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RESEARCH REPORT

ADDICTION SSA

Real-world effectiveness of pharmacological treatments of opioid use disorder in a national cohort

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Abstract

Aim: To investigate the real-world effectiveness of pharmacological treatments (buprenorphine, methadone) of opioid use disorder (OUD).

Design: A nation-wide, register-based cohort study.

Setting: Sweden.

Participants: All residents aged 16–64 years living in Sweden using OUD medication from July 2005 to December 2016 (n = 5757, 71.8% men) were identified from registers of prescriptions, inpatient and specialized outpatient care, causes of death, sickness absence and disability pensions.

Measurements: Main outcome: hospitalization due to OUD. Secondary outcomes: hospitalization due to any cause; death due to all, natural and external causes. Mortality was analyzed with between-individual multivariate-adjusted Cox hazards regression model. Recurrent outcomes, such as hospitalizations, were analyzed with within-individual analyses to eliminate selection bias. OUD medication use versus non-use was modelled with PRE2DUP (from prescription drug purchases to drug use periods) method.

Findings: Buprenorphine [hazard ratio (HR) = 0.73, 95% confidence interval (CI) = 0.54–0.97] and methadone (HR = 0.74, 95% CI = 0.59–0.93) use were associated with significantly lower risk of OUD hospitalization, but not any-cause hospitalizations, compared with the time-periods when the same individual did not use OUD medication. The use of buprenorphine and methadone were both associated with significantly lower risk of all-cause mortality (HR = 0.45, 95% CI = 0.34–0.59; HR = 0.51, 95% CI = 0.41–0.63, respectively), compared with non-use of both medications. Similar results were found for risk of mortality due to external causes (HR = 0.39; 95% CI = 0.27–0.54; HR = 0.40; 95% CI = 0.29–0.53, respectively), but not for mortality due to natural causes. The risk of OUD hospitalization and all-cause mortality was decreased in all duration categories of studied medications (< 30, 31–180, 181–365 and >365 days), except for methadone use less than 30 days.

Conclusions: The use of buprenorphine and methadone are both associated with a significantly lower risk of hospitalization due to opioid use disorder and death due to all and external causes, when compared with non-use.

KEYWORDS
Buprenorphine, effectiveness, hospitalization, methadone, mortality, opioid use disorder

INTRODUCTION

Opioid use disorder (OUD) is an increasing cause of morbidity and mortality world-wide [1–4]. The use of opioids is associated with severe health consequences, such as mental health disorders, HIV infection, hepatitis-related liver cancer and cirrhosis, overdose and premature death [2, 5]. In 2017, the use of opioids accounted for two-thirds of the 167 000 deaths attributed to drug use disorders [2]. Mortality rates associated with OUD are 10-fold higher than in the general population [6, 7]. Thus, the prognosis of OUD without treatment is poor [8]. Unlike for many other drug use disorders, there are several medications for the treatment of OUD [9]. Methadone, buprenorphine and naltrexone are the primary evidence-based treatments for OUD [10], of which opioid agonists buprenorphine and methadone are used in Europe [11]. Treatment with methadone or buprenorphine improves physical and mental wellbeing and reduces mortality [12–14]. Longer treatment duration is associated with better outcomes [15] and the rate of recurrent opioid use is high, if OUD treatment is discontinued prematurely [4]. The periods associated with highest risk of mortality are the induction onto methadone treatment and the period immediately after leaving both treatments [13]. Despite the effectiveness of these medications, they still are underused [1, 12, 16], possibly due to deficient understanding of pharmacotherapy used in the treatment of OUD and regulated prescribing policies [12, 17]. It has also been claimed that access to competent treatment is restricted because of the lack of physicians willing and able to provide it [18].

Buprenorphine and methadone are well-established in recent reviews and meta-analyses in reducing especially mortality and opioid use in cohort studies and randomized, controlled trials (RCTs) [13, 14, 19]. However, patients included in RCTs are highly selected populations and according to Santo *et al.*'s recent systematic review and meta-analysis, RCTs of opioid agonist treatment are underpowered to assess mortality risk [14]. Thus, the effectiveness of treatments in non-selected patient populations in real-world treatment settings is less studied. Molero *et al.* concluded in their real-world study in 2018 that medications used to treat OUD appeared to reduce suicidality and crime [20]. Also, Wakeman *et al.* found in their study in 2020 that treatment with buprenorphine or methadone was associated with a lower risk of overdose and serious opioid-related acute care utilization when compared to other treatments [4]. Nevertheless, little is known about overall long-term health outcomes (such as risks of hospitalization and all-cause mortality) associated with specific treatments in real-world circumstances.

The aim of this study is to test the hypothesis that the pharmacological treatments of opioid dependence reduce the (1) risk of hospitalization due to OUD as a main outcome, and (2) hospitalization due to any cause and death due to all natural and external causes as secondary outcomes. In addition, the aim was to investigate the effect of duration of use of these medications on the outcomes.

METHODS

Nation-wide register-based data were used to conduct a prospective population-based cohort study of patients with OUD treatment. The project was approved by the Regional Ethics Board of Stockholm (decision 2007/762–31). No informed consent is required for register-based studies using pseudonymized data.

Study population

Data were gathered prospectively from nation-wide Swedish registers. People who purchased OUD pharmacotherapy were identified from the Prescribed Drug Register (PDR) from July 2005. Dates of death were obtained from the Causes of Death Register and demographic characteristics for the cohort were obtained from the LISA register (the Longitudinal Integration Database for Health Insurance and Labor Market Studies), National Patient Register (NPR) and the MiDAS register (Micro Data for Analyses of Social Insurance). Information regarding the employment and source of income was also received from the LISA register held by Statistics Sweden.

All residents aged 16–64 years living in Sweden with registered OUD medication purchased between 1 July 2005 and 31 December 2016 were included into this study. Individuals were chosen based on not having a previous diagnosis of schizophrenia or bipolar disorder (based on diagnoses recorded in NPR since 1996). All Swedish residents have been assigned a unique personal identification number which enabled linkage between various registers.

Exposures

Medication use data were gathered from the PDR. Medication use information in the PDR is categorized according to the anatomical therapeutic chemical (ATC) classification [21] and the purchased amount recorded as defined daily doses (DDD), together with information on medication package and formulation. Exposure to OUD medications was categorized as buprenorphine (ATC N07BC01, N07BC51) and methadone (N07BC02). For methadone, the analysis considered only oral solution as OUD therapy (tablet forms possibly used for cancer-related pain). In addition to monotherapies of these medications, concomitant use of studied medications was also modelled (probably representing mainly switches between these medications), but could not be reported due to the low number of events (fewer than five). Exposure to buprenorphine and methadone, as well

as non-use of both medications (as a reference), was followed in time and people could switch between treatments and contribute person-time to both exposures.

Medication use periods (i.e. when medication use started and ended) were constructed using the PRE2DUP-method. The method is based on the calculation of sliding averages of daily dose (in DDDs), the purchased amounts of medications and personal medication use patterns [22]. The method takes into account hospital stays (when medication use is not recorded in the register) and stockpiling of medications when constructing use periods.

Outcomes

The main outcome measure was hospitalization due to opioid use disorder [OUD hospitalization, International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) code F11, as a main diagnosis]. Hospitalizations were derived from the NPR and defined as an inpatient stay of at least overnight (so that the date of admission is different than the date of discharge). The secondary outcomes were hospitalization due to any cause, all-cause mortality and death due to natural and external causes. Natural cause of death was defined as ICD-10 codes A00–R99 and external cause of death as ICD-10 code V01–Y98.

Covariates

Within-individual analyses were adjusted for temporal order of treatments, time since cohort entry (i.e. time since first dispensing of OUD pharmacotherapy) and use of psychotrophic medications; antidepressants, benzodiazepines and related medications, mood stabilizers and antipsychotics (Supporting information, Table S1). Between-individual analyses were additionally adjusted for baseline covariates age, gender, education, granted disability pension, long-term sickness absence during previous year (> 90 days) and time-varying covariates (i) medication-related: temporal order of treatment, concomitant use of psychotrophic medications, other medication use (opioid and non-opioid analgesics, cardiovascular medications, alimentary tract and metabolism medications, anti-epileptic medications and naltrexone; and (ii) comorbidities: the number of previous hospitalizations due to OUD, cardiovascular disease, diabetes, asthma/chronic obstructive pulmonary disorder (COPD), previous cancer, renal disease, previous suicide attempt, previous infections and other SUD than OUD (Supporting information, Table S1).

Statistical analysis

Hospitalizations were treated as recurrent events and analyzed using the within-individual Cox regression model [23, 24] (Supporting information, Figure S1). The within-individual model is a stratified Cox regression model in which each individual forms his or her own stratum. This reduces selection bias of different treatments. The follow-up time is reset to zero after each outcome event to allow comparison of treatment periods within each individual. Mortality was analyzed with the traditional multivariate-adjusted Cox regression model as between-individual analysis, and between-individual analyses were also used as sensitivity analyses for the main outcome and for analyses on duration of use and associated risk of OUD hospitalization and all-cause mortality. Only people having an event and variation in exposure status (on-medication/off-medication) over time contribute to the model in within-individual analysis, whereas all individuals contribute to the between-individual models. Dependence among repeated observations was corrected with robust sandwich estimator in between-individual analyses. The follow-up started at the first dispensing of OUD pharmacotherapy. The follow-up ended at death, emigration, diagnosis of schizophrenia or bipolar disorder, or end of study follow-up (31 December 2016). Subgroup analysis for the main outcome was performed by tightening the inclusion criteria by restricting analysis to people without any other substance use disorder (SUD) than OUD. Sensitivity analysis for the main outcome was conducted by including only incident cases ('first-time use'). Nominal *P*-values are displayed throughout the paper. Significance level was set at 0.05 using the Benjamini–Hochberg false discovery rate (FDR) method. The results are reported as adjusted hazard ratios (HR) with 95% confidence intervals (CIs), with non-use of buprenorphine and methadone as a reference. The primary research question and analysis plan were not pre-registered on a publicly available platform; thus, the results should be considered exploratory.

RESULTS

Cohort characteristics

In the total cohort, including 5757 people, 4136 (71.8%) were men; the mean age was 37.7 [standard deviation (SD) 10.1] years. The median follow-up time was 7.3 [interquartile range (IQR) 3.5–11.0] years. The follow-up started from the first purchase of OUD medication; however, according to the NPR, 4822 (83.8%) of the patients had a recorded diagnosis of OUD prior to or at the start of OUD medication. During the follow-up, 3766 (65.4%) of the patients used buprenorphine and 3245 (56.4%) used methadone. A total of 1017 (17.7%) patients had work income during the calendar year before cohort entry. Altogether, 791 (13.7%) of the patients were unemployed for 1–180 days and 213 (3.7%) for more than 180 days during the previous calendar year before cohort entry. Overall, 1857 (32.3%) of the patients were on disability pension at the time of cohort entry. A total of 4826 (83.8%) patients had no sickness absence during a year before cohort entry, 315 (5.5%) had sickness absence for 1–90 days and 616 (10.7%) for more than 90 days. The clinical and socio-demographic characteristics of the cohort are described in Supporting information, Table S2. Overall, 522 (9.1%) of the patients were diagnosed with schizophrenia or bipolar disorder after cohort entry and were censored at that point.

Outcomes

Table 1 shows the numbers of events for each exposure and outcome analyzed.

Primary outcome

During the follow-up, 798 (13.9%) patients had an OUD hospitalization. Buprenorphine (HR = 0.73, 95% CI = 0.54–0.97) and methadone (HR = 0.74, 95% CI = 0.59–0.93) were associated with significantly lower risk of OUD hospitalization compared to those time-periods when the same individual did not use any OUD medication (Figure 1). In between-individual analyses, the results were similar concerning buprenorphine, but methadone was not associated with lower risk of OUD hospitalization (buprenorphine HR = 0.53, 95% CI = 0.42–0.66, methadone HR = 1.09, 95% CI = 0.86–1.38, Table 2). When between-individual analyses were stratified according to duration of use, the risk of hospitalization due to OUD was significantly lower in all analyzed categories of treatment duration (< 30, 31–180, 181–365 and > 365 days) when the exposure was buprenorphine or any OUD medication compared to non-use of all OUD medication. The use of methadone during the first 30 days did not significantly reduce the risk of hospitalization due to OUD. The lowest risk of OUD hospitalization was associated with use of buprenorphine (HR = 0.38, 95% CI = 0.26–0.57), methadone (HR = 0.66, 95% CI = 0.50–0.88) or any OUD medication (HR = 0.55, 95% CI = 0.43–0.71) which had lasted for 181–365 days (Table 2).

Altogether, 2222 (38.6%%) patients with diagnosis of OUD were also diagnosed with some other SUD during the follow-up. The risk of OUD hospitalization did not significantly decrease with the use of buprenorphine or methadone in patients diagnosed with only OUD, but no other substance use disorders (HR = 0.62, 95% CI = 0.36–1.07; HR = 0.65, 95% CI = 0.42–1.01, respectively). The results were similar in sensitivity analyses, where only incident users were included. The risk of OUD hospitalization did not significantly decrease with the use of buprenorphine (HR = 0.97, 95% CI = 0.67–1.39) or methadone (HR = 0.81, 95% CI = 0.60–1.09) (Table 1).

Secondary outcomes

The risk of hospitalization due to any cause did not significantly decrease during use of either of the studied medications (Table 1). Overall, 843 (14.7%) of the patients died during the follow-up time. The use of buprenorphine and methadone were both associated with significantly lower adjusted risk of all-cause mortality (HR = 0.45, 95% CI = 0.34–0.59, HR = 0.51, 95% CI = 0.41–0.63, respectively) (Figure 2). The results were similar when the outcome was analyzed by duration of use of the studied medications. The risk of all-cause mortality was significantly lower in all analyzed categories of duration of use (> 30, 31–180, 181–365 and > 365 days) for all exposures (the risk of all-cause mortality reduced 28–78%). The lowest risk of all-cause mortality was associated with use of buprenorphine, methadone or any OUD medication, which lasted 181–365 days (a reduction 65, 78 and 74%, respectively) (Table 3). The use of buprenorphine (HR = 0.39, 95% CI = 0.27–0.54) and methadone (HR = 0.40, 95% CI = 0.29–0.53) was also associated with significantly lower risk of mortality due to external causes (i.e. suicides and overdoses). The risk of mortality due to natural causes did not significantly decrease during use of buprenorphine or methadone (HR = 0.73, 95% CI = 0.44–1.21, HR = 1.03, 95% CI = 0.72–1.48, respectively) (Figure 2).

TABLE 1 The numbers of events for each exposure and for each outcome analyzed

	Exposure					
	Buprenorphine			Methadone		
Outcome (*n* = individuals having this outcome at least once)	Events	HR (95% CI)	*P*-value (*)	Events	HR (95% CI)	*P*-value (*)
OUD hospitalization (*n* = 798)	275	**0.73 (0.54–0.97)**	**0.0328***	651	**0.74 (0.59–0.93)**	**0.0092***
Any hospitalization (*n* = 1236)	721	0.87 (0.74–1.02)	0.0838	1854	0.89 (0.78–1.01)	0.0644
All-cause mortality (*n* = 843)	76	**0.45 (0.34–0.59)**	**< 0.0001***	191	**0.51 (0.41–0.63)**	**< 0.0001***
Mortality, external cause (*n* = 466)	54	**0.39 (0.27–0.54)**	**< 0.0001***	97	**0.40 (0.29–0.53)**	**< 0.0001***
Mortality, natural cause (*n* = 377)	22	0.73 (0.44–1.21)	0.2194	94	1.03 (0.72–1.48)	0.8625
Sensitivity analysis OUD only (*n* = 681)	183	0.62 (0.36–1.07)	0.0854	361	0.65 (0.42–1.01)	0.0555
Sensitivity analysis incidents only	163	0.97 (0.67–1.39)	0.97	439	0.81 (0.60–1.09)	0.16

*Bold type denotes *P*-values significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons at a 0.05 threshold. Hazard ratios (HRs) with 95% confidence intervals (CIs), with non-use of both opioid use disorder (OUD) medications as a reference. OUD hospitalization: ICD-10 code F11 as a main diagnosis;
any hospitalization: ICD-10 code other than F11 as a main diagnosis;
mortality, external cause: the cause of death ICD-10 code V01–Y98;
mortality, natural cause: the cause of death ICD-10 code A00–R99;
sensitivity analysis OUD only: no other substance use disorder than OUD;
sensitivity analysis incidents only: first-time users of OUD medication since 1 July 2006.

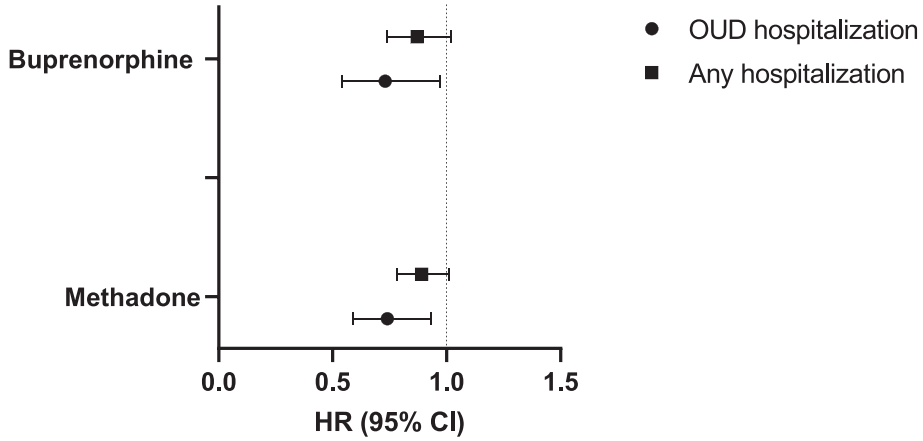

FIGURE 1 Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of hospitalization due to opioid use disorder (OUD) or any cause during pharmacotherapy compared with no use of medication in within-individual analyses

TABLE 2 The risk of OUD hospitalization in between-individual model and by duration of use for buprenorphine, methadone and any OUD medication. Dose stratified by the number of relapses experienced during the follow-up

The risk of OUD hospitalization	HR (95% CI)	*P*-value	*n* events
Buprenorphine	**0.53 (0.42–0.66)**	**< 0.0001***	275
Methadone	1.09 (0.86–1.38)	0.4995	651
Duration of medication use (days)	**HR (95%CI)**	***P*-value**	***n* events**
Buprenorphine			
≤ 30	**0.55 (0.43–0.71)**	**< 0.0001***	90
31–180	**0.46 (0.36–0.58)**	**< 0.0001***	122
181–365	**0.38 (0.26–0.57)**	**< 0.0001***	37
> 365	**0.36 (0.23–0.57)**	**< 0.0001***	26
Methadone			
≤ 30	0.93 (0.78–1.12)	0.4566	237
31–180	**0.77 (0.65–0.92)**	**0.0033***	279
181–365	**0.66 (0.50–0.88)**	**0.0041***	69
> 365	**0.70 (0.51–0.95)**	**0.0218***	66
Any OUD medication			
≤ 30	**0.79 (0.67–0.94)**	**0.0073***	327
31–180	**0.65 (0.55–0.76)**	**< 0.0001***	401
181–365	**0.55 (0.43–0.71)**	**< 0.0001***	106
> 365	**0.57 (0.43–0.74)**	**< 0.0001***	92

*Bold type denotes results significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons at a 0.05 threshold. Hazard ratios (HRs) with 95% confidence intervals (CIs), with non-use of both opioid use disorder (OUD) medications as a reference.

DISCUSSION

In this nation-wide cohort and with median follow-up of > 7 years, we found that use of either buprenorphine or methadone was associated with a reduced risk of hospitalization due to OUD and mortality due to any cause and external causes, in comparison to non-use periods of any OUD medications. To the best of our knowledge, no other prospective cohort study has investigated the long-term health outcomes (such as hospitalizations and all-cause mortality) associated with these medications in real-world circumstances. Using a within-individual design, we were able to reduce selection bias and study the effectiveness of medications in a non-selected patient population. A similar design was used in a study by Molero *et al*. 2018, in which the use of buprenorphine and methadone appeared to reduce suicidality and crime during treatment [20].

In this study, the use of either buprenorphine or methadone was associated with a significantly reduced risk of hospitalization due to OUD. To our knowledge, this risk has not been assessed previously. However, these results are in line with previous studies which have found buprenorphine and methadone to be effective in the treatment of OUD, especially in reducing overdose and serious opioid-related acute care use [4]. Buprenorphine has also been shown to reduce

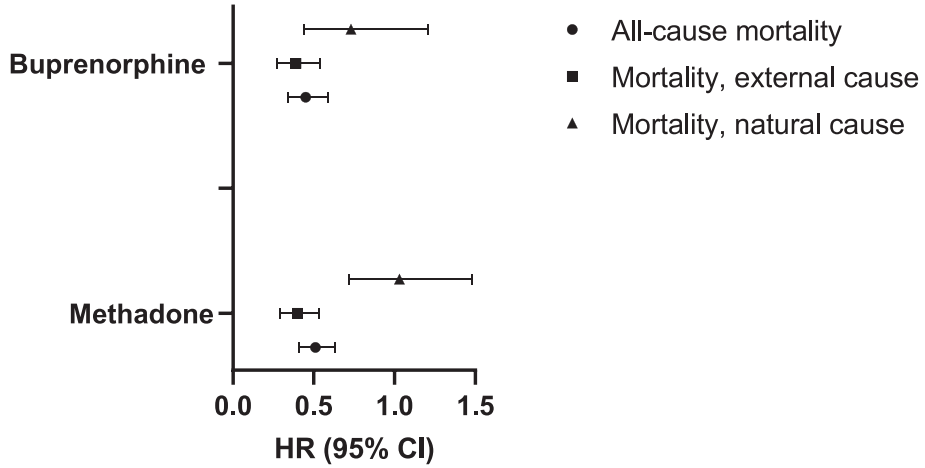

FIGURE 2 Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of mortality (all, external and natural causes). Between-individual model, adjusted for baseline covariates (age, gender, education, granted disability pension, long-term sickness absence) and time-varying covariates: (i) medication-related: temporal order of treatment, concomitant use of psychotrophic drugs, other medication use (opioid and non-opioid analgesics, cardiovascular medications, alimentary tract and metabolism medications, anti-epileptic drugs) and naltrexone, (ii) comorbidities: the number of previous hospitalizations due to opioid use disorder (OUD), cardiovascular disease, diabetes, asthma/chronic obstructive pulmonary disease (COPD), previous cancer, renal disease, previous suicide attempt, previous infections and other substance use disorders than OUD

TABLE 3 The risk of all-cause mortality in between-individual model and by duration of use for buprenorphine, methadone and any OUD medication. Dose stratified by the number of relapses experienced during the follow-up

The risk of all-cause mortality	HR (95% CI)	*P*-value	*n* events
Buprenorphine	**0.45 (0.34–0.59)**	**< 0.0001***	**76**
Methadone	**0.51 (0.41–0.63)**	**< 0.0001***	**191**
Duration of medication use (days)	**HR (95% CI)**	***P*-value**	***n* events**
Buprenorphine			
≤ 30	**0.50 (0.32–0.81)**	**0.0043***	20
31–180	**0.38 (0.25–0.56)**	**< 0.0001***	28
181–365	**0.35 (0.19–0.67)**	**0.0014***	10
> 365	**0.61 (0.37–1.00)**	**0.0479***	18
Methadone			
≤ 30	0.83 (0.62–1.11)	0.2114	68
31–180	**0.45 (0.33–0.60)**	**< 0.0001***	69
181–365	**0.22 (0.13–0.38)**	**< 0.0001***	15
> 365	**0.48 (0.33–0.69)**	**< 0.0001***	39
Any OUD medication			
≤ 30	**0.72 (0.55–0.95)**	**0.0177***	88
31–180	**0.42 (0.33–0.55)**	**< 0.0001***	97
181–365	**0.26 (0.17–0.40)**	**< 0.0001***	25
> 365	**0.51 (0.37–0.70)**	**< 0.0001***	57

*Bold type denotes results significant after Benjamini–Hochberg false discovery rate correction for multiple comparisons at a 0.05 threshold. Hazard ratios (HRs) with 95% confidence intervals (CIs), with non-use of both opioid use disorder (OUD) medications as a reference.

accidental overdoses [20]. Buprenorphine is usually well tolerated and, because of its high receptor affinity and only partial agonism, it protects against both overdose and reinforcing effects of full agonist opioids [8]. Conversely, as a full agonist, methadone has no ceiling effect compared to buprenorphine, which increases the risk for overdose when used at doses above the patient's tolerance [17].

However, our results suggest that the use of either of the studied medications seems safe and effective, considering their association with reduced risk of OUD hospitalization and as no association was found between studied medications and any-cause hospitalization (indicator of possible severe adverse effects).

Overall, 843 (14.7%) of the patients died during the follow-up time. The mortality rate in our study seems somewhat high compared to other studies regarding mortality among patients receiving opioid agonist treatment [14, 25, 26]. However, there is a limited number of studies within a similar setting. Studies are mainly RCTs or studies with a somewhat short follow-up time, which may explain the lower mortality rate compared with our results. The use of either buprenorphine or methadone was associated with a significantly reduced risk of mortality due to all and external causes. This association has also been previously reviewed [13], although the use of methadone has been linked to increased risk of accidental overdoses [20], which can cause death due to external causes. However, in this study methadone was also associated with a reduced risk of mortality due to external causes. No association with the risk of mortality were found due to natural causes and studied medications. This may be because the most commonly found causes of death among opioid users are overdose- or trauma and suicide-related (external causes), and disease-specific deaths (here presented as death due to natural cause) are far less common [27].

The risk for all-cause mortality and OUD hospitalization remained reduced when studied between analyses by the duration of any OUD treatment. The association of retention in OUD treatment and reduced mortality has also been observed in recent systematic reviews and meta-analyses [10, 14]. According to Sordo *et al*., the induction phase of methadone treatment and the time immediately after leaving treatment with both methadone and buprenorphine are periods of particularly increased mortality risk [13]. However, we did not find an increased risk of mortality or OUD hospitalization associated with any categorized duration of treatment, although methadone treatment during the first 30 days was not associated with a reduced risk of OUD hospitalization or mortality, unlike other duration categories. Evans *et al*. found in their cohort study in 2015 that exposure to detoxification and maintenance treatment (versus being out of treatment) was associated with lower risk of all-cause and cause specific mortality risk [25]. However, the median observation time was 2.6 years, and researchers assumed that observation over a longer time-period may reinforce knowledge of the cumulative protective effect of methadone maintenance treatment. Our results, with more than 7 years of follow-up, shows that the risk of all-cause mortality was significantly lower in all analyzed categories of duration of use for all exposures (the risk of all-cause mortality reduced from 28 to 78%). Thus, our findings extend knowledge of the effectiveness of OUD treatment during a longer period and offers valuable information to reduce the high mortality risk of OUD patients.

In Sweden, OUD treatment is basically available for all citizens at no or insignificant costs. However, an entry for maintenance treatment for OUD requires a diagnosis of OUD for at least 12 months. This inclusion criterion is stricter than in other Nordic countries [28] and may lead to a lower rate of pharmacological treatment for OUD. Low utilization rates of OUD pharmacotherapies have also been observed in other studies [1, 12, 16]. Despite Sweden's stricter inclusion criteria, entry for maintenance treatment does not require failed attempts of detoxification prior to opioid agonist treatment [28]. This seems reasonable, concerning the results of a large American cohort study reporting poor outcomes and decreasing odds of success in repeated attempts at detoxification [29]. The follow-up of this study started when a person purchased OUD medication for the first time, and thus we cannot make any conclusions regarding possible undertreatment of OUD in our study. However, only 83.8% of the patients had an OUD diagnosis, possibly indicating deficient diagnosing or recording of diagnoses of OUD.

Strengths and limitations

The main strength of this study is the data linkage of different registers and the nation-wide coverage of all actual OUD medication purchases (instead of data on prescriptions given to the patients) providing exceptionally wide data concerning medication use in real-world circumstances. Also, the follow-up time of up to 7 years was extensive. We analyzed the risk of hospitalization-based outcomes using within-individual design where each individual acts as his or her own control, which eliminates selection bias by accounting for factors remaining constant for an individual. Medication use was modelled with the PRE2DUP-method, which describes actual medication use well when compared with interview-reported use [30]. Even though the medical treatment of opioid use disorder is well established, our study provided new, pivotal information of the real-world effectiveness of buprenorphine and methadone on long-term health outcomes.

One of the limitations of this study is that some of the OUD medications are provided by the treatment centres and not dispensed through pharmacies; thus we could not acquire information on these treatments. However, in 2012 the number of opioid substitution treatment patients in Sweden was a little over 5000 [31], possibly indicating that the majority of patients using opioid substitution treatment is included in the cohort. Another limitation of this study is that we do not know whether people actually took medications they purchased. However, the medication use data take into account actually dispensed medications (from the pharmacy), not prescriptions for the medications. This provides more reliable information about the actual medication use.

In addition, there was no information on possible levels of illicit opioid use, so the effectiveness of studied medications was evaluated with secondary measures such as risk of hospitalization and death. However, these outcomes represent severe and significant consequences for both the individual and society. Another limitation is that we did not know whether an individual had psychosocial treatments during the use of medication. However, the effectiveness of non-pharmacological treatment is shown to be inferior to pharmacological treatment [4].

CONCLUSION

Buprenorphine and methadone were both associated with a significantly lower risk of hospitalization due to OUD and death due to all and external causes, when compared with no use of OUD medication. Thus, the results of our study imply the effectiveness of these pharmacological treatments of OUD. Regarding the analysis of the duration of medications, effectiveness seems to begin within the first month after initiation and remain similar during long-term treatment. Thereby, long-term use seems feasible, even for more than a year. Hospitalizations and mortality of individuals with OUD cause remarkable harm and costs for both individuals and society and, according to our findings, buprenorphine and methadone seem to reduce these outcomes. Increasing knowledge of the effectiveness of medications for OUD can encourage clinicians to steer their patients towards medical treatment of OUD and possibly strive societies for re-evaluating inclusion criteria for OUD treatment. Due to the increasing awareness of OUD medications being associated with favourable outcomes, societies may consider offering more low-threshold treatment to high-risk OUD patients.

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AUTHOR CONTRIBUTIONS

Milja Heikkinen: Conceptualization; data curation; formal analysis; investigation; methodology; software; supervision; validation; visualization. **Heidi Taipale:** Conceptualization; data curation; formal analysis; investigation; methodology; software; supervision; validation; visualization. **Antti Tanskanen:** Conceptualization; data curation; formal analysis; investigation; methodology; software; validation. **Ellenor Mittendorfer-Rutz:** Conceptualization; supervision. **Markku Lähteenvuo:** Conceptualization; formal analysis; validation; visualization. **Jari Tiihonen:** Conceptualization; formal analysis; funding acquisition; investigation; project administration; resources; supervision; validation.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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