antagonists, like buprenorphine. Pure agonists will give maximal biological response, whilst partial agonists will have less effect. Although the various opioids differ in terms of potency, pharmacokinetics and effect on various organ systems, they generally share some common properties. When used over a longer period there is a gradual tolerance development, in which the effect of the opioid decreases with time and higher doses are needed to reach the same level of effect. The use of higher doses is accompanied by increased dose-dependent side-effects. Acute discontinuation of the opioid after 14 days use or more will often lead to withdrawal symptoms such as anxiety, hyperventilation, sweating, dilated pupils and increased pain. Later on more severe symptoms like tachycardia, tremor, nausea, vomiting and diarrhoea may occur.

The therapeutic action of opioids is mainly analgesia, by which they have undisputed effect.[40] This is commonly their sole indication for use in medicine today. They have also been used therapeutically to suppress coughing, produce sleep and euphoria and prevent diarrhoea. Due to the spread of opioid receptors, opioids affect the various systems of the body and give rise to some common side-effects. All opioids reduce the sensitivity for carbon monoxide in the respiratory centre of the CNS, leading to respiratory depression. Gastrointestinal symptoms are also common, and include nausea, vomiting and constipation. Dizziness, sedation, unsteadiness and confusion occur at higher doses and are most often seen among the elderly. In the cardiovascular system, peripheral vasodilatation and inhibition of baroreceptor reflex leading to hypotension may result. Opioids release histamine from mast cells, by an action unrelated to opioid receptors. This histamine release can cause urticaria and itching of the skin, as well as bronchoconstriction and hypotension. Endocrine effects include increased sweating, as well as inhibition of secretion of luteinizing hormone

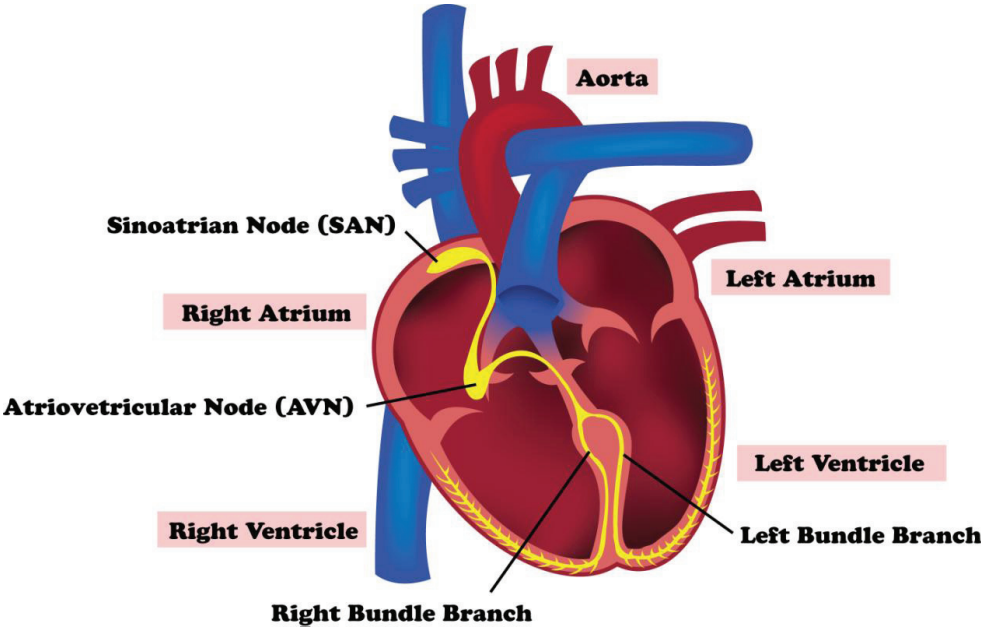
(LH) over time, leading to loss of ovulation and menstrual cycle in women and reduced testosterone production with low libido and erectile dysfunction in men.

In opioid maintenance treatment, the dose is slowly increased and then maintained at a steady level in which the patient can function optimally, avoiding both withdrawal symptoms and intoxication. Most patients who start on OMT are already opioid dependent and have developed opioid tolerance. Side-effects may still occur at the beginning of OMT, particularly sedation, nausea and constipation. Sweating and hormonal disturbances may rarely persist and require addressing. Usually the side-effects are minor compared to those of heroin addiction and most will disappear with time. However, when potentially harmful adverse effects of OMT are described, there is a cause for concern. Prolongation of the corrected QT (QTc) interval has received increased attention over the last decades and has been associated with some particular types of opioids, including methadone.

QTc interval prolongation and methadone

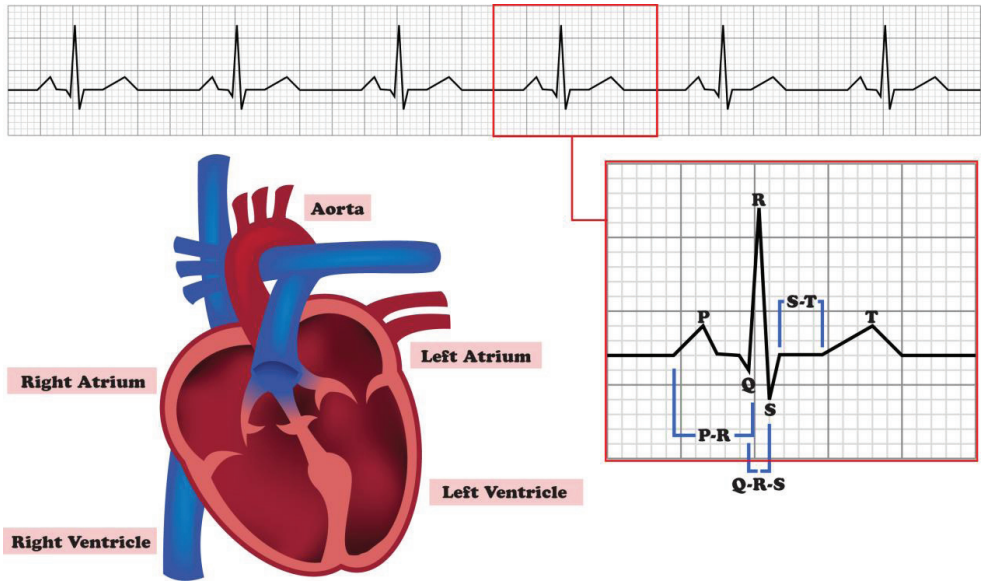
The electrical discharge of a normal cardiac cycle starts in a special area of the right atrium called the sinoatrial node (SAN).[41] Depolarization then spreads throughout the atrial muscle fibres. A delay occurs when the depolarization spreads through another special area in the atrium called the atrioventricular node (AVN). From there, the electrical discharge travels very rapidly down specialised conduction tissue; first a single pathway, the bundle of His, which then divides in the septum between the ventricles into the right and left bundle branches. Within the mass of ventricular muscle, conduction spreads somewhat more slowly, through specialised tissue called Purkinje fibres. This pattern is repeated for every cardiac cycle.

Figure 1. The anatomy of the heart with a normal cardiac conduction system



The electrical changes that occur during cardiac contraction can be detected by electrodes attached to the surface of the body when recording an electrocardiogram (ECG). The muscle mass of the atria is small compared with that of the ventricles, and the accompanying electrical changes is therefore small. On the ECG the atrial contraction is called the P wave. There is a large deflection on the ECG when the ventricles are depolarised and this forms the QRS complex. The T wave of the ECG is associated with the return of the ventricular mass to its resting electrical state (repolarisation).

Figure 2. Anatomy of the heart and appearance of a normal ECG



The QT interval is measured from the beginning of the Q-wave to the end of the T wave.[41] The QT interval represents the duration of activation and recovery of the ventricular muscles. This duration is reciprocal to the pulse and is measured in milliseconds (msec). Under normal conditions, this should be less than 450 msec when corrected for heart rate (QTc interval). Prolongation of the QTc interval is characterised by abnormal T-wave morphology seen on ECG and is associated with torsades de pointes (TdP).[42] In most cases TdP is self-terminating and causes a quick syncopal episode. If the TdP is more persistent and the rhythm does not spontaneously return to normal, ventricular fibrillation occasionally leading to cardiac arrest and sudden death can result. TdP is rarely associated with a QTc interval of less than 500 msec and this is generally considered the threshold for the risk of TdP development.[43]

Figure 3. Torsades de pointes (TdP)

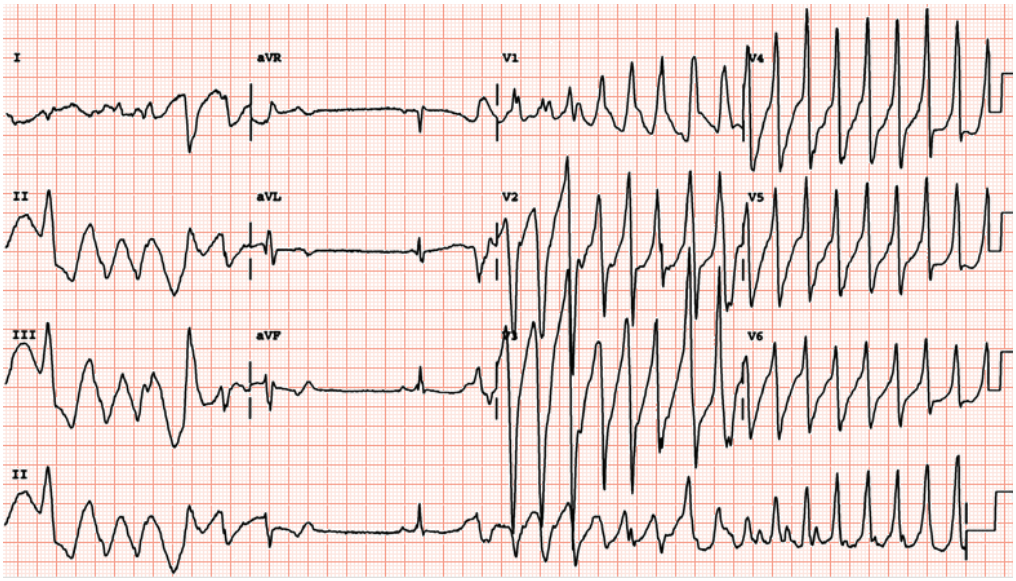


Image shows: A premature ventricular beat is followed by a pause and a subsequent supraventricular beat. Then a premature ventricular beat appeares, followed by an episode of polymorphic ventricular tachycardia showing a peculiar electrocardiographic pattern characterised by a continuous twisting in QRS axis around an imaginary baseline ("torsades de pointes" - TdP).

Drug-induced QTc prolongation is caused mainly by blockade of the slow component of the delayed rectifier potassium (K^+) current (I_{Kr}), a major repolarisation current in the heart. The I_{Kr} blockers, such as methadone, increase the dispersion in repolarisation. They often have a so-called reverse frequency-dependent effect on the QTc interval, in which the degree of prolongation is more prominent during slow heart rates.[44] In medical practice, this is a well-recognised adverse effect of certain drugs,[45;46] including anti-psychotics and anti-depressants.[47;48] The finding of an association between long-term use of opioid agonists and prolongation of the QTc interval was first demonstrated during maintenance treatment with levomethadyl hydrochloride acetate (LAAM), which was later redrawn from the market.[49]

Early studies reported an association between the use of methadone and QTc prolongation.[50-52] Several cross-sectional studies have since confirmed this association.[53-55] Ehret *et al* compared the electrocardiography (ECG) recordings of drug users on methadone with those of drug users not on methadone in a tertiary care hospital.[56] Of the MMT patients, QTc prolongation of 500 msec or more was detected in 16.2 %. No evidence of QTc prolongation was identified among those not receiving methadone. Wedam *et al* conducted a large randomized, controlled trial comparing the QTc effects of methadone, levomethadyl acetate (LAAM) and buprenorphine.[57] They found that the LAAM and methadone groups were significantly more likely to have a QTc greater than 470 msec (men) or 490 msec (women) or an increase from baseline in QTc greater than 60 msec.

Although several studies have demonstrated a dose-dependent relationship between methadone dose and QTc interval,[56;58;59] other researchers have not detected this effect. Peles *et al* found no correlation between QTc prolongation and methadone dose or serum levels.[55] Martell *et al* found significant increases in the QTc interval after initiation of methadone treatment, but these were unrelated to the amount of methadone used.[51] In their analysis of the mechanism of opioid influence on cardiac function, Katchman *et al* suggested that morphine and codeine had the largest safety margin,[60] while other authors have advocated the great safety of buprenorphine.[61;62] Today the association between methadone and QTc prolongation is well-established. However, there has been disagreement about whether a dose-dependent association exists. Furthermore, it has remained unclear whether time in treatment, gender or age has any influence on the QTc interval.

Both torsades de pointes and cardiac fibrillation have occasionally been reported among methadone patients.[62-65] A Danish cross-sectional study by Fanoe *et al* found a dose-response association between methadone and the length of the QTc interval, with increased methadone dose associated with a higher frequency of reported syncope.[66] After conducting a prospective evaluation of patients with sudden death in the community, Chugh and associates pointed toward an association between the use of methadone at therapeutic levels and the occurrence of sudden cardiac death.[67] A review of methadone-related adverse events reported to the Food and Drug Administration (FDA) between 1969 and 2002 identified 59 cases involving QT

prolongation or TdP. Of these, 28 resulted in hospitalisation: 5 of the 59 cases resulted in death.[68] Despite these studies, the clinical relevance and, importantly, whether there is mortality attributable to QTc prolongation in OMT have not been clearly established.

There are often multiple contributing factors to drug-induced QTc prolongation and ventricular arrhythmia, including hepatic cytochrome P450 inhibitors, structural heart disease and hypokalemia, as well as genetic predisposition.[69] These risk factors are often poorly identified among OMT patients before treatment with methadone is initiated. Despite extensive research on both congenital and acquired long QTc interval, to our knowledge, no previous study has specifically investigated whether congenital long QT syndrome (LQTS) mutation may pre-exist in patients on methadone maintenance treatment with prolonged QTc interval.

Congenital causes of QTc interval prolongation

Three major genes were identified as involved in congenital long QT syndrome (LQTS) as early as in 1995-96.[70] Currently, mutations in eleven different genes located in seven different chromosomes have been identified. The eleven genes code for subunits of various ion channels (potassium, calcium and sodium) and a structural anchoring protein. This forms the basis of the eleven known subtypes of LQTS (LQTS1-11), but most of the identified mutations occur in LQTS1, LQTS2 and LQTS3 genes.[71] Congenital long QT syndrome has both an autosomal dominant and a recessive trait of inheritance. When LQTS follows the dominant mode, it is commonly known as Romano-Ward syndrome. The recessive pattern is often referred to as Jervell and Lange-Nielsen syndrome and is characterised by a more severe phenotype and accompanied by congenital deafness.[72]

A recent study from Norway investigated the prevalence of LQTS mutations in the Norwegian population.[73] The researchers tested for mutations in the *KCNQ1, HERG, SCN5A, minK* and *MiRP1* genes, which all codes for subunits of cardiac ion channels. By performing cascade screening of 505 relatives of index patients with molecularly defined LQTS, they identified 251 mutation carriers. The observed

penetrance was 41 %. They estimated that the prevalence in Norway of heterozygous mutation carriers for the five genes could be somewhere between 1/100 and 1/300.[73]

The treatment of congenital LQTS has followed three classical modalities: beta-adrenergic blocking agents (beta-blockers), elective pacing (pacemakers) and left cervicothoracic sympathetic ganglionectomy.[71] Beta-blockers have been the standard therapeutic and preventative therapy of LQTS and are effective in about 60-70 % of patients in all age groups.[74] Pacemaker should be considered an adjunct to beta-blockers when there is evidence of pause or bradycardia-dependent arrhythmia and symptomatic bradycardia induced by beta-blocker therapy.[75] Left cardiac sympathetic denervation (ganglionectomy) is considered for LQTS patients suffering from cardiac events, despite treatment with beta-blockers, and in patients who experience arrhythmia storms with an implantable cardioverter-defibrillator (ICD).[76] An ICD will not prevent the precipitation of TdP, but will prevent sudden cardiac death when TdP persists or generate ventricular fibrillation. It has been used successfully when therapy with the classical modalities has failed.[71]

Both congenital (LQTS) and acquired prolongation of the QTc interval occur in all races and across all ethnic groups.[77] It is vital for patients with LQTS to avoid all drugs associated with QTc prolongation, which could increase the cardiac risk further.[71] Brink *et al* found that a QTc interval greater than 500 msec was associated with a 4-fold increased risk of syncope or sudden death in LQTS patients.[78] However, congenital LQTS is often an undetected condition. More specifically, if the LQTS mutation has previously been silent or undetected for other reasons, there is indeed a risk that the patient may be started on a QTc prolonging drug, such as methadone. Once identified, these patients should therefore always be provided with an updated list of potentially harmful drugs that must be avoided.[79]

Opioid maintenance treatment in Norway and research setting

In Norway, opioid maintenance treatment (OMT) was established by the government as a national system. The programme was designed to reach the population of severely addicted heroin users not benefiting from other types of treatment and was

first made nationally available in 1998.[80] At the time of our research one of the inclusion criteria for OMT was “several years of addiction dominated by opioid dependence”, verified prior to treatment. Additionally, it was also a requirement that the patient had made several failed attempts at abstinence-oriented therapy forms, prior to entering OMT. There was a 25 year age limit for inclusion, although exceptions were made. Persons with severe somatic or psychiatric co-morbidity were given priority. Treatment was based on cooperation between the social services, general practitioners (GPs) and specialised OMT centres.

Objectives

Overall research aims

There were two overall aims in this research. The first was to evaluate changes in mortality rate before, during and after opioid maintenance treatment (OMT) in association with overdose and non-overdose as causes of death. This is dealt with in paper 1. The second overall aim was to investigate QTc prolongation in OMT, with regards to prevalence, clinical relevance and manifestation, and presence of contributing risk factors, including genetic predisposition. This aim is approached in paper 2 and 3.

Objectives for each paper

Paper 1

Mortality prior to, during and after opioid maintenance treatment (OMT): A national prospective cross-registry study

Research objectives:

1. To assess differences in mortality rates prior to, during and after OMT.
2. To evaluate mortality reductions in an intention-to-treat perspective.
3. To examine the distribution of drug overdose versus non-overdose as cause of death.

Paper 2

Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: A mortality assessment study

Research objectives:

1. To investigate the prevalence of QTc prolongation among opioid maintenance treatment (OMT) patients in Oslo.
2. To assess any relation between QTc prolongation and type of agonist (methadone and buprenorphine), dose, gender and length of treatment.
3. To estimate the extent to which deaths occurring in the Norwegian OMT programme might be attributed to QTc prolongation.

Paper 3

Opioid maintenance patients with QTc prolongation:
Congenital long QT syndrome mutation may be a contributing risk factor

Research objectives:

1. To describe the findings of past medical history, drug and family history, focusing in particular on cardiac symptoms and other risk factors for QTc prolongation.
2. To conduct genetic testing for LQTS mutations among OMT patients with QTc interval > 500 msec.
3. To discuss in detail the findings from cardiac investigation and management of OMT patients found to have QTc prolongation.

Cross-register mortality study (Paper 1)

Sample

All opioid-dependent people who applied for and were accepted for OMT in Norway between 1 January 1997 and 31 December 2003 were included in the data for this study. This made a total of 3789 individuals with a total observation time of up to seven years. The design was a prospective cohort, where persons were included as they applied for OMT, resulting in individual and varying observation times; from inclusion until 31.12.2003, which was the time set for examination of mortality.

At the time of our mortality study, there was estimated to be between 8200 and 12500 injecting opiate addicts in Norway.[81] Of the patients accepted for OMT, 90-95 % were intravenous drug users. Buprenorphine was registered as a therapeutic OMT drug in 2001 and was used by 23% by the end of 2003. At the start of the observation period all patients were on methadone and in total during the whole period more than 9 out of 10 patients used methadone, according to the annual Norwegian OMT evaluations.[82]The average dosing of methadone and buprenorphine was 112 mg and 20 mg, respectively in 2005.[80;82;83]

Data collection

The sample was divided into pre-treatment (applicants qualifying for OMT, but prior to initiation of treatment = waiting list), in-treatment (in OMT) and post-treatment (after termination of OMT). A national OMT register including national ID numbers was established based on the electronic record system in each OMT centre. Each centre provided lists of all persons who had applied for, entered and left OMT during the observation period. These lists were sent to Statistics Norway and information on the date and cause(s) of any deaths were attached to the data files. Statistics Norway (SSB) is responsible for a national mortality register, based on all Norwegian death

certificates. The merging of data registers was performed towards the end of 2005. Thus, all deaths in the observation period (through to end of 2003) are included in the register.

Measures and definitions

All death certificates registered with Statistics Norway are completed by a medical doctor after examination of the deceased. In about one-third of cases, additional information as a result of autopsy is included.[84] Death certificates include one principal cause of death, and up to four underlying causes (ICD 10 codes).[84;85] Only the principal cause of death was used. Acute intoxications resulting in death from all substances were combined in an "overdose" category. These comprised ICD 10 codes F11.0, F19.0, X42.0 and X44.0 diagnoses. The non-overdose groups included both somatic and sudden/violent deaths (such as suicide, traffic accidents and homicide).

Some subjects included in the study (167 individuals) underwent several treatment periods. In-treatment refers in this study to the actual number of days in treatment (sum of days in treatment, excluding days after or between treatment periods). Post-treatment is the number of days out of treatment both between and following treatment periods within the study period. If subjects had several application dates, the first date was chosen.

The register initially contained some individuals that for varying reasons did not start treatment. Some did not fulfil the criteria of opioid dependence. Others chose long term drug free residential treatment and some chose not to start for other reasons. These subjects had application dates, but no treatment initiation within one year. The applications were all re-examined and verification of the application status confirmed. Subjects who were ineligible or withdrew their application for OMT constitute a mixed group that was termed "ineligible for treatment" (403 persons in total). Possible cases of misclassifications between pre-treatment and ineligible groups cannot be ruled out, although the utmost care was taken to reduce the problem by manually cross-checking the data with each centre. Mortality rate was not

calculated for this group as a whole, as no definite observation time was available. Some persons with application status (pre-treatment) between 1 and 365 days (included during the final year of observation 2003), may have withdrawn the application prior to commencing treatment or been found ineligible, without this being captured during data collection, as we have no information about the status of the subjects included beyond 31.12. 2003.
Intention-to-treat in this paper includes every person who ever started on OMT.

Analyses

Most analyses and descriptive statistics were performed by SPSS version 14.0.2. (Inc., Chicago, IL, USA). Mortality rates were calculated per 100 person years, in this equivalent case to percentage mortality per year, with 95% confidence intervals.

A Cox regression with a time-dependent covariate was performed (by SAS 9.2) (SAS Institute Inc.), to assess statistical differences between the treatment categories, as each individual could have changed status from pre-treatment to treatment and subsequently to post-treatment during the observation period. The time-dependent covariate was defined according to a subject's placement within the groups: pre-treatment, in-treatment and post-treatment. Calculated hazard ratios should be interpreted as the relative risk (RR) between groups.

ECG assessment study (Paper 2)

Sample

The prevalence of QTc prolongation was assessed in a normal clinical setting.
All OMT patients in Oslo are registered at the Oslo centre, LAR ØST. They are, however, mostly treated by GP in collaboration with the social service, and have dispensing of OMT medication at pharmacies. This enabled a cross-sectional study inviting all patients to have an ECG recording, either at the OMT centre or at the pharmacies. All opioid maintenance treatment patients in Oslo were eligible for the

QTc study. An ambulatory team consisting of a medical doctor and a nurse offered ECGs at selected pick-up locations for the OMT drugs. These included pharmacies and OMT services, where the appointed time of ECG recording was announced by posters and hand-outs a week in advance. The recruitment period lasted from October 2006 to August 2007. The average number of patients in treatment during this period was 976. Two hundred of these, roughly 20 % of the full treatment population, were recruited.

In the sample (n=200), 86.5 % were prescribed methadone and 13.5 % were prescribed buprenorphine: 68 % of the patients were men. The methadone patients were a few years older than those on buprenorphine and had spent a mean time of 2.8 years longer in treatment. The sample characteristics were similar to those of the broader national sample, based upon data from the Norwegian annual evaluation:[83] in the study period, 30.5 % of the OMT population were women and the mean age of the patients was 39.9 years: in Oslo, 82 % of the patients used methadone, while 18 % were on buprenorphine. The mean daily doses used during the study period were 110.2 mg for methadone and 17.3 mg for buprenorphine.

Procedure for QTc measurement

The patients were approached for an ECG recording between 8 and 10 am, after observed intake of their daily dose of OMT drug. When the patients had given verbal consent, a 12 lead ECG was recorded. This was done using the same ambulatory 6 channel ECG- apparatus for all the recordings; Siemens-Elema AB, model: 96 58 744, serial no: 0165, 50/60 Hz, 200 VA. Each patient was identified by a study number.

QT time was measured in lead V5 in most patients. In a few cases there were technical disturbances in V5 and QT time was measured in V4 or V6.
The cardiologist used a calliper and manually measured the QT and RR intervals of five consecutive QRS complexes. The mean values for both the QT and the RR intervals were estimated. Based on the mean RR and mean QT, the corrected QT (QTc) interval was then calculated by using to the formula of Bazett.[86] All the ECGs

were examined by the same cardiologist, who was blinded for all patient details, including type of OMT medication, as well as dose, age, gender, and time in treatment.

Prolonged QTc interval mortality study (Paper 2)

Sample

In the mortality assessment study, the results from crossing the two different national registers in the mortality study were used. The OMT register did not provide information on the type of OMT medication that the patients were using. However, at the start of the observation period all patients were on methadone and during the whole period more than 9 out of 10 patients used methadone, according to the annual Norwegian OMT evaluations.[82]

Analysis

Deaths were analysed according to time in treatment and cause of death.
Since cardiac arrhythmia might have been missed, or misdiagnosed for some deaths, the estimation of mortality which may have been due to cardiac arrhythmia (and hence QTc prolongation) was made by including those deaths in which these causes could not be excluded. The overdoses which were confirmed by post-mortem, and where fatal levels of various drugs had been detected in the blood, were excluded as possible cases of cardiac arrhythmia.

Cardiac and genetic investigations and management study (Paper 3)

Patients with QTc > 500 msec were identified and recruited from a QTc assessment study: ECG was recorded among 200 OMT patients [87], of whom 173 (53 women) were on methadone and 27 (9 women) on buprenorphine. The mean age was 41

years. The mean daily methadone dose of the sample was 111 mg (standard deviation (SD) 35 mg) and buprenorphine dose 19 mg (SD 5 mg).

The cardiologist, blinded to all patient details, used a calliper and manually measured the QT and RR intervals of five consecutive QRS complexes. Based on the mean RR and mean QT, the rate-corrected QT (QTc) interval was calculated using the formula of Bazett [86].

A detailed medical history was obtained from patients with QTc interval > 500 msec at the initial consultation. Previous cardiac symptoms and disorders were specifically requested, as were conditions like HIV, diabetes and liver disorders. All illegal and prescribed drugs ever used, particularly those associated with changes in QTc interval (e.g. cocaine and methamphetamine, antiarrhythmic, antipsychotic and antidepressive medications) were noted. The family history focused on known cardiac disorders, symptoms or treatment, sudden death, unexplained deaths or accidents, drowning or sudden infant death syndrome.

Standard dideoxy DNA sequencing was done on blood samples, in accordance with the manufacturer's instructions, using the 3.1 version of the Big Dye terminator cycle sequencing kit (Applied Biosystems, Foster City, California, USA). The testing was performed at the Department of medical genetics at Oslo University Hospital Rikshospitalet, checking for mutations in the following five genes:

- Potassium channel, voltage-gated, KQT-like subfamily, member 1 (*KCNQ1*) = LQTS1
- Human ether-a-go-go-related gene (*HERG*) = LQTS2
- Sodium channel, voltage-gated, type V, alpha subunit (*SCN5A*) = LQTS3
- Minimal potassium ion channel (*minK*) = LQTS5
- Minimal potassium ion channel-related peptide 1 (*MiRP1*) = LQTS6

PolyPhen® software was used to evaluate the pathogenicity of mutations detected [88]. Serum potassium levels were measured.

Patients were encouraged to attend the cardiac outpatient clinic at Oslo University Hospital Aker for an appointment with a consultant cardiologist. Investigations included ECG at rest, exercise ECG (bicycle) and 24 hours ECG (Holter) recording.

The final cardiac and genetic investigation and management study would not have been possible without the contributions of the cardiology department at Oslo University Hospital Aker, who willingly invited the patients to investigations and management in their facilities. Oslo University Hospital Rikshospitalet performed the genetic testing free of charge, which would otherwise not have been possible given our resources.

Ethical approval

The projects were all approved by the National Committees for Research Ethics and by the Data Inspectorate of Norway.

Overall findings

The main findings included a significant overall reduction in mortality risk between pre-treatment and in-treatment groups (hazard ratio 0.5, *P* = 0.001). Following treatment, males had significantly higher mortality than the pre-treatment levels. Risk for overdose death was significantly reduced with OMT, both for the in-treatment group separately and in the intention-to-treat analysis.

The prevalence of QTc interval above 500 msec was 4.6 % among the methadone patients. All the buprenorphine patients had QTc interval within the normal range. A dose-dependent association was found between methadone dose and the length of the QTc interval in the regression analysis. The maximum mortality rate potentially attributable to QTc prolongation was found to be 0.06 deaths per 100 patient years in OMT.

The cardiac investigations of the six patients revealed that QTc intervals fluctuated widely over 24 hours and during exercise. A man and a woman were identified as heterozygous carriers of mutations in LQTS1 and LQTS2 genes, respectively. The LQTS1 mutation carrier had already switched to buprenorphine and started on protective beta-blocker. None of the remaining five patients, including the women with the LQTS2 mutation, were willing to switch to buprenorphine or take other cardiac protective measures.

Results corresponding to the objectives of each paper

Mortality prior to, during and after opioid maintenance treatment (OMT): A national prospective cross-registry study

Research objectives:

1. To assess differences in mortality rates prior to, during and after OMT.

The study identified major differences in mortality rates prior to, during and after opioid maintenance treatment (OMT); per 100 person years in OMT the estimated mortality rates were 2.4 prior to OMT, 1.4 in OMT and 3.4 after OMT. In terms of hazard rates for death, there was an overall reduction in mortality risk between the pre-treatment and in-treatment groups (hazard ratio 0.5, $P = 0.001$). The post-treatment group as a whole was not significantly different from the pre-treatment group in regard to mortality. However, following treatment, males had significantly higher mortality than the pre-treatment levels. The post-treatment females had a non-significant tendency toward reduced mortality.

2. To evaluate mortality reductions in an intention-to-treat perspective.

An overall reduction in mortality risk between the pre-treatment and the intention-to-treat populations was found, with a hazard ratio of 0.6, $P = 0.004$.). In an intention-to-treat perspective the overdose mortality rate reduction per 100 person years was smaller than for the in-treatment group. Still a significant reduction was detected; 1.9 pre-treatment to 0.7 in the intention-to-treat group.

3. To examine the distribution of drug overdose versus non-overdose as cause of death.

In terms of overdose mortality, this comprised 79 % of the all pre-treatment deaths and 61 % of the all post-treatment deaths. In the in-treatment group, overdose mortality accounted for only 27 % of all deaths. In the overall mortality, all groups combined, overdose accounted for 53 % of all deaths. A significant reduction in overdose mortality rate for the group in OMT (1.4) compared with the pre-treatment group (2.4) was found. Overdose mortality rate was particularly prevalent among males who had ceased treatment (4.1).

Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: A mortality assessment study

Research objectives:

1. To investigate the prevalence of QTc prolongation among opioid maintenance treatment (OMT) patients in Oslo.

When investigating the prevalence of QTc prolongation in OMT, we found that 49.1 % (n=85) of the methadone patients had a QTc interval above 430 msec. Fifty patients (28.9 %) had a QTc above 450 msec. There were 15 % (n=16) with a QTc interval above 470 msec and 4.6 % (n=8) with a QTc above 500 msec. No patients on a dose of less than 120 mg were found to have a QTc above 500 msec. All the 27 patients on buprenorphine had QTc levels below 450 msec.

2. To assess any relation between QTc prolongation and type of agonist (methadone and buprenorphine), dose, gender and length of treatment.

A positive correlation was found between QTc interval and dose of methadone, both in the univariate ($r=0.37$, $p<0.00$) and multivariate analysis ($B=0.37$, $p<0.00$).

No statistically significant correlation was detected between QTc interval and time in treatment, age or gender. No statistically significant association was found between buprenorphine dose and the length of QTc interval.

3. To estimate the extent to which deaths occurring in the Norwegian OMT programme might be attributed to QTc prolongation.

The calculation of mortality potentially attributable to QTc prolongation included those deaths which were due to overdose and where post-mortem was not conducted, and deaths of unknown cause. Based on these figures, the estimated maximum mortality theoretically attributable to QTc prolongation was 4 deaths/6450 patient years in OMT = 0.06 deaths per 100 patient years in OMT. Only one death occurred that could possibly be attributed to cardiac arrhythmia within the first month of treatment. This corresponded to 1 death per 3850 OMT initiations.

Opioid maintenance patients with QTc prolongation:
Congenital long QT syndrome mutation may be a contributing risk factor

Research objectives:

1. To describe the findings of past medical history, drug and family history, focusing in particular on cardiac symptoms and other risk factors for QTc prolongation.

There were no cases of known HIV, liver disease, diabetes or other chronic disorders. No cardiac disorders had been diagnosed. There was no reported use of other illegal or prescribed drugs known to affect the QTc interval and no relevant family history for any of the participants. Two patients had histories of previous cardiac symptoms prior to OMT.

2. To conduct genetic testing for LQTS mutations among OMT patients with QTc interval > 500 msec.

Of the seven patients tested, two were found to be heterozygous carriers of two different LQTS mutations. Both had previously experienced cardiac symptoms prior to and during OMT, without receiving further cardiac or genetic investigations. One female patient was found to be heterozygous for a mutation in the R885C in exon 11 of the Human ether-a-go-go-related gene (HERG), known as LQTS2. One male was found to carry a heterozygous mutation in the Q530X of the Potassium channel, voltage-gated, KQT-like subfamily, member 1 (KCNQ1) gene, known as LQTS1.

3. To discuss in detail the findings from cardiac investigation and management of OMT patients found to have QTc prolongation.

The cardiac investigations revealed that QTc intervals fluctuated widely over 24 hours and during exercise for all patients. Three patients, without LQTS mutations detected, had reductions to their QTc interval from above to significantly below 500 msec with increased heart rate, illustrating the reverse frequency-dependent effect of drug-induced QTc prolongation. The LQTS1 mutation carrier had switched to buprenorphine and started on a protective beta-blocker. Despite expert advice, none of the other patients wanted to switch to buprenorphine, reduce the methadone dose or take other cardiac protective measures.

Cross-register mortality study

Discussion of results

This study illustrates reduced mortality during opioid maintenance treatment. It also highlights a change in causation, in which overdose mortality is dominant before and after treatment, and non-overdose mortality is most common in treatment.
Our approach enabled calculation of direct risk reductions in OMT in relation to the pre-treatment level, demonstrating significant reductions both in overdose deaths (RR 0.2) and all-cause mortality (RR 0.5). The mortality reduction may have been influenced by the particular characteristics of OMT in Norway at the time. Long term opiate addiction was a criterion to be found eligible for OMT. As a consequence, the patients admitted to the programme were long term, opioid dependent individuals. As the route of heroin administration in Norway is most commonly by injection, these were mainly needle users, with correspondingly poor health status.

The mortality pattern demonstrated in the study resembles findings from other studies previously reported in Amsterdam and Stockholm.[38;89;90] Although reduced from the pre-treatment level, overdose mortality was still found in treatment.
Our overdose mortality rate during treatment (0.4 per 100 person years) is similar to what has been reported by Caplehorn et al, who identified an overdose mortality of 0.5 per 100 person years during treatment.[91] It is reasonable to assume that these overdoses were caused by polydrug intoxications, in which illicit opiates may or may not have been involved. Unfortunately, the registers did not provide any information on the OMT drug and dose the patients who died of overdose during treatment were on.

Another noteworthy finding is that non-overdose deaths in the in-treatment group were dominating. Somatic health problems promoted swift acceptance into the programme. However, the cross-register data did not provide information on the health status of each individual patient. Exact figures for HIV prevalence in the study population were therefore unavailable in the dataset, but it is known to be relatively

low in Norway.[92] Estimated HIV prevalence based on available information, was in the range of 2–5 % among Norwegian OMT patients during the study period.

In addition to these findings, the study also demonstrated that a significant mortality risk reduction was found using the intention-to-treat perspective; in which mortality in drop outs was also included. In this perspective the overall mortality RR was 0.6 compared with the pre-treatment level. The benefits of OMT were supported also from the intention-to-treat perspective. However, as expected the benefit was less than when compared with the reduction found in the in-treatment group.
Studies focusing only on treatment results for completers will tend to overestimate the positive outcomes of OMT due to selection mechanisms. By including all patients who ever started on OMT in an intention-to-treat analysis, this selection bias can be ruled out.

The increase in mortality for the post-treatment group was mainly caused by an increased frequency of overdose deaths, corresponding with previous findings.[9;29] Patterns of mortality and mortality reductions were generally similar for both genders, with a couple of notable exceptions. Men who ceased OMT treatment had twice the risk of death as women in the same situation. The increase in overdose mortality post-treatment was more or less confined to males. Unfortunately, the dataset did not give information with regards to why individuals had stopped OMT, and whether this was voluntary or not. Thus, we have no data to provide an explanation for this gender-related pattern. However, males in the general population also appear to have about twice the age-adjusted mortality risk as females.[84] It is possible that the post-treatment group included individuals with the largest burden of psychiatric comorbidity, since it is generally accepted that it is the most heavily burdened and non-compliant patients who leave OMT.[30;38;93;94]

After the conductance of our study, Clausen and colleagues did further analyses of the cross-register data generated.[95] Mortality aspects among opioid users in relation to opioid maintenance treatment, age and causes of death were investigated.
They found that overdose deaths among all age groups were reduced during OMT. Whilst in treatment, older patients (≥50 years of age) were at higher risk for both somatic and traumatic deaths compared with the younger, and in general, deaths

during OMT were likely to be due to somatic causes. Before entering treatment, younger patients (≤ 34 years of age) had a greater risk of fatal overdose. After leaving treatment, it was the older patients (≥ 50 years of age) who faced the greatest risk of dying from an overdose. A recently published British paper, retrospectively investigated factors associated with mortality during methadone maintenance treatment for 2378 patients.[96] Overuse of methadone, a history of psychiatric admissions and comorbidity were all associated with increase in all cause mortality. More specifically, history of psychiatric admission, as well as previously been prescribed benzodiazepines, were found to be risk factors for drug dependent death. Fareed *et al* looked at chronic conditions as risk factors for premature death among older heroin addicts on MMT.[97] Diabetes mellitus, liver and gastrointestinal cancers were found to be associated with increased mortality. However, patients who remained in treatment showed significant improvement related to drug use, psychiatric, medical and legal problems compared to those who dropped out.

In the cross-register study, we did not exhibit information on the OMT drug the patients were on. More recent studies have investigated differences between methadone and buprenorphine maintenance treatment with regards to mortality. Bell and his colleagues published two large cross-register studies in 2009. In the first of these studies, they compared retention in OMT and mortality after initial entry to either methadone or buprenorphine treatment.[98] During induction, the risk of death was found to be lower with buprenorphine than methadone. The overall risk of death was lowest during treatment and significantly higher during the first 12 months after leaving both methadone and buprenorphine treatment. In the second paper, they looked at the risk of overdose whilst in OMT.[99] This study involved 13 718 patients on methadone and 2716 on buprenorphine. The main finding was that the risk of overdose death per thousand people in treatment was higher for methadone than buprenorphine (RR 4.25).

A Cochrane review published in 2009 by Mattick *et al* investigated methadone maintenance therapy (MMT) versus no opioid replacement therapy for opioid dependence.[100] They included 11 randomised clinical trials (RCTs), of which two were double-blind. The review concluded that MMT appeared statistically more effective on retaining patients in treatment and in suppressing heroin use.

However, they did not find significant differences in criminal activity or mortality. As mentioned in the introduction, RCTs may not be the most suitable design to study long-term effects of OMT on mortality, due to ethical aspects, as well as small number of participants and short follow-up periods. A recently published large Australian cross-register study involved 42 676 people entering OMT between 1985 and 2006.[101] The researchers here concluded that mortality was higher out of treatment than in, particularly during the first weeks out of OMT. During induction to treatment, mortality was elevated for methadone but not for buprenorphine, supporting the results of Bell *et al*. Compared to out of treatment, the overall mortality in treatment was reduced regardless of whether patients were receiving methadone or buprenorphine. Across the entire cohort, OMT was estimated to produce a 29% reduction in mortality.

Methodological considerations

The cross-register approach chosen in this study allowed for investigation of mortality differences prior to, during and post OMT, including an intention-to-treat perspective. It also enabled the separation of overall mortality into overdose and somatic mortality within the different groups. The use of intention-to-treat in this area of research may be regarded controversial. OMT is often considered to be a life long treatment. This does not, however, necessarily justify exclusion of mortality in treatment dropouts when estimating the benefits. Leakage of OMT drugs from the programme to persons outside OMT is a well-recognised problem that needs to be counteracted. Mortality reduction in treatment is therefore only one of several goals in an OMT programme, and has to be weighed against other issues. This underlines the importance of knowing the potential in reducing mortality risk for an entire population of opioid addicts eligible for OMT, not only those currently in treatment.

Cross-register studies are rational and efficient in evaluating mortality and other aspects of OMT. However, there are currently only a few countries, mostly Scandinavian, where such national registers exist and are feasible for this approach. The high quality of the data from the death register in Norway adds strength to our study. However, it is important to note that the mortality cause is dependent on the

individual practice of the doctor submitting the death certificate.
Misclassification of a true suicide as overdose would tend to cause overestimation of overdose as a cause of death. A limitation to the dataset is the lack of information about individual type of maintenance drug or dose. During the observation period for this study, methadone was the most widely used medication, whereas buprenorphine introduced in 2001 was used by 23% by the end of 2003. Additionally, no information on the subjects' drug use history was available, nor whether termination of treatment was voluntary or not. The relatively high age of the cohort may be explained by the age limit of 25 years. Notably, age was measured at the end of the observation time, not at inclusion.

Register-based studies are clearly dependent on the quality of the registers employed. In this study, the national OMT patient register was based on electronic patient records information from the regional OMT centres. For patients in treatment and for the post-treatment group, we believe that the information is up to date and of good quality, as budgets and monitoring of expenses are based on continuously updating the data. Despite thorough control of each individual that did not enter treatment (ineligible), some cases might wrongly have been classified as belonging to the pre-treatment group. Since the ineligible for treatment group had a low crude mortality rate, misclassifications could deflate mortality rates for the pre-treatment group. As the issue were thoroughly examined and manually checked, we find it unlikely that results were significantly affected.

The study population represents those who were found eligible to OMT in Norway during the study period. At the time this comprised between 1/3 and ½ of all injecting opioid dependants in Norway, characterised by a long-term and severe opioid dependence syndrome. As OMT programmes vary internationally in terms of different inclusion policy, availability and capacity, this will affect the degree to which the results apply to populations in other nations. The absolute levels of mortality reduction will vary accordingly across various populations. We believe that the relative level of risk reduction of mortality as a result of OMT is more comparable between different study groups, than the absolute mortality levels are.

ECG assessment study

Discussion of results

Eight of the 173 methadone maintenance patients (4.6 %) had an unequivocally prolonged QTc time above 500 msec, which placed them at increased risk of cardiac arrhythmia and TdP.[43] Methadone dose was found to be positively related to QTc prolongation, and all of the eight cases of with QTc prolongation greater than 500 msec were patients receiving methadone doses of 120 mg or more. The finding of a dose-dependent relationship between methadone and QTc prolongation points to causality and is consistent with results previously reported in other studies.[56;58]
No association was found between the QTc prolongation and age. We hypothesised that it was possible that the amount of time spent in methadone treatment might have had a cumulative effect on the QTc interval, but no such association was detected. In other studies, women have been found to be at greater risk for QTc prolongation than men.[102;103] We did not detect such a difference.

An Australian study looked at the QTc interval of OMT maintained subjects on moderate doses; n = 35 with mean daily methadone dose 69 mg (standard deviation +/- 29 mg) and n= 19 with mean daily buprenorphine dose 11 mg (standard deviation +/- 5 mg).[104] Despite methadone users having a longer QTc interval than the buprenorphine users, these were all well below 500 msec. They subsequently concluded that methadone and buprenorphine at commonly used daily doses remain safe agents for OMT. A study by Krantz investigated the QTc interval changes at baseline and 6 months after methadone induction.[105] The results highlighted the heterogeneity of QTc interval changes, where subjects exceeding 500 msec increased from 0 % to 2 %. Fonseca and colleagues performed a cross-sectional study among 109 methadone maintained subjects.[106] They found that 1.8 % exhibited a QTc interval above 500 msec and this was associated with higher daily methadone dose (median 120 mg). A dose-dependent correlation was observed.
In terms of plasma concentrations, no association was found between plasma concentration of (R)-methadone and (S)-methadone and the length of the QTc interval. However, a recently published study separated (R,S)-methadone into (R)- and (S)-methadone, and looked at the two components effect on the QTc interval.[107] (R)-methadone mainly mediates the opioid effect, whereas (S)-methadone is a more

potent blocker of the HERG potassium channel, which can cause QTc prolongation. They found that substituting (R,S)-methadone with (R)-methadone significantly reduced the length of the QTc interval.

Methodological considerations

In this study we used a cross-sectional approach. All the information was therefore gathered at the same time, as opposed to a cohort study, which follows individuals over time. The cross-sectional approach is not associated with the many difficulties affecting other designs, such as loss to follow-up and recall bias. There are, however, some problems associated with this type of study.[108] Sample selection must be considered. Often the interpretation of results is extended widely, despite research being carried out on a limited number of subjects. As the validity of the extrapolation depends on the representativeness of the sample, a random selection of individuals is the ideal method. Another problem faced by this approach is linked to the response rate, and indeed volunteer bias may occur. This is particularly well-recognised when surveys are distributed by post. In any study efforts should be made to increase the response rate as much as possible. Finally, the problem of cause or effect might occur with cross-sectional designs. Some case-control studies face similar problems, and a prospective study is the ideal way to investigate causation.

The final sample included approximately 20 % of the Oslo OMT population, which did not differ in characteristics from the OMT population of Oslo as a whole.
Most patients asked to participate appeared keen to have their heart checked and there were less than 10% who declined participation. We do not have any data on these individuals, but there was little to suggest from our observations that these were any different from the ones who participated. The external validity of our findings therefore seems well maintained.

A limitation associated with our data is the lack of additional information regarding the patients' concomitant use of illegal substances. The ability of cocaine to acutely prolong the QTc interval was recognised many years ago.[109] More recent studies have supported this finding.[110;111] Similarly, Haning and Goebert demonstrated QTc

prolongation at an abnormally high rate among methamphetamine dependents.[112] It is worth noting that, according to the Norwegian annual evaluations, in our sample and in the Norwegian OMT population as a whole, the use of cocaine and/or methamphetamine was close to non-existent, both in the QTc study period[83] and the mortality assessment period.[82] Another limitation of this study is that we do not have information about the nutritional status and life conditions of the patients in our sample, and severe malnutrition with hypokalemia can give rise to prolongation of the QTc interval.[113] Also, in the QTc assessment study the number of patients on buprenorphine was low (n=27). This makes it difficult to compare the two OMT drugs and to draw any firm conclusions with regards to the cardiac properties of buprenorphine. It adds strength to our study that all the ECGs were examined by the same cardiologist, who was blinded for all patient details, including type of OMT medication, as well as dose, age, gender, and time in treatment.

Prolonged QTc interval mortality study

Discussion of results

The estimated mortality potentially attributable to QTc prolongation was 0.06 deaths per 100 patient OMT years. The results also show that only one unexplained death occurred during the first month of OMT, which gave a figure of 1 death per 3850 OMT initiations. To our knowledge, this is the first attempt to estimate the potential impact on mortality from QTc prolongation in a large, national sample of OMT patients. These calculations add important information to the field as they indicate that the extent to which methadone gives rise to ventricular arrhythmias resulting in sudden death in OMT appears extremely low.

Methodological considerations

This study used the same data from the cross-register mortality study. The strengths stemming from large numbers in complete national registers therefore apply. Nevertheless, the potential mortality attributable to QTc prolongation should be interpreted with caution. It is an important point methodologically that only about one

third of the death certificates were supplemented with information supported by autopsy and toxicological analyses, hence the other 2/3 of cases are based on "external" examinations with the risk of misclassification. Deaths among patients with a known history of opiate addiction may well be misclassified as overdose rather than for example suicides or sudden cardiac deaths, as previously discussed by Gossop et al.[7] The mortality estimation was made by including the two cases of overdose without post-mortem and the two deaths of unknown cause. It is possible that not all of these four cases occurred as a result of ventricular arrhythmia associated with methadone, and in that case, the estimate of 0.06 deaths per 100 patient OMT years would represent an overestimation of the actual impact of QTc prolongation on mortality. Similarly, potential misclassification of the cause of death could also involve the deaths not included in the calculation. We have no information indicating differential classification between the outcome groups. In the absence of any evidence to support this, we believe that this is unlikely to have introduced any substantial bias into our reported calculation of mortality. Another limitation to this prolonged QTc interval mortality estimation is that the dataset did not provide relevant information on somatic health status, concurrent drug use or type of OMT drug and dose for the group in treatment.

Cardiac and genetic investigations and management study

Discussion of results

The main findings of this study involved identification of two heterozygous LQTS mutations carriers. QTc intervals fluctuated widely over 24 hours and during exercise for all the patients, ranging from below 500 msec to above 600 msec. Only one patient switched to buprenorphine and started on a beta blocker. None of the other patients wanted to switch to buprenorphine or take other cardiac protective measures.

To our knowledge, this is the first study to identify LQTS mutation as a potential pre-existing and contributing risk factor of QTc prolongation in OMT patients. Among the seven patients with QTc prolongation tested for LQTS, two heterozygous mutation carriers were identified. Both had previously experienced cardiac symptoms prior to

and during OMT. However, neither of the patients had ever had their QTc interval measured or had other cardiac investigations prior to the study. Family history did not prove a useful marker of mutation status, as it was negative for both patients. No other risk factors for QTc prolongation were identified.

The results of the cardiac investigations illustrate the diurnal fluctuations of the QTc interval. [114] In this study we recorded 24 hour ECGs, in which QTc intervals varied between markedly prolonged to below or down to 500 msec for all of the six patients. The exercise test further indicated the changes in QTc interval that can occur with increased heart rate. [115] Three patients without LQTS mutations detected, had reductions to their QTc interval from above to significantly below 500 msec with increased heart rate, illustrating the reverse frequency-dependent effect of drug-induced QTc prolongation. [116]

One male was found to carry a heterozygous mutation in the *KCNQ1* gene, known as LQTS1. He had earlier suffered two cardiac arrests requiring resuscitation during heroin withdrawal. Without knowledge of his genetic condition, he had switched to buprenorphine prior to the cardiac outpatient appointment. During the 24 hour tape recoding, the QTc interval fluctuated between normal values of 444 msec up to 601 msec at maximum heart rate. LQTS1 has been found to be more sensitive than LQTS2 and LQTS3 to sympathetic stimulation. [71] The underlying LQTS1 mutation, in combination with extreme stimulation of the sympathetic nervous system during heroin withdrawal, may have triggered the two episodes of cardiac arrest. As this resting QTc interval was normal on buprenorphine, it is uncertain whether the patient's genetic mutation would have been detected if he had not been treated with methadone when participating in the original study. Hinterseer *et al* has recently shown that increased short-term variability of QT interval of > 4.9 msec has a sensitivity of 83 % and specificity of 68 % in identifying new LQTS mutation carriers in people with a normal QTc interval. [117] They concluded that this non-invasive investigation could form a marker for diagnostic screening before results of genetic testing are available.

Clinical managerial issues were highlighted in this study. Only the patient with LQTS1 mutation, who already had switched to buprenorphine, was willing to take a

beta-blocker. None of the other patients wanted to switch to buprenorphine, reduce the methadone dose or take other cardiac protective measures, despite thorough information and strong medical advice. The cardiac symptoms experienced over many years by the two LQTS mutation carriers, highlights the importance of history taking prior to OMT.

Methodological considerations

The number of participants in this study was low. However, the identification of these patients required recruiting from a QTc assessment study with a much larger sample of 200 OMT patients, as the prevalence of QTc interval > 500 msec found to be 4.6 % among methadone maintained patients.[87] Given the nature of OMT in Oslo, the goal of reaching 200 OMT patients and recording their ECGs was satisfactorily achieved by stretching our resources.

This study is limited by the reduced sensitivity of a single ECG recording. Research has shown that 10-36 % of heterozygous mutation carriers are silent carriers and have a normal QTc interval on their ECG.[118] Consequently, there may have been missed cases of LQTS mutations among the remaining 165 methadone and 27 buprenorphine patients with QTc intervals < 500 msec in the QTc assessment study. This is indicated by the fact that the patient with the LQTS1 mutation exhibited a normal QTc interval at rest after switching from methadone to buprenorphine. Finally, even in patients referred for genetic testing following the most stringent criteria, a mutation is identified in approximately 70 % of the cases.[119;120] It implies that a substantial proportion of LQTS mutations have not yet been discovered and are subsequently not tested for.[71] In the future, it is expected that more mutations in LQTS candidate genes will be detected.

Ethical considerations in the research

In all research involving humans, ethical considerations safeguarding the subjects involved must be incorporated during the planning and conduction of a study.

Opioid dependent individuals form a particularly vulnerable group, which are often found to be in an exposed situation with increased prevalence of somatic diseases and mental illness.[10] Their need for treatment and desire for change are often substantial, but this may at the same time leave them more easily exposed to exploit. It is therefore crucial to base the treatment offered on evidence from research, with knowledge of associated risk factors and outcome. The cross-register mortality study is ethically important, as is yields information on OMT on crude measures of mortality and overdose prior to, during and after treatment. As a cross-register approach was used, this study did not involve any type of intervention for the patients.

In the ECG assessment study the patients were approached for participation after being thoroughly informed about the purpose of the ECG recording. The aspect of voluntary participation was emphasised and patients had to give informed consent before participating. The finding of a very low mortality rate that could potentially be attributable to QTc prolongation in OMT, was clinically important and confirms that patients are not being put on a treatment which itself carries a high mortality risk. In the final study the same approach with informed consent was practiced. Patients who decided to participate received cardiac and genetic investigations and were offered professional cardiac management based on findings by a senior cardiology consultant.

Implications for policy and treatment

The main finding of decreased mortality for patients in OMT compared to the period prior to and after treatment clearly has implications for OMT policy. The increased mortality, and particularly overdose rate, following treatment should warrant caution with regards to involuntary ending OMT. As death from somatic causes was most common whilst in treatment, this should be an indicator of the burden of somatic illnesses these patients carry. OMT provides an opportunity to address these problems, for a group of patients who otherwise rarely seek the help of health professionals. As of 2010 new guidelines for OMT have been implemented in Norway.[121] Compared to the previous guidelines, the age requirement has now been removed and although OMT should as a general rule not be the first treatment of

choice, failed attempts at abstinence-oriented treatment are no longer a requirement. Continuous drug-use or general lack of compliance with treatment requirements is not alone a satisfactory reason for involuntary eviction from OMT.

Our estimations indicate that the maximum mortality attributable to QTc prolongation and ventricular arrhythmia in opioid maintenance treatment is very low, despite a prevalence of QTc interval above 500 msec of nearly 5 % among methadone patients and indications of a dose-dependent relation.[87] Agreement on safe and rational cardiac management of methadone patients has so far proven contentious.
In Norway this discussion was raised in 2007 in the Journal of the Norwegian Medical Association by two general practitioners, who claimed that QTc prolongation due to methadone could be a cause of sudden cardiac deaths in OMT.[122] They advocated ECG screening prior to initiation of methadone maintenance treatment. After a review of the evidence based literature on this topic, an expert team recommended instead that ECG should be recorded during treatment and particularly if there were other risk factors for QTc prolongation present.[123] This was largely based on research done by Krantz, who was one of the first cardiologists to describe the phenomenon. Annals of internal medicine published in 2009 new recommendations by a team of researchers and clinicians, including the same Krantz. This time advocating a pre-treatment ECG, a follow-up ECG within 30 days and then annually.[124] At present, however, there are no widely accepted guidelines, and views regarding ECG screening are conflicting.[69]

Our findings do not point to ECG recording prior to OMT as a life-saving, cost-beneficial screening program. Rather, in the absence of firm guidelines, we suggest a practical approach for clinicians. A past medical history, focused particularly on cardiac symptoms and disorders, should always be obtained prior to treatment with methadone. If indicated by the history or in the presence of other known risk factors for QTc prolongation, the drug of choice is primarily buprenorphine. The patient should not be started on methadone without cardiac protection. An ECG, preferably over 24 hours, should be recorded at this stage. If this reveals QTc prolongation, the patients should be referred for genetic testing if available, along the same referral criteria as any other individual with similar findings. Further research should aim to clarify the costs and benefits of ECG screening in OMT prior to potential implementation.

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Mortality prior to, during and after opioid maintenance treatment (OMT): A national prospective cross-registry study

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Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: A mortality assessment study

Katinka Anchersen, Thomas Clausen, Michael Gossop, Viggo Hansteen, Helge Waal.

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Opioid maintenance patients with QTc prolongation:
Congenital long QT syndrome mutation may be a contributing risk factor

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Opioid maintenance patients with QTc prolongation:

Congenital long QT syndrome mutation may be a contributing risk factor

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Opioid maintenance patients with QTc prolongation:

Congenital long QT syndrome mutation may be a contributing risk factor

Objectives

This study investigates opioid maintenance treatment (OMT) patients found to have corrected QT (QTc) interval above 500 msec, with particular focus on past medical history, genetic testing and cardiac investigations.

Methods

Detailed medical and cardiac history was obtained, with particular focus upon risk factors. Cardiac investigations, including genetic testing for the five most common long QT syndrome (LQTS) mutations, exercise electrocardiography (ECG) and 24-hour ECG recordings, were performed.

Results

Of 200 OMT patients assessed with ECG, seven methadone maintained patients identified with QTc interval above 500 msec participated in this study. Two were identified as heterozygous LQTS mutations carriers. Both had experienced cardiac symptoms prior to and during OMT. No other risk factors for QTc prolongation were detected among the seven patients. Six of the seven patients underwent further cardiac investigations. QTc intervals fluctuated widely over 24 hours and during exercise for all patients. Only one of the LQTS mutation carriers switched to buprenorphine and started on a beta blocker. Despite strong medical advice and information, none of the other patients wanted to switch to buprenorphine or take other cardiac protective measures.

Conclusion

Findings indicate the importance of recording a thorough past medical history, focusing specifically on previous cardiac symptoms, and on other known risk factors for QTc prolongation, prior to initiating patients on methadone.

Keywords

Congenital long QT syndrome, genetic, management, methadone, QT prolongation

Opioid maintenance patients with QTc prolongation:

Congenital long QT syndrome mutation may be a contributing risk factor

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1. Introduction

The association between methadone and prolongation of the corrected QT (QTc) interval is well-established (Fonseca et al., 2009; Peles et al., 2007; Wedam et al., 2007). QTc prolongation is characterised by abnormal T-wave morphology seen on electrocardiogram (ECG) and is in itself asymptomatic. It is associated with torsades de pointes (TdP), which is often self-terminating and may cause a quick syncopal episode. If TdP is more persistent, ventricular fibrillation leading to cardiac arrest and sudden death can result (Vincent, 2000). As TdP rarely occurs with a QTc interval of less than 500 msec, this is generally considered the threshold of risk for TdP (Priori et al., 2003).

Drug-induced QTc prolongation is caused mainly by blockade of the slow component of the delayed rectifier K^+ current (I_{Kr}), a major repolarisation current in the heart. I_{Kr} blockers, such as methadone, increase the dispersion in repolarisation. They often display a reverse frequency-dependent effect, in which the degree of QTc prolongation is more prominent during slow heart rates (Chiang, 2004). A dose-response association between methadone and the QTc interval has been found, with increased dose associated with a higher frequency of reported syncope (Fanoe et al., 2007).

Multiple risk factors may contribute to QTc prolongation, including hepatic cytochrome P450 inhibitors, structural heart disease and hypokalemia, as well as genetic predisposition

(Chiang, 2004; Reddy et al., 2010). Three major genes involved in congenital long QT syndrome (LQTS) were identified in 1995 (De Ferrari & Schwartz, 2009). Most mutations occur in LQTS1, LQTS2 and LQTS3 genes (Markiewicz-Loskot et al., 2009). A study tested for mutations in the LQTS1, LQTS2, LQTS3, LQTS5 and LQTS6 genes, which all code for subunits of cardiac ion channels. The overall prevalence in the general population of heterozygous mutation carriers for the five genes was estimated to be between 1/100 and 1/300 (Berge et al., 2008).

Phenotypically silent or subclinical LQTS mutation carriers may become symptomatic in the presence of other risk factors (Chiang, 2004), including drugs with QTc prolonging properties such as methadone. However, the LQTS carrier status is often unknown to the individual and clinician prior to the risk exposure and subsequent clinical manifestation (Goldenberg & Moss, 2008). This study is a case series of OMT patients with QTc interval above 500 msec. A detailed medical and cardiac history was obtained, with particular focus upon risk factors. Cardiac investigations, including genetic testing for the five most common LQTS mutations, were performed.

2. Materials and methods

Patients with QTc > 500 msec were identified and recruited from a QTc assessment study: ECG was recorded among 200 OMT patients (Anchersen et al., 2009), of whom 173 were on methadone and 27 on buprenorphine. The mean age was 41 years. The mean daily methadone dose was 111 mg and buprenorphine dose 19 mg.

A medical history was obtained from patients with QTc interval > 500 msec at the initial consultation. Previous cardiac symptoms and disorders were specifically requested. All

substances (including alcohol) and medications ever used, particularly those associated with changes in QTc interval were noted. The family history focused on known cardiac disorders, symptoms and treatment.

Standard dideoxy DNA sequencing was done on blood samples, using the Big Dye terminator cycle sequencing kit. Testing was performed at the Department of medical genetics at Oslo University Hospital, checking for mutations in the following five genes:

- Potassium channel, voltage-gated, KQT-like subfamily, member 1 (*KCNQ1*) = LQTS1
- Human ether-a-go-go-related gene (*HERG*) = LQTS2
- Sodium channel, voltage-gated, type V, alpha subunit (*SCN5A*) = LQTS3
- Minimal potassium ion channel (*minK*) = LQTS5
- Minimal potassium ion channel-related peptide 1 (*MiRP1*) = LQTS6

Patients were encouraged to attend the cardiac outpatient clinic at Oslo University Hospital for an appointment with a consultant cardiologist. Investigations included ECG at rest, exercise ECG (bicycle) and 24-hour ECG recording.

The study was approved by the Regional ethics committee.

3. Results

Among the 200 OMT patients, eight methadone patients were identified with QTc >500 msec. One declined participation and was not included in this study. Seven patients (one woman, 6 men) attended the initial appointment, where a full medical history was obtained and blood tests for potassium level and genetic testing for LQTS mutations performed.

//Table 1//

Participants were aged 29 -53 years (mean 40.8 years). Daily methadone doses were 120-240 mg. Initial QTc ranged from 507-579 msec. All seven patients had normal serum potassium levels. Genetic testing revealed two heterozygous mutations for LQTS: both patients had histories of previous cardiac symptoms. No cardiac disorders had been diagnosed. There were no cases of known HIV, liver disease, diabetes or other chronic disorders. There was no reported use of other drugs known to affect the QTc interval and no relevant family history.

//Table 2//

Patient 7 dropped out of OMT after the initial appointment and testing. He did not undergo cardiac investigations and is excluded in further results. The remaining six patients received additional investigations. Patient 1 had a normal QTc at rest (444 msec). This increased to 535 msec on the exercise test and varied between 480-560 msec on the 24-hour recording. The other three patients without detected mutations had QTc intervals at rest >500 msec. The QTc interval of these three patients fell substantially <500 msec on the exercise test (460-477 msec). During the 24-hour recording, these patients had peaks >500 msec.

3.1. Patient with LQTS2 mutation

This patient was a 32 year old woman with longstanding injecting heroin use, until admitted to OMT 2 years previously when she was started on methadone. On the initial ECG recording, QTc was 532 msec. She received 120 mg of methadone/day. Genetic testing revealed that the patient was heterozygous for the LQTS2 mutation.

In her medical history, she described 5-6 episodes of syncope and daily episodes of dizziness, without palpitations. She had never consulted medical staff for this problem. Resting QTc interval was 501 msec. During exercise, heart rate reached a maximum of 138 bpm, while blood pressure remained unchanged at 93/78 mmHg. She had to stop after 4 minutes due to exhaustion. There was no chest pain or dizziness during the investigation and ECG showed no signs of arrhythmia or ischemia. QTc during the investigation increased to 507 msec. During the 24-hour recording QTc interval varied between 500-560 msec.

The patient did not wish to switch to buprenorphine. She declined to start on a protective beta-blocker or reduce the methadone dose. Finally, she turned down the offer of an implantable cardiac rhythm recorder.

3.2. Patient with LQTS1 mutation

This patient was a 30 year old man with longstanding injecting heroin use until admitted to OMT 4 years before the study. He was receiving 120 mg methadone/day. On the initial ECG, QTc was 513 msec. Genetic testing detected a heterozygous LQTS1 mutation.

After the prolonged QTc was detected, he requested transfer from methadone to buprenorphine. At the cardiac outpatient appointment he appeared in good health. His past medical history indicated two separate episodes of cardiac arrest prior to OMT: both occurred during withdrawal from heroin and required resuscitation. He had since experienced 3-4 episodes of syncope. Two years ago he had an episode of loss of consciousness resulting in hospital admission. He was discharged without any diagnosis or medication. QTc interval was not investigated at that time.

For resting ECG, the QTc was 441 msec. During exercise, heart rate reached a maximum of 138 bpm; blood pressure reached 142/78 mmHg. He was moderately out of breath at the end, but did not experience chest pain or dizziness. There were no signs of arrhythmia or ischemia on his ECG. QTc during the investigation remained unchanged. The 24-hour ECG recording revealed fluctuations of QTc between 444 msec at lowest heart rate up to 601 at maximum heart rate.

As the patient had already switched to buprenorphine, he was advised to start on a prophylactic beta-blocker based on his medical history, LQTS1 mutation and the 24 hour ECG recordings. He accepted this and was prescribed 50 mg metoprolol (Selo-Zok®) daily. The cardiologist also raised the possibility of an implantable cardiac rhythm recorder, which he declined.

3.3. Patients without LQTS mutations

The remaining four patients received individual follow-up appointments. One patient had experienced three non-specific episodes of loss of consciousness over the last 20 years, which were uncertain in origin. As no causation of QTc prolongation beyond methadone was established, these patients were advised to switch to buprenorphine, which all patients declined. They were recommended reduction of methadone dose, or alternatively a beta-blocker. These offers were also declined: all patients stated that they wished to continue the current methadone treatment. Finally, they were offered a small implantable cardiac rhythm recorder. No patient opted for this device. After information about possible risks, these patients chose to continue on the same methadone dose, without preventative measures.

4. Discussion

In this study we recorded 24-hour ECGs, in which QTc varied between markedly prolonged to 500 msec or less for all the patients. The exercise test further indicated the changes in QTc interval that can occur with increased heart rate (Extramiana et al., 2009). Results of our cardiac investigations illustrate diurnal fluctuations of the QTc interval (Harris & Steare, 2006) . Three patients without LQTS mutations detected, had reductions to their QTc interval from above to significantly below 500 msec with increased heart rate, illustrating the reverse frequency-dependent effect of drug-induced QTc prolongation (Chiang, 2004).

The study identified two heterozygous LQTS mutations carriers. The cardiac symptoms experienced over many years by these two patients, highlight the importance of history taking prior to OMT. Family history did not prove a useful marker of mutation status, as it was negative for both patients. No other risk factors for QTc prolongation were identified. Only one patient already on buprenorphine started on a beta blocker. None of the other patients wanted to switch to buprenorphine or take other cardiac protective measures.

One male was found to carry a heterozygous LQTS1 mutation. He had earlier suffered two cardiac arrests requiring resuscitation during heroin withdrawal. He had switched to buprenorphine prior to the cardiac outpatient appointment. During the 24-hour tape recording, the QTc interval fluctuated between normal values of 444 msec and 601 msec at maximum heart rate. LQTS1 has been found to be more sensitive than LQTS2 and LQTS3 to sympathetic stimulation (Markiewicz-Loskot et al., 2009). The underlying LQTS1 mutation, in combination with extreme stimulation of the sympathetic nervous system during heroin withdrawal, may have triggered the two episodes of cardiac arrest. It is uncertain whether the patient's genetic mutation would have been detected if he had not been treated with

methadone when participating in the original study. Increased short-term variability of QT interval of > 4.9 msec has recently been found to have a sensitivity of 83 % and specificity of 68 % in identifying new LQTS mutation carriers in people with a normal QTc interval (Hinterseer et al., 2009).

The marked diurnal fluctuations of the QTc interval among the patients clearly limit the reliability of a single ECG used for identification. Additionally, between 10-36 % of heterozygous mutation carriers are silent carriers and have a normal QTc interval on their ECG (Priori et al., 2003). Consequently, there may have been missed cases of LQTS mutations among the remaining 192 patients with QTc intervals < 500 msec in the QTc assessment study: it can not be excluded that the prevalence of LQTS mutations is the same in this group. Finally, even in patients referred for genetic testing following the most stringent criteria, a mutation is identified in approximately 70 % of the cases (Goldenberg & Moss, 2008; Napolitano et al., 2005). This implies that a substantial proportion of LQTS mutations have not yet been discovered and were subsequently not tested for. Further studies, including 24-hour ECGs and genetic testing, are needed in order to investigate the prevalence of QTc prolongation and associated risk factors among methadone maintained patients in more detail.

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Table 1. Patient characteristics, cardiac history and blood test results

	Gender	Age	Methadone dose	Months in treatment	QTc interval in study (msec)	Cardiac history	S-potassium mmol/L (ref.3.6-5.0)	Genetic testing for LQTS mutations
Patient 1	Male	46	140 mg	72	520	Nil	4.4	Nil found
Patient 2	Male	53	240 mg	96	579	3 episodes of loss of consciousness over 20 last yrs	3.9	Nil found
Patient 3	Male	35	140 mg	19	523	Nil	4.4	Nil found
Patient 4	Female	32	120 mg	25	532	5-6 episodes of syncope over last 12 years, daily episodes of dizziness	4.3	Heterozygote mutation R885C in exon 11 of the *HERG* gene
Patient 5	Male	47	150 mg	78	507	Nil	3.8	Nil found
Patient 6	Male	29	120 mg	38	513	2 episodes of cardiac arrest associated with abstinence, 3-4 episodes of syncope during last 10 years	4.5	Heterozygote mutation Q530X in the *KCNQ1* gene
Patient 7	Male	44	160 mg	39	528	Nil	4.9	Nil found

Table 2. Results of clinical examination and cardiac investigations

	General observations	Resting ECG at cardiac OP	Exercise ECG at maximum tolerance	24 hrs ECG (Holter)
Patient 1	H: 185 cm W: 104 kg HR: 74 reg BPs: 95/70 BPl: 120/80	SR, QTc 444 msec	QTc 535 msec, HR113 bpm, BP 129/65	SR 38-106 bpm, 1 pause: 2.01 sec, QTc 480-560 msec
Patient 2	H: 180 cm W: 92 kg HR: 75 reg BPs: 145/80 BPl: 145/80	SR, QTc 520 msec	QTc 477 msec, HR 112 bpm, BP 200/100	SR 55-119 bpm, QTc 480-520 msec
Patient 3	H: 200 cm W: 90 kg HR: 112 reg BPs: 106/78 BPl: 120/80	SR, QTc 502 msec	QTc 474 msec, HR 148 bpm, BP 134/86	SR 34-153 bpm, sinus bradycardia at night, QTc 480-505
Patient 4	H: 164 cm W: 68 kg HR: 70 reg BPs: 93/74 BPl: 100/80	SR, QTc 501 msec	QTc 507 msec, HR 163 bpm, BP 93/78	SR 44-136 bpm, QTc 500-560 msec
Patient 5	H: 179 cm W: 85 kg HR: 84 reg BPs: 154/98 BPl: 160/100	SR, QTc 506 msec	QTc 460 msec, HR 110 bpm, BP 195/89	SR 53-122 bpm, QTc 460-507 msec
Patient 6*	H: 186 cm W: 75 kg HR: 78 reg BPs: 108/78 BPl: 120/80	SR, QTc 441 msec	QTc 440 msec, HR 138 bpm, BP 142/78	SR 40-153, QTc 444-601 msec

SR = sinus rhythm, QTc= corrected QT interval, HR = heart rate, BP = blood pressure
H = height, W = weight, HR = heart rate in beats per minute (bpm), reg = regular, BPs = blood pressure sitting measured in mmHG, BPl = blood pressure lying measured in mmHG
*On buprenorphine during cardiac investigations