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A retrospective cohort study of medication dispensing at pharmacies: Administration matters!

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ABSTRACT

Background: Opioid agonist treatment (OAT) for opioid use disorders may be delivered at treatment clinics or dispensed from pharmacies, however the type of delivery may be associated with different risks and benefits. The aim of the study was to investigate whether dispensing of methadone or buprenorphine at pharmacies during treatment for opioid use disorders was associated with adverse outcomes.

Methods: Retrospective cohort study using a national, linked, population-level data set from Denmark. Patients included were between 18 and 75 years, living in Denmark, and admitted for treatment for opioid use disorders during 2000–2016 (n = 9299). Cox proportional hazards regression was estimated for convictions, non-fatal overdoses, and death, after the first dispensing of either methadone or buprenorphine from a pharmacy after starting treatment.

Findings: Of all patients, 68 % had methadone and 31 % had buprenorphine dispensed at a pharmacy. Compared with the time prior to pharmacy dispension, the risk of criminal convictions increased after having methadone dispensed from a pharmacy (adjusted hazard ratio (aHR) = 1.22, 95 % confidence interval (CI) = 1.16-1.28), non-fatal overdoses (aHR = 1.55, CI 1.41-1.71), and all-cause mortality (aHR = 1.54, CI = 1.43-1.76). After having buprenorphine dispensed at a pharmacy, risk of criminal convictions increased (aHR = 1.08, CI = 1.01-1.16) and non-fatal overdoses (aHR = 1.31, CI = 1.18-1.45), but not all-cause mortality (aHR = 1.07, CI = 0.94–1.23).

Conclusions: For almost all outcomes investigated across medication type, the risk of adverse events increased following a switch from clinic dispension to pharmacy dispension of medications in OAT. Medically responsible and safe provision of OAT may often require more clinical follow-up than what is typically provided when medication is dispensed at pharmacies.

1. Introduction

Opioid use disorder (OUD) is a medical condition with substantial and increasing contribution to the global disease burden (Degenhardt et al., 2014). Illicit opioid use is associated with risk of infections, such as HIV and hepatitis C, poly-substance use, psychiatric comorbidity, criminal activity, and premature death (Degenhardt et al., 2019; United Nations Office on Drugs and Crime, 2019).

Opioid agonist treatment (OAT) with methadone, buprenorphine, or buprenorphine plus naloxone, has been shown to be effective at reducing use of illicit opioids, preventing drug-related deaths, and reduce overall healthcare costs for individuals with an OUD (Bukten et al., 2012; Sordo et al., 2017; Srivastava et al., 2017). However, a growing body of evidence suggests that mortality during and after OAT is time varying and differs by type of medication and quality of treatment (Evans et al., 2015; Kimber et al., 2015), and is related to gender, age, ethnicity, psychiatric problems, and area of residence (Brady et al., 2017; Martins et al., 2015).

The delivery of OAT varies considerably across countries and jurisdictions (Jin et al., 2020), including eligibility criteria, types of drugs, doses, use of urine testing to monitor treatment, and access to unsupervised intake.

Evidence suggests that OAT clinics and family doctors are equally effective at treating OUD (Fudala et al., 2003; Gibson et al., 2003; King

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et al., 2002). However, an important question is whether a patient should have the OAT medication dispensed at the clinic or at a pharmacy away from the clinic (Gauthier et al., 2018). Intake of medication under clinical supervision may reduce the patients' personal freedom, but at the same time allows for regular patient-clinician interactions and for the clinicians to observe clinical development and intervene accordingly (Cousins et al., 2011). Some argue that outpatient low threshold OAT is a feasible and safe clinical practice (Bhatraju et al., 2017), and that patients who find it difficult to attend the clinic regularly due to work, education or family commitments, are better treated by receiving their OAT medication at a pharmacy with take-home dosages, thereby reducing risk of dropout (Fingleton et al., 2015). However, take-home medication from a clinic and OAT medication dispensed from pharmacies with or without supervision present considerable risks. Studies indicate that patients who are dispensed OAT medication outside the context of clinics are at higher risk of fatal overdose (Daubresse et al., 2017; Delorme et al., 2016). In addition, there is a risk that medication is diverted (Johnson and Richert, 2015), contributing to increasing misuse of these medicines among persons outside of OAT (Bukten et al., 2019; Casati et al., 2012).

1.1. Is the current state of OAT in Denmark a liberal practice with flaws?

Denmark has taken a unique approach to handling the issue of OUD since the year 2000, which has been described as a shift from abstinence orientation towards harm reduction, and from a psychosocial approach towards a medical approach (Frank et al., 2013). Treatment for drug use disorders (DUD), including OUD, is publically funded and without co-payment (The Danish Health Authority, 2017), and the Danish law states that the local authorities must initiate treatment and formulate a treatment plan for OUD within two weeks of a treatment request from a patient (The Danish Health Authority, 2017). Within these two weeks, the patient must see a medical doctor, who assesses the treatment need of the patient and makes the final referral to the relevant type of treatment.

According to the Danish national guidelines, intake of OAT medication should be under clinical supervision at least once a week, depending on the patient's level of functioning and stability (The Danish Health Authority, 2017, p. 53). Other factors, such as the use of contingencies for take-home doses are at the discretion of clinic management, and varies considerably between the 98 municipalities in Denmark. The typical clinic employs a multidisciplinary team of social workers, nurses, a doctor, onsite medicine dispension services, and has at a minimum some level of wrap-around services, such as counselling, linkage with employment, housing and family services, and other municipal and regional services.

There are no specific guidelines regarding supervised intake when the medication is dispensed at a pharmacy; all pharmacies outside of public hospitals are private, and each pharmacy can decide whether supervised intake is offered as a service to the patient or not. The degree to which pharmacies are willing to observe medication intake varies considerably throughout Denmark, with none of the pharmacies in the capital area offering this service, and some offering it in other urban areas.

Despite the relatively low threshold access to OAT, and the implementation of a faster process between initial request and upstart in treatment, Denmark has for years ranked among the countries in Europe with the highest opioid overdose mortality rate (European Monitoring Center for Drugs and Drug Addiction, 2018; Simonsen et al., 2015). In a recent study, almost two-thirds of the deceased with methadone-related overdose death received methadone agonist treatment at the time of death, of which more than three-quarters did not have a supervised intake (Tjagvad et al., 2016). Against this background, it is of interest to explore if patients who receive OAT from pharmacies in Denmark fare better or worse than when they receive the medication from the clinics, with staff experienced with DUD.

The aim of the study was to investigate whether dispensing of methadone or buprenorphine at pharmacies in Denmark were associated with a higher or lower risk of later adverse outcomes. Specifically, we wanted to test whether risks of adverse outcomes increased or decreased after the first pharmacy-based dispensing of the medication. The adverse outcomes considered were convictions, non-fatal overdoses, and all-cause mortality.

2. Methods

2.1. Design

This was a retrospective cohort study utilizing a nation-wide dataset. Data for this study were drawn from multiple Danish registers. All the registers were linked, using the unique identification number assigned to each individual at birth or at first entry to Denmark as an immigrant. Consecutive admissions for treatment for DUD from 2000 to 2016 were included.

The Registry of Drug Abusers Receiving Treatment was used to identify patients who were enrolled in treatment for DUD (Pedersen et al., 2013). The register was established in 1996, and contains socio-demographic information, information concerning past year drug use and dates of starting treatment and discharge. Only the first episode for each patient in the time period was included. At the time of admission, a preliminary type of treatment is entered into the database (i.e., drug free treatment, OAT with methadone, OAT with buphenorphine, OAT with other opioid).

The Danish National Prescription Registry was used to identify prescription of drugs, and is a complete register of all prescribed medication dispensed through non-hospital based pharmacies since 1994 (Kildemoes et al., 2011). The medicines are classified according to the Anatomical Therapeutic Chemical (ATC) classification. Two variables were constructed to indicate dispensing of respectively methadone or buprenorphine in the year prior to treatment and after admission to treatment. The variables representing prescription after admission were codes as days elapsed since starting treatment.

The Danish National Patient Register was used to extract dates of hospital contacts, including inpatient and accident and emergency admissions (A&E), and admissions for non-fatal overdoses (Schmidt et al., 2015). The register is one of the world's oldest nationwide hospital registries, containing administrative and clinical data from public and private hospitals data from all Danish hospitals since 1977 with complete nationwide coverage since 1978.

The Danish Cause of Death Register (Helweg-Larsen, 2011) was used to identify dates of death.

The Central Criminal Register contains records on offenses and offenders in criminal cases for use in criminal procedures, and was used to obtain information on convictions. (Lund, 1990).

The Psychiatric Central Research Register was used to obtain information on psychiatric care. The register contains information for all outpatient, inpatient, and emergency contacts at psychiatric hospitals, including the dates of treatment admission and discharge, and mode of admission, and psychiatric diagnoses (Mors et al., 2011).

We followed the patients from their first registered treatment admission to December 31st 2016 or death, whichever occurred first. When multiple treatment episodes were recorded for the same patient, we used the first registered treatment episode for that patient.

2.2. Inclusion criteria

Patients were included if they were enrolled in publicly funded treatment for DUD in Denmark between January 1st 2000 and December 30th 2016, were between 18 and 75 years old at time of admission to treatment, and reported opioid use as the primary problem. Patients were excluded if information on substances were missing for both the past year use and the primary drug of use, or if their date of death was

invalid, e.g. if the date of birth exceeded the date of death. Fewer than five patients were excluded due to invalid data. We included only patients with an opioid as the primary drug, as patients seeking treatment who occasionally use opioids would not be likely to receive OAT.

2.3. Outcome variables

We considered the following types of events: convictions, hospital contacts with opioid overdose as diagnosis, and death. Patients were classified as having been convicted, if they had a record of conviction, regardless of type of offence. Patients were classified as having experienced an opioid related non-fatal overdose if they were registered with any hospital wcontact with a diagnosis of T40 (followed by any of the numbers 0–4 or 6) (Thylstrup et al., 2020).

2.4. Control variables

Information on all substances used by the individual patient 12 months prior to admission in the first registered treatment episode were extracted from The Registry of Drug Abusers Undergoing Treatment. Further, we included a treatment substitution predictor that indicated whether patients had initially been referred for methadone, buprenorphine, drug free treatment, and other types of substitution treatment (e.g., Levacetylmethadol or slow-release morphine). Based on the admission form, we also used a categorical predictor indicating previous DUD treatment versus no previous DUD treatment, or missing information on previous DUD treatment.

Using information from the National Patient Register, we constructed two dummy variables representing treatment in the past 12 months leading up to the first treatment, one for any record of admission to a hospital in Denmark, and one for A&E visits. Dummy variables for psychiatric care with no substance-related diagnosis and for conviction during the year prior to treatment admission were constructed, using psychiatric and criminal registers respectively.

Using Statistics Denmark, we constructed variables for participants representing gender, age (as a continuous variable), immigrant status (born in Denmark or not), civil status (married or not), living with children, and not in education, employment, and training (NEET) in the calendar year of admission.

2.5. Analyses

Descriptive statistics are reported as percentages for dichotomous variables and means with standard deviations for all other variables. Time-to-event analyses were conducted using the Cox proportional hazards model.

For all three outcome variables, i.e. conviction, non-fatal overdose, and all-cause mortality, we considered only the first event during the observation period (date of first enrolment to December 31st 2016 or death). Subjects were coded as having experienced one of the events if they had a record of one of events at any point after admission to OAT, and as censored if they had not experienced any of the events by December 31st 2016.

Total survival time for each type of event was calculated from the time of first registered OAT admission to the time of one of the first events or censoring. The STATA *stsplit* command was used to split the records between time at risk before and after the first pharmacy-based dispensing of methadone and buprenorphine respectively (Cleves et al., 2016). This method is appropriate in situations where a patient's health status or treatment regime change during an observation time for a time to event. When clustering for individuals is applied, the hazard of an event occurring before and after the change in health status or treatment regime can be directly compared using standard time to events models.

For the purpose of parameter estimation (estimation of the chosen parameters in the selected distribution), each original record was converted into two new observations, corresponding to before and after the first pharmacy-based dispensing of medication using the Stata *stsplit* command. The final analyses was conducted using clustering on ID. In this way, subjects functioned as controls until the date they received their first pharmacy prescription at a pharmacy. The *stsplit* command has been used in previous medical research (Almeida et al., 2016a, b; Leiva et al., 2017).

Post hoc power analyses were conducted to assess the minimal and maximal hazard ratio that could be detected given N, the r^2 of the main predictor with the remaining co-variates, and the standard deviation for the co-variates. Given a fail rate of 20 % (the lowest observed, for non-fatal overdoses), a multiple r^2 of 0.10, and a hazard ratio of 1.20, the power with 9299 observations was 0.96. Adequate power was obtained for hazard ratios greater than or equal to 1.16.

We produced Kaplan–Meier observed survival curves with fitted curves from Cox regression analyses on the same graph for all outcomes by both primary predictors, and compared the Kaplan-Meier graphs to the Cox graphs visually. The graphs are available as Supplementary material 2. As can be seen from the graphs, none of the curves showed visible signs of deviation from each other, indicating that the proportional hazards assumption for the Cox model was met in all cases.

All p-values were 2-tailed, and level of significance was assessed as a Type I error with a rate of alpha 0.01 due to multiple testing. All statistical analyses were performed using Stata 15 StataCorp (StataCorp, 2017).

Data are stored on secure servers at Statistics Denmark, and procedures were approved by the Danish Data Protection Agency. Since the data used for this study were collected and stored for monitoring and quality assurance in Denmark, no ethics evaluation for the present study was needed under the Danish law. The STROBE guidelines were used to

Table 1
Description of the sample at baseline (n = 9299).

Variable Substance use variables[1]	N	%
Injected	6582	70.8%
Heroin	5806	62.4%
Cannabis	4009	43.1%
Alcohol	1952	20.1%
Benzodiazepines	2314	24.9%
Cocaine	1645	17.7%
Amphetamine	927	10.0%
Prescription variables year prior to treatment[2]		
Methadone from pharmacy	2054	22.1%
Buprenorphine from pharmacy	1006	10.8%
Healthcare data[2]		
Psychiatric care	246	2.7%
Non-fatal overdose	416	4.5%
Inpatient hospitalization	1305	24.8%
A&E	4417	50.7%
Criminal record[2]		
Conviction	3881	41.7%
Socio-demographics[2]		
Female gender	2326	25.0%
Age (mean/standard deviation)	36.2/9.7	
Not in employment education, or training	7828	84.2 %
Danish background	8243	88.6 %
Household variables[2]		
Single	7347	79.0%
Living with children	1249	13.4%
Treatment type[1]		
No substitution/drug free	3560	38.3%
Buprenorphine	1080	11.6%
Methadone	4514	48.5%
Other substitution	145	1.6%
Previously treated[1]		
Yes	5338	57.4%
No	3722	40.0%
Missing information	239	2.6%

Note: [1]Based on the Registry of Drug Abusers in Treatment. 2 Based on record linkage.

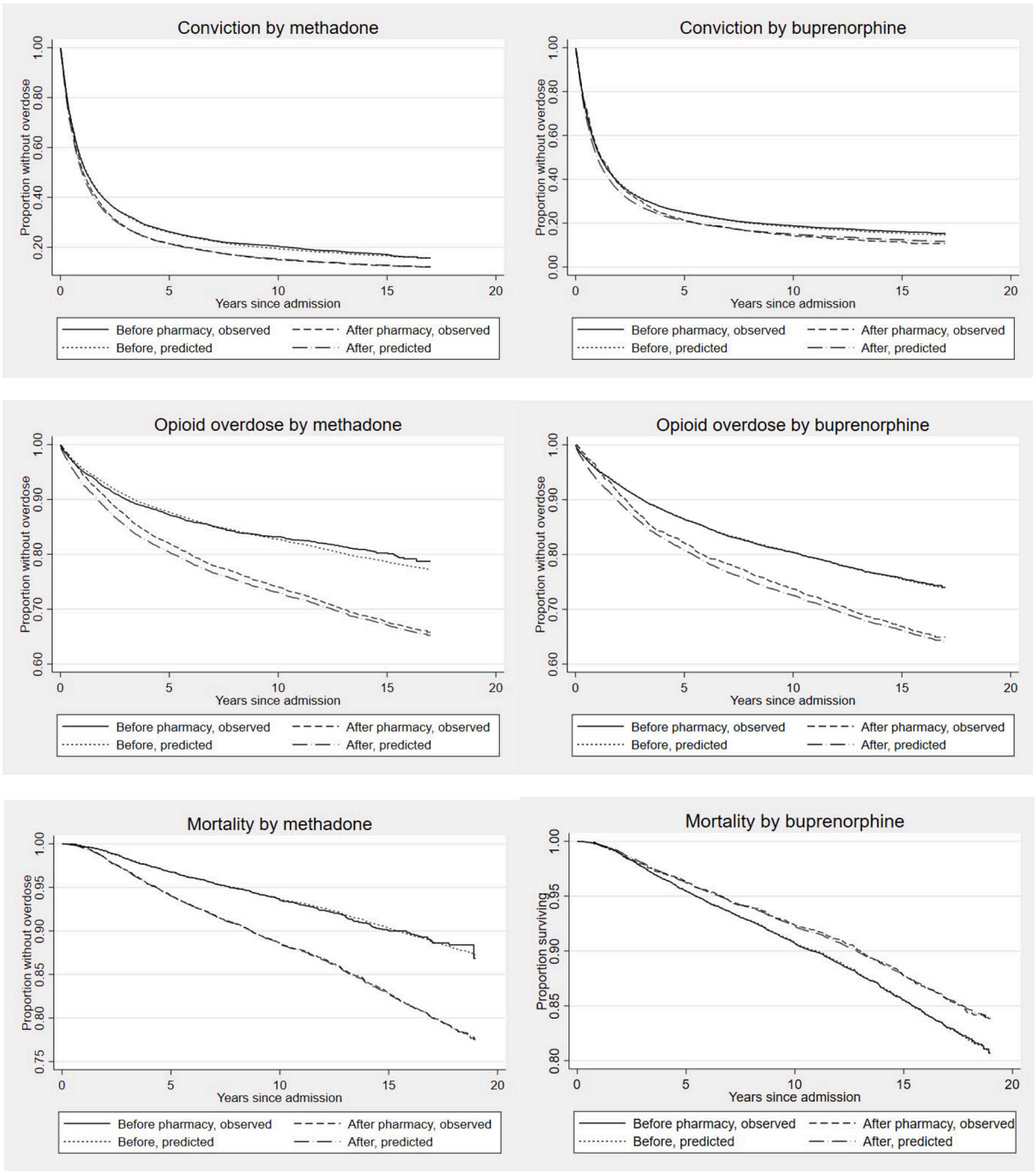

Fig. 1. Kaplan-Meier graphs of all five outcomes after admission for DUD treatment.
Notes: Full lines represent proportion surviving after first pharmacy pick-up, dashed lines represent proportion surviving before first pharmacy pick-up

ensure the reporting of this cohort study (Cuschieri, 2019).

3. Results

3.1. Study population

During the study period, a total of 9299 unique patients were admitted to treatment with an opioid as their primary drug and were eligible for the analyses. Characteristics of the sample at first admission are shown in Table 1. Most patients were men (75.0 %), born in Denmark (88.6 %), lived alone (74.9 %), lived in households without children (86.6 %), and were not in employment, education, or training (84.2 %). The mean age at treatment inclusion was 36.2 years (standard deviation = 9.7).

3.2. Pharmacy pick-up

In the study period, 7410 patients had OAT medication dispensed from a pharmacy at least once (i.e., either methadone or buprenorphine, 79.6 %). 68.2 % of the patients had had methadone dispensed from a pharmacy at some point (6339/9299), and 34.9 % had had buprenorphine dispensed from a pharmacy (3248/9299). Among those who were dispensed methadone, the median time from admission to first dispensing of methadone was 253 days (inter-quartile range = 27–991

Table 2
Cox-Regression multivariate analyses predicting conviction, non-fatal overdose, and all-cause mortality, among patients admitted to DUD treatment after methadone prescription (Denmark 2000-2016, N = 9299).

	Conviction		Non-fatal overdose		All-cause mortality	
Primary predictors[1]	HR	CI	HR	CI	HR	CI
Change in hazard after methadone prescription (unadjusted)	1.17	1.13–1.23	1.89	1.75–2.05	2.09	1.87–2.34
Change in hazard after methadone prescription (adjusted)	1.22	1.16–1.28	1.55	1.41–1.71	1.54	1.34–1.76

Notes: HR: hazard ratios CI: 95 % confidence intervals. Adjusted hazard ratios are adjusted for age, gender, injection drug use, use of heroin, cannabis, alcohol, benzodiazepines, cocaine, amphetamine, having picked up methadone from a pharmacy in the year prior to treatment, having picked up buprenorphine from a pharmacy in the year prior to treatment, having had psychiatric care in the year prior to treatment, having been convicted of a crime in the year prior to treatment, having been hospitalized in a general hospital in the year prior to treatment, having been in an acute and emergency unit in the year prior to treatment, having been working or studying in the year prior to treatment, being single at treatment admission, number of children in the household, being born in Denmark, having had previous treatment for drug use disorders.

days). For the patients who had buprenorphine dispensed from a pharmacy, the median time to first buprenorphine was 581 days (interquartile range = 105–176 days).

Among patients initially referred for methadone treatment, 80.0 % picked up methadone from a pharmacy at some point after admission to treatment (3633/4514), while 42.6 % of the patients who initially were referred for buprenorphine treatment picked up methadone (460/1080), and 61.9 % of the patients initially referred for drug free treatment picked up methadone from a pharmacy (2204/3560). Finally, 29.0 % of the patients initially referred for another type of OAT picked up methadone (42/145).

Among patients initially referred for buprenorphine treatment, 58.3 % picked up buprenorphine from a pharmacy at some point after admission (630/1080), 23.3 % among patients initially referred for methadone treatment picked up buprenorphine after admission (1054/4514), while 42.2 % among patients referred for drug free treatment did so (1502/3560). Finally, 42.8 % among patients referred for another type of OAT picked up buprenorphine at the pharmacy at some point after admission (62/145).

3.3. Outcomes

During follow-up, 7498 (80.6 %) of the patients had at least one conviction, corresponding to an incidence rate of 2539 per 10,000 observation years, while 2221 (23.9 %) of the patients had at least one hospital admission with a drug-related diagnosis, corresponding to an incidence rate of 237 per 10,000 observation years. Furthermore, 2776 (29.9 %) patients died during the follow-up period, corresponding to an incidence rate of 237 per 10,000 observation years. Fig. 1 shows the Kaplan-Meier and Cox estimates for all three outcome variables before and after first pharmacy pick-up. As can be seen from Fig. 1, in all cases the Cox and Kaplan-Meier functions are nearly identical, indicating that the proportional hazards assumption is not violated in any case.

Table 2 shows the regression results for methadone. In univariate analysis, the risk of conviction increased after the first methadone pick-up (hazard ration [HR] = 1.17, 95 % CI 1.13–1.23, $p < 0.01$). After adjusting for co-variates, the association remained significant (adjusted hazard ration [aHR] = 1.22, CI = 1.16–1.28, $p < 0.01$). The risk for non-fatal overdose was increased after the first pick-up of methadone (HR = 1.89, CI = 1.75–2.05, $p < 0.01$). After adjusting for co-variates, the association remained significant (aHR = 1.55, CI = 1.41–1.71, $p < 0.01$). The risk of all-cause mortality increased after pick-up of medication in the unadjusted analysis (HR = 2.09, CI = 1.87–2.34, $p < 0.01$). After adjusting for co-variates, this association remained significant (aHR = 1.54, CI = 1.34–1.76, $p < 0.01$).

Table 3 shows the regression results for buprenorphine. In univariate analysis, the risk of conviction increased after the first buprenorphine pick-up from a pharmacy (HR = 1.12, CI 1.05–1.19, $p < 0.01$). After adjusting for co-variates, the association was no longer significant (aHR = 1.08, CI = 1.01–1.16, $p < 0.01$). The risk for non-fatal overdose was increased after the first pick-up of buprenorphine (HR = 1.47, CI = 1.35–1.60, $p < 0.01$). After adjusting for co-variates, the association remained significant (aHR = 1.31, CI = 1.18–1.45, $p < 0.01$). The risk of all-cause mortality was lower after pick-up of medication in the unadjusted analysis (HR = 0.83, CI = 0.74–0.93, $p < 0.01$). After adjusting for co-variates, this association was reversed, and no longer significant (aHR = 1.07, CI = 0.94–1.23, not significant).

4. Discussion

The present study findings highlight the risks associated with referrals to dispensing of OAT medication at pharmacies, and maybe more so for the full-agonist methadone than for the partial agonist buprenorphine. We found that after having methadone or buprenorphine dispensed at a pharmacy, patients in treatment increased their risk for convictions, A&E visits, inpatient hospitalizations, and hospital visits due to non-fatal overdoses for methadone, and non-fatal overdoses for buprenorphine, as well as all-cause mortality. The results were significant even after controlling for potential confounders.

While induction of methadone may be a particular high-risk period for overdoses (Sordo et al., 2017), our findings show that multiple adverse outcomes, including overdose, are very likely to persist if OAT medication is dispensed at a pharmacy with little opportunity to observe and monitor the individual patient's clinical development on a regular

Table 3
Cox-Regression multivariate analyses predicting conviction, non-fatal overdose, and all-cause mortality, among patients admitted to DUD treatment after buprenorphine prescription (Denmark 2000-2016, N = 9299).

	Conviction		Non-fatal overdose		All-cause mortality	
	HR	CI	HR	CI	HR	CI
Change in hazard after buprenorphine prescription (unadjusted)	1.12	1.05–1.19	1.47	1.35–1.60	0.83	0.74–0.93
Change in hazard after buprenorphine prescription (adjusted)	1.08	1.01–1.16	1.31	1.18–1.45	1.07	0.94–1.23

Notes: HR: hazard ratios CI: 95 % confidence intervals. Adjusted hazard ratios are adjusted for age, gender, injection drug use, use of heroin, cannabis, alcohol, benzodiazepines, cocaine, amphetamine, having picked up methadone from a pharmacy in the year prior to treatment, having picked up buprenorphine from a pharmacy in the year prior to treatment, having had psychiatric care in the year prior to treatment, having been convicted of a crime in the year prior to treatment, having been hospitalized in a general hospital in the year prior to treatment, having been in an acute and emergency unit in the year prior to treatment, having been working or studying in the year prior to treatment, being single at treatment admission, number of children in the household, being born in Denmark, having had previous treatment for drug use disorders.

basis (Daubresse et al., 2017; Delorme et al., 2016).

The fact that more than half of all patients in this study had methadone dispensed at a pharmacy at some point after their first admission to OAT, while around one in three had buprenorphine dispensed at a pharmacy, underlines that the treatment for OUD in Denmark is best characterized as liberal (Tjagvad et al., 2016), although countries may be difficult to compare due to multiple differences (Jin et al., 2020).

Regardless of the variations in the delivery of OAT across countries and jurisdictions, the findings in this study underline that transferring patients with an OUD to pharmacy dispensing of OAT medication is likely to come with a considerable risk of adverse events. While the pharmacy may be an important location for providing treatment for some patients with an OUD, such a model is far from a feasible and safe clinical practice for all patients. Psychosocial treatment should be an integrated part of OAT and involve regular patient contact in the stabilizing phase and in critical periods with at least some minimal level of ongoing relevant services (Kraft et al., 1997; McLellan et al., 1993). With regard to the Danish OAT model, the study findings underline that dispensing of OAT medication at pharmacies should primarily be an option for patients who have been stable in OAT provided at the clinics for a longer period, both with regard to misuse of substances, general health condition, and possible criminal behavior. Another possibility is to make all types of take home medication contingent on progress in other forms of rehabilitation, such as working or other meaningful daily activities (King et al., 2002; Ohlin et al., 2015).

The identification of pharmacy-based OAT as a potential risk factor for adverse outcomes is important and should be dealt with by both public health and clinical strategies in order to mitigate such risk. For example, pharmacy-based treatment may be improved by strategies similar to those implemented by Scotland in the 1990ties, where pharmacies took on the responsibility to monitor patients and ensure observed medication intake (Roberts and Hunter, 2004). Future research must be conducted to properly compare OAT provided at the pharmacy and in the clinic, and, if possible, include periods in and out of each treatment. Future research should address mechanisms by which various models of treatment improve or fail to improve outcomes.

4.1. Limitations and strengths

The study had a number of strengths. The largest strength is the national coverage and the unique opportunity to use multiple national registers to study treatment-seeking individuals with OUD over a long period to observe outcomes from treatment. The registers used for outcomes are all considered to be of excellent quality (Kildemoes et al., 2011; Lund, 1990; Mors et al., 2011). Furthermore, the data from the Danish national registers enabled us to adjust for many potential confounders.

However, a number of limitations exist as well. First, there may be periods in which some individuals have missing information in the treatment registries, or during which a small number of individuals are missing. Second, questions on the admission form that is used to record information about patients as they enter treatment for DUD in Denmark are not standardized and may not be optimal (i.e. simply asking participants if they used a substance in the past year). Similarly, when type of treatment was recorded in The Registry of Drug Abusers Receiving Treatment, a social worker would in many cases enter a preliminary referral into the database, before the patient had seen a physician and received the final referral to type of treatment. Further, it is a limitation in the study that there are no national guidelines regarding supervised intake when the medication is dispensed at a pharmacy.

Finally, while the register data from pharmacies, crime, and time of death are of high quality, they do not provide a level of data that is necessarily optimal to characterize treatment services. For instance, the existence of a record indicating that a patient picked up methadone or buprenorphine is only an indicator that the level of monitoring was decreased at that point in time. Some patients may have received considerable support and monitoring from pharmacies, while others may have received little or no monitoring or support from clinics. However, that there is no central data collection on this, it is impossible for us to say to what extent pharmacies and clinics collaborated on supporting patients.

5. Conclusions

In order to reduce adverse consequences related to OUD, there is a need for more clinical follow-up during OAT than what is typically provided when medications are dispensed at pharmacies. OAT without appropriate clinical follow-up may be harmful to patients, either because staff is unable to monitor treatment, or because medication is diverted from pharmacy-based treatment. Given the high rate of methadone related deaths in Denmark while in OAT, a review of the current clinical practise in treatment of people with OUD may be warranted.

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Data statement

All data used for this study is the property of the Danish Government, and can be obtained by applying to the Danish Health Data Authority (The Danish Health Authority, 2017).

Authors' contributions

Authors' contributions for "How Opioid Agonist Treatment medications are administrated to patients matters! A retrospective cohort study of medication dispensing at pharmacies"

MH initially conceived of the study. MH and AK conducted initial statistical analyses, and all authors conducted literature searches, added perspectives, and suggested additional analyses. All authors read and revised the final manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2021.108792.

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