Changes in somatic disease incidents during opioid maintenance treatment: results from a Norwegian cohort study

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ABSTRACT

Objectives: To examine the effect of opioid maintenance treatment (OMT) on somatic morbidity in a cohort of OMT patients.

Design: Retrospective cohort study.

Setting: OMT programme in two Norwegian counties.

Participants: 200 OMT patients, participation rate 71.2%.

Main outcome measures: Incidence rates (IR) before, during and after OMT for acute/subacute hospital-treated somatic disease incidents (drug-related, non-drug-related, injuries) and rates for inpatient days and outpatient treatment contacts.

Results: IR for drug-related hospital treatment episodes were 76% lower during compared to before OMT (before versus during incidence rate ratio (IRR) 4.2 (95% CI 2.9 to 6.2), \( p<0.001 \)) and 11 times higher after compared to during OMT (after versus during IRR 11.1 (6.6 to 18.5), \( p<0.001 \)). For non-drug-related treatment episodes, IR were 35% higher during than before OMT (before versus during IRR 0.7 (0.6 to 1.0), \( p=0.02 \)) and 32% higher after compared to during OMT (IRR 1.4 (0.9 to 2.2), \( p=0.15 \)), while injuries showed little change compared to OMT status. Although patients with on-going drug-taking during OMT showed less reduction in drug-related hospital-treated incidents during treatment than patients not using illicit drugs, the quartile with most drug-taking showed a significant reduction (before versus during IRR 3.6 (2.4 to 5.3)). Patients who had experienced cessation of OMT showed a significant reduction in drug-related treatment episodes during OMT (before versus IRR 1.7 (1.0 to 2.9)), although less than patients without OMT interruptions (before versus during IRR 6.1 (3.6 to 10.6)), and a significant increase after OMT cessation compared with during OMT (IRR 5.4 (3.0 to 9.7)).

Conclusion: Acute/subacute drug-related somatic morbidity is reduced during compared to before OMT. This was also found for patients with on-going drug-taking during OMT. However, acute drug-related health problems show an increase after OMT cessation, and this is a matter of concern. Further studies on somatic morbidity after OMT cessation should be carried out.

INTRODUCTION

Dependent opioid users, especially those injecting heroin, have increased somatic and psychological morbidity and reduced health-related quality of life. Injecting drug users are prone to chronic bloodborne viral infections, especially HIV/AIDS and chronic hepatitis B and hepatitis C as...
well as acute and subacute bacterial infections and other complications related to injecting. Opioid dependence is associated with social marginalisation, criminality and socioeconomic deprivation accompanied by malnutrition, chronic diseases and generally impaired health as well as exposure to overdoses and trauma. Mortality among injecting drug users is much greater than in the general population, with a standardised mortality ratio ranging from 5 to 30 in studies from several countries. The main causes of death (in descending order) are overdose, diseases, trauma and suicide.

Maintenance treatment, hereafter called opioid maintenance treatment (OMT), has been the most widely used treatment for opioid dependence for the last number of decades. The specific changes in physical and mental health that occur during OMT have received surprisingly little detailed research attention. Maintenance treatment leads to reduced use of illegal opioids and less injection. It also induces tolerance to opioids and a corresponding decline in drug-related morbidity including overdoses should be expected. Some studies report improved somatic health during OMT based on interviews, clinical assessment and reduced consumption of inpatient care due to infections, but relatively few studies have investigated OMT-related somatic health effects and morbidity patterns. In a previous study we found reductions in somatic disease incidents treated in hospital or by general practitioners during OMT compared to ‘not in treatment’. Drug-related incidents were reduced by about two thirds, but non-drug-related incidents showed a non-significant increase (possibly due to closer contact with health services) and injuries showed no change during treatment. These findings were, however, based upon a small sample of patients from one municipality. In order to evaluate the effects of maintenance treatment, it is necessary to study morbidity prior to, during and after OMT. Such studies are scarce, and very few include long-term follow-up.

The present study investigates how somatic morbidity varies according to OMT status (before, during and after OMT) in a group of 200 patients. The main hypothesis to be tested was that somatic morbidity is reduced during OMT. More detailed research questions were: (1) What changes in somatic morbidity are found during OMT compared to before and after treatment, and what types of disease incidents are reduced? and (2) How is the effect of OMT status on somatic morbidity influenced by various patient characteristics?

**MATERIALS AND METHODS**

**Design, sample and setting**

Methadone and buprenorphine are used as substitution medications in the national Norwegian OMT programme, which began in 1998. On 13 December 2009, 5383 people were in treatment, and 55.7% were receiving methadone and 44.3% buprenorphine. Norway has a population of 4.9 million and the target group for OMT is estimated to be about 10 000.

The study has a retrospective cohort design. The cohort was established in 2007–8 and consists of those admitted to OMT from 1998 until the end of June 2007 in two counties (Hedmark and Oppland) in Norway (figure 1). The participants were recruited through their treatment contacts. Out of a total of 319 patients who started OMT, 38 had no contact with local health or social services at the time of invitation and were regarded as ineligible for this study. Of the remaining 281, 13 who died after their first OMT entry were included. Among the 268 eligible subjects still alive, 187 consented to participate and 81 did not, and so the cohort consisted of 200 persons. The participation rate was 71.2%, 68.8% among patients in treatment versus 73.7% among those not in treatment when invited.

**Measures**

A somatic disease incident was defined as any acute or subacute health problem leading to inpatient or outpatient hospital treatment, henceforth called hospital treatment episodes. The numbers of hospital treatment episodes, inpatient days and outpatient hospital contacts were recorded. Incidence rates and rates of inpatient days and outpatient contacts for the periods before, during and after OMT were calculated. Incidence rate ratios before versus during treatment and after versus during treatment were estimated. Only records from somatic departments were examined. Psychiatric disease incidents were only considered if they caused a somatic condition, for example due to self-harm. Hospital contacts for chronic somatic disorders were not included, but acute treatment episodes caused by an underlying chronic disease were assessed. One episode could lead to more than one contact, for instance follow-up of a fracture or an abscess. One episode documented in records from several hospitals was only counted once.

**Figure 1** Participants: patients starting opioid maintenance treatment between 1998 and June 2007. The studied cohort consists of the 200 included patients.
Incidence rates were analysed by means of a Poisson regression model. Dependencies in the data, due to the fact that each participant was measured repeatedly (before, during and after OMT), were handled by generalised estimating equations with unstructured working correlation and robust variance estimation. With regard to drug-related treatment episodes, we investigated the possible influence of different patient characteristics on the effect of OMT by including the interaction between OMT and the characteristic in question in the model, one by one. Incidence rate ratios with 95% CIs were estimated. The significance level was set to 5%. All analyses were performed in SPSS v 15.

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. Exemption from the duty of confidentiality and professional secrecy for those who had died was granted by the Norwegian Directorate of Health.

RESULTS

Cohort characteristics
Sixty-six per cent of the cohort were men and the mean age at the first entry to maintenance treatment was 37 years. Methadone was prescribed to 67% and buprenorphine to 33% at the point of entry to the study. Mean dosage for methadone was 122 mg and 17.6 mg for buprenorphine. Fifty-one out of 200 (26%) had left maintenance treatment once or more during the observation period, while the rest had been in continuous treatment since they were included. Mean age of first use of heroin was 21.1 years, and mean duration of opioid dependence before OMT was 12.3 years. Thirty-four per cent reported more than 10 overdoses during their lifetime, 54% between one and 10, and 12% reported none. Seventeen per cent had not completed 9 years of compulsory schooling, 50% had completed 9 years and 33% had 12 or more years of education. Twenty-three per cent had <1 year of employment, 28% between 1 and 5 years and 49% had more than 5 years of work experience.

Among the patients who had experienced interruption of maintenance treatment, 15% were assessed as stable and drug-free when leaving OMT for the first time, while 85% were assessed as unstable and taking drugs.

Changes in somatic disease incidents during opioid maintenance treatment

Table 1 shows the rates of hospital treatment episodes due to acute and subacute somatic disease incidents and the rates for inpatient days and outpatient hospital contacts for the various categories of episodes before, during and after OMT. Table 2 displays the statistical significance of these changes by showing the incidence rate ratios according to different OMT status; before versus during OMT and after versus during OMT, respectively. A total of 1021 somatic disease incidents were registered: 605 before, 310 during and 106 after OMT.

The rate of all treatment episodes was 37% lower during compared to the period before treatment (before versus during OMT incidence rate ratio (IRR) 1.6 (95% CI 1.3 to 1.9), p<0.001). The rate in the post-OMT period was 197% higher compared to the period during OMT (after versus during treatment IRR 2.8 (95% CI 2.1 to 3.9), p<0.001).

During treatment, the rate of all inpatient hospital treatment days was 38% lower (before versus during
treatment IRR 1.7 (95% CI 1.1 to 2.4), p=0.01) and the overall rate of outpatient hospital treatment contacts was 27% lower (before versus during treatment IRR 1.4 (95% CI 1.0 to 1.8), p=0.04). After treatment the rate of inpatient days was 5.1 times higher than during treatment (IRR 5.9 (95% CI 3.6 to 9.6), p<0.001) and the rate of outpatient hospital treatment was 2.6 times higher (IRR 2.0 (95% CI 1.1 to 3.8), p=0.03).

Drug-related disease incidents
The rate of drug-related hospital treatment episodes was 76% lower during treatment than before (before versus during IRR 4.2 (95% CI 2.9 to 6.2), p<0.001). The rate of injecting-related episodes was 83% lower (IRR 5.9 (95% CI 3.1 to 11.4), p<0.001) and the rate of overdoses was 64% lower (IRR 2.8 (95% CI 1.6 to 5.0), p<0.001) than before OMT. Among the injecting-related episodes, local and systemic bacterial infections were the most common. The rate of drug-related inpatient days was 84% lower (IRR 6.3 (95% CI 3.4 to 11.8), p<0.001) and the rate of outpatient contacts was 79% lower during treatment compared to the pre-treatment period (IRR 4.8 (95% CI 2.7 to 8.3), p<0.001).

The post-OMT rate for drug-related treatment episodes was higher than the rate before or during treatment. Compared to the period during OMT, the rate was 10.1 times higher (IRR 11.1 (95% CI 6.6 to 18.5), p<0.001). Overdoses after OMT were double those before OMT and the overdose rate was 5.6 times higher compared to the period during OMT (IRR 5.8 (95% CI 2.7 to 12.3), p<0.001). The rate of injecting-related episodes was 14.2 times higher after than during treatment (IRR 12.6 (95% CI 4.3 to 36.8), p<0.001), the rate of inpatient days due to drug-related episodes was 23.8 times higher (IRR 25.2 (95% CI 13.1 to 48.7), p<0.001) and the rate of outpatient contacts was 10.3 times higher (IRR 10.6 (95% CI 4.7 to 25.9), p<0.001).

Non-drug-related disease incidents
Non-drug-related treatment episodes were 35% more frequent during treatment compared to the pre-OMT period.
The incidence rate ratios indicate the statistical significance of the changes in incidence rates demonstrated in Table 1, estimated by Poisson regression (generalised estimating equations). Patient-years at risk: 1000 before, 813 during and 91 after OMT. Number of incidents: 605 before, 310 during and 106 after OMT. IRR, incidence rate ratios; OMT, opioid maintenance treatment; TCRR, treatment contact rate ratios.

Subgroups in italic.

Interaction between OMT status and patient characteristics
From the data in Table 1 it is evident that changes according to OMT status in the total number of hospital treatment episodes are associated with changes in drug-related treatment episodes. In the analysis of how the effect of OMT status is influenced by various patient characteristics, we therefore concentrated on drug-related episodes alone. Table 3 shows the interaction between the effect of maintenance treatment (OMT status) and various patient characteristics, that is the incidence rate ratio between the periods before and during OMT for drug-related treatment episodes adjusted for these characteristics.

In a comparison of patients who received continuous maintenance treatment throughout the during-OMT observation period versus those who left treatment once or more, those with continuous treatment showed greater incidence rate reduction during treatment than those with interrupted treatment, although the latter still showed significant reduction versus the pre-treatment period. After treatment, the group with interrupted treatment showed an increase, with the incidence rate ratio between the periods after and during OMT for this group being 5.4 (3.0 to 9.7) (not shown in the table). Patients with ongoing illicit drug-taking during OMT showed less reduction in incidence rate during treatment than patients not using illicit drugs. Even so, the quartile taking most drugs showed a significant reduction during versus before OMT (before versus during IRR ratio 3.6 (2.4 to 5.3)).

Among the pre-OMT patient characteristics, only employment history and years of opioid dependence before OMT showed a significant interaction with OMT status in the period before versus during OMT. Individuals with less work experience and fewer years of opioid dependence, respectively, showed less reduction in incidence rates during compared to before treatment. Interaction was also tested for gender, age at OMT start, lifetime number of overdoses, years of education and age at heroin debut without showing any statistically significant interaction (p>0.1).

**DISCUSSION**

The study shows a substantial reduction in drug-related hospital-treated incidents of somatic disease during maintenance treatment compared to the pre-treatment period. The reduction consists of less overdoses, and fewer injecting-related and other drug-related treatment episodes.

Overdoses are the most frequent cause of death among dependent opioid users, and the 64% reduction in overdoses during treatment is an important finding. Several studies have documented reduced mortality during OMT compared to the pre-OMT period and after leaving OMT and the reduction in overdoses found in the present study supports previous findings of reduced mortality during OMT.

| Table 2 | Acute/subacute hospital-treated somatic disease incidents: crude incidence rate ratios and treatment contact rate ratios of inpatient days and outpatient hospital contacts |
|-----------------|-----------------------------|-------------------------|
| **Before versus during OMT, during OMT as reference** |
| **Incidence rate = 1** |
| All incidents | 1.6 (1.3 to 1.9) | <0.001 |
| Drug-related | 4.2 (2.9 to 6.2) | <0.001 |
| Overdoses | 2.8 (1.6 to 5.0) | <0.001 |
| Injecting-related | 5.9 (3.1 to 11.4) | <0.001 |
| Other | 5.7 (2.8 to 11.9) | <0.001 |
| Non-drug-related | 0.7 (0.6 to 1.0) | 0.02 |
| Injuries | 1.2 (0.9 to 1.5) | 0.23 |
| **Inpatient days** |
| Drug-related | 6.3 (3.4 to 11.8) | <0.001 |
| Non-drug-related | 0.5 (0.3 to 1.0) | 0.04 |
| Injuries | 2.1 (0.7 to 5.7) | 0.17 |
| All | 1.7 (1.1 to 2.4) | 0.01 |
| **Outpatient contacts** |
| Drug-related | 4.8 (2.7 to 8.3) | <0.001 |
| Non-drug-related | 0.7 (0.4 to 1.2) | 0.18 |
| Injuries | 1.1 (0.7 to 1.6) | 0.78 |
| All | 1.4 (1.0 to 1.8) | 0.04 |
| **After versus during OMT, during OMT as reference** |
| **Incidence rate = 1** |
| All incidents | 2.8 (2.1 to 3.9) | <0.001 |
| Drug-related | 11.1 (6.6 to 18.5) | <0.001 |
| Overdoses | 5.8 (2.7 to 12.3) | <0.001 |
| Injecting-related | 12.6 (4.3 to 36.8) | <0.001 |
| Other | 16.7 (6.5 to 42.7) | <0.001 |
| Non-drug-related | 1.4 (0.9 to 2.2) | 0.15 |
| Injuries | 0.8 (0.3 to 1.8) | 0.57 |
| **Inpatient days** |
| Drug-related | 25.2 (13.1 to 48.7) | <0.001 |
| Non-drug-related | 1.1 (0.5 to 2.3) | 0.78 |
| Injuries | 4.6 (0.8 to 28.5) | 0.98 |
| All | 5.9 (3.6 to 9.6) | <0.001 |
| **Outpatient contacts** |
| Drug-related | 10.6 (4.7 to 25.9) | <0.001 |
| Non-drug-related | 1.6 (0.7 to 3.7) | 0.26 |
| Injuries | 1.1 (0.4 to 3.1) | 0.87 |
| All | 2.0 (1.1 to 3.8) | 0.03 |

The changes in incidence and treatment contact rates for injuries were minor and non-significant.
Injecting-related treatment episodes were also substantially reduced (by 85%) during OMT. This may have been due to those OMT patients who stopped injecting and to others who continued to inject but at a less frequent rate than before treatment. The reduction includes all kinds of injecting-related episodes among which local and systemic bacterial infections are by far the most frequent. The local skin infections often require surgical treatment and may give rise to severe systemic infections as sepsicaemia, fasciitis, endocarditis, osteomyelitis, discitis and others. Most of these conditions are rare, but they are much more frequent among injecting drug users than among the general population. Such infections may be life-threatening and may result in severe and permanent health problems, and often necessitate complex, long-lasting and expensive hospital treatment. When injecting-related health problems among drug users are considered, these apparently less serious conditions are often overshadowed by the focus on HIV and hepatitis C. However, some studies indicate that the burden on the healthcare system due to injecting-related local and systemic bacterial infections may be even greater than that due to bloodborne infections. The present study found that such bacterial infections were frequent among dependent opioid users and that they were substantially reduced during maintenance treatment.

Non-drug-related treatment episodes were found to increase (by 35%) during OMT as compared to the pre-OMT period. Inpatient days increased by 98% and outpatient treatment contacts increased by 40%. The reason for this may be closer contact with health services during maintenance treatment. Within the OMT programme, patients may receive healthcare that was not previously available to them, leading to the diagnosis and treatment of health problems that were previously not identified. If so, this increase in non-drug-related episodes may reflect improved access to health services and not an increase in morbidity. It is theoretically possible that this increase is due to adverse effects of OMT, but we have found no evidence of this in our scrutiny of the hospital records.

Drug-related treatment episodes and related inpatient days and outpatient hospital contacts were more frequent in the period after OMT compared to the periods before OMT and during OMT. These rates apply only to those patients who had left OMT. Although some patients may remain drug-free after leaving OMT, it is likely that many leave OMT, voluntarily or involuntarily, because of ongoing drug-taking, opposition to programme rules and control measures, or instability in taking their OMT medication. Our data show that only 15% of those who left OMT were assessed as stable and drug-free at the time of leaving treatment. Patients with interrupted maintenance treatment may therefore constitute a patient subgroup with higher levels of risk-taking behaviour and/or more serious health problems, and the post-OMT results may be influenced by selection bias. We therefore examined the interaction between OMT status (incidence rates before versus during OMT) and OMT cessation (having experienced OMT cessation or not) and found less reduction in drug-related treatment episodes in the cessation group compared to the group with continuous treatment. Nevertheless, even the cessation group experienced a significant reduction in episodes of about 40%. After OMT cessation, however,
they experienced a more than fivefold increase compared to the period during OMT. The high post-OMT incidence rates, therefore, reflect an increase in acute drug-related health problems after OMT cessation among patients with treatment interruption, and cannot be fully explained by selection effects. This is an important finding that should stimulate increased efforts to study the health effects of OMT cessation and to improve responses to minimise the harmful consequences.

Even the quartile taking most illegal drugs during OMT showed a significant 72% reduction in drug-related treatment episodes during versus before treatment. This indicates that not only patients with successful maintenance treatment, but also patients with poor rehabilitation results experience health improvement during OMT.

The present study focuses on acute/subacute hospital treatment episodes. Injecting drug users experience increased chronic morbidity that reduces their quality of life and some studies based on interviews and clinical assessment show a reduction in chronic health problems during OMT. However, considering the high mortality rate among injecting drug users, the often life-threatening acute disease incidents comprise a substantial—and perhaps the most important—part of the morbidity pattern within this group.

The study has some limitations. First, the study assessed acute/subacute hospital-treated disease incidents and not morbidity as such. A key question is whether changes in incidence and treatment rates according to OMT status (before, during and after OMT) reflect a change in morbidity; in other words, whether these rates can be regarded as a proxy indicator for morbidity. Information on hospital treatment outside the local area was based on patient recall and some disease incidents prior to treatment may have been overlooked. In addition, closer contact with health services during OMT probably increases patients’ help-seeking, resulting in hospital treatment for health problems that would not have been treated before OMT. Further, the patients were 5 years older during than before OMT, resulting in an age-dependent increase in morbidity. Even so, we found a significant reduction in treatment episodes during OMT. Therefore, our findings most probably reflect a ‘true’ reduction in acute/subacute incidents of somatic disease, and hence in acute/subacute somatic morbidity, during compared to before OMT.

Another limitation is that primary healthcare contacts were not included in this study. In our previous study, however, general practitioner contacts were registered and we found that about 80% of all acute somatic disease incidents assessed as severe resulted in hospital treatment both before and during OMT. The focus on hospital treatment episodes should therefore provide an adequate assessment of OMT-related changes in severe acute health problems within the cohort. Also, the cohort is relatively old, with a mean age at first OMT entry of 37 years and mean duration of opioid dependence before the first admission to OMT of 12 years. This reflects the late introduction of OMT to Norway in 1998 with an accumulated demand for maintenance treatment by older patients at programme start and a high recommended age limit for OMT admittance during the first years. The cohort is typical of Norwegian OMT patients, but the age distribution is no doubt characterised by specific historical traits of the Norwegian OMT programme and this might be a possible limitation to the external validity of the study. However, we did check the effect modification of age at OMT entry (no significant interaction) and duration of opioid dependence before first OMT entry (less reduction among patients with fewer years of dependence) on the rates of drug-related treatment episodes before versus during OMT.

Yet another limitation is that the list of diagnoses to differentiate whether treatment episodes were drug-related or not has not been validated by external researchers and we could find no similar list in the literature. There may be some uncertainty about whether some episodes were drug-related or not; however, inter-rater reliability scores were high. There were also analytical problems due to the fact that the post-OMT observation period was only 91 years versus 1000 before and 813 during OMT. This is mainly due to the high retention in OMT in Norway. The relatively few post-OMT years at risk is a limitation in the study, but with this design and the given retention in treatment, the post treatment period will nevertheless be unbalanced compared to the periods before and during OMT.

The study also has certain strengths. These include the high participation rate among patients in as well as out of maintenance treatment at the time of invitation, the access to all hospital records and the long observation period. The overall participation rate was high (71%) and more than 99% of requested hospital records were obtained. Hence, selection bias was probably of limited importance in the study. Further, the evaluation of morbidity changes is based on in-depth assessment of full-text hospital records which could be expected to give more robust data than interview data or register data alone.

Despite possible limitations in the study design, the findings document a substantial reduction in acute and subacute drug-related disease incidents leading to hospital treatment during OMT compared to the period before OMT. This reduction in somatic morbidity during treatment seems also to be valid for patients with ongoing drug-taking during OMT. However, acute drug-related health problems show an increase after OMT cessation, and this is a matter of concern. Further studies on somatic morbidity after OMT cessation should be carried out.

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Contributors IS had the original idea for the study, took part in the planning and developed the questionnaire and the list of diagnoses, carried out interviews (not authors). Hermansen (sociology student at the University of Oslo) performed the planning of the study, interpretation of data and revision of the article. ML supervised the study and took part in the planning of the study, interpretation of data and took part in revision of the article. MG contributed to the interpretation of data and took part in revision of the article. MT took part in the revision of the article. ER took part in the interpretation of data and revision of the article. HW is project leader and the main supervisor of the study and participated in the planning of the study, interpretation of data and revision of the article.

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