BMJ Open  Opioid maintenance treatment in the Czech Republic, Norway and Denmark: a study protocol of a comparative registry linkage study

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INTRODUCTION

Globally, opioid use disorders (OUDs) are a major public health concern, associated with high costs to the society, the healthcare system, and at the individual level for both the opioid users and their close ones.1–3 OUD is associated with high somatic comorbidities, including infectious diseases, such as HIV and hepatitis,3,4 high rates of psychiatric comorbidities,5,6 criminal activities,7,8 social exclusion and low quality of life of opioid users and significant others, economic costs, and loss of social cohesion.9–11 Furthermore, the rate of drug-related mortality is high3,12 including overdose deaths among young people with OUD.13

OUD requires long-term treatment that typically consists of opioid maintenance treatment (OMT) as the method of choice, including OMT medications in combination with psychosocial care.14 Methadone and buprenorphine are currently the most widely used opioids in OMT in Europe and elsewhere.15 Recent reports show that in Europe, methadone is received by 61%, buprenorphine by 37% and other types of medication by 2% of patients in OMT.16 OMT

Strengths and limitations of this study

► International registry linkage-based study design minimises selection and recall bias and makes it possible to follow individuals over time in treatment and out of treatment without loss to follow-up.
► The wide range of nationwide data from health and population-based registers in the Czech Republic, Norway and Denmark increases the generalisability of common findings.
► The possibility of performing meta-analysis of the results from multiple countries increases statistical power and makes it possible to study differences between the different opioid maintenance treatment (OMT) drugs (methadone, buprenorphine and buprenorphine with naloxone).
► The main limitation is that important information can be under-reported, reported in insufficient format or completely lacking in the national health registers.
► In Norway, OMT is defined by dispensed OMT drugs as recorded in the prescription database, while both the Czech Republic and Denmark have specific detailed registers for OMT treatment.
is a well-established treatment approach for OUD, and has proven positive effects on a number of outcomes in various subpopulations, including positive effects on stabilisation of people with OUD, reducing the risk of relapse to illicit opioid use, health-related variables such as (co)morbidity and mortality, social-related variables such as criminality, and well-being and quality of life. Treatment participation (retention in treatment) improves outcomes of OMT, while cycling in and out of OMT seems to be a common trajectory for many people with OUD.

However, OMT is not a static and well-defined treatment modality. The current evidence base consists of a wide variation in outcome measures of treatment of people with OUD, across time and settings, which reduces comparability of results. Therefore, OMT must be evaluated over the same time period as well as in different national health system and clinical contexts, in order to consistently provide high-quality care and improve our understanding of the dynamics of OMT and outcomes. Especially, in countries from the former Eastern European region, data regarding the efficacy, tolerability and predictors of outcome for OMT remain scarce. In addition, evidence based on comparisons of the same outcomes in several risk populations and across national treatment systems is lacking. For example, an increased risk in overdose death during the induction/cessation of treatment was observed, indicating that patients are especially vulnerable during periods of treatment transition, while others have observed very low rates of mortality during the first period after treatment start and treatment termination. Therefore, use of data from multiple nationwide health and population registers is an important new approach with great potential to further improve the knowledge base. Further, use of multiple national data prevents potential confounding and classification bias in comparison with mortality risk between OMT, including periods of cycling in and out of treatment. Finally, linking data from multiple registers allows for large unselected study populations, and for identification of relevant comparison groups and comparable outcome indicators.

The aim of this project is to identify factors associated with important beneficial outcomes for OMT patients across settings, in order to further improve treatment practices and our understanding of the key elements of treatment success.

**Project objectives**

The main objective is to study OMT adherence trajectories, comorbidity and mortality, based on large patient cohorts in the Czech Republic, Norway and Denmark. Specifically, in the national OMT cohorts, we plan to:

1. Describe OMT, OMT patients, OMT adherence trajectories and predictors of these trajectories.
2. Study comorbidity in OMT patients while observing other somatic and mental morbidities.

3. Investigate crude mortality rate for all cause and cause-specific mortality.

Different OMT adherence trajectories will be characterised by OMT entry, drop-out, re-entry, time in OMT and OMT termination.

All three objectives will involve stratified analysis with regard to treatment with methadone, buprenorphine and buprenorphine in combination with naloxone, or switching between the different OMT medications.

**METHODS AND ANALYSIS**

**Project period**

Data cleaning and the first analyses are planned for the period between February and May 2021. The planned end date of the project is December 2024. The project period may be extended with additional funding.

**Treatment settings**

**Czech Republic**

OMT was introduced in one treatment facility in the Czech Republic in 1997 and became a national standard treatment modality in 2000. In prison, OMT was piloted in 2006 and has been used regularly since 2008. Two OMT medications, methadone and buprenorphine, both administered orally, are used, and these are represented by six products on the current market. Methadone is available to patients through specialised OMT clinics with varying levels of threshold, but is in general accompanied by psychosocial services. Medication that contains buprenorphine can be prescribed by the physician, and its use is more widespread but with less formal follow-up services. However, the availability and affordability of OMT is limited, since methadone is used only in 12 specialised centres in the country, and buprenorphine is subject to a strict health insurance scheme, so that a majority of the patients in reality have to pay full price for their medication. Provision of OMT is monitored and governed by the Standard of Substitution Treatment issued by the Ministry of Health in cooperation with Society for Addiction Treatment of the Czech Medical Association.

**Norway**

OMT was implemented as a national programme in 1998. Treatment is initiated at the specialist (secondary care) level. In most cases, after a period of stabilisation, the patient is transferred to the primary care level with regular follow-up and prescriptions by the general practitioner and the social services in the municipality. The Norwegian OMT programme has gradually become more low-threshold and harm reduction oriented, with very few patients discharged from treatment, regardless of ongoing drug use during enrolment. There is no time limit on OMT in Norway, and patients may be provided with treatment in a lifelong perspective. The Norwegian OMT model has a clear ‘rehabilitative’ goal that includes the provision of psychosocial services, and aims that patients improve their health and well-being to best reach their
individual potential. Since 2010, the Norwegian OMT has had a national OMT guideline, issued by the Directorate of Health (scheduled for an update in 2021). OMT is free and publicly funded for all patients in Norway.

**Denmark**

OMT was introduced as a treatment option for patients with OUD in Denmark in 1970. At first, methadone was the only available OMT medication, but since 2008, buprenorphine has also been available. In addition to buprenorphine and methadone, heroin-assisted treatment has been available in Denmark since 2009. As part of the Danish welfare services, OMT is free and publicly funded, and the Danish law states that the municipalities must initiate treatment and formulate a treatment plan for OUD within 2 weeks of the first treatment request. Although two different sets of policies govern OMT in Denmark—health regulations and social service regulations—practitioners consider OMT as an integrated treatment that includes both healthcare and psychosocial services. The aim of OMT is to support the patients in having a meaningful and satisfying life in a way that is defined and controlled by the patient themselves. This may also include a lifelong involvement in OMT.

**Design**

All research questions will be answered using a national cohort approach, linking the registers’ data sources by using the unique personal identification number (the so-called birth number) assigned to all residents at birth in the Czech Republic, Norway and Denmark.

**Data sources**

The overview with description of relevant national registers in the Czech Republic, Norway and Denmark is presented in [table 1](#). In all countries, physicians and pharmacies are obliged by law to report data to the nationwide registers. Data are collected prospectively and without informed consent. Earlier studies indicate that the quality of data in the registers from Norway and Denmark is moderate to high, depending on the condition or treatment studied.41–46

**Study population and size**

The Czech Republic cohort

Using data from the entire Czech Republic, the OMT population will be obtained from the National Register of Addiction Treatment (table 1). Approximately 4000 men and 1700 women enrolled in OMT in the period 2000–2020 will be included in the study. More than half of the patients were between 30 and 39 years.

The Norwegian OMT cohort

In Norway, the OMT population will be defined by the Norwegian Prescription Database (table 1). By 2020, there was around 7900 patients enrolled in treatment, of which 30% were women, with a mean age of 46 years.

The Danish registry cohort

The OMT population will be defined by the Danish Registry of Drug Abusers Undergoing Treatment (table 1). By 2018 (latest data), 6656 patients had been enrolled in OMT. During 2018, 737 patients enrolled in OMT, of which 21% were women, with a mean age of 46 years.47

**Comparison groups**

Regarding objectives 2 and 3, patients with OUD (International Classification of Diseases, 10th Revision (ICD-10), F11 code—opioids-related disorders) not receiving OMT, patients with other drug use disorders (ICD-10, F10–F19 codes—mental and behavioural disorders due to psychoactive substance use, except F11), and the general drug non-using populations will be used as comparison groups. In some analyses, the different OMT adherence trajectories will be compared with each other.

**Patient and public involvement**

The study team members are in contact with patients and public representatives regarding design, running the study and interpretation of the study findings. Moreover, the patient representatives will be encouraged to disseminate the findings within their patient networks.

**Outcome variables**

The following outcome variables will be obtained from the respective registers (see table 1).

**OMT adherence trajectories**

Characterised by OMT entry, drop-out, re-entry, time in OMT and OMT termination.

**Comorbidity**

Somatic and psychiatric comorbidity (eg, infections, immune disorders, cardiovascular and respiratory diseases, epilepsy and neoplasms, neurological disorders, anxiety, depression, sleep problems) (based on ICD-10 codes (secondary care), International Classification of Primary Care, Second Edition codes (primary care), and prescribed/dispensed drugs as proxy of disease).

**Mortality**

All-cause mortality and specific mortality (eg, overdose deaths, accidents, cardiovascular disease/cancer, others) (based on ICD-10 codes).

**Analysis strategy**

All data will be analysed using an individual participant data meta-analyses method. Methodologically, this approach allows for applying consistent inclusion/exclusion criteria applied across countries, an approach that has successfully been applied in other studies. This method has several advantages, among others: (a) as data are analysed locally in the first step, it overcomes the privacy hurdles associated with sharing individual-level data across countries and jurisdictions; (b) involvement of local researchers provides an opportunity to convey the

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Table 1  Potential data sources used in the OMT registry-based study in the Czech Republic, Norway and Denmark

|               | Czech Republic | Norway | Denmark |
|---------------|----------------|--------|---------|
| Information about OMT user and OMT drug | National Register of Addiction Treatment; Information about patients who receive OMT, date of treatment initiation and termination and type of OMT drug | The Norwegian Prescription Database (NorPD); Prescription drugs dispensed at pharmacies, all opioids dispensed to outpatients are registered. OMT opioids can be identified by use of ATC codes and Nordic article number. It is estimated that about 90% of the OMT patients are identified using the NorPD. Use of prescription drugs as proxy of disease is possible in two different situations. For reimbursed drugs, the ICD-10 or ICPC-2 diagnosis code of the disorder that is treated has to be written on the prescription. The other option is to use drugs that only have one indication like for instance insulin for treating diabetes. | The Danish Registry of Drug Abusers Undergoing Treatment; Information on patients who are enrolled in outpatient treatment for drug use disorders, including information about patients who receive OMT, date of treatment initiation/termination and type of OMT drug |
| Information about comorbidity | National Register of Inpatient Treatment; Information on every episode of all types of hospitalisations, including information on dates of admission and discharge from hospital. All diagnoses (primary and secondary) and procedures (ICD-10). | National Primary Care Reimbursement System; Diagnosis (ICPC-2) from claims from general practitioners and other health service providers, such as emergency rooms, date of consultation | The Danish National Prescription Register; Information on all individual prescription drugs dispensed through pharmacies to patients outside of institutions such as hospitals and drug treatment facilities |
| Information System Infections (EPIDAT) | Information on all notifications of selected serious infections—verified cases, suspected diseases, carrier of an infection and deaths. | The National Patient Register | The Danish National Patient Register |
| National Register of Reimbursed Health Services | Also includes information on prescribed drugs reimbursed within the health insurance system. | Information on all patients receiving hospital-level care in both inpatient and outpatient facilities, and acute and emergency services for mental and somatic illnesses. Primary and secondary diagnoses (ICD-10), date of admission, date of discharge | Information on all patients receiving hospital-level care in both inpatient and outpatient facilities, and acute and emergency services for somatic illnesses. Primary and secondary diagnoses (ICD-10), date of admission, date of discharge |
| Information about death and cause of death | National General Mortality Register; Cause of death diagnosis (ICD-10), date of death | Cause of Death Registry; Cause of death diagnosis (ICD-10), date of death | Cause of Death Registry; Cause of death diagnosis (ICD-10), date of death |
| Information about socioeconomic status | Czech Statistical Office; Demographic data, country of birth, education, work situation, income, disability pension | Statistic Norway; Demographic data, country of birth, education, work situation, income, disability pension | Statistic Denmark; Demographic data, country of birth, education, work situation, income, disability pension |
| Information about income, disability pension | The Danish Psychiatric Central Research Register; Information on all patients receiving hospital-level care in both inpatient and outpatient facilities, and acute and emergency services for mental illnesses. Primary and secondary diagnoses (ICD-10), date of admission, date of discharge | The National Health Insurance Service Registry; Information on individual services undertaken by general practitioners |

ATC, Anatomical Therapeutic Chemical; ICD-10, International Classification of Diseases, 10th Revision; ICPC-2, International Classification of Primary Care, Second Edition; OMT, opioid maintenance treatment.

nuances of local and national data; (c) allows for consistent and realistic adjustment for confounding factors that may explain differences in findings across countries; and (d) allows for increased clinical relevance of findings by providing the opportunity to explore clinical questions across different national contexts and times.48 50

Objective 1: OMT adherence trajectories

First, we will identify all OMT patients in each country. Following this, we will describe the national OMT cohorts in general with regard to pharmacological treatment provided and background characteristics of the patients. In addition, we will identify different OMT adherence
trajectories based on entry to treatment, drop-out, re-entry, total time in OMT and OMT termination. We will study associations between health, demographic and socioeconomic factors, different OMT adherence trajectories, and psychiatric and somatic comorbidity.

**Objective 2: comorbidity**
We will investigate comorbidity and use of healthcare services in the different national OMT cohorts by studying the number of contacts with healthcare services for the OMT groups and the comparison groups. Also, we will study somatic and psychiatric comorbidity by studying different specific diagnoses and compare them with comorbidity among the comparison groups.

**Objective 3: mortality and cause of death**
We will compare mortality and causes of death in the national OMT cohorts. Patients in OMT will be compared with patients who have been in OMT, but have dropped out of or terminated treatment. Mortality will also be compared with mortality among patients with drug use disorders not in OMT and with the general population.

Regarding all three objectives, harmonised and firm-level data will be pooled across countries in order to investigate between-country variations in a fully consistent manner but with respect to privacy and confidentiality restrictions on micro-data.

**Statistical analyses**

**Descriptive analysis**
Statistical analyses will include descriptive analyses of the pharmacological OMT treatment and the characteristics of the study populations in the different national cohorts.

**OMT adherence trajectories**
First, we will do explorative examinations of OMT with respect to initiation, time in treatment, number of drop-outs and re-entries, and terminations in the different national cohorts. Based on these results, we will assign patients to different OMT adherence trajectory groups. Potential factors associated with different treatment trajectories groups will be examined using multinomial logistic regression analysis. The coefficients will be interpreted in terms of relative risk ratios with 95% CIs. We will run univariate models for all covariates and one multivariate model. In the multivariate model, age, gender, psychiatric and somatic comorbidity, and use of other prescription drugs with abuse potential will be adjusted for.

**Comorbidity**
We will study comorbidity in a defined period before OMT initiation, during treatment and after termination of treatment. Comorbidity will be measured as number of contacts and diagnosis from primary (Czech Republic and Norway) and secondary healthcare. The number of contacts and proportions with selected groups of diagnosis will be compared by t-test or $\chi^2$ test. For selected diagnosis, we will also study the proportion (with 95% CI) receiving adequate prescription drug treatment. We will compare comorbidity in OMT patients in the different national cohorts. All analyses will be stratified by gender and age group.

**Mortality**
Patients initiating OMT often cycled in and out of treatment. We will estimate the crude mortality rates (CMRs) and 95% CIs as number of deaths per 1000 person-years in-treatment and post-treatment. We will define the following time at risk periods: in-treatment: the period between treatment start and death, from treatment start to termination of treatment, or from treatment start and the end of the observation period. As the same patient may contribute to multiple observation periods, all treatment periods are included in the analysis. Post-treatment: the period between termination of treatment and death, from termination of treatment to another treatment start, or from termination of treatment to the end of the observation period. The same patient can contribute to several out-of-treatment periods between treatment episodes, and all these between-periods are included in the analysis. In order to compare CMRs between in-treatment and post-treatment, crude rate ratios will be calculated by dividing one mortality rate by another.

We will also compare CMRs between different subgroups, for example, women and men and age groups, and between patient groups receiving methadone, buprenorphine, and buprenorphine and naloxone patients. To compare mortality between OMT patients and the general population, standardised mortality ratio will be calculated.

Statistical analyses will be performed on SPSS (V.24) and Stata packages (V.14.2). Analysis and publication of results will follow the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

**Ethics and personal data protection**
Approval from the respective ethics committees in: the Czech Republic (36/19/GrantAZVVES20201.LFUK) and Norway (REK number 2019/656/REK sør-vest C) has already been obtained. In Denmark, ethical evaluation is not required by law, but was approved by the national data authority (journal number: 2013540288, updated 13 March 2020). All disseminations from the project will be on-group-based information, and no individual participants will be recognisable.

All relevant national registers include independent and prospectively collected information on the health and socioeconomic status of all inhabitants in the Czech Republic, Norway and Denmark. Data of our interest are already available in the national registers. Data in the project will be used in pseudo-anonymised form. Each country will manage its own country-specific data. Applicable to all, data will be directly loaded to and saved on an information technology platform specifically dedicated to secure storage of sensitive research data at the respective institutions.
Data management
Original data received from the health registers’ data administrators will be checked for consistency, and series of automatic range checks will be performed until the database is considered clean; all data procedures in this phase will be tracked. A data backup will be performed periodically during the study. Only designated investigators will be allowed access to data.

Strengths and limitations
Nationwide registers provide a great potential to study large cohorts and examine longitudinal outcomes with less selection bias and reduced risk of recall bias compared with clinical studies. At a global level, only some countries have nationwide registers that cover both health data and socioeconomic status. The Scandinavian countries and the Czech Republic have such registers. Registry-based cohort studies enable us to control for important confounding factors, such as socioeconomic and health status. The Czech and Scandinavian registers are comparable and provide great opportunities to conduct innovative research, for instance, comparing OMT patients with similar characteristics across national cohorts. Further, the Czech and Scandinavian registers provide a wealth of comparable data regarding relevant ICD-10 health conditions that allows us to study comorbidity and mortality in OMT populations on a national level and across countries, and to compare data with the general population and other subpopulations. In addition, the current evidence regarding OMT is insufficient in the countries representing the former Eastern European region. Last but not least, the study will allow us to examine and compare different treatment traditions in OMT, for example, the more liberal OMT in Denmark, the historically restrictive OMT, however, with gradual transition into a more liberal since 2010 in Norway, and the less available and affordable OMT in the Czech Republic.

Larger patient cohorts increase the statistical power, and the analyses of combined multiple data sources increase the richness of information available and enable control to important factors across countries, such as culture-specific factors and differences in country-specific healthcare systems. Furthermore, an international registry-based study design increases the generalisability of the findings.

There are, however, some drawbacks of registry cohort studies. The main limitations are that important information can be under-reported, reported in insufficient format or be lacking in the national health registers (eg, use of licit and illicit drugs). Furthermore, there may be potential limitations in controlling for all sources of bias and unmeasured confounders (eg, lifestyle factors that may potentially affect the outcomes in people with OUD).

We define OMT patients in a different way in the Norwegian data than in the Czech Republic and Denmark. By using prescription data for OMT medication, uncertainty of the date of initiation and termination of treatment may arise. However, preliminary analyses show that OMT patients are mainly dispensed OMT medication quite frequently (weekly or every second week). So we assume that as long as the patients are being prescribed OMT medication, they are enrolled in OMT.

Norway and Denmark have prescription databases that have been used for research purposes for years. In the Czech Republic, data on prescription drugs for the past 10 years were made available in 2020, and there is limited experience in using this data in research. This project will be the first to use such data.

Implications for interventions and future policy
Physicians and other healthcare providers within the healthcare system need updated and latest evidence-based knowledge regarding the models of care and benefits of OMT and treatment of OUD in general. The project will provide invaluable information, not only in the respective countries, but internationally.

The research outcomes will improve the quality of OMT for people with OUD and contribute to the reduction of health burden of disease and mortality, improved quality of life and reduce social exclusion of people with OUD. It is also important to identify risk factors associated with treatment discontinuation, relapse to drug use, causes of premature death, and psychiatric and somatic disorders. Research in this field has the potential to identify significant areas of benefit, to break the relapsing nature of OUD and, thus, reduce public health burden among people with OUD.

The project has great potential for improving the utilisation of the national registers by providing feedback on the quality and validity of the collected data. The project is unique in its utilisation of the number of nationwide registers in a database-linkage project, and will be the first in the history of the health information system in the Czech Republic and European Union—except Scandinavian countries.

Comorbidity should be generally accepted as a complex multifactorial issue, and its individual components cannot be completely separated in any research. Similarly, the treatment models vary between countries and within countries, both by region and over time. Despite the complexity, it is well known that OMT (using well-tested opioid agonists of defined quality, dosage, release form, effects) reduces the harm related to OUD in comparison with ongoing use of illicit drugs outside of treatment.

In conclusion, we present a comparative international project initiative to study OMT in the Czech Republic, Norway and Denmark. Investigations will improve our knowledge of how national treatment systems evolve over time regarding patient flow and OMT participation and outcomes. By identifying profiles and time phases of models of OMT and its outcomes, we can better guide clinicians and inform decision-makers and policymakers.
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